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Origin and evolution of the neuroendocrine control of reproduction in vertebrates, with special focus on genome and gene duplications

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130 **Abstract**

131 In human, as in the other mammals, the neuroendocrine control of reproduction is ensured by
132 the brain-pituitary gonadotropic axis. Multiple internal and environmental cues are integrated
133 *via* brain neuronal networks, ultimately leading to the modulation of the activity of
134 gonadotropin-releasing hormone (GnRH) neurons. The decapeptide GnRH is released into the
135 hypothalamic-hypophyseal portal blood system, and stimulates the production of pituitary
136 glycoprotein hormones, the two gonadotropins, luteinizing hormone (LH) and follicle-
137 stimulating hormone (FSH). A novel actor, the neuropeptide kisspeptin (Kiss), acting
138 upstream of GnRH, has attracted increasing attention in recent years. Other neuropeptides,
139 such as gonadotropin-inhibiting hormone (GnIH) / RF-amide related peptide (RFRP), and
140 other members of the RF-amide peptide superfamily, as well as various non-peptidic
141 neuromediators such as dopamine and serotonin also provide a large panel of stimulatory or
142 inhibitory regulators. This paper addresses the origin and evolution of the vertebrate
143 gonadotropic axis. Brain-pituitary neuroendocrine axes are typical of vertebrates, the pituitary
144 gland, mediator and amplifier of brain control on peripheral organs, being a vertebrate
145 innovation. The paper reviews, from molecular and functional perspectives, the evolution
146 across vertebrate radiation of some key-actors of the vertebrate neuroendocrine control of
147 reproduction, and traces back their origin along the vertebrate lineage and in other metazoa
148 before the emergence of vertebrates. A focus is given on how gene duplications, resulting
149 from either local events or from whole genome duplication events (WGD), and followed by

150 paralogous gene loss or conservation, might have shaped the evolutionary scenarios of current
151 families of key-actors of the gonadotropic axis.

152

153 **1. Introduction**

154 The neuroendocrine control of reproduction has been extensively investigated in mammals
155 (for review: (370)). Two pituitary hormones, the gonadotropins, *i.e.* luteinizing hormone (LH)
156 and follicle-stimulating hormone (FSH), are released in the general blood circulation and
157 regulate gonad activity. The synthesis and release of gonadotropins is mainly controlled by a
158 neuropeptide, gonadotropin-releasing hormone (GnRH), produced by hypothalamic
159 neurosecretory neurons and released into the portal blood system connecting the median
160 eminence to the adenohypophysis. GnRH neuron activity is itself regulated by various brain
161 neuromediators, which allows the integration of multiple environmental and internal cues in
162 the course of developmental or seasonal control of reproduction (Figure 1).

163 Other major physiological functions in mammals are similarly controlled by brain-pituitary-
164 peripheral gland axes, such as the thyrotropic axis (brain-pituitary-thyroid) for development
165 and metabolism, the somatotropic axis (brain-pituitary-liver) for body growth, the
166 corticotropic axis (brain-pituitary-adrenal gland) for stress and metabolism. The pituitary
167 gland and its role as a relay between the brain and peripheral glands or peripheral organs, is
168 considered as an innovation of the vertebrate lineage (for review: (641, 738, 740)). The
169 pituitary gland with its production of pituitary hormones under the control of brain
170 neurohormones is a common feature to all vertebrates, even though some anatomical
171 variations in the brain-pituitary relationships are observed. In mammals as in other tetrapods,
172 hypophysiotropic neurons project to the median eminence and neurohormones are released
173 into the pituitary portal system which irrigates the adenohypophysis, while, in teleost fishes,
174 hypophysiotropic neurons directly project up to the adenohypophysis which exhibits a high

175 regionalization of pituitary cell types (231, 287). In cyclostomes (hagfish and lamprey), brain
176 neuropeptides reach the adenohypophysis by diffusion from the third ventricle, which may
177 represent the ancestral pattern of connection between the hypothalamus and the pituitary in
178 vertebrates (for review: (738)).

179 We review here current information and hypotheses on the origin, conservation and variations
180 of the key actors of the vertebrate brain-pituitary control of reproduction, with a special
181 attention to the impact of gene and genome duplication events in the evolutionary scenario of
182 their molecular families.

183

184 **2. Looking for the origin and evolution of the neuroendocrine control of reproduction**

185 **2.1. Objectives**

186 Comparative biologists have been investigating the control of reproduction as well as of other
187 physiological functions in non-mammalian vertebrates and other metazoa. Comparative
188 studies not only provided specific information on species of interest, but also led to major
189 advances for basic research. A remarkable example concerns the “neurosecretion” process,
190 *i.e.* the ability of certain neurons to synthesize and release hormones, a property exhibited for
191 instance by GnRH neurons. Hypothalamic neurosecretory neurons were first described in
192 1928 in a teleost fish species, *Phoxinus laevis*, by Ernst Scharer (679), who established the
193 concept of “neurosecretion”, a few years after the description by Carl Speidel (1919) (742) of
194 some “glandular” neurons in the spinal cord of chondrichthyan fish, the skates (for reviews:
195 (665, 678)). In the same line, the first RF-amide peptide, designated after the C-terminal
196 arginine (R) and amidated phenylalanine (F) residues, has been isolated in 1977 from the
197 ganglia of a mollusk, the Venus clam, *Macrocallista limbosa* (623). Since then, an increasing
198 number of RF-amide peptides have been identified in all metazoa, constituting the RF-amide

199 superfamily and including some brain peptides involved in the neuroendocrine control of
200 reproduction in vertebrates (see section 5).

201 Comparative and evolutionary reproductive neuroendocrinology is arousing interest for
202 various disciplinary fields, thanks to the variety of biological models investigated and the
203 availability of tools such as genome sequences. There is an increasing attention to teleosts
204 (*e.g.* zebrafish) as vertebrate models for biomedical research, and an increasing diversity of
205 species investigated worldwide for their relevance to agriculture, aquaculture, conservation,
206 or environmental assessment. Comparative and evolutionary neuroendocrinology aims at
207 tracing back the roots and the evolution of the neuroendocrine systems, from molecular and
208 functional perspectives, and at inferring their roles in the evolution of metazoan species and
209 lifecycles. For agronomic sciences, it contributes to increase basic and applied knowledge for
210 sustainable control of reproductive cycles in captivity, for understanding domestication
211 processes, for diversifying cultured species such as in aquaculture, and promoting sustainable
212 agro/aqua-systems. For conservation biology, it provides new knowledge for understanding
213 the role of neuroendocrine systems in species adaptation and adaptability to environmental
214 factors, a crucial topic in the context of global, climatic and anthropogenic changes. In
215 biomedical sciences, comparative and evolutionary neuroendocrinology contributes to
216 innovative advances by providing alternative vertebrate models suitable for experimentation
217 such as zebrafish, by revealing the evolutionary conservation of key neuroendocrine actors
218 and of their sequences, the mutation of which may lead to severe pathologies, or by
219 highlighting common processes in the impact of environmental stressors and pollutants
220 leading to the disruption of the reproductive capacity of wild species, domesticated animals or
221 humans, in the frame of the “One health” concept.

222

223 **2.2 Bases of phylogeny**

224 In order to investigate and compare neuroendocrine systems in an evolutionary perspective, it
225 is necessary to relate the data obtained in a given species to the phylogenetical position of this
226 species. Phylogeny of vertebrates and metazoa is by itself an ongoing research topic, based on
227 multiple disciplinary fields such as paleontology, comparative anatomy, embryology, and
228 more recently molecular systematics and phylogenomics. We are using, in the present
229 manuscript, recent and largely consensual advances in vertebrate and metazoa phylogeny.

230

231 2.2.1. Phylogeny of vertebrates (Figure 2)

232 All vertebrate species belong to a monophyletic clade, *i.e.* a group of species that consists of
233 all the descendants of a common ancestor. Among the vertebrate clade, several “subclades”
234 can be distinguished. The most ancient (or most basal) is represented by cyclostomes (such as
235 lampreys and hagfish). Cyclostomes are the sister clade of all other vertebrates characterized
236 by the innovation of the jaws and therefore called gnathostomes. The gnathostome clade is
237 further divided into two sister clades, the chondrichthyans (such as sharks and ray fishes) and
238 the osteichthyans. The osteichthyan clade is further divided into two major sister clades: (i)
239 the actinopterygian clade that encompasses teleost fishes (the largest current group of
240 vertebrates with more than 25,000 species including most fisheries, aquaculture and model
241 fish species) and some other “fish” clades such as holosteans (gar); (ii) the sarcopterygian
242 clade that encompasses the tetrapods including mammals, and also some “fish” species such
243 as the coelacanth, representative species of actinistia, a basal group among sarcopterygians.
244 The current vertebrate phylogeny highlights in particular that the name “fish” is not by itself
245 phylogenetically relevant, as it may apply to species from very distinct vertebrate clades, such
246 as cyclostomes (lampreys), chondrichthyans (sharks), actinopterygians (gar, zebrafish), and
247 sarcopterygians (coelacanth). Thus, human and coelacanth are phylogenetically closer than
248 coelacanth and zebrafish or than human and zebrafish.

249

250 2.2.2. Phylogeny of metazoa (Figure 3)

251 While the broad lines of vertebrate phylogeny remained similar to the traditional classification
252 based on paleontology, comparative anatomy and embryology, the recent advances in
253 molecular systematics and phylogenomics largely challenged the classification of other
254 metazoa (8, 170). We present here a most consensual phylogeny of the major clades of
255 metazoa. Bilateria, the major clade among metazoa, gather animals with a bilateral symmetry
256 (at least at the embryonic stage) and with three tissue layers (endoderm, mesoderm, ectoderm)
257 during embryogenesis so that they are also called triploblastics. Besides bilateria, the
258 respective classification of the basal groups of metazoa, such as cnidaria (corals), porifera
259 (sponges), and others, is still largely under debate. Bilateria encompass two major clades, on
260 the one hand, deuterostomes which include chordates and among chordate the vertebrates, and
261 on the other hand, protostomes which include two major sister clades, ecdysozoa (flatworms,
262 insects, crustaceans,..) and lophotrochozoa (annelids, mollusks, ...) (8, 608).

263

264 2.2.3. Phylogeny of molecular families versus phylogeny of species

265 Phylogenetical analyses of protein families of interest, such as hormones / neuropeptides /
266 receptors / enzymes, potentially involved in the neuroendocrine control of reproduction, are
267 performed in order to compare sequences between various vertebrate or metazoa species.
268 Phylogenetic trees of molecular families highlight protein sequence conservation or
269 divergence and lead to hypotheses on evolutionary relationships between sequences and
270 possible functional variations. The phylogenetic tree of a given protein family does not
271 always follow the phylogenetic tree of the corresponding species, which makes it possible to
272 infer further hypotheses on the duplication, divergence, convergence and loss of
273 corresponding protein-coding genes.

274

275 **2.3. Origin and fate of duplicated genes**

276 Gene duplications produce so-called paralogous genes, and are considered as major drivers of
277 evolution, as they provide new gene pools allowing the emergence of novel functions, organs
278 and regulatory processes.

279

280 **2.3.1. Intra-gene duplication**

281 Besides gene duplication, intra-gene duplication of exons also contributes to the evolution of
282 neuroendocrine systems, as exemplified by the multiple copies of thyrotropin-releasing
283 hormone (TRH) peptide coded by the TRH gene (397), or by up to three homologous
284 gonadotropin-inhibiting hormone (GnIH) peptides coded by the GnIH gene (see section 5).
285 Intra-gene peptide duplication may lead to the amplification of peptide production or, after
286 mutations of some of the duplicated sequences, to the production of distinct peptides with
287 potentially differential activities.

288

289 **2.3.2. Local gene duplication**

290 Gene duplication produces paralogous genes and may originate from local genomic events,
291 targeting either a specific gene or a limited genomic region. If no major genomic
292 restructuration occurs afterwards, local duplication events can be traced back in extant species
293 genomes by tandem position or by a relatively close position of the paralogous genes on the
294 same chromosome. For instance, a local gene duplication in early gnathostomes is
295 hypothesized to be at the origin of the two gonadotropin receptors, LH receptor and FSH
296 receptor, positioned in tandem in tetrapods, including human, as well as in basal
297 sarcopterygian (coelacanth) and basal actinopterygian (gar) (468). The conservation of the
298 tandem position throughout vertebrate evolution may be related to conserved coordination of

299 gene expression, *via* chromatin accessibility and common regulatory factors. In the primate
300 lineage, a specific gene duplication of the LH beta subunit (LH β) gene, that occurred much
301 more recently, is at the origin of the chorionic gonadotropin beta subunit (CG β), involved
302 in the regulation of an innovative reproductive organ, the placenta; further CG β duplications
303 led to up to six hCG β genes in human arranged in a gene cluster together with the LH β gene
304 on chromosome 19 (for review: (522)) (see section 3).

305

306 2.3.3. Whole genome duplication

307 Gene duplications may also originate from whole genome duplication events (WGD), as
308 proposed by Ohno in vertebrates (548). Gene paralogs stemming from WGD are thus named
309 “ohnologs” by certain authors. It is now consensually admitted that two successive WGD,
310 referred to as “1R” and “2R”, for “first round” and “second round” of whole genome
311 duplications, have occurred at the base of the vertebrate lineage (Figure 2), even though the
312 exact timing of the second WGD is still under discussion (for review: (284)). These 1R and
313 2R WGD, which occurred about 450 Million years ago, are still traceable in the current
314 human genome, by fourway paralogous regions (paralogons) covering a large proportion of
315 the human genome (145). It has been advanced that the two rounds of WGD may have
316 contributed to the evolutionary success of the vertebrate lineage.

317 Genome sequencing of teleost fish models, such as medaka, fugu or zebrafish, revealed an
318 additional WGD, referred to as 3R (for 3rd round of WGD) (for review: (484)) (Figure 2).

319 When occurred this 3R WGD in the actinopterygian lineage event, remained under debate
320 until recently, as more genomes became available including for species of key phylogenetic
321 positions such as a non-teleost actinopterygian, an holostean, the spotted gar (72), or a basal
322 teleost, an elopomorph, the eel (273, 274). These studies concluded that, in the course of
323 actinopterygian evolution, the 3R would have specifically occurred in the teleost lineage, in

324 an early teleost ancestor before the emergence of the basal group of elopomorphs. This 3R
325 event is thus also referred to as TWGD or TGD (teleost whole genome duplication) (586), and
326 is hypothesized to have contributed to the diversification of this group, the largest among
327 vertebrates.

328

329 2.3.4. Definition of homologous, orthologous, paralogous, or ohnologous genes

330 These definitions are important in order to analyze the molecular and functional relationships
331 and diversification processes among molecular families including those involved in
332 neuroendocrine systems. Homologous genes are present in the same or different species, and
333 all derive from a common ancestral gene. Homologous genes include orthologous, paralogous
334 and ohnologous genes. Orthologous genes are genes present in different species and evolved
335 from a common ancestral gene in the course of speciation (emergence of new species over the
336 course of evolution). Paralogous genes are present in the same or in different species and
337 result from the duplication of a common ancestral gene, either *via* local gene specific
338 duplication or *via* WGD. Ohnologs are paralogs resulting from WGD.

339

340 2.3.5. Fate of duplicated genes

341 Gene duplication produces two paralogs, which initially exert the same redundant function. In
342 most cases, this redundancy leads to a rapid loss of one of the two paralogs, *via* accumulation
343 of mutations due to redundancy-related lack of selective pressure. However, both paralogs
344 may be conserved after duplication due to evolutionary selection related to amplification of
345 initial function, or sharing of initial pleiotropic functions (subfunctionalisation), or emergence
346 of a new function (neofunctionalisation). Duplications followed by gene amplification,
347 subfunctionalisation, neofunctionalisation, or loss, are involved in the evolutionary scenarii of
348 the neuroendocrine gonadotropic axis.

349

350 **3. Origin and evolution of gonadotropins, the pituitary relay between brain and gonads**
351 **in vertebrates**

352 **3.1. Vertebrate gonadotropins**

353 3.1.1. Discovery of pituitary gonadotropins

354 A role of pituitary gland activity on the development of gonads was suggested as far back as
355 1910 (132) by studies showing that hypophysectomy leads to an atrophy of genital organs.
356 The first experiment describing the stimulatory effects of bovine pituitary extracts on rat
357 ovarian growth and luteinization was published in 1922 (180), demonstrating that the anterior
358 part of the pituitary gland contains a gonadotrophic factor. It took a decade before this factor
359 appeared to be composed of two distinct fractions in ewes, one responsible for growth of
360 ovarian follicles and the other for luteinization (190). These two fractions were accordingly
361 named follicle-stimulating hormone (FSH) and luteinizing hormone (LH), respectively.
362 Technical improvement in glycoprotein purification methods, and notably the development of
363 ion-exchange chromatography, made possible a better assignment of the roles of LH and
364 FSH. In hypophysectomised rats, it was found that FSH acts on granulosa cells of the
365 Graafian follicles and LH on the *theca interna* and ovarian interstitial tissue, the combination
366 of the two stimulating estrogen secretion, ovulation and *corpus luteum* formation (834). The
367 dimeric nature of LH, first suggested by Li and Starman (1964), was confirmed by Papkoff
368 and Samy (1967) (576) who characterized two dissimilar subunits in ovine LH. The
369 biological activity of the reconstituted dimer was finally demonstrated by De la Llosa and
370 Jutisz (1969) (382).

371 Another factor was also purified from the bovine pituitary gland that stimulates the thyroid
372 (126). Homology between this thyroid-stimulating hormone (TSH) and the gonadotropins was
373 suggested after experiments demonstrating that mammalian LH and FSH are able to stimulate

374 the thyroid of teleost fish (203, 204). Soon after, it was established that LH, FSH and TSH
375 have one interchangeable subunit, the glycoprotein hormone (GPH) α subunit, whereas the β
376 subunit determines the hormonal specificity (609). The first amino acid sequence of an LH α
377 subunit was deciphered in 1971 (428) and its identity with the FSH α subunit was
378 demonstrated in 1974 (710). The first sequences of β subunits also appeared in the early 70s
379 ((428) for LH; (417) for TSH; (710) for FSH), confirming the homology between thyrotropin
380 and gonadotropin β subunits. It was thus established by the mid-seventies that the two
381 pituitary gonadotropins and the thyrotropin belong to a family of dimeric glycoproteins that
382 share the α subunit, whereas the three β subunits, which confer hormonal specificity, are
383 derived from a common evolutionary ancestor.

384 The demonstration of the existence of two pituitary gonadotropins was laboriously extended
385 to all tetrapod groups (for review: (309)); teleosts ((758), for review: (407); chondrostei (628);
386 dipnoi (627); chondrichthyans (629)), showing that all jawed vertebrates are provided with
387 the same pituitary gonadotropic molecules. Up to now, a single gonadotropin has been
388 discovered in the cyclostomes, in hagfish (819) and in lamprey (741) even though, in this later
389 species, the α subunit has still to be identified (739). Glycoprotein hormones (*stricto sensu*),
390 like all other pituitary hormones, are not found before the emergence of vertebrates (83).

391

392 3.1.2. Non-pituitary gonadotropins

393 The presence of a luteotrophic factor in urine of pregnant women was first observed in 1927
394 (24), leading to the development of the first pregnancy detection test. This gonadotropic
395 factor was shown to be produced by placental cells in culture (327) and more specifically by
396 syncytiotrophoblast cells (485) and named human chorionic gonadotropin (hCG). The
397 similarity with LH in terms of biological activity was rapidly observed (439) and its ability to
398 bind the same receptor as LH was later demonstrated (92), hence the LH-CG receptor naming.

399 Eventually, the close structural relatedness of hCG to LH was confirmed when sequencing
400 data were made available (765). The human CG β subunit has later been found to be expressed
401 in the pituitary (61) and testis (53, 583). Pregnant mare serum was also shown to contain a
402 gonadotropic factor (123) that was called pregnant mare serum gonadotropin (PMSG) before
403 its origin as a chorionic cell product was recognized and its name changed to equine chorionic
404 gonadotropin (eCG). It was later demonstrated that, unlike their human counterparts, eCG and
405 eLH β subunits are encoded by the same gene (702). LH β subunit expression also occurs in
406 the placenta of a marsupial (482) and possibly in diverse eutherian mammals (119).

407

408 3.1.3. Extra-pituitary expression of LH and FSH

409 LH and FSH are also expressed in the gonads and the brain. The first report of gonadal
410 expression of gonadotropin described the immunological detection of LH in human and rat
411 Leydig cells and that of FSH in Sertoli cells (849). LH β subunit transcripts were further
412 characterized in elongated spermatids in the rat (910), and were found to possess an extended
413 5' UTR end resulting in the same coding sequence as the pituitary transcript apart from the
414 first three amino acids of the signal peptide (909). In female rat, FSH β , LH β and the common
415 α subunits are produced by theca cells, *corpora lutea* and oocytes, whereas granulosa cells
416 only express LH subunits. The ovarian LH β subunit gene uses the same alternative promoter
417 as in the testis (680). Expression of this transcript is reduced by administration of PMSG,
418 which activates both LH and FSH receptors in non-equine species (249, 419). Interestingly, *in*
419 *vitro* granulosa cell expression of LH β mRNA is also decreased in response to a GnRH
420 agonist, likely through FSH receptor activation (425). Both LH and FSH are expressed in the
421 Siberian hamster ovary with levels varying according to the estrus cycle but in an opposite
422 fashion as in the pituitary (699). No specific role has been described for these gonadal
423 gonadotropins. Whether gonadal expression of gonadotropins is a common feature in

424 mammals or other tetrapods remains to be clarified but this seems to be the case in teleosts (4,
425 172, 626, 705, 706, 728, 879, 882). It has to be noted that the seabream ovarian LH β subunit
426 transcript is also extended in its 5' end, suggesting the existence of a conserved alternative
427 and gonadal-specific promoter for the LH β gene. However, the expression of the two ovarian
428 gonadotropins is up-regulated by GnRH in the sea bream (879). Ovarian LH β subunit
429 expression in the sole also varies according to the ovarian maturation stage, like in the
430 pituitary (706).

431 Another important site of expression of gonadotropins in teleosts is the brain (172, 496, 580,
432 705). It was notably observed in a cichlid that the two gonadotropins expressed in the preoptic
433 area potentially play a regulatory role on pituitary expression of gonadotropins (574). LH is
434 also expressed in rat hypothalamus in a manner that depends on the presence of a functioning
435 pituitary (177). Brain gonadotropins may be involved in neuronal regulation of steroid
436 synthesis (427).

437

438 3.1.4. Main regulators of gonadal function

439 Genetic mice models where either the FSH β (380) or LH β (442) subunit or the FSH (1) or LH
440 (908) receptor is deleted show that ovarian differentiation and growth are not dependent on
441 pituitary gonadotropin stimulation even if FSH stimulates proliferation of granulosa cells in
442 pre-antral follicles. In teleosts, timing of pituitary gonadotropin expression as compared to
443 gonadal differentiation also pleads for a process that does not involve gonadotropins (518).
444 Mammalian FSH receptors are expressed in granulosa cells from the secondary follicle stage
445 (follicles with at least two layers of granulosa cells) onward and LH receptor expression on
446 theca cells rapidly follows. After puberty onset, FSH is indispensable for the cyclic
447 recruitment of follicles (after oocytes have reached their maximal size) and terminal
448 folliculogenesis. LH is involved in the final steps of pre-ovulatory follicle maturation,

449 allowing meiosis to resume and inducing ovulation (6, 239, 474). LH is responsible for the
450 production of aromatizable androgens by theca cells. These androgens then reach granulosa
451 cells where they are converted into estrogens under the stimulatory action of FSH (371, 708).
452 At mid-cycle, granulosa cells of recruited follicles acquire LH receptor expression and initiate
453 progesterone production, the stimulation of which is later relayed by hCG. Progesterone is
454 essential for ovulation and for preventing further follicle maturation.

455 As for the ovary, pituitary gonadotropins are not required for testicular differentiation but
456 FSH stimulates proliferation of Sertoli cells in prepubertal testis (399, 448). At puberty onset,
457 FSH promotes Sertoli cell function but its importance for spermatogenesis depends on
458 taxonomic groups (297). LH stimulates proliferation of adult-type Leydig cells responsible
459 for the production of steroid hormones (792) and activates steroidogenesis and therefore,
460 spermatogenesis.

461

462 3.1.5. A role for gonadotropin subunit monomers or homodimers?

463 The gonadotropin receptors are poorly activated by gonadotropin subunit monomers or
464 homodimers. However, the hCG β subunit is produced in large excess in most epithelial
465 cancers and is believed to play an autocrine angiogenic and anti-apoptotic role, possibly
466 through interacting with components of cysteine-knot growth factor (and notably TGF β)
467 receptor complexes (124, 303). Free glycoprotein hormone α subunit is also produced in
468 excess by the pituitary and secreted throughout the menstrual cycle (255) and by the placenta
469 (635). In the placenta, the free α subunit is much more potent than the intact hCG in acting
470 synergistically with progesterone to induce decidualization of endometrial stromal cells (512)
471 and stimulates prolactin release from human decidual cells (65). Interestingly, the free α
472 subunit stimulates differentiation and proliferation of prolactin-producing cells in the foetal
473 and postnatal mammalian pituitary gland (31, 42, 95) and prolactin release by frog pituitary

474 cells in culture (544). The action of the free α subunit is not mimicked by LH or hCG
475 heterodimer, demonstrating that the free α subunit, like hCG β , may have a specific role
476 independent on the activation of the gonadotropin receptors.

477

478 **3.2. Structural characteristics of gonadotropins**

479 The glycoprotein hormones are non-covalently linked heterodimers composed of an α subunit
480 that is common to all gonadotropins and TSH and a specific β subunit that confers biological
481 specificity. In all species, the pituitary gonadotropin subunits are transcribed from single
482 genes although some teleost fishes may be provided with two α subunit genes, resulting from
483 genome duplication in recent ancestors (407). The α subunit gene contains four exons, the
484 first of which encoding the 5' untranslated region, the three others coding for a 92-100 amino
485 acid-long protein excluding the signal peptide. All pituitary glycoprotein hormone β subunit
486 genes contain three exons, the first one coding for the 5' untranslated region and, in some
487 species, part of the LH β signal peptide. The second intron-splicing site is located at the same
488 position in all β subunit genes.

489

490 **3.2.1. Global folding and general characteristics**

491 The most obvious characteristics shared by the α and all β subunits are the presence of one or
492 two glycosylation sites at conserved position and a conserved arrangement of cysteine
493 residues. The crystal structure of hCG was resolved almost simultaneously by two different
494 laboratories (390, 883). The structure of FSH was later deciphered (206) demonstrating that
495 the overall folding pattern of the two glycoprotein hormone dimers is very similar. Taking
496 into account the high degree of conservation of the glycoprotein hormone subunits in
497 vertebrates and in particular the special cysteine arrangements (with the exception of teleost
498 FSH β subunit as related below), it is tempting to assume that this organization is conserved

499 among vertebrate gonadotropins. Both the α and β subunits belong to the large cysteine-knot
500 family of proteins and more specifically to the TGF- β subfamily (13, 28, 271). They present a
501 similar folding producing flat elongated structure organized in a head to tail orientation in the
502 dimer. Each subunit contains four antiparallel β strands tightened with a central cysteine-knot
503 motif from which three hairpin loops are deployed so that loops 1 and 3 from one subunit are
504 intertwined with loop 2 of the other subunit. The determining knot motif involves six cysteine
505 residues from each subunit (Figure 4). Four of them bridge β 2 and β 4 strands with two
506 disulphide bonds forming an eight-residue ring through which penetrates a third disulphide
507 bond linking the two other cysteine residues from the β 1 and β 3 strands. The α subunits
508 contain a total of 10 cysteine residues, the two additional pairs linking the β 1 to β 2 and β 3 to
509 β 4 strands tying the amino- and carboxy-termini to the core molecule. The β subunits have
510 twelve cysteine residues. In addition to those involved in the knot, two of them form a
511 disulphide bridge linking together the tips of loop 1 and loop 3 and two others, seven amino
512 acids apart from each other, are involved in an intra-chain bonding located at the end of the
513 β 4 strand. The last two cysteine residues form a disulphide bridge between loop 1 and the C-
514 terminal extremity that constitutes the buckle of the “fastening belt” that wraps the carboxy-
515 end of the β subunit around the α subunit loop 2. This latter structure is of crucial importance
516 for maintaining the stability of the dimer at the low concentrations encountered in the
517 peripheral circulation (13, 888).

518

519 3.2.2. α subunits

520 The α subunit is globally well conserved across vertebrates, a feature that is expected since a
521 mammalian α subunit is able to associate with a teleost LH β subunit to produce a heterodimer
522 that retains most of the biological activity of the native teleost LH (78, 201). Such stability in
523 structure probably results from the constraints imposed on the α subunit that has to efficiently

524 associate with three different β subunits. The α subunits show alternate variable and
525 conserved regions. The variable regions, where insertions/deletions are encountered, are
526 located at the level of loop 1 and loop 3 as well as in the amino-terminal end of the protein.
527 On the contrary, the most conserved regions lie in $\beta 2$, $\beta 3$ and $\beta 4$ strands and in loop 2. Great
528 apes α subunit sequences are characterized by a 4-amino acid-long deletion in the amino-
529 terminal end, at an intron-splicing site. Some teleostean or chondrosteian sequences also show
530 deletions at this site. Surprisingly, mutations of cysteine codons occur in some sequences.
531 This is particularly the case in hagfish (*Epatretus atami*) where cysteines C2 and C4 are
532 replaced by an arginine and a tyrosine, respectively. C2 is usually involved in the disulphide
533 bridge with C7 that is part of the cysteine knot motif whereas C4 bridges with C1 to move $\beta 1$
534 and $\beta 2$ strands closer to each other (Figure 4). There is only one clone identified and
535 sequenced in hagfish (819), so these apparent mutations might result from artefacts in the
536 cloning or sequencing process. Nevertheless, a different assignment of the cysteine residues
537 may be operating in this subunit with C1 replacing C2 in the bonding with C7 and the absence
538 of bonding between $\beta 1$ and $\beta 2$ strands. Substitutions in cysteine residues are also observed in
539 the α subunit of the Elephant shark (*Callorhynchus milii* - NCBI NM001292594.1) where C9
540 is replaced by an arginine, of the Tiger salamander (*Ambystoma tigrinum* - CN048018.1) with
541 C6 also replaced by an arginine, and the Arabian camel (*Camelus dromedarius* -
542 XM010987723.1) (but not *C. bactrianus* - XM_006178591.1 and *C. ferus* -
543 XM_010948966.1) with C2 replaced by an aspartic acid. Whether these substitutions
544 correspond to sequencing errors or to true mutations remains to be clarified. Two
545 glycosylation sites are overall conserved except in crows (*Corvus cornix* - XM010404527.2,
546 *C. brachyrhynchus* - XM_08640241.2 and *C. macrorhynchus* - AB563175.1) where the
547 asparagine at the junction of loop 2 with the $\beta 3$ strand is replaced by an aspartic.
548 Carbohydrate side chains are predicted to impact on synthesis and storage, on receptor

549 binding and signal transduction, and eventually on metabolic clearance of gonadotropins
550 (271). Since three species at least out of this taxonomic group share this substitution, a
551 compensatory mechanism should occur for these gonadotropins to assemble and elicit full
552 biological activity.

553

554 3.2.3. LH β subunits

555 LH β subunits are 112-121 amino acid-long, with the exception of equine LH β where a 10
556 nucleotide-long deletion induces a shift in the reading frame leading to an extension of the
557 carboxy-terminal end in very much the same as for hCG β (702). The lamprey gonadotropin β
558 subunit (*Petromyzon marinus* - AY730276.1) is also extended at the carboxy-terminal side. If
559 it is an ancestral characteristic, it has not been conserved in the hagfish (*Eptatretus atami* -
560 AB546741.1), another cyclostome species. In comparison to the α subunit, there are no major
561 insertions/deletions within the mature proteins apart for single or two amino acid-long
562 deletion events in some species, occurring in the region of loop 2. The degree of conservation
563 at the amino acid level is lower than in the α subunit. In addition to the twelve cysteine
564 residues, conserved amino acids are found mostly within the β strands but also in the loops
565 that seem to be more constrained than in the α subunit. LH and TSH β subunits usually have
566 one glycosylation site conservatively located in the β 1 and the β 2 strand, respectively,
567 whereas FSH β subunits have both of them. One glycosylation site is actually found in a
568 conserved position in almost all LH β subunits. It is to be noted that, in the spotted green
569 pufferfish (*Tetraodon nigroviridis* - CR706772.2) and in the fugu *Takifugu rubripes* -
570 XM_003963794.2), two related species, the unique glycosylation site is displaced to the
571 carboxy-terminal end, between C10 and C11, two cysteine residues that are linked by a
572 disulphide bridge. The zebrafish (*Danio rerio* - BC162111.1) LH β subunit has a second site
573 also at this position. Two glycosylation sites are also found in LH β subunits in primates

574 except in human. The two sites are located as in FSH β subunits. Remarkably, the
575 gonadotropin β subunit of cyclostomes, the most basal extant vertebrate species, is provided
576 with the same two glycosylation sites. It is not known whether cyclostomes have only one or
577 two pituitary gonadotropins. All TSH β subunits have two additional amino acids inserted in
578 loop 2 (467) so that the hormone identified in cyclostome that do not have these two
579 additional amino acids most likely belongs to the gonadotropin lineage. It is not known if this
580 GTH is homologous to LH or FSH or is ancestral to LH and FSH, hence the naming GTH for
581 gonadotropic hormone (739, 741, 819). A third potential glycosylation site is found in the
582 lamprey GTH β subunits in their specific carboxyl extension.

583

584 3.2.4. CG β subunit

585 The primate CG β subunit genes arose from a duplication of the LH β subunit gene just before
586 the divergence between New World and Old World Monkeys (see 3.3 Origin and evolution of
587 gonadotropins). These sequences are characterized by a frame shift in the coding sequence
588 due to a single nucleotide deletion, 8 codons before the LH β stop codon. This event generated
589 a carboxyl extension of the encoded protein including several serine residues that are O-
590 glycosylated in trophoblast cells. One of the consequences of this higher glycosylation level is
591 the higher half-life of hCG in the blood when compared to hLH (112).

592 Equine CG β subunits are encoded by the LH β subunit gene expressed in the trophoblast.
593 Surprisingly, a similar carboxyl extension phenomenon occurred in equidae albeit due to a
594 different mechanism. In equidae, a ten nucleotide-long deletion occurred, leading to the same
595 frame shift as in primates (702).

596

597 3.2.5. FSH β subunit

598 The less conserved subunit is the β subunit of FSH. This is mainly due to their high

599 evolutionary rate in the teleost lineage (627). Up to twelve amino acid residues are deleted in
600 the most derived teleosts, the acanthomorphes, essentially in the loop regions. The most
601 spectacular feature of the teleost FSH β subunits is the rearrangement of the cysteine residues.
602 Although conserved in most basal teleosts including ostariophyses (carp and catfish related
603 species), cysteine C3, which is involved in the latch of the seatbelt loop with C12, is then lost.
604 The seatbelt loop is determinant for the ability of the dimer to keep associated once diluted in
605 the general circulation. Teleosts have developed alternative means to ensure the seatbelt to be
606 fastened. In more recently emerged taxonomic groups (clupeocephala), an additional cysteine
607 (which will be referred to as C0) is found at the amino-terminal end that is extended to the left
608 and includes amino acids aligned to the signal peptide in other taxonomic groups
609 (elopomorphes (341); salmonids (758, 761); percomorphes (225, 226, 373, 553, 866)). It was
610 found by mutating the hCG β subunit so as to reproduce this teleost-type cysteine pattern that
611 the seatbelt could be latched by a disulphide bridge between C0 and C12 (888). In
612 cyprinodontiformes, the mature sequence after cleavage of the signal peptide does not include
613 C0 (709). Instead, another cysteine residue is found either two amino acids downstream of the
614 usual C3 position or just following C5, and it is likely that these subunits use the natural
615 gonadotropin β subunit folding pattern. The cleavage site of the signal peptide has not been
616 characterized so far in ostariophyses. If the mature protein includes C0, their sequence would
617 totalise 13 cysteine residues. Another striking feature in FSH β subunits is the more flexible
618 position and number of glycosylation sites. FSH β subunits usually have two glycosylation
619 sites. The one on the β 1 strand is generally well conserved except in some teleosts. The other
620 site is absent or displaced to variable regions in most teleost species. In an extreme case, the
621 Atlantic halibut (AJ417768), the FSH β subunit is deprived of any glycosylation site. At the
622 opposite, a third site is occasionally found in some sharks, teleosts, turtles, birds and
623 crocodiles. The unique pattern of cysteine arrangements or glycosylation states of teleost

624 FSHs offers remarkable examples to investigate structure-function relationships. It is to be
625 noted that most of these studies have been performed on mammalian hormones expressed in
626 mammalian cells cultured at 37°C and thus, far from the low temperature at which most
627 teleost gonadotropin assemble and act.

628

629 **3.3. Origin and evolution of gonadotropins**

630 3.3.1. Recent discovery of additional members of GPH family in mammals

631 In search for ligands for orphan G-protein-coupled receptors in the human genome, Hsu and
632 his colleagues identified two new glycoproteins, also present in other vertebrate genomes, that
633 share numerous characteristics with the glycoprotein hormone subunits (293). They were
634 called GPA2 (GPHA2) and GPB5 (GPHB5) as for the second glycoprotein hormone related α
635 subunit and the fifth glycoprotein hormone related β subunit. GPA2 and GPB5 are able to
636 associate into heterodimer and the heterodimer is able to stimulate the TSH receptor but not
637 the gonadotropin receptors (523). The heterodimer was therefore named thyrostimulin.

638

639 3.3.2. Ancient origin of GPA2/GPB5 before the emergence of vertebrates

640 These glycoproteins, which are found in most bilateria (293, 581, 640, 645, 663), are now
641 referred to as GPA and GPB in invertebrates that lack the classical glycoprotein hormone
642 subunits (83). In most investigated invertebrates, the genes encoding GPA and GPB are
643 located close to each other without intervening genes (662), suggesting a functional or
644 regulatory link between them. A leucine-rich repeat-containing receptor related to the
645 glycoprotein hormone receptors (279, 437) was also identified in several invertebrate species
646 (645). The fly receptor (LGR1) binds and is activated by the fly GPA/GPB heterodimer (749).
647 Interestingly, in the parasitic wasp *Nasonia* (266), the leech *Helobdella* (832) and the
648 myriapode *Strigamia* (833), three species that lack GPA and GPB, the homologous receptor is

649 also absent. Altogether, these data strongly suggest that the vertebrate glycoprotein hormone
650 α and β subunits derive from a duplication of GPA and GPB, respectively, early after the
651 emergence of vertebrates.

652

653 3.3.3. A limited role for vertebrate GPA2/GPB5 in reproduction

654 No consensus role for GPA and GPB in invertebrates have been proposed to date even if they
655 may have been involved in specific functions in different species (640). In vertebrates, few
656 data are yet available. Like GPH α , GPA2 harbours two glycosylation sites, the position of the
657 one just after loop 2 being conserved. The other one is located on the β 1 (by analogy with
658 GPH α) strand. GPA2 lacks the cysteine residues involved in the bonding between β 1 and β 2
659 strands. It contains, in addition to the six residues composing the cystine-knot motif, two
660 cysteine residues that are believed to form a disulphide bridge between loops 1 and 3. These
661 loops appear longer than in GPH α . GPB5 is encoded by two exons with the same intron/exon
662 splicing site as for GPH β subunits. It harbours only one glycosylation site, located on the β 3
663 strand, just following the cysteine knot motif. The main difference between the GPB5 and
664 GPH β subunits is the absence of the carboxy extension that constitutes the seat belt. As
665 mentioned earlier, this seat belt is essential for the stability of the dimer so it is believed that a
666 GPA2/GPB5 dimeric structure may not be maintained once diluted into the general
667 circulation (13). The thyrostimulin naming of the GPA2/GPB5 dimer is based on the ability
668 of the recombinant dimer to stimulate the TSH receptor but not gonadotropin receptors (523,
669 552). It is further supported by the hyperthyroid phenotype observed in mice chronically
670 injected with the recombinant dimer (552) and in mice ubiquitously overexpressing GPB5
671 (443). In the latter case, the thyrotropic effect was attributed to the dimer formed by the
672 overexpressed GPB5 with the GPA2 naturally expressed in the thyroid to activate the TSH
673 receptor. However, the thyrostimulin concept is not supported by the absence of obvious

674 thyroid phenotypes in GPB5 knocked-out mice (443, 552) except for a transient
675 hypothyroxinemia in juveniles (907). Surprisingly, no GPA2-knocked-out mice have been
676 described. The GPA2/GPB5 dimer is 10 to 20 times more active than TSH in stimulating TSH
677 receptor (552). Taking into account the wide variety of tissues expressing GPA2 and/or GPB5
678 (293, 520, 523, 552) and the TSH receptor (874), it is conceivable that the GPA2/GPB5 dimer
679 may act as a local activator of TSH receptor. However, numerous tissues do not seem to co-
680 express GPA2 and GPB5 so that, as for the free α and hCG β subunits, other modes of action
681 as monomer or homodimer must be explored for GPA2 and GPB5. In any case, no
682 abnormalities in fertility were mentioned in GPB5 knocked-out mice (443, 552, 906, 907) so
683 that a major role of the GPA2/GPB5 dimer or of GPB5 by itself in the control of reproduction
684 is very unlikely.

685

686 3.3.4. Evolution of the GPH family in vertebrates

687 Taking advantage of the availability of sequenced genomes from species of phylogenetical
688 significance, comparative synteny analysis between amphioxus (a pre-vertebrate chordate)
689 and vertebrate glycoprotein hormone subunit loci allowed the reconstruction of their
690 evolutionary history in vertebrates (467, 663). A first local duplication of a tandemly
691 organized GPA and GPB locus occurred just before the radiation of vertebrates and the
692 emergence of cyclostomes, giving rise to the vertebrate forms of GPA and GPB (GPA2 and
693 GPB5) and to the ancestral glycoprotein hormone (ancGPH) α and β subunits (Figure 5). The
694 *ancgpha* gene was maintained close to *gpa2-gpb5* whereas the *ancgph β* gene was translocated
695 soon after the duplication. After the first round of WGD (1R), one copy each of *gpa2* and
696 *gpha* was lost from one of the duplicated *gpa2-gpha-gpb5* loci, leaving two copies of *gpb5*,
697 *i.e.* *gpb5a* in the remaining *gpa2-gpha* locus and *gpb5b*. After the second WGD (2R), only
698 one copy of the duplicated *gpb5b* was retained. From the duplicated *gpa2-gpb5a-gpha* locus,

699 one copy of the duplicated *gpha* and one copy of the duplicated *gpa2-gpb5a* were lost,
700 leaving a single *gpha* encoding gene and the remaining single copies of the tandemly
701 organized *gpa2* and *gpb5a*. These two genes were kept in tandem in teleosts (663) and in the
702 Coelacanth (Ensembl scaffold JH127632; unpublished data). *gpb5a* was lost in tetrapods that
703 only retained *gpb5b*. The ancestral form of *gphβ* that was somehow parted from its original
704 environment soon after the original, local duplication was duplicated at the 1R giving rise to
705 an ancestral the gonadotropin β subunit gene (*ancgthβ*) and to an ancestral TSHβ subunit gene
706 (*anctshβ*) (Figure 5). The 2R duplicated the *ancgthβ* to generate *lhβ* and *fshβ* genes. One of
707 the duplicated copy of the *anctshβ* gene (encoding TSHβ2) was retained in chondrichthyes
708 and in lungfish and coelacanth but was lost before the radiations of teleosts and tetrapods
709 (467). Of note, after the Teleost-specific WGD (3R), of all duplicated *gph* genes only the
710 duplicated *tshβ1* gene was maintained (encoding TSHβ3 or TSHβ1b according to a recent
711 nomenclature), all other duplicated glycoprotein hormone subunit genes being lost (467, 663).
712 As mentioned earlier, two copies of GPHα subunit-encoding genes may have been generated
713 in some teleost species, resulting from recent, specific tetraploidization events.

714 While a tandem duplication was at the origin of the glycoprotein hormone family in
715 vertebrates, the most recently appeared glycoprotein hormone, CG, was also generated by a
716 tandem duplication that occurred during the radiation of primates, just before the divergence
717 between New and Old World monkeys, some 35 to 55 Million years ago (272, 460).
718 Subsequent gene duplications led to a rising number of CGβ duplicates, that are not all
719 functional (in human, 4 out of 6 CGβ genes are functional), up to about 50 copies in gorilla
720 (169). The New World monkeys have only one CGβ and one LHβ subunit gene. Surprisingly,
721 in the marmoset and probably in all New World monkeys, the LHβ gene has lost its pituitary
722 functionality, and it is the CGβ gene that is expressed in the pituitary and in the placenta from
723 specific promoters (514). The first duplication event probably affected only the LHβ gene but

724 subsequent duplications also concerned the neurotrophin NTF4 gene (also called NTF5 or
725 NTF6) although only one copy retained its functionality. Surprisingly, phylogenetic analysis
726 of LH β and CG β transcripts showed that CG β sequences tend to group with the LH β
727 sequence from the same species instead of with CG β sequences from closely related species.
728 This phenomenon was shown to be due to gene conversion *i.e.* nonreciprocal transfer of
729 sequence information, where the LH β gene sequence and notably its first and second exons
730 act as the parent for *cg β* genes conversion (460).

731

732 **4. Origin and evolution of GnRH, brain conductor of reproduction in vertebrates**

733 **4. 1. Introduction**

734 In the late 1920s, once the involvement of the pituitary in the processes of reproduction was
735 demonstrated, systematic investigations were initiated to decipher the link between the
736 hypothalamus and pituitary gonadotropin secretion (491, 614). Harris was the first to propose
737 the hypothesis of neurohumoral regulation of gonadotropin secretion (192). The question that
738 remained to be resolved was how information perceived in the CNS would be communicated
739 to the pituitary gland. In the early 1960s, several investigators reported, in crude hypothalamic
740 extracts, the existence of substances that specifically stimulated the secretion of luteinizing
741 hormone (LH) or folliculo-stimulating hormone (FSH), and that were probably polypeptides
742 (367). It was concluded therefore that the hypothalamus regulates the release of LH and FSH
743 by means of two releasing hormones (LH-RH and FSH-RH), transported to the anterior
744 pituitary *via* the hypothalamic portal circulation. From that moment, several teams devoted
745 their efforts to the isolation and identification of LH- and FSH-releasing hormones. The
746 isolation of the single substance able to stimulate the synthesis and secretion of both
747 gonadotropins was independently achieved in 1971 from porcine and ovine brain by the
748 groups of Schally (465) and Guillemin (16, 77), respectively. It was a decapeptide that was

749 initially termed LH-releasing hormone (LHRH) or LH-releasing factor (LRF), but the
750 molecule is now generally referred to as gonadotropin-releasing hormone (GnRH). For this
751 seminal discovery, Schally and Guillemin were awarded the Nobel Prize in Physiology or
752 Medicine in 1977.

753

754 **4.2. Origin and evolution of GnRH**

755 4.2.1. GnRH in mammals

756 The first GnRH form isolated from pig and sheep is an amidated decapeptide with the
757 sequence pQHWSYGLSPGamide (77, 465). This sequence is identical in almost all
758 mammalian species investigated so far (556). As other neuropeptides, GnRH is synthesized as
759 part of a larger precursor molecule called pre-proGnRH. The full-length cDNA encoding this
760 precursor was initially cloned from a human placental library (687). In human, pre-proGnRH
761 is a protein of 92 amino acids that consists of the decapeptide, extended at the N-terminus by
762 a signal peptide, and at the carboxy-terminus by a Gly-Lys-Arg sequence necessary for
763 enzymatic cleavage and carboxy-terminal amidation of GnRH. The 56 aa-residue sequence
764 located in the C-terminal region of the precursor is called the GnRH-associated peptide
765 (GAP). The architecture of pre-proGnRH is conserved in other mammals.

766 The mammalian GnRH gene is composed of four exons and three introns (688). Exon 1
767 contains a part of the 5'-UTR. Exon 2 encodes the rest of the 5'-UTR, the signal peptide, the
768 GnRH decapeptide, the amidation/proteolytic processing motif and the N-terminal part of the
769 GAP. Exon 3 encodes the central portion of the GAP. Exon 4 encodes the C-terminal part of
770 the GAP along with the 3'-UTR.

771 Immunofluorescence and immunohistochemical studies using specific antibodies revealed
772 that GnRH is primarily localized in neurons located in the hypothalamus, particularly in the
773 arcuate-median eminence region and the preoptic area (36, 403). In the median eminence,

774 GnRH nerve terminals secrete directly into portal capillaries. The peptide is then delivered by
775 the portal circulation to the adenohypophysial gonadotrope cells (614). An important feature
776 of the secretory activity of GnRH neurons is its pulsatile nature (43). The frequency and
777 amplitude of secretory episodes are essential for the release as well as the synthesis of LH and
778 FSH by gonadotrope cells (784).

779 It was shown that GnRH neurons arise from the nasal placode and migrate to their target
780 regions in the hypothalamus during development (682, 881); for review:(880)) This finding is
781 in agreement with the observations that humans deficient in GnRH also lack their sense of
782 smell and with studies showing a loss of GnRH cells in animals with olfactory placode
783 ablation (871, 880).

784 In 1994 was reported, for the first time in mammals, the occurrence of a second GnRH gene
785 (347). Details regarding this second gene will be provided in the next section since it encodes
786 a peptide whose sequence was already described in chicken since 1984 (500).

787

788 4.2.2. GnRH in other vertebrates: contribution to the discovery of multiple GnRHs

789 For a long time after it was discovered, GnRH was thought to have an invariant sequence
790 because all mammalian peptides that were characterized were identical (643). This view was
791 invalidated in 1982 when the first GnRH variant, containing the substitution Arg⁸→Gln, was
792 isolated from chicken hypothalami (364, 365, 498, 499). Several other molecular isoforms
793 were subsequently identified through peptide purification, cDNA cloning, and more recently
794 data mining. They were primarily found in teleosts, but also in amphibians, elasmobranches
795 and cyclostomes, and even in mammals (for review: (556)). They were generally named
796 according to the species in which they were initially isolated. However, a given form found in
797 a particular species or group can exhibit a much wider distribution, making this nomenclature
798 particularly confusing. For example, salmon GnRH (sGnRH) (703) is present in many other

799 teleost species, including medaka and zebrafish (381, 555). Likewise, the mammalian form of
800 GnRH (mGnRH) is also found in frogs (127, 269) and fishes (228, 558) but not in the guinea
801 pig (323).

802 In 1984, the occurrence of a second GnRH was demonstrated in the chicken, called chicken
803 GnRH-II (cGnRH-II) in addition to cGnRH-I (500). Since then, it became evident that almost
804 all vertebrate species are able to produce more than one GnRH form, each encoded by a
805 peculiar gene (for review: (556)): two in most of them, including human (868) and even three,
806 notably in teleosts (870) but also in lampreys (349, 704, 715, 737, 757). Very interestingly,
807 cGnRH-II is present in all gnathostomes with exactly the same structure. As a result, in
808 species that express two GnRH forms, the cGnRH-II variant is systematically present in
809 combination with a second one which corresponds to mGnRH in most mammals (870), some
810 amphibians (127) and fishes (228), or cGnRH-I in birds (498, 500) and reptiles (436). In
811 teleost species possessing three forms, cGnRH-II is often associated with the sGnRH variant,
812 plus a third form whose structure is more variable (619).

813 The peptides belonging to the GnRH family share several characteristics: (i) They all are
814 decapeptides with residues 1, 4, 9 and 10 perfectly conserved as well as modified amino-
815 (pGlu) and carboxy-terminus (NH₂) (248) (Table 1). (ii) They originate from preproGnRH
816 precursors that exhibit the same features as those of mammals (248). (iii) The general
817 organization of their genes is similar (188), suggesting they all share a common ancestral
818 gene.

819 In the brain of species containing several GnRH forms, each variant exhibits a peculiar
820 distribution. In gnathostomes, three major GnRH neuronal systems were recognized (163).
821 The first one, called the ventral forebrain GnRH system, is composed of neurons mainly
822 located in the preoptic area of the hypothalamus and projecting toward gonadotrope cells in
823 the pituitary. The GnRH molecular form synthesized by these neurons is variable depending

824 on the species: *e.g.* mGnRH, cGnRH-I, frog GnRH (fGnRH), sea bream GnRH (sbGnRH) or
825 guinea pig GnRH (gpGnRH). Functionally, this peptide corresponds to the hypophysiotropic
826 GnRH form initially characterized by Schally and Guillemin. The second GnRH system,
827 called midbrain GnRH system, is composed of neurons located in the midbrain tegmentum
828 near the third ventricle. These neurons project throughout the brain, especially in the midbrain
829 and hindbrain, but also in the pituitary in some teleost and amphibian species. They produce
830 the cGnRH-II form. The third system, called the terminal nerve GnRH system, has so far been
831 identified only in teleosts. Neurons of this system are mainly located in the terminal nerve
832 ganglion near the olfactory bulb, and project primarily to the telencephalon but also widely
833 into the whole brain, including the retina and the olfactory epithelium. They specifically
834 express the sGnRH variant (556). It is to note that, in some teleost species, cells from the
835 hypothalamic GnRH systems and cells from the terminal nerve GnRH system clearly overlap
836 in the forebrain (232, 233, 502). It was also shown that neurons from both systems share a
837 common embryonic origin: they arise in the olfactory system and migrate into the forebrain
838 (2, 3, 233, 234, 557, 869).

839

840 4.2.3. Evolution of GnRH genes in vertebrates: impact of WGD

841 Because GnRHs are short peptides, their evolutionary relationship was difficult to establish
842 solely on the basis of their primary structure (337). In 1998, a phylogenetic analysis of GnRH
843 prepro-hormones from 23 species of bony fish and mammals revealed the existence of three
844 evolutionarily distinct GnRH groups, named GnRH1, GnRH2 and GnRH3 (869). These three
845 groups globally coincide with the three GnRH forms identified on the basis of their location
846 in the brain: releasing form localized to the hypothalamus (GnRH1), form previously
847 localized solely to midbrain nuclei (GnRH2), and form localized to the telencephalon in
848 teleosts (GnRH3) (188).

849 Subsequent phylogenetic studies including newly discovered sequences confirmed this
850 categorization, which is now widely accepted and is at the basis of the current nomenclature
851 (248, 337, 556). The occurrence of three GnRH paralogous genes is also supported by
852 synteny analysis (360, 381, 555, 643, 644, 790) since each GnRH gene is positioned in
853 genomic regions containing common neighbors across teleost and tetrapod species.

854 GnRH1 and GnRH2 are clearly two “old” genes since the peptides they encode exhibit a very
855 well conserved structure among gnathostomes. In contrast, GnRH3 has long been considered
856 as a teleost-specific gene, suggesting a more recent emergence, possibly through the teleost-
857 specific whole-genome duplication (3R) (248, 337, 556). However, this hypothesis was
858 rejected when it appeared that genes surrounding GnRH3 in teleosts are also present in
859 tetrapods (360, 381, 555, 790). The view that GnRH3 arose by an ancient duplication before
860 the teleost-tetrapod split was recently confirmed by the finding of a GnRH3 ortholog in
861 coelacanth and several species of elasmobranches (219, 644, 903).

862 In lamprey, three members of the GnRH family of neuropeptides have been identified, named
863 lamprey GnRH-I (lGnRH-I), lGnRH-II and lGnRH-III (349, 704, 715, 737, 757). The precise
864 relationship between lamprey peptides and the three subtypes of GnRH in other vertebrates
865 was difficult to resolve. Phylogenetic analysis initially led Sower et al. (2009) (740) to
866 propose that lGnRH-II may represent a vertebrate GnRH2 ancestral form and to classify
867 lGnRH-I and lGnRH-II in a fourth group of vertebrate GnRH peptides. Once again, both
868 assumptions were refuted by synteny analysis showing that lGnRH-II is a GnRH2 ortholog
869 while lGnRH-I and lGnRH-III are two copies of GnRH3 that probably arose through tandem
870 duplication (143, 252, 644, 725). It should be noted that the presence of GnRH was suggested
871 in the hagfish hypothalamus by both radioimmunoassay and immunohistochemistry, but the
872 identity of the peptide remains to be determined (541).

873 It is now well accepted that the three GnRH paralogs appeared together through the 2R. In
874 strong support of this view is the observation in the genome of many species that GnRH1,
875 GnRH2 and GnRH3 loci, in addition to a fourth locus without GnRH but sharing homologous
876 neighboring genes, are part of a same tetra-paralogon (360, 790, 903). Moreover, a GnRH-
877 like gene recently characterized in amphioxus is positioned in a locus surrounded by syntenic
878 homologs of the human GnRH tetra-paralogon (642). Taken together, these data suggest that
879 four GnRH paralogs, including a putative GnRH4, were present in the last common vertebrate
880 ancestor (360, 790) (Figure 6).

881 After 2R, the history of the GnRH family was driven, across vertebrate evolution, by multiple
882 and independent gene loss events, leading to the diversity of GnRH currently known.

883 The GnRH1 gene occurs in all gnathostomes but not in cyclostomes, suggesting gene loss
884 specifically in this latter lineage. The GnRH2 gene is currently the most represented GnRH
885 gene in living vertebrates. No GnRH3 gene has so far been isolated from any tetrapod, while
886 it is present in several groups of fish. It thus appears that this gene was likely deleted during
887 the early evolution of the tetrapod lineage. Finally, the putative GnRH4 gene probably
888 disappeared shortly after 2R without leaving any trace in current species (Figure 6).

889 Apart from these general considerations, additional species-, genus- or family-specific losses
890 of a GnRH form subsequently occurred independently in different vertebrate lineages. For
891 example, some teleosts lost GnRH1 (salmon, trout, goldfish, zebrafish, arowana) or GnRH3
892 (eel, catfish, butterfly fish). In elephant shark, only GnRH1 and GnRH2, but not GnRH3,
893 were identified (536, 644). Also, certain mammalian species lost GnRH2 (rat, mice, cattle,
894 sheep, chimpanzee), and thus now possess only GnRH1 (746). It is to note that no effect of
895 the 3R can be recorded on the current number of GnRH genes in teleosts, suggesting massive
896 gene losses after 3R. In contrast, two GnRH3 are present in sockeye salmon (25), probably

897 due to the salmon-specific whole-genome duplication (4R) (420), while two tandemly
898 arranged GnRH1 exist in elephant shark (219) (Figure 6).

899 The detailed evolutionary relationship between the three GnRH paralogs is still not
900 completely understood. Phylogenetic analysis shows that GnRH1 and GnRH3 sequences
901 group into the same clade, suggesting they share a common ancestor (248, 349, 800).
902 Moreover, in teleosts, GnRH1 and GnRH3 neuronal systems exhibit striking similarities
903 regarding both their embryonic origin and their distribution in the brain (337, 556). Taken
904 together, these data support the notion that 1R generated on the one hand the GnRH1-GnRH3
905 ancestor and on the other hand the GnRH2-GnRH4 ancestor. Although appealing, this
906 scenario remains to be confirmed.

907

908 **4.3. Origin and evolution of GnRH receptors**

909 4.3.1. GnRH-R in mammals

910 GnRH receptors (GnRH-R) were initially characterized in the pituitary and several other
911 tissues such as the brain, placenta and gonads, as specific binding sites with high affinity for
912 mGnRH1 and its potent agonist or antagonist analogs (747). Some immortalized cell lines
913 derived from neoplastic tissues also proved to be an important source of GnRH-R (747). One
914 of them, the mouse pituitary α T3 gonadotrope cell line, led to the molecular isolation of the
915 first GnRH receptor sequence, by expression screening for electrophysiological (809) or
916 calcium responses (634) in *Xenopus* oocytes. This sequence provided the basis for the cloning
917 of GnRH-R in several other species (506, 686).

918 GnRH-R is mainly expressed in gonadotrope cells of the pituitary, in agreement with its role
919 in the synthesis and release of gonadotropins, but it is also present in extra-pituitary tissues
920 including the brain (320), placenta, gonads, prostate, uterus and breast (108, 637). GnRH-R is
921 also expressed in cancer tissues, either related (*i.e.* prostate, breast, endometrial, and ovarian

922 cancers) or unrelated (*i.e.* melanoma, glioblastoma, lung, and pancreatic cancers) to the
923 reproductive system. Activation of GnRH-R was shown to inhibit proliferation of transformed
924 cells making this receptor a therapeutic target for direct action of GnRH analogues on certain
925 proliferating cells (422, 450).

926 Analysis of the primary sequence identifies the GnRH receptor as a member of the rhodopsin
927 β -like G protein-coupled receptor (GPCR) family, which contains a characteristic seven
928 transmembrane (TM)-domain structure (686). Unlike most GPCRs, which are intronless, the
929 GnRH-R gene is composed of three exons and two introns (181).

930 A hallmark feature of the mammalian GnRH-R is the absence of a cytoplasmic carboxy-
931 terminal domain, which is unique among GPCRs (686). As a result, this receptor is resistant
932 to rapid desensitization and internalizes very slowly (142, 597). The extracellular loops (EC)
933 and superficial regions of the transmembrane domains (TM) are responsible for receptor-
934 ligand recognition and binding while the intracellular loops are involved in interacting with G
935 proteins for signal transduction (196, 490).

936 In gonadotrope cells and gonadotrope-lineage cells, activation of the GnRH receptor
937 stimulates a variety of intracellular signalling pathways (99, 525, 600). However, it is
938 generally accepted that the primary effect of GnRH binding to its receptor is the activation of
939 phospholipase C β (PLC β) through the G_{q/11} G protein and the hydrolysis of
940 phosphatidylinositol 4,5-bisphosphate (PIP₂) into diacylglycerol (DAG) and inositol 1,4,5-
941 trisphosphate (IP₃), which stimulates calcium release and activates protein kinase C (PKC)
942 (247). These events lead to the synthesis and release of gonadotropins (747).

943 The presence of at least two GnRHs in most vertebrates, including mammals, suggested the
944 existence of several cognate GnRH receptor subtypes (793). In support of this view, the
945 occurrence of a second GnRH-R subtype (called GnRH-RII, as opposed to the first subtype
946 now renamed GnRH-RI) was reported in non-human primates (488, 530). It is noteworthy

947 that the GnRH-RII subtype is either partially or completely silenced in a number of
948 mammalian species (human, chimpanzee, sheep, cow, rat, and mouse) (487, 506, 507).

949 A study carried out in marmoset showed that the type II GnRH receptor is more widely
950 distributed than type I receptor (488). As expected, GnRH-RI exhibits greater sensitivity to
951 the hypophysiotropic GnRH form, GnRH1, than to GnRH2. Conversely, the GnRH-RII
952 shows greater sensitivity to GnRH2 than to GnRH1 (304, 449, 488).

953

954 4.3.2. GnRH-R in other vertebrates: contribution to the discovery of multiple GnRH-R

955 The first non-mammalian GnRH-R was isolated from catfish in 1997 (778). Remarkably, this
956 receptor exhibits a 49-amino acid cytoplasmic carboxy terminal domain that is lacking in the
957 mammalian receptors. Moreover, it possesses a much higher affinity for GnRH2 than for
958 GnRH1. A number of subsequent studies described the cloning of GnRH receptors in several
959 other species, including trout (447), *Xenopus* (794), and chicken (754). In some species, such
960 as in goldfish (305), bullfrog (855) and sea bass (503), the coexistence of two, three and even
961 five distinct GnRH-R subtypes was reported, respectively. Three GnRH-R were also
962 characterized in lamprey (330, 716). GnRH binding sites in GnRH-R type I and II forms are
963 highly conserved but several amino acid residues in the second and fourth transmembrane
964 domains confer selectivity toward GnRH1 and GnRH2 (122, 205).

965 Interestingly, at both the structural and functional levels, non-mammalian GnRH receptors
966 resemble more closely the mammalian type II receptors than the mammalian type I receptors.
967 Indeed, they all have a carboxy-terminal tail and a higher affinity (although sometimes
968 modest) for GnRH2 than for GnRH1 (337). Moreover, in contrast to GnRH-RI, they show an
969 Asp residue in transmembrane domain 2 that is conserved among members of the GPCR
970 family. This Asp residue, that is replaced by an Asn residue in the mammalian GnRH-RI, is
971 required for receptor activation (406, 488).

972 As the mammalian GnRH-RII, non-mammalian GnRH receptors are expressed in numerous
973 tissues, in particular in reproductive organs. In species possessing several GnRH-R subtypes,
974 each receptor exhibits a distinct expression pattern (248). Both mammalian GnRH-RII and
975 non-mammalian GnRH receptors generally couple to the Gq protein and therefore mediate the
976 intracellular production of inositol phosphates (99, 337).

977

978 4.3.3. Evolution of GnRH-R genes in vertebrates: impact of WGD

979 The evolutionary relationship between vertebrate GnRH receptor is still obscure, making it
980 difficult to propose a consensual nomenclature (see (613) for a detailed review of the different
981 nomenclatures proposed over time). As mentioned above, vertebrate GnRH receptors were
982 generally subdivided into two major types (I and II) on the basis of both their structural
983 (presence or not of a C-terminal tail) and functional (selectivity to individual GnRH peptides)
984 features. Type I GnRH-R only contains the mammalian « tail-less » sequences, while type II
985 GnRH-R includes all remaining sequences, from both mammalian and non-mammalian
986 species. Such a categorization is well supported by numerous phylogenetic analyses in which
987 GnRH-RI and GnRH-RII sequences actually group into two separate major clades (302, 613,
988 643, 644, 690, 776, 873).

989 Until recently, GnRH-RI sequences were only found in mammals, suggesting that this
990 receptor evolved after lineage-specific gene duplication in early mammals (337, 643). This
991 concept was eventually invalidated when sequences of GnRH-RI were found in coelacanth,
992 elephant shark and little skate (644, 690, 873), indicating that the gnathostome ancestor
993 already possessed a type I GnRH-R. Thus, functionally, the absence of the cytoplasmic tail in
994 type GnRH-RI can no longer be viewed as an adaptation to mammalian physiology (873), as
995 previously suggested by some authors (142, 794).

996 In contrast to the type I clade, the type II clade is characterized by a wide heterogeneity, since
997 it includes sequences from species of very diverse origins. This heterogeneity is reinforced by
998 the fact that most of these species possess multiple type II receptor forms, *e.g.* three in
999 lamprey, some teleosts and amphibians, and up to four in coelacanth. Hence, recent studies
1000 subdivided type II clade into two major clades, called IIa and IIb (613, 644, 873). IIa and IIb
1001 can be further split into three and two groups, respectively. The first type IIa GnRH-R clade
1002 contains all three of the lamprey GnRH-R sequences plus one of the coelacanth paralogs. The
1003 second type contains the mammalian type II GnRH-R plus one of the coelacanth paralogs,
1004 while the third type contains GnRH-R sequences from teleosts, coelacanth, amphibians,
1005 reptiles and birds. The first type IIb clade also contains GnRH-R sequences from teleosts,
1006 coelacanth, amphibians, reptiles and birds, while the second type is exclusively composed of
1007 teleost sequences. It is noteworthy that the two IIb subtypes are not discriminated in the
1008 Williams's study.

1009 At first sight, the logic of this breakdown is not obvious. Indeed, phylogenetic analyses,
1010 alone, are not perfectly suitable to explain the origin of the different GnRH receptor subtypes,
1011 and their evolutionary relationships. Recently, several studies have tried to revisit the history
1012 of the GnRH-R family in light of the 2R theory (360, 644, 690).

1013 Following up a previous work (360), Sedifeh et al. (2014) (690) examined the conserved
1014 synteny of chromosomes harboring GnRHR genes. They identified three pairs of GnRH-R
1015 subtypes in three paralogous linkage groups, suggesting that an ancestral pair emerged
1016 through local duplication before 2R. According to their model, 2R thus led to the generation
1017 of 6 subtypes of GnRH-R in the vertebrate ancestor. However, this model is based on a
1018 phylogenetic analysis whose conclusions have been recently strongly challenged (644, 873).
1019 For instance, Roch et al. (2014) proposed that all three major GnRH receptor subtypes (types
1020 I, IIa and IIb) were already present in the vertebrate ancestor before 2R (644). These three

1021 receptors would have been the products of two successive events of tandem duplication.
1022 According to their model, 2R theoretically led to the generation of 12 GnRH-R subtypes
1023 (Figure 7). However, due to multiple gene losses, only six of them were preserved.
1024 Thereafter, further losses could occur in the different vertebrate lineages, eventually leading
1025 to the current situation. This model is in good agreement with phylogenetic data, which
1026 identify a total of six GnRH-R subtypes. However, on the basis of practically the same data,
1027 Williams et al. (2014) propose a totally different scenario, in which only three GnRH-R genes
1028 were present in the gnathostome ancestor (873). By contrast, they argue that the current data
1029 do not resolve the number of GnRH receptors in the common ancestor of vertebrates and the
1030 actual impact of 2R.

1031 Taken together, this information shows that further studies, combining both phylogenetic and
1032 syntenic data, will be needed to fully understand the evolution of the GnRH-R family in
1033 vertebrates.

1034

1035 **4.4. Origin of the GnRH system before the emergence of vertebrates**

1036 In order to gain more insight into the origin of GnRH, intensive efforts have been made to
1037 hunt out GnRH-related peptides in phyla other than vertebrates.

1038

1039 **4.4.1. GnRH and GnRH-R in non-vertebrate chordates**

1040 The first molecular evidence that GnRH occurs outside vertebrates was provided by the
1041 characterization of multiple GnRH-like peptides in tunicates, encoded by one or two different
1042 genes, depending on the species (5, 264, 618, 644). In several species examined, such as
1043 *Ciona sp.* or *Halocynthia sp.* (5, 264), pre-proGnRHs are multifunctional precursors, each
1044 containing the sequence of two to three tandemly arranged peptides. However, despite the
1045 unique organization of their precursor, almost all tunicate GnRH forms identified so far are

1046 decapeptides including the six invariant amino acids, in positions 1–4, 9 and 10, found in
1047 vertebrates (644) (Table 1). It is noteworthy that the occurrence of both mGnRH and cGnRH-
1048 I reported by Di Fiore et al. (2000) (193) in *Ciona* could not be confirmed (5).

1049 Search of the *Ciona* genome also led to the identification of four GnRH receptors (775). All
1050 these receptors possess a C-terminal tail similar to vertebrate type II GnRH-R, as well as
1051 several other structural features shared with vertebrate GnRH-Rs (643). At the functional
1052 level, only one tunicate receptor is able to activate the $G_{q/11}$ pathway and to trigger IP3
1053 accumulation, while the three others provoke an increase of cyclic AMP formation through
1054 stimulation of G_s (775). At the evolutionary level, the four *Ciona* GnRH receptors cluster into
1055 a single clade at the root of the vertebrate GnRH-R one (644). Taken together, these data
1056 demonstrate unequivocally the existence in tunicates of a GnRH system homologous to that in
1057 vertebrates.

1058 The occurrence of a functional GnRH system was also reported in amphioxus. However, the
1059 first Blast searches of the amphioxus genome allowed the identification of only GnRH-like
1060 receptor but not peptide sequences (776). Of the four amphioxus GnRH-R sequences found,
1061 only two, GnRH-R1 and GnRH-R2, cluster as expected, at the root of the chordate GnRH-R
1062 tree (642, 644). In contrast, the two others, GnRH-R3 and GnRH-R4, appear much more
1063 distant and do not group with chordate GnRH-R sequences (see below for more details).
1064 Nevertheless, the four amphioxus GnRH-R genes are positioned in the same locus surrounded
1065 by syntenic homologs of the vertebrate GnRH-R paralogon (642).

1066 In 2009, a peptide with GnRH sequence identical to mammalian GnRH1 was purified from
1067 amphioxus (96) but this result proved to be artifactual (642). The occurrence of a genuine
1068 amphioxus GnRH-like gene was reported only five years later by using a more sensitive
1069 search methodology with hidden Markov models (642). The GnRH identity of this gene was
1070 confirmed by synteny analysis. However, the GnRH-like peptide encoded by this gene

1071 exhibits a very atypical structure, pQILCARAFTYHTWamide, since of its 14 amino acids
1072 (aa) (and not 10), 3 only are conserved at positions 1, 5, and 7 with vertebrate GnRH2
1073 residues (Table 1). It has been proposed that the amphioxus GnRH-like peptide may be
1074 cleaved to form a more active 7 aa-peptide (785). The amphioxus GnRH-like peptide acts as a
1075 ligand for amphioxus GnRH-R3 (642), but does not activate any of the three other amphioxus
1076 GnRH-R subtypes (642), indicating that the natural ligands of the latter receptors remain to be
1077 identified. It is to note that amphioxus GnRH-R1 and GnRHR-2 can be activated by
1078 vertebrate GnRH (642). Interestingly, a second GnRH-like peptide has been identified in the
1079 amphioxus genome (called GnRHv), but this peptide does not activate any of the four known
1080 amphioxus GnRH-R (642).

1081

1082 4.4.2. GnRH-like peptides and GnRH-R in other non-vertebrates

1083 The first non-vertebrate GnRH-like molecule, at least clearly presented as such, was
1084 characterized in 2002 from a cephalopod mollusk, the common octopus (313). Octopus
1085 GnRH is a dodecapeptide that shares 7 residues with vertebrate GnRH2 from which it mainly
1086 differs by the insertion of two amino acids after position 1 (Table 1). The overall organization
1087 of the octopus GnRH precursor is the same as that of vertebrate pre-proGnRHs. Its cognate
1088 receptor was identified soon after and was demonstrated to have numerous similarities with
1089 chordate GnRH receptors (344).

1090 Closely related peptides were subsequently identified in several other species of mollusks (58,
1091 831, 912), annelids (832) and echinoderms (649, 695) (Table 1). All these newly identified
1092 peptides, together with the amphioxus GnRH-like peptide, were proposed to be classified as
1093 invertebrate GnRHs (invGnRHs), as opposed to vertebrate GnRHs (that also include the
1094 tunicate ones) (644). However, recent studies have shown that invGnRHs are probably not
1095 orthologous to GnRHs and should be renamed (see below) (613, 905).

1096

1097 4.4.3. Other GnRH-related peptides (AKH, CZR, ACP) and their receptors

1098 In 1998, the occurrence of a receptor structurally related to vertebrate GnRH receptors was
1099 reported in *Drosophila* (267). Several years later, the ligand for this *Drosophila* GnRH-type
1100 receptor was characterized and identified as a member of the adipokinetic hormone (AKH)
1101 family (745). Such a result was totally unexpected since AKH has been well known for a long
1102 time in insects (470, 748) but without apparent relationship with GnRH. However, taking a
1103 closer look, GnRHs and AKHs appear to share the N-terminal pyro-Glu residue and the C-
1104 terminal amide plus various identical residues depending on the species, in particular a
1105 conserved Trp at the third last position. It thus appears reasonable to consider peptides of the
1106 AKH family as possible GnRH homologs.

1107 AKH is an insect peptide first isolated from the locust *corpura cardiaca*, a functional
1108 equivalent of the pituitary gland in insects (835), for its ability to mobilize lipids from the fat
1109 body during flight (748). Many different forms (8-10 residues) of this peptide hormone were
1110 subsequently described in various insect species, with even two or three gene copies in some
1111 of them (216) (Table 1). AKH is also known as the red pigment-concentrating hormone
1112 (RCPH) isolated several years earlier in crustaceans (189) The first RCPH receptor has been
1113 recently characterized from *Daphnia* (456).

1114 In 1989, an AKH-like peptide was identified in the cockroach and named corazonin (CRZ,
1115 “corazon” being the Spanish word for ‘heart’) on the basis of its cardioacceleratory properties
1116 (830). Although slightly larger in size (11 residues), CRZ share several structural features
1117 with AKH (Table 1). Furthermore, their preprohormones have a similar organization
1118 indicating that the two neuropeptide precursor genes must have a common evolutionary origin
1119 (829). Like AKH, CRZ is expressed in neurosecretory neurons of the protocerebrum and
1120 transported to the storage lobes of the *corpura cardiaca* (622). The CRZ receptor was initially

1121 characterized in *Drosophila* by a reverse pharmacology strategy (94, 582). Sequence analyses
1122 showed that CRZ, AKH and GnRH receptors are all evolutionarily related.

1123 In 2006 Belmont et al. (2006) isolated from *Anopheles* a receptor with strong similarities to
1124 the AKH receptor but which is activated neither by AKH nor by CRZ (45). The natural ligand
1125 for this receptor was subsequently characterized as a new peptide called AKH/corazonin-
1126 related peptide (ACP) due to its intermediate structural features with AKH and CRZ (261).

1127 In all species examined so far, AKH, CRZ and ACP originate from precursors that exhibit the
1128 same overall organization as those of vertebrate GnRHs, with the mature peptide immediately
1129 after the signal peptide. However, despite their structural similarities with other non-
1130 vertebrate GnRH-like receptors, the AKH receptors are specific for AKH and are not
1131 activated by ACP or CRZ. Similarly, the ACP receptors are specific for ACP and the CRZ
1132 receptors are specific for corazonin, showing that AKH, ACP and CRZ are three independent
1133 signaling systems (411).

1134 For a long time, AKH, CRZ and ACP were thought to be confined to the arthropod clade,
1135 where they often (but not systematically) coexist in the same species (411). In 2009 the
1136 existence of an AKH-like peptide and its cognate receptor was reported in the nematode *C.*
1137 *elegans* (424), suggesting an older origin of the AKH signaling system. This notion was
1138 backed up soon later when it appeared that a functional AKH system is also present in
1139 mollusks (164, 265, 411), hemichordates (905) and echinoderms (785). Regarding the CRZ
1140 system, the same conclusion can be drawn from a recent study showing the presence of CRZ
1141 and its receptor in hemichordates and echinoderms (644, 785). In contrast, so far, ACP has
1142 been identified only in arthropods (905).

1143

1144 4.4.4. Evolutionary relationships between GnRH- and AKH-CRZ-ACP-like systems

1145 The view that AKH, ACP, CRZ and GnRH peptides form a superfamily is generally well
1146 accepted (265, 318, 423, 492, 613, 644, 905). However, the precise relationships between
1147 CRZ, AKH, ACP and GnRH are poorly understood as illustrated by a very confused
1148 nomenclature (265, 613, 644, 801, 905). One of the major issues is whether AKH and CRZ
1149 neuropeptides can be both considered as orthologs to the vertebrate GnRH system.
1150 Unfortunately, this issue is not really addressed by phylogenetic analyses. In contrast, it
1151 appears likely that the invGnRH group previously defined by Roch (2014) (644) is not a
1152 monophyletic group (613, 801). It has thus been proposed to limit the name of GnRH
1153 exclusively to deuterostome GnRHs (613).

1154 Regarding the receptors, the situation is also unclear. Phylogenetic analyses generally agree to
1155 recognize three major clades (265, 613, 644, 785). The first clade includes all chordate
1156 GnRH-Rs, except amphioxus GnRH-R3 and GnRH-R4, plus GnRH-R-like sequences from
1157 echinoderms, in other words most deuterostome GnRH-Rs. The second clade contains all
1158 arthropod CRZ-R sequences. It also encompasses amphioxus GnRH-R3 and GnRH-R4 plus
1159 some GnRH-R-like sequences from echinoderms and lophotrochozoans (annelids and
1160 mollusks). Surprisingly, among this second clade, are the octopus and *Aplysia* GnRH
1161 receptors, initially thought to belong to the GnRH-R group, as indicated by their name (344,
1162 348). Finally, the third clade encompasses all arthropod ACP-R plus AKH-R sequences from
1163 arthropods, nematodes and lophotrochozoans. Depending on the authors, different clusterings
1164 of these clades were proposed and formed the basis of two main evolutionary scenarios (654)
1165 (Figure 8). The first scenario states that an ancestral CRZ-R, which was conserved in the
1166 ambulacrarians (echinoderms and hemichordates) and the lophotrochozoans (annelids and
1167 mollusks), duplicated twice independently and thus generated two lineages: the first leading
1168 to CRZ-R and AKH-R, subsequently AKH-R generated arthropod ACP-R in ecdysozoans,
1169 and the second leading to GnRH-R in chordates (Figure 8A). The second scenario states that

1170 GnRH-R and CRZ-R might have been arisen via gene duplication in a common ancestor of
1171 bilaterians, and that a second gene duplication of GnRH-R might have generated AKH-R and
1172 ACP-R during the divergence between lophotrochozoans and ecdysozoans (arthropods and
1173 nematods) (Figure 8B). The main difference between the two models is that, in the first one,
1174 AKH-R/ACP-R and GnRH-R are not orthologous since they arose independently while, in the
1175 second one, they are orthologous. In contrast, both models agree that the CRZ-R gene was
1176 probably lost in urochordates, vertebrates and nematodes.

1177 The second scenario was particularly detailed by Zandawala et al. (2018) who thus proposed
1178 to totally reconsider the classical nomenclature of the GnRH- and AKH-CRZ-ACP-like
1179 systems (905). According to these authors, who distinguish two major types of GnRH-like
1180 receptors, *i.e.* the (true) GnRH-R type and the CRZ-R type, the term AKH-R should be left
1181 out and replaced by GnRH-R in all bilaterian species, since AKH-R and GnRH-R are
1182 orthologous. Nevertheless, they suggest keeping AKH-R specifically in arthropods, together
1183 with that of ACP-R, its co-paralog. They also propose to change all the nomenclature of ~~the~~
1184 invertebrate GnRH-like peptides on the basis of the receptor type that they activate. For
1185 example, the octopus GnRH, as well as its counterparts in other lophotrochozoans, should be
1186 renamed as CRZ because their cognate receptor clearly belongs to the CRZ-R type (344).
1187 Likewise, all AKHs from lophotrochozoans and non-arthropodian ecdysozoans (*e.g.*
1188 nematodes) should be renamed as (true) GnRHs.

1189 As already mentioned, receptors of GnRH-R (GnRH-R1 and GnRH-R2) and CRZ-R (GnRH-
1190 R3 and GnRH-R4) types, have been characterized in amphioxus (776). In contrast, only one
1191 GnRH-like peptide was found in this group (642), that probably corresponds, for the reasons
1192 given above, to CZR. These data clearly suggest the existence of an authentic amphioxus
1193 GnRH that remains to be discovered.

1194 All in all, the Zandawala's scenario appears very attractive, since it is based on the hypothesis
1195 of co-evolution between peptides and receptors, a process generally observed for
1196 neuropeptidergic signaling systems (492). However, further studies are needed to confirm this
1197 model, in particular to characterize the ligand-binding properties of the receptors in a larger
1198 number of species. For example, such studies would help to clarify the phylogenetic status of
1199 the different peptides recently identified in prawn (756), particularly the so-called GnRH,
1200 whose place in the Zandawala's nomenclature remains to be determined. The same remark
1201 applies regarding the so-called AKH2 and GnRH2 found in the marine annelid *Platynereis*
1202 *dumerilii* (129).

1203 Phylogenetic analyses show that receptors of the GnRH/CRZ superfamily have close
1204 evolutionary relationships with receptors of the vasopressin (VP)/ocytocin (OT) family (492,
1205 643). Interestingly, although they are not structurally related, GnRH2, OT and VP genes are
1206 tandemly arranged in several vertebral species (252, 360, 643, 790), also suggesting a
1207 possible common origin.

1208

1209 4.4.5. GnRH and GnRH-R before bilateria?

1210 The nervous system in cnidarians is well known for its peptide wealth (245). As a matter of
1211 fact, a large number of neuropeptides have been isolated from different groups of cnidarians
1212 (211). Several reports show that coral tissues contain GnRH-like compounds (18, 812) but
1213 they have not been characterized yet. The occurrence of GnRH-like peptides has also been
1214 reported in the sea anemone genome (19). However, recent investigations failed to identify
1215 any GnRH-R-like sequence in cnidarian genomes (265, 613), suggesting that the GnRH-CRZ
1216 signaling system is a bilaterian innovation.

1217 It is noteworthy that an earlier origin of the GnRH system was formerly proposed after the
1218 finding that yeast α -mating factor shows some structural and functional similarities to

1219 vertebrate GnRHs (435). However, evolutionary relationships between both peptides are
1220 unlikely since α -mating factor is known to activate a receptor that does not belong to
1221 rhodopsin β -like GPCRs (329).

1222

1223 **4.5. Functions of GnRH-like peptides: evolutionary perspectives**

1224 **4.5.1. Reproductive functions of GnRH in chordates**

1225 In vertebrates, GnRH1 is the main GnRH form targeted to the pituitary. Its stimulatory effect
1226 on gonadotropin release is well established in many species. GnRH1 is thus considered as the
1227 major regulator of the hypothalamo–pituitary–gonadal axis whose stimulation leads to
1228 gametogenesis and steroid production in the gonads (556, 643, 921). Consistent with this
1229 notion, studies conducted in mice and humans show that GnRH1 null mutations result in
1230 hypogonadotropic hypogonadism and infertility (93, 97). In teleosts species lacking GnRH1,
1231 such as zebrafish, GnRH3 is believed to assume the hypophysiotropic role of GnRH1 (3,
1232 744).

1233 The action of GnRH1 is thus closely linked to the presence of a pituitary, which is a
1234 vertebrate innovation (643, 740). However, GnRH1 is also produced in and acting on other
1235 reproductive tissues. This is particularly the case in the gonads where, in numerous species of
1236 fish, amphibians, birds, reptiles and mammals, GnRH1 acts as a paracrine factor involved in
1237 the control of both gametogenesis and steroidogenesis (475, 477). This is also the case in the
1238 placenta (therefore specifically in mammals) where GnRH1 promotes trophoblastic cell
1239 invasion and regulates chorionic gonadotropin biosynthesis (670). In addition to its
1240 physiological actions, GnRH1 also regulates reproductive behaviors, including female
1241 lordosis (656) and male mating behavior (638) in rats.

1242 As mentioned above, GnRH2 is primarily expressed in the vertebrate midbrain and is
1243 generally thought to have neuromodulatory actions (337, 556). Thus, intracerebroventricular

1244 administration of GnRH2 promotes female reproductive behavior in various mammalian
1245 species (556). Likewise, GnRH2 stimulates female spawning behavior in goldfish (843).
1246 However, in some teleost and amphibian species, GnRH2 fibers originating from the
1247 midbrain were found to project, directly or indirectly, to the pituitary (125, 611, 921). As a
1248 matter of fact, GnRH2, as GnRH1, stimulates gonadotropin synthesis and secretion by
1249 pituitary gonadotrope cells (148, 489, 554).

1250 GnRH3 is implicated in the control of reproductive behavior in teleosts. For instance, in
1251 cichlid fish, GnRH3-immunoneutralization decreases nest-building ability of males (542).
1252 Similarly, in medaka, terminal nerve GnRH3 neurons have an essential role for activating
1253 mating preferences based on familiarity (559).

1254 In tunicates, GnRH induces the release of gametes, probably *via* a direct action on the gonads
1255 (779), suggesting that GnRH already exerted reproductive functions in the olfactores ancestor
1256 (the common ancestor of urochordates plus vertebrates), before the appearance of the
1257 pituitary.

1258

1259 4.5.2. Non-reproductive functions of GnRH in chordates

1260 Both, GnRHs, and their receptors are expressed in numerous non-reproductive tissues in the
1261 central nervous system (cerebral cortex, hippocampus, cerebellum, ...) and in peripheral
1262 organs (bladder, adrenal, heart, ...) (722), suggesting that GnRH may have a variety of non-
1263 reproductive activities. In fact, GnRH1 is released in significant concentrations into the
1264 cerebrospinal fluid (CSF) to potentially act outside the hypothalamus (86, 721). GnRH1 can
1265 affect pituitary cells other than gonadotropes (722). In particular, GnRH1 stimulates GH
1266 release in goldfish (455) and chicken (677). A role of GnRH2 and GnRH3 on early brain
1267 regionalization and eye development has also been revealed by knockdown experiments in
1268 zebrafish (886). At the behavioral level, GnRH1 is involved in the control of anxiety and

1269 depression was reported both in human and rodents (579), while GnRH2 influences feeding
1270 behavior (461, 777).

1271 Interestingly, a role of GnRH in the control of metamorphosis has been recently observed in
1272 tunicates (342), suggesting that, even in the olfactores ancestor, GnRH is not just a
1273 reproductive hormone.

1274

1275 4.5.3. Roles of GnRH-like peptides in non-chordates

1276 The first two GnRH-like peptides to be characterized in non-chordates were identified from
1277 octopus (313) and *C. elegans* (424). According to the new Zandawala's nomenclature (see
1278 above, 2018), these peptides correspond to CRZ-type and true GnRH-type forms,
1279 respectively. At the time of their discovery, both peptides were logically investigated for their
1280 reproductive functions. As a matter of fact, the octopus peptide was shown to stimulate
1281 oviduct contraction and gonadal steroidogenesis (312, 344), while the nematode peptide was
1282 described as a regulator of egg-laying behaviour (424). These findings were thus taken as a
1283 strong support to consider both peptides as GnRH homologs (in addition to the fact that they
1284 bind to GnRH-like receptors) (423). However, further studies showed that the reproductive
1285 functions of GnRH-like peptides are often marginal in non-chordate species.

1286 As mentioned above, AKH- and CRZ-type signalling systems were first characterized in
1287 arthropods. Therefore, most of the functional data currently available are from this group,
1288 especially from *Drosophila* (905). In insects, AKH mainly regulates carbohydrate
1289 homeostasis, and lipid and carbohydrate mobilization, particularly during flight (216). AKH
1290 is also involved in other physiological processes related to locomotion and stress (265), but is
1291 generally not linked to reproduction (905). Only a few studies in the cricket (434) and the
1292 locust (509) indicate that AKH may have a role in reproduction. In crustaceans, RPCH, the
1293 AKH ortholog, modulates gut motility in the lobster (151) and ovarian maturation in the

1294 crayfish, in addition to its role in background color adaption initially reported in the prawn
1295 (189). The functions of AKH-like peptides in other taxa are still poorly characterized. AKH
1296 has been recently identified in *Aplysia* (324) and functional assays indicate that it may
1297 modulate metabolism, feeding and gut motility, and also affect some gonadal parameters.
1298 Although this peptide is considered as a true GnRH according to the Zandawala's
1299 nomenclature (2018) (905). While the functions of ACP, the closest paralog of AKH in
1300 arthropods, are still unclear, in a recent study, ACP was shown to play a role in lipid
1301 metabolism and inhibition of oocyte proliferation in prawn (756).

1302 As already indicated, CRZ was originally isolated from cockroach on the basis its
1303 cardiotropic properties (830). However, such an activity has been so far only documented in a
1304 few species. Since then, CRZ has been implicated in a wide range of functions in insects,
1305 including the initiation of ecdysis behaviors in the moth (362), induction of cuticular
1306 pigmentation in the locust (771), reduction of the spinning rate and pupal development in the
1307 silkworm (767), testicular development and spermatogenesis in the prawn (711). In ants, CRZ
1308 controls social behavior and caste identity (236). As for GnRH, the functions of CRZ in other
1309 taxa are still poorly known. The reproductive functions of CRZ in octopus have been
1310 mentioned above, but octopus CRZ (according to the Zandawala's nomenclature) has also
1311 non-reproductive functions, in particular on the heart and muscles (312, 344). In *Aplysia*,
1312 CRZ affects many processes including motor function, feeding and neuronal activities but has
1313 no significant effect on reproduction (753, 802).

1314 Overall, GnRH-type and CRZ-type peptides are pleiotropic hormones that have both
1315 overlapping and specific properties, but do not exhibit clear patterns of functions emerges,
1316 thus making difficult to infer their ancestral functions in Urbilateria, the last common ancestor
1317 of bilaterians. The only (quasi) certainty is that the critical role of GnRH as a reproductive

1318 activator is a characteristic unique to vertebrates (654), likely related to the innovation of the
1319 pituitary gland in this group.

1320

1321 **5. Origin and evolution of brain RF-amide peptides in the limelight for reproduction**

1322 Two types of brain peptides, namely kisspeptin and GnIH/RFRP, have been subjected to most
1323 attention in the field of reproductive physiology since the early 2000s. Both belong to the
1324 superfamily of RF-amide peptides and have been proposed as new major actors in the
1325 neuroendocrine control of reproduction in vertebrates.

1326

1327 **5.1. History and evolutionary relationships of the RF-amide peptides**

1328 5.1.1 Discovery of RF-amide peptides in mollusks

1329 In 1972, a substance, designated peak C, was isolated in all major classes of the phylum
1330 Mollusca for its cardioexcitatory activity (9). Five years later, peak C was purified from
1331 cerebral ganglion extracts of the sunray venus clam, *Macrocallista nimbosa* (623). The
1332 neuropeptide identified, FMRFamide, was named after the letter abbreviations of its four
1333 amino acids, phenylalanine, methionine, arginine and phenylalanine, and its amidated C-
1334 terminal sequence (623). Since then, FMRFamide along with its structurally related
1335 neuropeptides named FMRFamide-related peptides (FaRPs) or FMRFamide-like peptides
1336 (FLPs) remains the best-investigated family of neuropeptides in mollusks.

1337

1338 5.1.2. RF-amide peptides superfamily in vertebrates

1339 The first vertebrate member of the RF-amide family (peptides ending with Arg-Phe-NH₂) was
1340 isolated and sequenced (Leu-Pro-Leu-Arg-Phe-NH₂: LPLRFamide) from chicken brain in
1341 1983 (152). This peptide was subsequently recognized as a fragment of a longer RF-amide
1342 peptide, gonadotropin-inhibitory hormone (GnIH) (for review: (806). Since 1983, a number

1343 of neuropeptides sharing the typical C-terminal RF-amide (RFa) signature were discovered in
1344 all major animal phyla (174, 318, 904).

1345 Dockray (2004) suggested designating the mammalian RF-amide genes, *farp-1* to *farp-5* in
1346 the chronological order they were described (153): the *farp-1* gene (601, 841) encodes two
1347 peptides, neuropeptide FF (NPFF) and neuropeptide AF (NPAF) (896); the *farp-2* gene (280)
1348 encodes prolactin-releasing peptide (PrRP) (280); the *farp-3* gene (281, 426) encodes two
1349 peptides, RFRP-1 and RFRP-3 also referred to as neuropeptide VF (NPVF) or GnIH (281);
1350 the *farp-4* gene (227) corresponds to the Kiss-1 gene encoding kisspeptin (or metastin)
1351 peptides (375, 549); the *farp-5* gene (104, 213, 322) encodes 26RFa, also named P518 or
1352 QRFP (104, 213, 322). These five distinct genes thus encode seven peptides in mammals
1353 (153, 630). The *farp* nomenclature based on chronology of discovery has not been followed
1354 by other authors (630). However, a similar classification into five groups has been adopted
1355 (for review: (826)) and further validated by phylogenetical analyses performed on sequences
1356 from various vertebrates including mammals, other tetrapods, teleosts and lamprey (570).
1357 These groups of RF-amide peptides were named by the authors: PQRFa (NPFF) group
1358 corresponding to *farp-1*; PrRP group corresponding to *farp-2*; LPXRFa (GnIH) group
1359 corresponding to *farp-3*; metastin (kisspeptin) group corresponding to *farp-4*; and QRFP
1360 (26RFa) group corresponding to *farp-5* (for review: (805)).

1361 All the RF-amide peptides bind to G protein-coupled receptors (GPCRs). Dockray suggested,
1362 as for *farp*s, to designate the receptors to the RF-amide peptides in the order they were
1363 identified as putative RFamide receptors: accordingly, *rfr-1* for PrRP (*farp-2*) receptor (280);
1364 *rfr-2* for RFRP-1 and RFRP-3/NPVF/GnIH (*farp-3*); *rfr-3* for NPFF and NPAF (*farp-1*)
1365 receptors (68, 176, 281); *rfr-4* for metastin/kisspeptin (*farp-4*) receptor (375, 513, 549); *rfr-5*
1366 for QRFP/26RF (*farp-5*) receptor (213, 322). Using phylogenetical analyses of more than 800
1367 human GPCR sequences, Fredriksson (2003) showed five main families of GPCRs in human,

1368 which they named glutamate, rhodopsin, adhesion, frizzled/taste2 and secretin (208). The
1369 rhodopsin family was divided into four groups: α , β , γ and δ (208). Kisspeptin receptor (also
1370 named GPR54 or *rfr-4*) belongs to the γ group, more specifically to the SOG receptor cluster,
1371 together with the receptors for non-RFamide peptides, somatostatin (S), opioid (O) and
1372 galanin (G) (208). Receptors of NPFF (*rfr-3*), GnIH/RFRP (*rfr-2*), PrRP (*rfr-1*) and QRFP
1373 (*rfr-5*) cluster within the β group, with receptors for non-RFamide peptides, neuropeptide Y
1374 (NPY), cholecystokinin, GnRH, tachykinin, ghrelin, and neuromedin U (208).

1375 Several studies, based on synteny analysis and phylogenetic relationships of RF-amide
1376 peptides and receptors, provide new insights into the RF-amide peptide superfamily (for
1377 review: (904)). A gene encoding a PQRFa peptide has been identified in a cephalochordate,
1378 the amphioxus, indicating the presence of a *pqrf* gene at least in a chordate ancestor (565).
1379 This ancestral gene likely gave rise to *gnih* (*farp-3*) and its sister gene *npff* (*farp-1*), via one of
1380 the two rounds of whole genome duplications (1R/ 2R) that occurred early in the vertebrate
1381 lineage ((565); for reviews: (807, 904)). The authors also reported phylogenetical
1382 relationships between NPFF, GnIH and QRFP (*farp-5*), suggesting a close evolutionary
1383 relationship between these three groups of RF-amide peptides (904). Kisspeptin (*farp-4*) has
1384 been proposed to be evolutionary more related to non RF-amide peptides, galanin and spexin,
1385 than to other RF-amide peptides, and proposed to be classified as a member of the
1386 galanin/spexin family ((359); for review: (904)). PrRP receptors likely share a common
1387 ancestry with NPY receptors as reported by Lagerström and collaborators (385), linking the
1388 PrRP group (*farp-2*) more to a non-RF-amide peptide family than to the other RF-amide
1389 peptide groups. The grouping of the various RF-amide peptide subfamilies/groups in a same
1390 RF-amide superfamily is thus currently a matter of debate (Figure 9).

1391

1392 **5.2. GnIH (*farp-3*) and evolutionary-related peptides (NPFF and QRFP) (*farp-1* and -5)**

1393 5.2.1. Discovery of GnIH in birds: direct inhibitory role on pituitary gonadotropins

1394 In 2000, Tsutsui and collaborators reported the isolation and characterization, from quail
1395 brain, of a novel neuropeptide, having an RFa motif at the C-terminus, which dose-
1396 dependently inhibits the gonadotropin, luteinizing-hormone (LH), release *in vitro* from quail
1397 anterior pituitaries. They named this peptide gonadotropin-inhibitory hormone (GnIH) (808).

1398 In the quail, starling and duck, the GnIH precursor mRNA encodes a polypeptide that can
1399 potentially be cleaved into three mature peptides with a C-terminal LPXRF-amide sequence
1400 (X=L or Q), named GnIH-related peptide-1 (GnIH-RP1), GnIH and GnIH-RP2 (quail: (671);
1401 starling: (814); duck: (207); for review: (378)). GnIH was identified as a mature endogenous
1402 peptide by mass spectrometry analyses, in the brain of quail (808), starling *Sturnus vulgaris*
1403 (814), zebra finch *Taeniopygia guttata* (788) and chicken (472), while GnIH-RP2 was also
1404 identified in the brain of quail (671).

1405 In 2005, Tsutsui and colleagues identified a GnIH receptor (898), using primers designed
1406 from the sequence of GPR147, a novel GPCR, also called NPPF receptor 1 (NPPFR-1) since
1407 its discovery together with another NPPF receptor (NPPFR-2 or GPR74) in mammals (68).
1408 As GnIH has higher affinity for NPPFR-1, the latter is considered to be the primary receptor
1409 for GnIH (68, 426).

1410 The direct inhibitory action of quail GnIH on LH release was confirmed in another bird, the
1411 chicken. An inhibitory effect of GnIH on LH release by pituitary slices was reported in the
1412 sexually immature female White Leghorn while it was not observed *in vitro* in sexually
1413 mature birds and nor on FSH release at both stages (446). In a hybrid of White Leghorn and
1414 Silkie Breed, GnIH inhibits LH release (but not mRNA expression), as well as FSH release
1415 and mRNA in pituitary explants (117).

1416 The direct effect of GnIH at the pituitary level is also supported by the detection of *gnih*
1417 mRNA in the pituitary of various bird species (quail: (898); starling and quail: (51)) and by

1418 the colocalization of GnIH receptor immunoreactivity with LH β or FSH β mRNA expression
1419 in the chicken pituitary gland (446).

1420

1421 5.2.2. GnIH inhibitory role at the brain and gonadal levels in birds

1422 GnIH may also directly influence GnRH secretion as GnIH-ir fibers are observed in contact
1423 with GnRH-ir neurons in many bird species (sparrow: (50); for review: (49); European
1424 starling: (814); zebrafinch: (788)). Moreover, GnIH receptor mRNA is expressed in different
1425 parts of the brain in quail and starling as shown by PCR (51), and more specifically in both
1426 GnRH-I and GnRH-II neurons in European starling *Sturnus vulgaris* as shown by ISH/ICC
1427 (814).

1428 Injection of GnIH rapidly reduces plasma LH and attenuates GnRH-induced rise in plasma
1429 LH in sparrow (49, 569). In quail, continuous administration of GnIH for 2 weeks decreases
1430 LH β mRNA levels (818). In the Pekin duck, icv injection of GnIH reduces plasma LH
1431 concentrations, while administration of GnIH-RP1 has no effect (207). One study reported no
1432 effect of GnIH on LH plasma levels in a bird species: in the Rufous-winged sparrow, GnIH
1433 does not affect basal or GnRH-stimulated plasma LH levels (149).

1434 PCR analyses reveal the presence of GnIH as well as GnIH-R mRNAs in the testis, ovary and
1435 accessory reproductive organs (oviduct, epididymis and *vas deferens*) in starling and quail
1436 (51). Similarly, transcripts for GnIH and GnIH-R are detected in the testis of house sparrow
1437 *Passer domesticus* ((476); for review: (475)). In this latter species, GnIH decreases
1438 testosterone secretion from cultured testis (476). This indicates possible local,
1439 autocrine/paracrine actions of GnIH in the gonads in birds.

1440

1441 5.2.3. GnIH in mammals

1442 The discovery of GnIH in birds has prompted investigations in mammals. The GnIH
1443 precursor cDNAs identified from mammalian brain encode two GnIH peptides, also known as
1444 RFamide-related peptides (RFRP): RFRP-1 and -3 (for reviews, see (804–806); rat: (281,
1445 822); mouse : (281); Siberian hamster (813); bovine (212, 281, 900); monkey (815); human
1446 (281, 816)). Like avian GnIH and GnIH-RPs, all these peptides possess a common C-terminal
1447 LPXRFamide (X=L or Q) motif, with RFRP-1 being a C-terminal LPLRFamide peptide and
1448 RFRP-3 a LPQRFamide peptide (for review: (807)). In human and bovine (not in rat and
1449 mouse), a third peptide, RFRP-2, is also predicted, but is a LPLRSamide peptide or a
1450 LPLRLamide peptide, respectively (281). This RFRP-2 peptide could not be detected in an
1451 extract of human hypothalamus by using an avian GnIH antibody-conjugated immunoaffinity
1452 column and mass spectrometry, possibly due to its different C-terminal motif or because it is
1453 not processed from the precursor (816). The rat GPR147 does not respond to hRFRP-2,
1454 showing the importance of the C-terminal RFamide for the binding to the receptor (281, 816).
1455 The RFRP-2 sequence is absent from the RFRP precursor in the Siberian hamster (813). Li
1456 and collaborators suggested that the pig GnIH precursor encodes three RFRP peptides, two
1457 with an LPLRFamide C-terminal sequence and one with an LPQRFamide C-terminal motif
1458 (416). The authors reported also similar characteristics in the rabbit and golden hamster GnIH
1459 precursors (416).

1460 In all mammalian species, as in birds, RFRP fiber terminals form close appositions with
1461 GnRH neurons (hamsters (377); rats (325, 377); mice (377, 885); sheep (726); monkeys
1462 (815); humans (816)). In the mouse, direct application of RFRP-3 on cultured brain slices
1463 decreases the firing rate of a subpopulation of GnRH neurons, and this effect is maintained
1464 when amino acid transmission is blocked, suggesting a direct suppressive action of RFRP-3
1465 on the excitability of GnRH neurons (165).

1466 In addition to its effects on GnRH neurons, GnIH may also act directly at the pituitary level

1467 via its release in the portal blood in mammals as in birds. GPR147 (also referred to as
1468 NPFFR-1), is expressed in the pituitary in rat (281), Syrian hamster (230) and human (816),
1469 and RFRP-ir fibers are observed in the external layer of the ME in hamsters (230), sheep
1470 (118) and humans (815, 816). However, other studies using a different antiserum failed to
1471 detect RFRP-ir in the ME of rat brain and ip injection of the retrograde tracer Fluorogold did
1472 not label RFRP cell bodies (639). RFRP-3 inhibits GnRH-stimulated gonadotropin synthesis
1473 in pituitary gonadotropes in sheep *in vitro* (664), supporting a potential action at the pituitary
1474 level. In Artiodactylae, RFRP-3 inhibits GnRH-induced, but not basal, LH and FSH secretion
1475 and expression by primary cultures of pituitary cells (ewe: (118, 664); bovine: (332); pig:
1476 (415)). In rat, Pineda et al (2010) observed an inhibitory effect of RFRP-3 on both basal and
1477 GnRH-stimulated LH secretion (610), while other studies reported no effect (20) or an effect
1478 only on GnRH-stimulated LH release (517). In the Syrian hamster, Ancel et al. (2012) found
1479 no effect on either basal or stimulated LH release (17).

1480 The presence of GnIH and its receptor in the mammalian gonads (Syrian hamster testis (914);
1481 human ovary (550); pig ovary and testis (416, 916)) suggests, like in birds, possible
1482 autocrine/paracrine regulations via a local gonadal GnIH system. Indeed, in the mouse, *in vivo*
1483 and *in vitro* studies show that GnIH/RFRP-3 treatment inhibits follicular development and
1484 ovarian steroidogenesis in the female (719), as well as testicular steroidogenesis and
1485 spermatogenesis in the male (22). Similarly, GnIH/RFRP-3 inhibits the synthesis and release
1486 of estradiol by ovarian granulosa cells (415) and of testosterone by Leydig cells (916) *in vitro*
1487 in pigs. Interestingly, a recent study investigating the role of RFRP-1 on ovarian activities
1488 reported a stimulatory effect of RFRP-1 on ovarian steroidogenesis at proestrus in the mouse,
1489 but an inhibitory action on ovarian folliculogenesis (141).

1490 Using a mouse line with genetic inactivation of NPFFR-1, it has been demonstrated that the
1491 NPFFR-1 pathway is dispensable for preserved puberty and fertility ((401); for review:

1492 (402)). To the best of our knowledge, there is no report on the possible impact of *gnih* (*npvf*)
1493 gene inactivation in mice.

1494

1495 5.2.4. Current studies on the presence and role of GnIH in the reproduction in other
1496 vertebrates

1497 a. In other sauropsids

1498 In sauropsids, apart from birds, three GnIH peptides (GnIH, GnIH-RP-1 and GnRH-RP-2)
1499 have been characterized in the red-eared slider turtle *Trachemys scripta elegans* (821), in the
1500 Chinese softshell turtle and in the anole lizard (for reviews: (566, 807)), and they all possess
1501 the common C-terminal LPXRFamide motif, like the avian and mammalian peptides.
1502 However, few studies have investigated their potential physiological roles. Brain localization
1503 of GnIH by ISH and/or immunohistochemistry has been reported in the Japanese grass lizard
1504 *Takidromus tachydromoides* (350) and the red-eared slider turtle (821). In the lizard *Calotes*
1505 *versicolor*, ovarian localization of GnIH has also been reported and GnIH is able to suppress
1506 ovarian GnRH receptor expression (718).

1507 b- In amphibians: a GH-releasing factor (for review: (315))

1508 In the bullfrog *Rana catesbeiana*, a RF-amide peptide, isolated from hypothalami, showed
1509 high (75%) sequence identity with quail GnIH (372). It was designated fGRP for “frog GH-
1510 releasing peptide” as it exhibits growth hormone-releasing activity (372). In parallel, the same
1511 peptide was isolated from the brain of the European green frog *Rana esculenta*, and named R-
1512 RFa for “Rana-RFamide” (104). The cloning of a cDNA for fGRP revealed that the deduced
1513 precursor encodes one fGRP and three putative fGRP-related peptides (fGRP-RP1, -RP2 and
1514 -RP3) (672). These four peptides were all identified as mature peptides and found to have a
1515 common C-terminal LPXRFamide with avian and mammalian GnIHs (824). Two of these
1516 peptides (fGRP and fGRP-RP2) stimulate GH and/or PRL release *in vivo* and *in vitro*, while

1517 the other two (fGRP-RP1 and fGRP-RP3) have no effects ((372, 824); for review: (823)).
1518 None of them is able to modify the release of gonadotropins (372, 824). The localization in
1519 the amphibian brain is in agreement with other vertebrate distribution as positive neurons (cell
1520 bodies) are present in the periventricular region of the hypothalamus (372, 612, 673). In
1521 contrast, nerve fibers are widely distributed throughout the brain (612) notably in the
1522 olfactory system ((194, 612). An urodele, the Japanese red-bellied newt *Cynops pyrrhogaster*
1523 possesses four GnIH peptides (nLPXRFa-1, nLPXRFa-2, nLPXRFa-3 and nLPXRFa-4) but
1524 no functional studies have been performed yet (114). The GnIH system and its functional
1525 significance in amphibians has been recently reviewed (315).

1526 c- In basal sarcopterygian and actinopterygian

1527 In a basal sarcopterygian, the coelacanth *Latimeria chalumnae*, a GnIH precursor gene has
1528 been identified, encoding three putative LPXRFamide peptides and one LPXRFamide-like
1529 peptide, which align with human RFRP-1/quail GnIH-RP1, human RFRP-2/quail GnIH,
1530 human RFRP-3, and quail GnIH-RP2, respectively (for review: (516)).

1531 In a basal, non-teleost actinopterygian, the spotted gar *Lepisosteus oculatus*, a GnIH precursor
1532 encodes three putative LPXRFamide peptides, which align with human RFRP-1/quail GnIH-
1533 RP1, human RFRP-2/quail GnIH, and human RFRP-3, respectively (for review: (516)).

1534 d - In teleosts: positive and negative effects on gonadotropins

1535 Up to now, in teleosts, only a single gene for GnIH has been identified as in the spotted gar.
1536 However, owing to the teleost specific WGD (3R), two GnIH genes would have been
1537 expected. This suggests the loss of one of the 3R-GnIH duplicated paralogs shortly after the
1538 3R event.

1539 Most of the teleost GnIH precursors encode three LPXRFamide or LPXRFamide-like
1540 peptides which align with human RFRP-1/quail GnIH-RP1, human RFRP-2/quail GnIH, and
1541 human RFRP-3, respectively (for reviews: (516, 807)). In some species, the precursor

1542 encodes only two peptides which align with human RFRP-1/quail GnIH-RP1, and human
1543 RFRP-2/quail GnIH, respectively. Most GnIHs identified in teleosts possess the common C-
1544 terminal LPXRFamide motif observed in other vertebrate GnIHs.

1545 Concerning the physiological role of GnIH in the control of the gonadotropic axis, the
1546 situation appears more complex in teleosts than in other vertebrates. In the goldfish, GnIH
1547 inhibits GnRH-stimulated *lhβ* and *fshβ* expression by primary cultures of pituitary cells, with
1548 no effect on basal gonadotropin expression (625), while other studies describe either
1549 stimulatory, inhibitory or no effect on both basal and stimulated LH (release and expression),
1550 depending on the gonadal stage (510, 511). A stimulatory effect of goldfish LPXRa was
1551 observed on LH and FSH release by salmon pituitary cells (14). Similarly, goldfish LPXRa
1552 stimulates *lh* and *fsh* expression by whole pituitaries of grass puffer (700). In tilapia,
1553 treatment of pituitary cells in primary culture with tilapia LPXRfa-2 induces a significant
1554 increase in both FSH and LH release (60). In *Cichlasoma dimerus*, homologous LPQRfa-1
1555 decreases LH and FSH release, while LPQRfa-2 is able to stimulate FSH release (whole
1556 pituitaries: (899)). In a basal teleost, the eel *Anguilla anguilla*, ongoing studies indicate that
1557 the three peptides encoded by the eel *gnih* gene exert an inhibitory effect on *lhβ* mRNA
1558 expression by eel pituitary cells.

1559 e- In cyclostomes (agnathans)

1560 Tsutsui and colleagues in collaboration with Sower's laboratory (563) have cloned the
1561 lamprey GnIH precursor cDNA that encodes a precursor encompassing three GnIH peptides
1562 (lamprey LPXRfa-1a, LPXRfa-1b and lamprey LPXRfa-2). The lamprey GnIH peptides
1563 have a C-terminal PQRfamamide motif, unlike most GnIHs, but like NPFF, in gnathostomes. *In*
1564 *vivo* administration of one of the lamprey GnIHs (lamprey LPXRfa-2) stimulates the
1565 expression of lamprey GnRH (GnRH3) in the hypothalamus and gonadotropin β mRNA in
1566 the pituitary (563). Thus, the authors suggest that GnIH may have emerged in agnathans as a

1567 stimulatory neuropeptide that subsequently diverged to an inhibitory neuropeptide during the
1568 course of evolution from basal vertebrates to later-evolved vertebrates, such as birds and
1569 mammals (563).

1570

1571 5.2.5. Origin and evolution of GnIH and its receptors in vertebrates

1572 Osugi and collaborators showed that agnathans possess both GnIH and NPF genes, with the
1573 common C-terminal PQRamide motif (563, 570).

1574 Tsutsui and colleagues hypothesized that vertebrate GnIH and NPF genes may derive from a
1575 common ancestral gene present in protochordates (for review: (807)). In protochordates, a
1576 precursor cDNA of amphioxus PQRamide peptides was then identified. This precursor
1577 encodes three mature peptides characterized by immunoaffinity purification and mass
1578 spectrometry (565). The conserved syntenic region around the loci of the amphioxus
1579 PQRamide peptide gene, as well as of the GnIH gene and NPF gene in vertebrates (565),
1580 suggests that GnIH and NPF paralogous genes may originate from WGD in early vertebrates
1581 (for review: (567)) (Figure 9). As amphioxus PQRamide peptides inhibit forskolin-induced
1582 CRE-luciferase activity in COS-7 cells expressing the amphioxus PQRa receptor 1 (565),
1583 the authors suggested that the common ancestral peptide of GnIH and NPF has played an
1584 inhibitory role in reproduction in ancestral chordates (807). The inhibitory role of the
1585 ancestral peptide would have been conserved for GnIHs in mammals, birds and some teleosts,
1586 whereas a change from inhibitory to stimulatory role would have occurred in agnathans and
1587 some teleosts (807). In fact, the GH- and PRL-releasing activity of GnIH in amphibians with
1588 the lack of effect on gonadotropin secretion suggests a larger flexibility in the possible
1589 physiological roles of GnIH peptides in the course of vertebrate evolution.

1590 Concerning GnIH receptors, two GPCRs have been identified in birds and mammals:
1591 (LPXRF-R or NPF1R or GnIHR or OT7T022) considered as the primary GnIH receptor

1592 and GPR74 (PQRF-R or NPFFR-2) with a lower affinity for GnIH (for review: (543)).
1593 In teleosts, up to three different GnIH receptor genes (*gnihr1*, *gnihr2* and *gnihr3*), that share
1594 high sequence identity with the mammalian and avian GPR147, have been isolated in
1595 zebrafish (913), goldfish (625) and common carp (599). This may reflect the impact of teleost
1596 specific WGD (3R) or of the additional WGD that occurred in some cyprinids (4R in goldfish
1597 and some carps). However, in most teleosts, only one receptor has been identified so far
1598 (grass puffer LPXRF-R (700); tilapia LPXRF-R (60); orange-spotted grouper GnIHR (858);
1599 clownfish GnIHR (113); tongue sole LPXRFa-R (853)). Further investigations are thus
1600 clearly needed.

1601 Elphick and Mirabeau have identified a GnIH/NPFF-type receptor gene in the genome
1602 database of the hemichordate *Saccoglossus kowalevski* (174). Phylogenetic analyses grouped
1603 the receptors of vertebrates into NPFFR-1 (GPR147) and NPFFR-2 (GPR74), and the
1604 receptors of insects into SIFR (817). Deuterostomian NPFFR genes have already been
1605 proposed to share a common evolutionary origin with protostomian SIFR genes (492).

1606

1607 5.2.6. NPFF (PQRF) group (*farp-1*)

1608 The first NPFF (PQRF) peptide to be reported was isolated from the bovine brain and
1609 characterized as a pain modulatory peptide (896). NPFF peptides possess a similar C-terminal
1610 structure (PQRFamide motif) as some GnIH peptides (for review: (577)). As previously
1611 discussed, *npff* and *gnih* genes are paralogous genes that likely emerged from WGD in early
1612 vertebrates. As GnIH precursors, the PQRFa precursor encompasses two to three putative
1613 mature peptides: NPFF and NPAF in mammals, NPFF and NPAF in teleosts, and PQRFa,
1614 PQRFa-RP1 and PQRFa-RP-2 in agnathans (lamprey and hagfish) (for review: (577)).

1615 NPFF peptides have been largely investigated for their role in the control of nociception (for
1616 review: (29)). Other actions have been also reported such as increasing arterial blood pressure

1617 and water intake, while decreasing food intake in mammals (for review: (577)). Compared to
1618 GnIH or kisspeptin, few studies have been carried out to investigate the possible role of NPDF
1619 in reproduction. In teleosts, one study reported that bath application of medaka NPDF inhibits
1620 the pacemaker activity of terminal nerve GnRH neurons in the dwarf gourami (653). In
1621 agnathans, one of the hagfish NPDF peptides directly stimulates pituitary expression of
1622 gonadotropin β mRNA (568), while the lamprey peptides appear to possess a stimulatory
1623 effect only on GnRH2 secretion (140). These data suggest that PQRamide peptides may play
1624 a role in the reproductive system of lower vertebrates and that they might have adopted new
1625 functions during the course of vertebrate evolution (568).

1626

1627 5.2.7. QRFP (26RFa) group (*farp-5*)

1628 In 2003, a new peptide family was simultaneously identified by three different laboratories
1629 (104, 213, 322). The first research group isolated the peptide from a frog brain extract, and
1630 named it 26RFa after its 26 amino acid sequence and RF terminal motif (104). The other two
1631 research groups identified the peptide while searching for ligands to an orphan GPCR
1632 (GPR103 also referred to as AQ27 or SP9155) (213, 322). Fukusumi and collaborators named
1633 it QRFP, after its pyroglutamylated arginine-phenylalanine-amide signature; the peptide
1634 consists of 43 amino acid residues (213). Jiang and collaborators (2003) named it P52 and its
1635 precursor protein, P518 (322). Comparative studies indicated that amphibian 26RFa and
1636 mammalian QRFP/P52 are orthologs (825). Phylogeny analyses of RF-amide peptides and
1637 receptors suggested a close relationship between QRFP (26RFa) (*farp-5*) on the one hand and
1638 the GnIH and NPDF groups (*farp-3* and *farp-1*) on the other hand, likely resulting from local
1639 gene duplication, preceding vertebrate WGD (904) (Figure 9).

1640 A QRFP (26RFa) gene has been described in amphioxus (492, 889), suggesting that the gene
1641 existed in chordates before the emergence of vertebrates. As all vertebrates studied so far

1642 possess a single gene, this suggests that duplicated paralogs resulting from the successive 1R,
1643 2R WGD in early vertebrates and from 3R WGD in early teleosts, might have been lost (for
1644 review: (404)).

1645 The main role reported for 26RFa/QRFP is the control of feeding behaviour with a potent
1646 orexigenic effect in mammals and birds, while it may also exert other various functions (for
1647 reviews: (102, 103, 105, 404, 825)). Concerning reproductive functions, *in vitro* and *in vivo*
1648 studies support the involvement of 26RFa in the control of the gonadotropic axis in mammals
1649 (528). 26RFa dose-dependently stimulates basal and GnRH-induced LH secretion by male
1650 and cyclic female rat pituitaries *in vitro* (528). Similarly, *in vivo* (icv or systemic) injection of
1651 26RFa induces a significant increase of serum LH levels in cyclic and ovariectomized females
1652 (528). Patel and collaborators tested the more potent GPR103 ligand, QRFP43, *in vivo* and *in*
1653 *vitro* (594). They reported that icv injection of QRFP43 to male rats increases plasma LH and
1654 FSH levels; in contrast, intraperitoneal administration does not influence circulating
1655 gonadotropin levels (594). *In vitro*, QRFP43 stimulates GnRH release from hypothalamic
1656 explants from male rats and from the immortalized hypothalamic GnRH-producing neurons
1657 (GT1-7 cells) (594). In teleosts, one study in the goldfish reported that intraperitoneal
1658 injection of 26RFa increases plasma LH levels; the peptide may exert its action at the brain
1659 level, since 26RFa has no direct effect on LH release *in vitro* by primary cultures of pituitary
1660 cells (431).

1661

1662 **5.3. A raising star in mammalian reproduction: Kisspeptin (*farp-4*)**

1663 5.3.1. Discovery of Kiss in mammals

1664 In 1996, a metastasis suppressor gene for melanoma cells was identified and called Kiss-1...
1665 as a tribute to the chocolate speciality of the city of the authors (227). Then, in 1999, the
1666 cDNA of a novel GPCR was isolated from rat brain and named GPR54 (396). Since the

1667 highest identity of this orphan GPCR was observed with the galanin receptors and since its
1668 cerebral distribution was similar to those of galanin receptors, the authors suggested that the
1669 endogenous ligand of GPR54 may have a peptidergic nature (396). Two years later, the
1670 natural ligands of GPR54 were isolated from human placenta (375). The Kiss-1 gene encodes
1671 a 54 amino-acid peptide which may be further processed into shorter peptides of 14 and 13
1672 amino-acids (290, 549), all designated as kisspeptins (375). The peptide of 54 amino-acid
1673 residues was also named metastin (549). The 10-amino acid C-terminal fragment of
1674 kisspeptins (or kiss peptides) carries the biological activity (375). The functional importance
1675 of the C-terminal amidation was shown by the lack of binding and functional response for
1676 non-amidated synthetic kisspeptins (375).

1677 A few years later, a pivotal role of kisspeptin in the control of reproduction was revealed. The
1678 discovery by three research groups (214, 648, 693) that inactivation of kisspeptin receptor
1679 (GPR54) leads to hypogonadotropic hypogonadism in human patients (loss-of-function
1680 mutations) and in mice (knock-out, KO) retained attention of reproductive endocrinologists
1681 and initiated intensive research on kisspeptin for many years. Hypogonadotropic
1682 hypogonadism was also observed in *Kiss1* KO mice (135). Conversely, mutations leading to
1683 higher resistance of kisspeptin to degradation (714) or prolonged activation of GPR54 (774)
1684 can induce precocious puberty onset in humans (for review: (714)).

1685

1686 5.3.2. Role of Kiss in the control of reproduction in mammals

1687 a- Stimulation of GnRH neurons

1688 Peripheral (subcutaneous, sc) or intracerebroventricular (icv) injection of kisspeptin increases
1689 plasma levels of gonadotropins and this response is abolished by the use of a GnRH
1690 antagonist (icv, mice: (237); icv, rats: (307); sc, rats: (464); icv, monkeys: (698)), suggesting
1691 a stimulatory effect of kisspeptin on gonadotropins via activation of hypothalamic GnRH

1692 neurons. In addition, coexpression of GPR54 mRNA by GnRH neurons is observed in rat
1693 (307) and mouse (483). Icv administration of kisspeptin in sheep also induces a robust release
1694 of GnRH into the cerebrospinal fluid (483). Intraperitoneal (ip) injection of kisspeptin in
1695 wild-type mice stimulates LH and FSH release, but has no effect in *gpr54*^{-/-} mice (483). All
1696 these data define the kisspeptin system (ligand and receptor) as a major stimulator of the
1697 gonadotropic axis *via* induction of GnRH in mammals (rodents, sheep and primates). In rats
1698 and mice, two distinct subpopulations of kisspeptin neurons with different roles on
1699 GnRH/gonadotropic axis have been identified: the hypothalamic arcuate nucleus
1700 subpopulation is involved in the pulse mode of GnRH/LH release while the anteroventral
1701 periventricular nucleus subpopulation is implicated in the surge mode of GnRH/LH release (for
1702 review: (820). A direct action of kisspeptin on GnRH neurons was demonstrated *in vitro*, as
1703 kisspeptin induces GnRH release from mediobasal hypothalamus (MBH) explants, while this
1704 did not occur in MBH explants from *Gpr54* null mice (770). Primary cultures of whole fetal
1705 rat brain respond to exogenous kisspeptin with increased *gnrh* mRNA expression (750).
1706 Using mouse GnRH-secreting neuronal cell lines (GT1-7 cells: (480); GN11 cells: (631)), two
1707 studies also showed a stimulatory effect of kisspeptin on GnRH secretion and mRNA levels
1708 (GT1-7 and GN11 cells: (540); GT1-7 cells: (780)); in contrast, another study using GT1-7
1709 cells showed that kisspeptin fails to stimulate GnRH expression while increasing GnRH
1710 receptor transcriptional activity ((751); for review: (343)).

1711 b- Direct action on pituitary and gonads

1712 The expression of GPR54 in the pituitary gland and in particular on LH β cells in rat, ovine
1713 and human suggests a potential direct action on pituitary cells (for reviews: (218, 636)). In
1714 most mammals, kisspeptin-10 is able to stimulate LH secretion *in vitro* (rat: (527); bovine and
1715 porcine: (759); ovine: (727); baboon: (440)). However, other studies in rats have been unable
1716 to find any detectable action of kisspeptin on LH directly at the pituitary level (464, 783).

1717 Few data are available on *in vitro* FSH regulation by kisspeptin in mammals. Either no effect
1718 on FSH release (baboon: (440)) or moderate stimulation of GnRH-enhanced FSH secretion
1719 (526) has been reported. Concerning the transcriptional regulation of gonadotropins, Witham
1720 and collaborators showed, using both the mouse pituitary gonadotrope cell line L β T2 and
1721 murine primary pituitary cells, that kisspeptin induces LH β and FSH β expression through the
1722 activation of KissR-1 signaling via PKC (876).

1723 Expression of kisspeptin, as well as GPR54, in mammalian ovary (rat: (91); swine: (37)) and
1724 testis (mice: (854); goat: (660); primate: (306)) supports a role of the local kisspeptin system
1725 at the gonadal level. *In vitro* studies on the functional role of the kisspeptin system in gonads
1726 have so far given contradictory results in mammals, with no (mouse Leydig cells: (479, 854);
1727 Rhesus monkey testes: (769)) or stimulatory effect on steroidogenesis (swine granulosa cells:
1728 (38); goat Leydig cells: (661)). In addition, kisspeptin was shown to stimulate fertilization
1729 capacity of mouse spermatozoa (292).

1730

1731 5.3.3. Multiple Kiss and Kiss receptor genes in vertebrates: impact of WGD

1732 a- 1R and 2R WGD origin of multiple Kiss genes followed by gene losses during vertebrate 1733 evolution (Figure 10)

1734 While, in rodents, a single gene (*Kiss1*) is present, up to three *Kiss* genes have been identified
1735 in other vertebrate lineages including cyclostomes (2 genes), chondrichthyes (2 or 3 genes),
1736 actinopterygians (1 or 2 genes), basal sarcopterygian (coelacanth: 3 genes), amphibians (up to
1737 3 genes), sauropsids (0, 1 or 2 genes), as well as in non-rodents mammals (1 or 2 genes).
1738 Phylogenetic analysis classified the identified *Kiss* genes into three different clades (i.e., *Kiss1*,
1739 *Kiss2* and *Kiss3* clades, leading to a phylogenetically-based nomenclature according to
1740 Pasquier and collaborators (587, 592). The current three *Kiss* genes may derive from a single
1741 ancestral gene duplicated through the two successive WGD (1R and 2R) in early vertebrates

1742 (for review: (587)). These 1R and 2R events should have yielded four different *Kiss* genes in
1743 vertebrates, and syntenic analysis supports the potential existence of a fourth *Kiss* gene
1744 (*Kiss4*) in early vertebrates (587, 592).

1745 The current diversity of *Kiss* gene numbers (from 0 to 3) in extant vertebrate species is the
1746 result of multiple and independent pseudogenization processes and gene loss events during
1747 vertebrate evolution that occurred after the 1R and 2R events (for review: (587)). The loss of
1748 the putative *Kiss4* gene would have occurred early in vertebrate evolution (shortly after the
1749 2R) as it is absent in all extant species of key phylogenetical positions. Additional *Kiss* gene
1750 loss events would have happened, as only a few extant representative species of
1751 chondrichthyans (elephant shark) and sarcopterygians (coelacanth and *Xenopus*) possess three
1752 *Kiss* genes. *Kiss3* would have been lost independently in early actinopterygians and early
1753 amniotes, while *Kiss1* would have been lost independently in some teleosts and sauropsids,
1754 and *Kiss2* in some sauropsids and some mammals. The *Kiss1* and *Kiss2* genes are thus the
1755 most frequent *Kiss* genes in extant vertebrates. Among sauropsids, both *Kiss1* and *Kiss2*
1756 genes are present in some groups such as chelonians (turtle) and crocodylians, while *Kiss1* has
1757 apparently been lost independently in some squamates (anoles) and in birds. Furthermore,
1758 *Kiss2* has undergone pseudogenisation and loss during bird evolution, leading to the lack of
1759 *Kiss* in some species such as the chicken, falcon or parrot (591). In mammals, *Kiss1* and
1760 *Kiss2* are both present in a prototherian mammal (platypus), while *Kiss2* has undergone
1761 pseudogenisation and loss in metatherian (opossum) and eutherian mammals (for review:
1762 (587)). Although a *Kiss2*-like gene is present in the genomes of primates including humans,
1763 due to the lack of amidation signal in the precursor, the endogenous *Kiss2* peptide may not be
1764 functional or produced (564).

1765 While teleost 3R WGD (TWGD) should have generated additional *Kiss* paralogs, extant
1766 teleost species do not possess more *Kiss* genes than a non-teleost actinopterygian (spotted gar)

1767 (*Kiss1* and *Kiss2*) (592). The lack of impact of TWGD suggests a massive loss of 3R-Kiss
1768 paralogs shortly after the 3R event. Furthermore, additional loss of *Kiss1* led to the presence
1769 of a single Kiss gene (*Kiss2*) in some teleosts such as the tetraodon and stickleback (587).

1770 b- 1R and 2R WGD origin of multiple Kiss receptor genes followed by gene losses during
1771 vertebrate evolution (Figure 11)

1772 While, in mammals, only a single gene encodes kisspeptin receptor (*KissR*), several *KissR*
1773 genes have been identified in other vertebrates including chondrichthyes (2 genes), teleosts (1,
1774 2 or 3 genes), amphibians (3 genes) and sauropsids (0, 1 or 2 genes) (for review: (587)). As
1775 for *Kiss* genes, the multiple *KissR* genes may arose from 1R and 2R, so that the potential
1776 existence of four *KissR* paralogs in vertebrates has been hypothesized (361, 398). Actually, a
1777 fourth *KissR* has been discovered in extant representative species of basal sarcopterygians
1778 (coelacanth) and actinopterygians (spotted gar). Phylogenetic analysis classified the identified
1779 *Kiss* genes into four different clades (*i.e.*, *KissR1*, *KissR2*, *KissR3* and *KissR4* clades),
1780 according to the nomenclature by Pasquier and colleagues (587, 589). Phylogenetic and
1781 syntenic analyses indicate that these four paralogs likely resulted from 1R and 2R WGD
1782 ((589, 592). This suggests that a *KissR* ancestral gene was present before the emergence of
1783 vertebrates. In agreement with this hypothesis, *KissR* homologous genes have been identified
1784 in non-vertebrate deuterostomes (174). The *KissR1* and *KissR3* clades are more closely
1785 related to each other than to *KissR2*, and likely represent sister clades stemming from 2R
1786 (587). A phylogenetic reconstruction of a gene family associated with the *KissR* paralogon,
1787 the PALM family (298), also supports the hypothesis that 2R gave rise to *KissR1* and *KissR3*
1788 sister paralogons on the one hand, and of *KissR2* and *KissR4* sister paralogons on the other
1789 hand.

1790 As for the *Kiss* genes, after the 1R and 2R events, the history of the *KissR* family was driven,
1791 throughout vertebrate evolution, by multiple gene loss events leading to the current diversity

1792 of KissR. *KissR4* has been lost independently in the actinopterygian and sarcopterygian
1793 lineages. In actinopterygians, this event has likely occurred in a teleost ancestor after the
1794 emergence of holosteans (e.g. the spotted gar still possesses the four KissRs). Among
1795 sarcopterygians, *KissR4*, which is still present in a basal species (coelacanth) in some
1796 sauropsids (chelonian and squamates) and in prototherian mammals (platypus), has been lost
1797 independently in the amphibian lineage, in some sauropsids (crocodilians) and in the common
1798 ancestor of metatherian and eutherian mammals, including human which possesses a single
1799 KissR (*KissR1*).

1800 As for Kiss, due to massive gene losses, no effect of the teleost-specific TGWD can be
1801 recorded on the current number of *KissR* in teleosts (587, 589, 592). This is further supported
1802 by a recent study in pejerrey *Odonthesthes bonariensis* including phylogenetic analyses (791).

1803 c- Gene conservation or losses and variations in Kiss/KissR couples

1804 Comparison of the evolutionary histories of *Kiss* and *KissR* families (Figures 10 and 11)
1805 highlights both common features and divergences (587). Four *Kiss* and four *KissR* genes
1806 arose from 1R and 2R early in the vertebrate lineage, followed by repeated independent gene
1807 loss events throughout vertebrate radiation. As a consequence of the independent and
1808 asynchronous losses of *Kiss* genes, as well as of *KissR* genes, the extant vertebrate species
1809 present various combinations of putative Kiss and KissR couples. For example, the same two
1810 *Kiss* genes (*Kiss1* and *Kiss2*) have been conserved in a prototherian mammal (platypus) and
1811 in some teleosts (e.g. zebrafish, seabass) but together with the conservation of different
1812 receptors (*KissR1* and *KissR4* in platypus, versus *KissR2* and *KissR3* in zebrafish). Likewise,
1813 unmatching numbers of *Kiss* and *KissR* genes are present in some species, such as three *Kiss*
1814 genes versus four *KissR* genes in a basal actinopterygian, the spotted gar and a basal
1815 sarcopterygian (coelacanth), or two *Kiss* genes versus three *KissR* genes in a basal teleost, the
1816 eel (587, 592). Such variations in the putative couples between Kiss and KissR paralogs

1817 reveal a lack of maintenance and co-evolution of specific Kiss/KissR couples during
1818 vertebrate evolution. This may have been favored by the promiscuity of Kiss receptors
1819 towards various Kiss peptides, related to the high conservation of the 10 amino-acid C-
1820 terminal biologically active sequence (kisspeptin-10 or Kp-10) (398, 413, 561). In species
1821 where multiple *Kiss* and *KissR* paralogous genes have been conserved, differential
1822 physiological roles related to subfunctionalisation or neofunctionalisation may have emerged
1823 between paralogs.

1824

1825 5.3.4. Current studies on the role of Kiss in reproduction in non-mammalian vertebrates

1826 a- In amphibians and reptiles

1827 In amphibians and reptiles, few functional studies are available and concern the action of
1828 kisspeptin on the gonads. In the anuran amphibian *Rana esculenta*, *in vitro* Kp-10 treatment
1829 induces testicular expression of both *gpr54* and estrogen nuclear receptor α , *ER α* (109). In
1830 this species, *ex vivo* treatment of testis with Kp-10 stimulates spermatogenesis (110, 111) and
1831 upregulates the expression of testicular *ER β* , *gnrh 1* and 2, as well as the three types of *gnrh*
1832 receptors (110). All the effects of Kp-10 in amphibians are counteracted by Kp-234, a
1833 kisspeptin antagonist (109, 110). In the reptile *Uta stansburiana* (side-blotched lizard), intra-
1834 coelomical treatment with kisspeptin up-regulates plasma testosterone levels (531).

1835 b- In teleosts: positive and negative effects on reproduction

1836 Even before the demonstration of colocalization of GPR54 on GnRH neurons in mammals
1837 (483), Parhar and collaborators reported that kisspeptin receptor (KissR2) localizes to
1838 hypothalamic GnRH neurons in tilapia, using laser-captured single GnRH neurons (578).
1839 Similarly, in the cichlid fish *Astatotilapia burtoni* (246) and striped bass *Morone saxatilis*
1840 (919), GnRH1 neurons express KissR2 mRNA. In the chub mackerel *Scomber japonicus*,
1841 GnRH1 neurons in the preoptic area co-express KissR1, but not KissR2 (545). Kiss1 and

1842 Kiss2 neurons show differential connections with GnRH neurons in the zebrafish brain (697,
1843 732).

1844 In agreement with the expression of KissR by GnRH neurons, effects of kisspeptins on GnRH
1845 neurons have been demonstrated in various teleost species. Kiss1 and Kiss2 peptides have
1846 opposite effects on the electrical activity of hypophysiotropic GnRH3 neurons in adult
1847 zebrafish: Kiss1 stimulates, while Kiss2 inhibits neuronal activity (915). In the striped bass
1848 *Morone saxatilis*, only Kiss2 (but not Kiss1) upregulates the expression of the
1849 hypophysiotropic *gnrh1* by *in vitro* brain slices (920). In contrast, in hypothalamic explants of
1850 the half-smooth tongue sole, Wang and colleagues showed that Kiss2 has no effect on either
1851 *gnrh2* or *gnrh3* mRNA levels (852). *In vivo* studies reported either no (zebrafish *gnrh 2* and *3*:
1852 (366); grouper *gnrh3*: (707); hybrid bass *gnrh 2* and *3*: (919); yellowtail kingfish *gnrh1*:
1853 (535); male chub mackerel *gnrh1*: (546, 691, 692)), stimulatory (grouper *gnrh1*: (707)) or
1854 inhibitory (striped bass *gnrh1*, *2* and *3*: (918)) effects of Kiss peptides on brain transcript
1855 levels of *gnrh*. Depending on the administration routes, in the female chub mackerel, both
1856 stimulatory (sc (692)) and inhibitory (icv (546)) effects of Kiss2 have been reported on brain
1857 *gnrh1* mRNA levels. These *in vitro* and *in vivo* studies thus indicate variable effects of
1858 kisspeptins on GnRH in teleosts.

1859 Concerning the effect of kisspeptin on the pituitary in teleosts, direct (*in vitro*) stimulatory
1860 action of kisspeptin 2 (Kp2) on pituitary LH secretion was reported in goldfish (895), striped
1861 bass (918, 920) and sea bass (179), but no effect of Kp1 was observed in goldfish (413) and
1862 sea bass (179)). In contrast, in the European eel, heterologous and homologous Kiss peptides
1863 all directly inhibit the expression of *lh*, with no effect reported on *fsh* (588, 590). In the
1864 striped bass also, Kp1 is generally ineffective but, at high doses, can inhibit *lh* expression
1865 (918, 920). A few studies also report a stimulatory effect of kisspeptins on FSH (striped bass,
1866 Kp1 and Kp2 (918, 920); sea bass, Kp2 (179)).

1867 *In vivo* stimulatory (goldfish (413); sea bass (185); seahorse *Hippocampus erectus* (911)) or
1868 no (goldfish (524)) action of kisspeptins on gonadotropins have been described in teleosts. In
1869 the striped bass, kisspeptin action depends on the stage of development, as intramuscular
1870 injection of Kp1 has no effect on LH at the pubertal stage, while both Kp1 and Kp2 increase
1871 LH levels at gonadal recrudescence (919). In both sexes (adult immature stage) of the chub
1872 mackerel *Scomber japonicus*, icv administration of Kp2, but not Kp1, increases *fsh β* and *lh β*
1873 mRNA levels (546, 547).

1874 The role of Kiss was further investigated in knocked-out fish models. Two studies reported
1875 normal fertility in KO fishes for kisspeptin-related genes (zebrafish: (768); medaka: (524)).
1876 In KO medaka for *kiss1*, *kiss2*, *gpr54-1* or *gpr54-2*, ovaries and testes develop normally as
1877 compared to wild-type fish, with full-grown and late-vitellogenic follicles, and spermatozoa
1878 being observed, respectively (524). There are also no significant differences in the expression
1879 levels of both *lh β* and *fsh β* between the kisspeptin-related gene KO lines and wild-type (524).

1880 Similarly, zebrafish with mutations for *kiss1*, *kiss2*, *kissr1* or *kissr2* show normal
1881 gametogenesis and reproductive capability, as well as normal expression levels of *gnrh2*,
1882 *gnrh3*, *lh β* and *fsh β* (768). Double mutation (*kiss1*^{-/-}; *kiss2*^{-/-}), which prevents the
1883 compensation between ligands, causes lower expression of *gnrh3*, *lh β* and *fsh β* , supporting
1884 that kisspeptin signalling stimulates the expression of these genes in zebrafish (768).

1885 However, these decreases had no impact on the phenotypes of the fish, as normal reproductive
1886 performance was reported (768). As compared to the induction of hypogonadotropic
1887 hypogonadism in mammals by loss-of-function mutation (human) or KO (mice) of *gpr54* or
1888 *kiss1* KO, these observations suggest a dispensable role of Kiss in the neuroendocrine control
1889 of reproduction in teleost models (zebrafish and medaka).

1890 Interestingly, a study readdressed this question in mice by using ablation of kisspeptin
1891 neurons or of *gpr54*-expressing neurons (469). Differently from KO experiments, the authors

1892 observed no impact on the timing of puberty, suggesting that kisspeptin neurons play a role in
1893 the optimization of reproductive success, by integrating various cues and relaying this
1894 information to GnRH neurons, but are dispensable for puberty onset, activation of GnRH
1895 pulses and fertility.

1896 c- Loss of kiss function in birds?

1897 As mentioned above (§ 5.2.3 a, b), phylogenomic studies suggest that two Kiss genes (*Kiss1*
1898 and *Kiss2*) have been inherited from the amniote ancestor. In the course of amniote evolution,
1899 *Kiss1* has likely been lost early in the bird lineage, while it has been conserved in some other
1900 sauropsids and in mammals. The existence of a *Kiss2*-like gene has been demonstrated in the
1901 genomes of several bird species, mallard duck, zebra finch, and rock pigeon (591). These
1902 avian *Kiss2*-like sequences diverge from those of other vertebrates and are not found in the
1903 genomes of chicken, falcon and parrot (591), revealing the processes of *Kiss2* gene
1904 pseudogenisation and loss in the avian lineage. Together with the loss of *Kiss1*, these results
1905 support the absence of any functional kisspeptin in birds. Concerning Kiss receptors, two
1906 genes (*KissR1* and *KissR4*) would have been inherited from the amniote ancestor. Synteny
1907 studies demonstrate the loss of *KissR1* in the bird lineage, but cannot conclude for the
1908 presence or not of *KissR4* with the current databases. Altogether, current phylogenomic
1909 analysis suggests the loss of *Kiss* genes in birds and a possible conservation or loss of a Kiss
1910 receptor (*KissR4*) (still to be found).

1911 Immunocytochemical studies reported the presence of kisspeptin-like immunoreactive
1912 neurons in the medial preoptic nucleus of the hypothalamus in the mallard drake in close
1913 proximity to GnRH fibers and almost all these neurons co-express aromatase (658). This may
1914 correspond to the derived sequence identified in the duck even though the peptide mutations
1915 and the variations in gene structure suggest a pseudogenisation (591). Kisspeptin
1916 immunoreactivity is also observed in ovarian granulosa cells of hens (887), while genomic

1917 and syntenic analyses support the loss of Kiss in this species (591). In goose, immunoreactive
1918 kisspeptin is also detected in the ovary (granular layer and theca of the follicle) and in the
1919 plasma where concentrations vary during the reproductive cycle (295). This raises the
1920 question as to whether the detection of immunoreactive kisspeptin in birds may result from
1921 cross-reactions with other RF-amide peptides.

1922 A few functional studies using mammalian kiss peptides have been performed in birds.
1923 Central (icv) administration of kisspeptin-52 is able to increase plasma LH levels in the
1924 mallard drake, and pretreatment with a GnRH receptor antagonist prevented this increase in
1925 LH levels (658). Kisspeptin also increases plasma LH levels in the white-crowned sparrow
1926 (cited in (533)). However, in adult male chicken, human Kp-10 has an inhibitory effect, as
1927 intravenous injections of Kp-10 suppress plasma testosterone levels (847). Kisspeptin-10
1928 treatment stimulates progesterone secretion in cultured chicken granulosa cells (887).
1929 Repeated injections of Kp-10 advance the initiation of egg-laying in the juvenile female quail
1930 (533) by increasing lipid synthesis as well as upregulating estrogen receptor protein and
1931 lipogenic gene expression in the liver (884). In the hypothalamus, Kp-10 induces an up-
1932 regulation of *cgnrh-I* expression and a down-regulation of *gnih* expression. In the pituitary,
1933 Kp-10 increases *lhβ* and *gnrh-rII* and decreases *fshβ* expression (533). Further studies are
1934 warranted to investigate whether these actions of heterologous kisspeptin in birds are
1935 mediated by a potential Kiss receptor (KissR4; still to be identified in birds) or by other RF-
1936 amide peptide receptors.

1937

1938 5.3.5. Kiss before vertebrates

1939 In deuterostomes, in addition to vertebrates, two other sub-phyla constitute the phylum of
1940 chordates: the urochordates and the cephalochordates. Neither kisspeptin nor kisspeptin
1941 receptors have been found in urochordates (such as ascidians). In contrast, four kisspeptin-

1942 type precursors and 16 kisspeptin-like receptors have been identified in the cephalochordate
1943 amphioxus *Branchiostoma floridae* (492), suggesting that multiple gene duplication events
1944 specifically targeted Kiss and KissR in this lineage. In *B. floridae*, one of the reported genes
1945 encodes three putative peptides, suggesting additional intra-gene duplication of peptidic
1946 sequences, while the other genes encode a single peptide (492). More recently, 27 putative
1947 KissR-like genes were identified in *B. floridae* (856). Further expression and functional
1948 studies were performed in the amphioxus *B. japonicum* on one kiss-like gene (*BjkissL-2*) and
1949 one kissR-like gene (*Bjgpr54L-1*) (856). Using qPCR and immunohistochemistry, the authors
1950 showed that *BjkissL-2* mRNA and protein levels are higher in notochord/nerve cord, and
1951 especially in the anterior region of the nerve cord (cerebral vesicle) and Hatschek's pit (856).
1952 *Bjgpr54L-1* expression is predominantly observed by qPCR in the notochord/nerve cord,
1953 moderate expression is seen in the testis and ovary, and lower expression in gill, muscle,
1954 hepatic caecum and hind-gut (856). Two amphioxus peptides show functional interaction with
1955 *Bjgpr54L-1*, while the receptor exhibits higher affinity for zebrafish Kiss peptides (856).
1956 Amphioxus synthetic Kiss peptides induce LH release in sexually mature female zebrafish
1957 and, in amphioxus, trigger the expression of *gpb5* mRNA, the glycoprotein subunit related to
1958 vertebrate glycoprotein hormones (see section 3), suggesting an ancestral role of Kiss-KissR
1959 in the neuroendocrine control of reproduction (856).
1960 In non-chordate deuterostomes, echinodermata and hemichordata are sister phyla in a clade
1961 known as ambulacraria (285). The occurrence of kisspeptin-type receptors has been reported
1962 in ambulacrarian species, the sea urchin *S. purpuratus* (phylum echinoderms) and the acorn
1963 worm *Saccoglossus kowalevskii* (phylum hemichordates) (318, 492). Recently, kisspeptin-
1964 type precursors have also been identified in ambulacrarians, the starfish *Asterias rubens*, *S.*
1965 *purpuratus* and *S. kowalevskii* (694, 695). These precursors comprise two putative kisspeptin-
1966 like peptides.

1967 Concerning protostomes, some kisspeptin-type receptors, but not yet a peptide precursor,
1968 have been found in lophotrochozoa (mollusca and annelida) (87, 318, 492). Precisely,
1969 kisspeptin-like receptors are present in mollusca, bivalvia (oysters, *Crassostrea gigas* and
1970 *Pinctata fucata* and mussel, *Mytilus galloprovincialis*) and gastropoda (limpet, *Lottia*
1971 *gigantea*; slug, *Aplysia californica*), as well as in annelida (worm, *Capitella teleta*) (87). The
1972 occurrence of kisspeptin-like receptors in lophotrochozoan invertebrates suggests the
1973 existence of kisspeptin-like peptides in these animals.

1974 According to Elphick and collaborators, the evolutionary ancestry of kisspeptin-type receptors
1975 can be traced back to the common ancestor of the bilaterians, but with subsequent loss in
1976 urochordate deuterostomes and ecdysozoan protostomes (for reviews: (174, 175)). However,
1977 based on phylogenic and syntenic analyses using *Anopheles* mosquitoes (ecdysozoan), it
1978 appears that allostatin type A receptors (AST-ARs) and KissR emerged from a common gene
1979 ancestor after the divergence of galanin receptors (GALRs) in the bilaterian genome,
1980 suggesting that invertebrate AST-ARs and ligands shared a common evolutionary origin with
1981 vertebrate kisspeptin/galanin receptors and ligands (186).

1982

1983 5.3.6. Kisspeptin, more related to galanin/spexin than to other RF-amide peptides

1984

1985 Originally, the kisspeptin receptor was discovered for its high degree of sequence similarity
1986 with galanin receptors (396). Kim and collaborators found that spexin (*SPX*), galanin (*GAL*)
1987 and kisspeptin (*KISS*) genes are on the same reconstructed vertebrate ancestral chromosome
1988 (359). Their family genes are distributed among four 2R-generated paralogs (four linkage
1989 groups). Three linkage groups contain *SPX1* and *KISS2*, *SPX2* and *GAL*, and *KISS3* and
1990 galanin-like peptide (*GALP*), respectively. The fourth linkage group has *KISS1* alone. The
1991 ancestral forms of *KISS*, *GAL* and *SPX* are proposed to arise by local tandem duplications
1992 before 2R (Figure 9) and to expand their family members through 2R (359). Likewise,
1993 *KISSRs* and *GALRs* have probably emerged through local duplications before 2R, producing

1994 three subgroups in vertebrates: KISSRs (4 KISSRs), GALR1 (GALR1a and GALR1b), and
1995 GALR2/3 (GALR2a, GALR2b and GALR3)(for review: (904). SP1 and SPX2 are functional
1996 ligands for GALR2 and GALR3 and are even more potent than GAL in activating GALR3
1997 (359). The evolutionary origin of the KISS (*farp-4*)/SPX/GAL family is far distant from those
1998 of the NPF (*farp-1*)/QRFP(*farp-3*) and PrRP(*farp-2*)/NPY families, so that some authors
1999 propose that kisspeptin should be classified separately (for review: (904)). This infers that
2000 common peptide sequences such as the C-terminal sequence shared by the RF-amide peptide
2001 super-family may reflect conservation but also convergences of peptide sequences especially
2002 suitable for bioactivity.

2003 The galanin peptide family is constituted of galanin, galanin message-associated peptide
2004 (GMAP; encoded by the same gene as galanin), galanin-like peptide (GALP; encoded by a
2005 distinct gene) and alarin (encoded by a splice variant of GALP gene) (for review: (389)).
2006 Spexin (SPX; now renamed SPX1) was discovered in 2007 in human proteome (493). A
2007 second form, SPX2, has been characterized in all vertebrates except mammals (359). GALR2
2008 and GALR3, but not GALR1, have been shown to be the cognate receptors for SPX (359).
2009 Regarding functional roles of these peptides, they share an involvement in the control of
2010 reproduction, especially as a link between metabolism and reproduction, which have been
2011 previously reviewed in depth by other authors (for reviews: galanin family, (182, 478);
2012 GALP, (393); spexin, (441)).

2013

2014 **5.4. Prolactin releasing peptide (PrRP) group (*farp-2*)**

2015 The search for the ligand of the human orphan pituitary receptor, hGR3, led to the
2016 identification of a new peptide from bovine hypothalamic extract that acts as a prolactin-
2017 releasing factor in rat anterior pituitary cells and was thus named prolactin releasing peptide,
2018 PrRP (280). The prepro-protein generates at least two forms of mature peptide, PrRP31 and

2019 PrRP20 (a C-terminal fragment of PrRP-31) (280)). At the same time, another RF-amide
2020 peptide, with a similar amino acid sequence, was isolated from the brain of a teleost, the
2021 Japanese crucian carp, and named Carassius-RFa (C-RFa) (210). C-RFa homologs have been
2022 characterized in other teleosts as well as in chicken, *Xenopus* and lamprey, but not in
2023 mammals, and C-RFa had been considered as a teleost PrRP (for review: (762)). However,
2024 while looking for PrRP and C-RFa in chicken, Wang et al (2012) found that PrRP and C-RFa
2025 are encoded by distinct genes in non-mammalian vertebrates, originating through duplication
2026 of an ancestral gene (386). Tachibana and Sakamoto (762) thus proposed that the widely used
2027 name of PrRP/C-RFa in lower vertebrate species be renamed PrRP2, as previously suggested
2028 by Wang and collaborators (859).

2029 Data in non-mammalian vertebrates indicate that PrRP and C-RFa/PrRP2 are able to stimulate
2030 PRL release *in vitro* (teleosts: C-RFa in tilapia, (685); C-RFa in rainbow trout, (508, 646))
2031 and *in vivo* (bird: comparison C-RFa et mPrRP, (763); amphibian: PrRP, (655); teleost:
2032 (508)). In contrast, after the initial finding of Hinuma and collaborators (280), other studies in
2033 mammals questioned the role of PrRP as a prolactin releasing factor and thus led to the
2034 hypothesis that this role of PrRP may be ancient and even lost in mammals. In fact, there is
2035 now clear evidence that PrRP is involved in the control of feeding behavior and energy
2036 expenditure in mammals as well as in other vertebrates (for reviews: (154, 762)).

2037 Several studies support a role of PrRP in the neuroendocrine control of reproduction in
2038 mammals. Icv injection of PrRP to male rats increases plasma LH, FSH and testosterone
2039 levels (684), while icv administration of an anti-rat PrRP serum causes a reduction of LH
2040 surge (283). As PrRP is not able to induce release of LH and FSH directly from dispersed
2041 male pituitary cells *in vitro*, but instead can increase the release of GnRH from hypothalamic
2042 explants (684), it was suggested that PrRP could stimulate gonadotropin secretion *via* a
2043 hypothalamic mechanism involving the release of GnRH in male rat. The control of GnRH1

2044 neurons by PrRP in rat is further supported by the presence of PrRP fibers in the medial
2045 preoptic area and of PrRP receptors in GnRH1 neurons (187). To the best of our knowledge,
2046 no data are yet available for such a role in other vertebrates.

2047 Phylogenetic, pharmacological and paralogon analyses reveal that prolactin releasing
2048 hormone receptor (PrRP-R) shares a common ancestry with neuropeptide Y (NPY) receptors
2049 (385). In fact, NPY binds to PrRP-R1 and inhibits response of PrRP-R1-expressing cells to
2050 PrRP, behaving as an antagonist. NPY-type peptides have an ancient origin in bilaterians as
2051 they are present both in protostomes (328) and deuterostomes. An ancestral PrRP peptide
2052 probably started coevolving with a redundant NPY receptor, which then became PrRP-R,
2053 approximately 500 Million years ago (385). The distinct PrRP/NPY family genes and their
2054 receptor genes emerged by local gene duplication during early vertebrate evolution (for
2055 review: (904)) (Figure 9). NPY has been largely recognized for its involvement in the
2056 interactions between food intake, metabolism and reproductive function (for reviews: (146,
2057 473, 519)).

2058

2059 **5.5. Conclusion on RF-amide peptides**

2060 While RF-amide peptides, which all share a conserved C-terminal RF-amide signature, have
2061 been described as a family of neuropeptides encoded by five different genes in mammals,
2062 phylogeny and synteny analyses suggest that they do not all derive from a common ancestor
2063 and perhaps should not be seen as a family.

2064 As reviewed above, RF-amide peptides, such as GnIH and kisspeptin, are critically involved
2065 in the control of reproduction and puberty. Most RF-amide peptides (GnIH, kisspeptin,
2066 QRFP/26RFa, PrRP) and non-RF-amide peptides which they are related to, such as NPY for
2067 PrRP and galanin/spexin for kisspeptin, are also major regulators of food intake and
2068 metabolism (for reviews: (153); GnIH, kisspeptin (848); kisspeptin (877); QRFP/26RFa

2069 (404); PrRP (762) ; galanin, spexin (182, 441) ; NPY (519)), which can be closely linked to
2070 reproduction (452). Modulation of nociception is mainly exerted by NPFF and, to a lesser
2071 extent, by other RF-amide peptides such as QRFP/26Rfa (for reviews: (29, 404)).

2072 Some data point out that RF-amide peptides display low selectivity toward the different RF-
2073 amide peptide receptors, within and between receptor families. Cross-activities between RF-
2074 amide peptides and their various receptors have notably been demonstrated *in vitro*. For
2075 instance, PrRP has high affinity, and higher efficacy than NPFF, at the NPFFR-2 receptor
2076 (178); 26Rfa interacts with a receptor distinct from GPR103 (26Rfa receptor) that may be
2077 NPFFR-2 (74); Kisspeptin-10 exhibits high binding affinity and receptor activation towards
2078 NPFFR-1 and NPFFR-2 (551). PrRP, kisspeptin and 26Rfa activate NPFFR-1 and NPFFR-2
2079 and thus may modulate nociception (171).

2080 Together, these data highlight the complexity of the diversification of neuropeptides and their
2081 receptors via local and whole genome duplications, conservation, losses and convergences,
2082 and the putative variety of interactions between multiple paralogs of ligands and receptors.

2083

2084 **6. Non-peptidic neuromediators and the control of reproduction**

2085 **6.1. Introduction**

2086 In addition to GnRH and some other peptides, non-peptidic neurotransmitters such as
2087 monoamines (catecholamines, indolamines and histamine), acetylcholine, and amino acids
2088 (glutamic acid and gamma-aminobutyric acid, GABA) may also play a more or less
2089 prominent role in the neuroendocrine control of reproduction (for reviews: (34, 222, 621, 840,
2090 864, 875, 921)). This chapter will focus on the role of dopamine, norepinephrine, serotonin,
2091 histamine, and GABA in the control of reproduction.

2092

2093 **6.1.1. Ancient, multifunctional neuromediators**

2094 In the nervous system of adult vertebrates, neurotransmitters act as chemical mediators of
2095 intercellular communication by the activation of specific receptors and second messengers in
2096 postsynaptic cells. This specialized role appears to have evolved from more ancestral
2097 functions in primitive organisms where these substances were used as both intra- and
2098 intercellular signals. Indeed, a number of 'classical' neurotransmitters are present in primitive
2099 organisms and early embryos in the absence of a nervous system (79) and it has been
2100 suggested that these molecules “initially functioned as intracellular regulators, then became
2101 local hormones, and finally acquired the role of synaptic transmitters” (80, 811).

2102 It is now clear that in vertebrates, that most known central nervous system neurotransmitter
2103 substances may also participate in the regulation of pituitary secretion and that in some
2104 instances “neurotransmitters” behave like releasing hormones. The best example is dopamine
2105 (DA) which, in mammals, is released from nerve endings of tuberoinfundibular DA (TIDA)
2106 neurons in the median eminence and pituitary stalk to activate DA receptors at the pituitary
2107 level after being transported there by portal blood vessels. Hence, the definitions of
2108 neurotransmitters and neurohormones are partially intermingled (810). Neurotransmitters can
2109 participate in the control of pituitary secretion by serving as a neurotransmitter input, or
2110 releasing factor output, of hypothalamic neuroendocrine transducer cells; they can act also
2111 within these cells, or act as neurotransmitter within a nerve tract that impinges upon the
2112 hypothalamus (23).

2113 a- Monoamines

2114 Monoamines (such as catecholamines, serotonin, histamine) are evolutionary ancient
2115 molecules. They are present in metazoa and also in some protozoa (811). They control neural
2116 and endocrine systems in both non-vertebrates and vertebrates. In vertebrates, physiological
2117 and pharmacological evidences make it clear that monoamines are involved in the regulation
2118 of anterior pituitary hormone secretion, including gonadotropins (LH and FSH).

2119 -The catecholamines, dopamine (DA), norepinephrine (NE) and epinephrine (E) are major
2120 neurotransmitters found in most, if not all, metazoan species, although the nature of the
2121 catecholamines may differ between animal phyla. Their role as neuromediators or
2122 neurohormones is documented in a limited number of species: While the neuromodulatory
2123 functions of DA appears to be conserved in all bilaterians (505), that of NE is clearly
2124 demonstrated only in vertebrates. In mammals, both have been implicated in the regulation of
2125 GnRH secretion (222, 339).

2126 -The indoleamine, serotonin (5-hydroxytryptamine; 5-HT), first identified as a
2127 neurotransmitter-signaling molecule in mammals, is ubiquitous across all forms of life. Cells-
2128 containing 5-HT have been found in representatives from all major metazoan clades, *e.g.*,
2129 cnidarians, plathyhelminths, nematodes, arthropods, annelids, mollusks, echinoderms,
2130 tunicates and vertebrates (30, 137, 268) suggesting an early appearance during animal
2131 evolution. As regards reproductive functions, various studies in vertebrates have
2132 demonstrated a role of 5-HT in the secretion of reproductive neurohormones and sexual
2133 behaviors (for review (621)).

2134 -Histamine (HA): Classically established as a “peripherally” important mediator of
2135 inflammation, HA is now accepted to play a role in neurotransmission (254). The brain
2136 histaminergic system is a phylogenetically old group of neurons that project to most regions
2137 of the central nervous system (253).

2138 b- GABA

2139 GABA (gamma amino butyric acid) is known as the main inhibitory neurotransmitter in the
2140 brains of mammals (144). Such a function appears ancestrally derived, as GABA exerts
2141 similar inhibitory functions in the nervous system of even the most primitive animals (238).
2142 GABA plays a key role in the control of pituitary hormone release, including gonadotropins,
2143 in mammals (414, 839) as in fish (799).

2144

2145 6.1.2. Non-peptidic neuromediators produced via enzymatic synthesis: phylogeny of enzymes
2146 to retrace their evolutionary history

2147 Nonpeptidic neuromediators are decarboxylated derivatives of amino acids: DA and NE are
2148 synthesized from tyrosine, 5-HT from tryptophan, HA from histidine, and GABA from
2149 glutamic acid, in one or more enzymatically catalysed reactions of which the first serves as
2150 the rate-limiting step.

2151 α -Aromatic Amino acid hydroxylases (AAAH)

2152 The first step in catecholamine and indoleamine biosynthesis is the ring hydroxylation of the
2153 aromatic amino acid substrates (tyrosine or tryptophan respectively) catalysed by a class of
2154 rate-limiting enzymes, the aromatic amino acid hydroxylases (AAAH). These proteins belong
2155 to a family of tetrahydrobiopterin (BH₄)-dependent monooxygenases, which in vertebrates
2156 includes one phenylalanine hydroxylase (PAH), two tyrosine hydroxylases (TH1 and TH2)
2157 and two tryptophan hydroxylases (TPH1 and TPH2).

2158 AAAHs are present in phylogenetically distant taxonomic groups such as bacteria, insects and
2159 mammals (85). The TH, TPH, and PAH genes are found in all sequenced genomes of
2160 bilaterians, supporting the presence of each of the AAAH family members long before the
2161 divergence of chordates (595). Phylogenetic studies suggest that the AAAHs originated by
2162 duplication and divergence of a common ancestral gene at the base of the eukaryotic tree.
2163 Some lineage-specific intron loss or gain events have occurred during the expansion of
2164 AAAH genes and generated diversity of gene structures (85). The high level of sequence
2165 identity between different subfamilies suggests evolutionary conserved functions.

2166 In eukaryotes, these enzymes are composed of a homologous central catalytic domain to
2167 which is attached discrete N-terminal regulatory domains and a short C-terminal
2168 tetramerization domain, whereas the bacterial enzymes lack the N- and C-terminal domains.

2169 Therefore it is believed that the C-terminal portions of all three enzymes arised from a
2170 common ancestor, and represent the catalytic core (243) while the amino terminal regions are
2171 responsible for substrate specificity. The eukaryotic hydroxylases are all homotetramers (see
2172 (195, 773).

2173 -TH catalyzes the hydroxylation of tyrosine to L-dihydroxyphenylalanine (L-DOPA),
2174 the first and rate-limiting step in the biosynthesis of catecholamine neurotransmitters DA, NE
2175 and E (409). Two paralogous genes encoding TH are found in teleost fishes, amphibians,
2176 birds and non-eutherian mammals. They emerged as a consequence of a WGD which
2177 occurred before the divergence of jawed vertebrates (probably 2R-WGD), but TH2 was
2178 secondarily lost in eutherian mammals (893). The history of TH gene evolution within
2179 vertebrates may be also shared by the other AAAH (893).

2180 -TPH catalyzes the hydroxylation of tryptophan to 5-hydroxytryptophan, the first and
2181 rate-limiting step in the biosynthesis of serotonin (321).Two distinct molecular isoforms of
2182 TPH, TPH1 and TPH2, resulting from a whole genome duplication (WGD) which occurred in
2183 the vertebrate lineage, are present in the brains of zebrafish (44) as well as humans, mice and
2184 rats (851). The TPH isoform discovered first is referred to as TPH1 and is primarily found in
2185 the pineal gland of mammals (243, 421). By contrast, the second TPH isoform, TPH2 first
2186 cloned from the rat pineal gland (139) is strongly expressed in 5-HT-producing neurons of the
2187 raphe nucleus in mammals (593, 851), and also of the hypothalamus in teleosts (632).
2188 Sequence homology analysis of vertebrate TPHs indicates that the sequence identity between
2189 TPH1 and TPH2 within a species is low, whereas the sequence identities between TPH1s or
2190 TPH2s from different species are relatively high. While two TPH genes (*tph1* and *tph2*), are
2191 found in most groups of jawed vertebrates, in teleost fishes (for instance, in zebrafish,
2192 stickleback and medaka) three paralogs (*tph1a*, *tph1b* and *tph2*) that likely result from the
2193 teleost-specific whole genome duplication (TWGD), have been described (for review (421)).

2194 b- Amino acid decarboxylases (ADC)

2195 The aromatic amino acid decarboxylase (AADC), also called DOPA decarboxylase, is
2196 encoded by the *ddc* gene, and transforms L-DOPA into DA. AADC also transforms 5-HTP
2197 into 5-HT. AADC is a member of the large family of decarboxylases which include other
2198 enzymes involved in the synthesis of neurotransmitters, such as histidine decarboxylase
2199 (HDC) for histamine and glutamate decarboxylase (GAD) for GABA (651). HDC is highly
2200 conserved throughout metazoa (254). AADC is present in both protostomes and
2201 deuterostomes, suggesting its presence in ancestral bilaterians. AADC has been duplicated in
2202 insects leading to two paralogous genes (*ddc* and *amd*). In mammals, alternative splicing
2203 generates various *ddc* transcripts, one being specific to the nervous system (894).

2204 Glutamic acid decarboxylase (GAD) catalyzes the decarboxylation of glutamate, the (*single*
2205 *and*) rate-limiting step in the biosynthesis of GABA. Throughout the vertebrate taxa, GAD
2206 exists as two major isoforms, GAD65 and GAD67 (for review (799)). They are thought to
2207 derive from 2 paralogous genes that arose in early vertebrates at least in a gnathostome
2208 ancestor as both GAD65 and GAD67 paralogs have been cloned from two chondrichthyan
2209 species; in contrast a single GAD appears to be present in non-vertebrate chordates,
2210 urochordates (ascidians) and cephalochordates (amphioxus) in which the GAD sequence are
2211 highly divergent (70, 391). There is also evidence for a third GAD gene in a teleost, the
2212 armoured grenadier, although this paralog does not classify with either GAD 65 or 67. It is
2213 found throughout the grenadier brain including the hypothalamus but its importance there
2214 remains unexplored (799).

2215

2216 6.1.3. Origin and evolution of neuromediator receptors: direct phylogeny

2217 Neurotransmitter receptors are critical elements in intercellular signaling within the central
2218 nervous system and are divided into two major types, based on their molecular structure and
2219 biophysical properties.

2220 a- G-protein-coupled receptors (GPCRs)

2221 Most of, if not all, the physiological actions of catecholamines, indolamines and histamine, as
2222 well as some actions of GABA (via GABA_B receptors) are mediated by receptors which
2223 belong to the largest membrane protein family known so far, the seven transmembrane (7-
2224 TM) segment receptors coupled to heterotrimeric G-protein (G-protein-coupled receptors or
2225 GPCRs). This family of receptors transmits the effect of agonist binding to the various
2226 intracellular effectors by interacting with an intermediary G-protein (532). The diversity of
2227 receptor subtypes inside this neurotransmitter receptor superfamily, observed in many animal
2228 species, is the result of a long and complex evolutionary process consisting in gene
2229 duplications and continuous accumulation of mutations. GPCRs are believed to have evolved
2230 through a series of gene duplication and divergence events that started with a single ancestral
2231 gene (209): the first event was the divergence of the catecholamine receptors from the
2232 muscarinic acetylcholine receptors, which occurred prior to the divergence between
2233 deuterostomes and protostomes, since they are present at least in arthropod and vertebrate
2234 lineages. Subsequently, the ability to activate specific second-messenger pathways diverged
2235 independently in both the muscarinic and the catecholamine receptors (209).

2236 The calculation of phylogenetical distances between bioamine receptors revealed two main
2237 periods of diversification: the first one likely occurred in the Precambrian before the
2238 separation between the protostomes and deuterostomes and corresponds to the appearance of
2239 the main subtypes of bioamine receptors. The second one, might have accompanied the
2240 cephalization of the CNS in vertebrates (836).

2241 b- Ligand-gated ion channels

2242 Ligand-gated ion channels, also called ionotropic receptors, are transmembrane ion-channel
2243 proteins, which after binding of their ligands, allow the passing through of permeant ions
2244 (such as sodium, potassium, chloride and calcium), leading to changes in membrane potential.
2245 This superfamily of proteins is found in almost all forms of life (238), with strong structural
2246 similarities despite the variety in ions gated and in ligands (850). Two subtypes of GABA
2247 receptors (GABA_A and GABA_C) and the subtype 3 of serotonin (5-HT₃) receptors are
2248 members of this superfamily. They are composed of five homologous subunits. Evolutionary
2249 scenario of the family of GABA_A and glycine-like receptors (GRL), suggests the presence of
2250 an ancestral receptor in bilateria and that a set of local gene duplications, WGD rounds in
2251 early vertebrates (1 R and 2 R) and gene loss led to current set of GLR subunits in extant
2252 vertebrates including human (803).

2253

2254 **6.2. A key-neuromediator: dopamine**

2255 6.2.1. Major brain neuromediator in human and other mammals

2256 Dopamine (DA) is a neurotransmitter broadly distributed in the vertebrate central nervous
2257 system (CNS) (311). After its discovery as a neurotransmitter in the CNS of vertebrates ((88,
2258 89), DA has raised large interest for its various roles in brain functions and its involvement in
2259 severe human pathologies. DA systems regulate sensory perception, motor function, memory,
2260 emotion, food intake, and various hypothalamic functions including the neuroendocrine
2261 control of pituitary hormones. Pathologies related to the multiple functions of DA include
2262 Parkinson's disease (291), schizophrenia, Tourette Syndrome, addiction to drugs, and
2263 pituitary adenoma (for reviews (63, 311, 681)). The involvement of DA in diverse brain
2264 functions is ensured by independent dopaminergic systems (894).

2265 a - Multiple brain dopaminergic systems; multiple brain functions; multiple receptors

2266 The dopamine systems in vertebrates are highly diversified anatomically and also molecularly
2267 as regards DA biosynthesis enzymes and receptors. Gene duplications and losses have
2268 contributed to this diversification (891–893). The mammalian brain contains ten
2269 neuroanatomically distinct dopaminergic systems (named A8 to A17) located in the forebrain
2270 and midbrain (64). The (A8-A10) DA neurons are involved in initiation of movement and
2271 behavioral responses as well as in drug addiction. The A11 DA neurons are involved in
2272 autonomic motor regulation, and the A12-A15 neurons in neuroendocrine regulation. The
2273 A16 DA cell bodies in the olfactory bulb and A17 in the retina are involved in olfactory and
2274 visual perceptions, respectively (63, 64, 724). Comparative anatomical and functional studies
2275 highlight both conservation and divergences of DA forebrain and midbrain systems across
2276 vertebrates (345, 724, 894).

2277 The pleiotropic activity of DA also relies on a diversity of receptors. DA exerts its actions on
2278 target cells by activating specific membrane receptors belonging to two structurally and
2279 functionally different classes of GPCRs, termed D1 and D2, and originally distinguished by
2280 their ability to activate (D1 class) or inhibit (D2 class) adenylyl cyclase (351). D1 and D2
2281 receptors also regulate other signal transduction pathways including calcium and potassium
2282 channels and arachidonic acid synthesis [reviewed in (314, 494, 712, 828)]. D1 and D2
2283 receptors both belong to the group A (rhodopsin-like) of the GPCR superfamily but have
2284 different structural features. D1 receptor genes are intronless, and D1 receptor proteins exhibit
2285 a short third cytoplasmic loop and a long C-terminal tail. They are coupled to the Gs family of
2286 G proteins, and D1 receptor agonists promote adenylyl cyclase activity. In contrast, D2
2287 receptor genes contain several introns and encode a long third cytoplasmic loop and a short C-
2288 terminal tail. D2 receptors are coupled to the Gi/Go family of G proteins, and D2 receptor
2289 agonists inhibit adenylyl cyclase activity.

2290 Each class of DA receptors comprises two to five subtypes depending on the vertebrate
2291 species: in mammals, the D1 class comprises two receptor subtypes (D1 and D5), while the
2292 D2 class comprises three receptor subtypes (D2, D3 and D4). However, in non-mammalian
2293 species, additional DA receptor genes have been found. Phylogenetic analyses strongly
2294 suggest that the common ancestor of Osteichthyans possessed four subtypes in the D1-class
2295 (D1, D5, D6 and D7), and five subtypes in the D2-class (D2, D3, D4, D8/D2₁ and D9/D4_{rs};
2296 (891, 892). While multiple gene losses have largely reduced the number of DA receptors in
2297 mammals, many DA receptor genes have been conserved in other vertebrates; moreover,
2298 teleost-specific WGD (3R) further increased the number of DA receptor genes in this lineage
2299 (891).

2300 Notably, D1 and D2 DA receptors are phylogenetically not more related to each other than to
2301 other monoamine receptors (82, 131, 892). This suggests that the ability to bind DA, shared
2302 by the two receptor classes, was acquired independently reflecting a convergence process
2303 during metazoan evolution.

2304 b- Neuroendocrine functions (e.g. major inhibitory regulator of pituitary prolactin via
2305 dopamine D2 receptors)

2306 In mammals, DA represents the major nonpeptidergic agent exhibiting well-defined
2307 neuroendocrine functions and its role as an inhibitor of pituitary lactotroph cell secretion
2308 became recognized in the 1970s: based on the evidence of dopaminergic nerve terminals in
2309 the median eminence (215), McLeod and coworkers (445) proposed that DA may be released
2310 into the pituitary portal system, and thereby act as a hypothalamic hormone (distinct from its
2311 neurotransmitter role in other systems). They demonstrated that dopaminergic agonists were
2312 effective at suppressing prolactin (PRL) secretion *in vivo*, and *in vitro* from isolated pituitary
2313 glands (445). DA was subsequently detected in the pituitary portal blood (340), and variations
2314 of DA levels in the portal blood were shown to account for changes in PRL secretion in

2315 various physiological conditions (47, 48, 229, 242). DA receptors of the D2 class were
2316 identified on anterior pituitary lactotroph cells (453). Finally, the observation that mice
2317 lacking the DA D2 receptor are hyperprolactinemic (352, 652), clearly demonstrated the
2318 critical role of DA in suppressing endogenous PRL secretion. Interestingly, in all hormonal
2319 systems studied so far, whether at the hypothalamic, posterior pituitary, or anterior pituitary
2320 level, DA functions as an inhibitor via DA receptors of the D2 class (for reviews (46, 241)).
2321 While DA is now established as the primary regulator of PRL gene expression and release in
2322 both mammals and teleost fish (46, 241, 872), it also exerts some negative control on the
2323 release of growth hormone (GH), thyroid-stimulating hormone (TSH) and melanocyte-
2324 stimulating hormone (α -MSH) (for review (810)) in the pituitary of both mammals and teleost
2325 fish, despite differences in the neuroanatomical organization of the hypothalamo-pituitary
2326 axis between these vertebrate classes (32). An additional neuroendocrine action of DA,
2327 initially discovered in teleosts and later demonstrated in various vertebrate species, is the
2328 inhibitory control of gonadotropin secretion and reproductive function ((168, 603); see
2329 section 6.2.4).

2330

2331 6.2.2. Evolution of tyrosine hydroxylase, key-enzyme of dopamine synthesis

2332 a- Biosynthetic pathway of dopamine

2333 Dopamine is synthesized from the aromatic amino acid tyrosine through two enzymatic steps.
2334 The first and limiting step is catalyzed by an aromatic amino acid hydroxylase (tyrosine
2335 hydroxylase [TH]), and the second step by the aromatic amino acid decarboxylase (AADC),
2336 often called DOPA-decarboxylase.
2337 TH, as the other AAAHs, has at least one homolog in all bilaterian species studied so far. TH
2338 probably evolved from an ancestral AAAH that did not have a regulatory domain and gave
2339 rise to all three present-day AAAH (394).

2340 b- Tyrosine hydroxylase 1 and 2 in vertebrates

2341 The gene coding TH has been identified in species of several vertebrate groups, including
2342 humans (521), rats (244), mice (301), bovines (136), quails (184), chicken (90) and lamprey
2343 (35). Whereas only one gene encodes TH in mammals (with two to four proteic isoforms
2344 generated by alternative splicing), two non-allelic TH genes (th1 and th2) exist in several
2345 teleost species (84). Phylogenetic analyses showed that both th1 and th2 genes are not only
2346 found in teleosts but also in all studied non-eutherian vertebrates, therefore in all vertebrates
2347 except placental mammals (893). It is thus likely that the ancestral vertebrates possessed TH1
2348 and TH2 DA-synthesizing cells.

2349 The existence of two paralogous TH genes in teleost fishes, amphibians, birds and non-
2350 eutherian mammals suggests that the gene duplication giving rise to the two TH genes is
2351 ancient in the vertebrate lineage (35) probably as a consequence of the second round (2R) of
2352 WGD (548, 575, 713). While TH2 is still found in prototherian (platypus) and metatherian
2353 mammals (opossum), it may have been lost in the eutherian mammalian lineage which
2354 possess a single TH, TH1 (893). Genomes of many eutherians are fully sequenced, and the
2355 chromosomal localizations of the TH genes and their syntenic genes support the loss of TH2
2356 in the eutherian mammals. Indeed, apart from the absence of TH2 in the eutherian mammals,
2357 the order of the neighbouring genes (IGF1, PAH, and ASCL1) at the locus is highly
2358 conserved.

2359 c-Tyrosine hydroxylase in metazoa

2360 Tyrosine hydroxylation, and its regulation, is an ancient and critical biochemical pathway.
2361 The hydroxylation of tyrosine to form L-3, 4-dihydroxyphenylalanine is an enzymatic
2362 pathway utilized not only throughout animal phyla but in plants as well. TH, as the other
2363 AAAH, has at least one homolog in all bilaterian species studied so far (505).

2364 The gene coding TH has been identified from various species of non-vertebrates, including
2365 schrimps (454), fresh water crab (*D pagei*; (615)), parasitic helminthes (*Schistosoma mansoni*
2366 (258); *Schistosoma japonicum* (294), and insects, [*Drosophila* (760); moth (300); cricket
2367 (862)]. In several species of insects, as in mammals, different isoforms of TH produced by
2368 alternative splicing have been identified (in the cricket (862), in *D. melanogaster* and the
2369 armyworm *M. separata* (62, 534). Since the drosophila TH protein exhibits similar kinetic
2370 parameters and regulatory mechanisms to its mammalian counterpart, it is likely that very
2371 strong evolutionary constraints have been placed on the biochemical mechanism (529).

2372

2373 6.2.3. Evolution of Dopamine D2 receptors

2374 The D2 receptors have been diversified as a consequence of genome duplications in early
2375 vertebrates. In mammals, three DA receptors (D2, D3 and D4) are classified as the D2 class.
2376 The classification and nomenclature of DA receptors has been initially based on the set of
2377 receptors found in eutherian mammals. When more DA receptors have been found in other
2378 groups of vertebrates, the necessity of revisiting DA receptor classification was raised by
2379 some authors (147, 891, 892).

2380 a- Impact of WGD

2381 The number of DA receptors subtypes has been multiplied by the two major rounds (1R/2R)
2382 of WGD that took place in early vertebrates (286, 296, 438). Additional duplication of DA
2383 receptor gene occurred in the teleost fish lineage *via* TWGD (3R) (15, 316, 617, 772).
2384 Duplicated paralogous genes were maintained in some vertebrate groups, probably by the
2385 acquisition of some differential functional properties, specific of each subtypes, as well as by
2386 discrete changes in their expression patterns in the brain (for reviews (861,862)).

2387 b- Multiple genes in teleosts

2388 Five subtypes of D2 receptor genes (*D2*, *D3*, *D4*, *D8* (also named *D2_l* for *D2_{like}*) and *D9* (also
2389 named *D4_{rs}* for *D4- related sequence*) exist in teleosts. The *D2_l* and *D4_{rs}* genes would have
2390 originated in the ancestor of gnathostomes (562). Phylogenetic analyses strongly suggest that
2391 the ancestral Osteichthyes (bony jawed vertebrates) possessed five D2-class of DA receptors
2392 (*D2*, *D3*, *D4*, *D8* and *D9*) likely resulting from 1R/2R with a possible additional specific
2393 duplication (891, 892). In eutherian mammals, only three D2-class DA receptors are found
2394 (*D2*, *D3*, *D4*) due to multiple DA receptor gene loss in this lineage (891). In contrast, up to
2395 seven D2 class DA receptors (*D2a*, *D2b*, *D8*, *D3*, *D4a*, *D4b*, *D9*) have been identified in the
2396 zebrafish (66, 67, 891), the additional receptors (*D2a/D2b*, *D4a/D4b*) likely resulting from
2397 TWGD.

2398

2399 6.2.4. Dopamine as a major inhibitory regulator of gonadotropin secretion in teleosts

2400 A major neuroendocrine action of DA, initially discovered in teleosts and later demonstrated
2401 in various vertebrate species, is the inhibitory control of gonadotropin secretion and
2402 reproductive function (167, 168, 603). This inhibitory role of DA appears to be a powerful
2403 counterpart to the well-known stimulatory role of GnRH in the neuroendocrine control of
2404 reproduction.

2405 a- Discovery in goldfish

2406 The discovery by Peter and colleagues, using brain lesion approaches, of the presence of a
2407 gonadotropin release-inhibiting factor (GRIF (604)) in the hypothalamus of goldfish has been
2408 previously reviewed (167). GRIF neurons were subsequently shown to originate from the
2409 preoptic area (POA) and project to the pituitary (606). *In vivo* experiments aimed at
2410 investigating the effect of various DAergic agonists and antagonists on LH secretion and
2411 ovulation strongly suggested that DA could be the GRIF (100). Immunocytochemical and
2412 neuroanatomical studies supported this conclusion by revealing DA cell bodies in a specific

2413 region of the POA, the nucleus preopticus anteroventralis (NPOav), with projections in the
2414 proximal pars distalis of the pituitary where gonadotrope cells are located (333, 606). Lesions
2415 of the NPOav induce a surge of LH and subsequent ovulation (336). Finally, *in vitro* studies
2416 on primary cultures of goldfish pituitary cells revealed that DA inhibits both basal and GnRH-
2417 stimulated LH release by acting directly on gonadotropes, through binding to receptors
2418 pharmacologically-related to the mammalian D2 receptors (101). In addition, in goldfish, DA
2419 exerts inhibitory effects on GnRH neurons, blocking the synthesis of the peptide or its release
2420 from the pituitary nerve terminals (602, 901). The discovery of a dual control of reproduction
2421 led to a major application in aquaculture: the development of a spawning induction method
2422 based on combined treatments with a DA antagonist and a GnRH agonist that has been
2423 widely used to induce spawning in captivity of a certain number of species (LINPE method,
2424 named after the scientists R. Peter and HR Lin (for review (603))).

2425 b- Evidence in various teleosts

2426 As a matter of fact, the role of DA as a GRIF, originally demonstrated in the goldfish, a
2427 cyprinid, has been later on observed in various other teleost species, including other
2428 cyprinids, but also in species belonging to other teleost subgroups such as silurids, salmonids,
2429 percomorphs, mugiliforms, elopomorphs (for review (167)) and pleuronectiforms (251).

2430 In some teleost species, however, this physiological role of DA was not found (for review
2431 (168)). It is worth noting that the intensity of the dopaminergic inhibition varies according to
2432 the species, from a drastic barrier in cyprinids (603, 605) or in prepubertal eel (166, 837) to a
2433 milder control in salmonids (659).

2434 As in the goldfish, DA actions on gonadotrope cells are mediated by receptors of the D2 class
2435 in all species studied (European eel (326, 838), tilapia (408) catfish (26), grey mullet (10) and
2436 zebrafish (202)). In zebrafish, ISH and ICC studies reveal that the TWGD-paralogs D2a and
2437 D2b as well as D8 are expressed in LH-producing cells, suggesting that the three receptors are

2438 involved in mediating DA inhibitory control in this teleost (202). In the eel, the TWGD-
2439 paralog D2b is predominantly expressed as compared to D2a in LH and FSH cells (326). The
2440 expression of D2a and D2b is differentially regulated by sex steroids (585) and the two
2441 receptor subtypes are differentially involved in the onset of puberty (319). These data
2442 suggested a functional differentiation of the TGWD-D2 paralogs in the eel, with a major role
2443 of the D2b receptor in the control of gonadotropic function (326).

2444

2445 6.2.5. Dopamine as an inhibitory regulator of gonadotropic axis in other vertebrates

2446 A dopaminergic inhibition of GnRH-induced pituitary gonadotropin secretion has also been
2447 found in a chondrostean fish, the white sturgeon (*Acipenser transmontanus*; (596)). This
2448 indicates that the role of DA in the inhibitory control of reproduction may have a more
2449 ancient evolutionary origin, in an actinopterygian ancestor, common to teleostean and
2450 chondrostean fishes.

2451 The inhibitory influence of DA on gonadotropin secretion and reproduction is not restricted
2452 to fish (584, 837): A dopaminergic inhibitory control of reproduction has been shown also in
2453 representative species of various other classes of tetrapods as demonstrated in amphibians,
2454 birds, and mammals (for review (168)).

2455 In amphibians, some data point to an important role for dopaminergic inhibition in the
2456 regulation of seasonal reproduction. In the frog, *Rana temporaria*, lesions of the infundibular
2457 hypothalamus in hibernating preovulatory females cause advanced ovulation (734, 735). This
2458 effect is mimicked by a dopaminergic antagonist and blocked by administration of a
2459 dopaminergic agonist (736). More recent studies indicate that the inhibitory effects of DA on
2460 reproduction are conserved in frogs: for instance, in the wood frog, injection of quinpirole in
2461 females delays or inhibits oviposition (844). The release of sperm and eggs is induced in
2462 several anurans and salamanders by the co-injection of a GnRH agonist and the selective DA

2463 receptor D2 antagonist metoclopramide (termed “the amphiplex method” (121, 240, 795, 796,
2464 845). The technique has also been successfully applied in small-scale trials to several other
2465 amphibian species (796).

2466 In birds, there is similar evidence for an inhibitory role of DA on reproduction (for review
2467 (168)). For instance, in laying hens, the anovulatory state induced by food withdrawal, is
2468 caused by a dopaminergic inhibition of GnRH release at the median eminence level, where a
2469 dense concentrations of DA and GnRH-containing processes is observed, providing
2470 opportunities for synaptic interactions between them (128).

2471 In mammals, DA is involved in the modulation of pulsatile LH release in some species. This
2472 effect has been extensively studied in seasonal mammals notably in sheep, in which DA
2473 participates in the inhibition of gonadotropic activity before puberty (73) as well as in adults
2474 during seasonal anestrus (for reviews (221, 781)) by acting on GnRH neurons at the median
2475 eminence level (379), through D2 receptors (55). In rat, GnRH neurons are directly innervated
2476 by catecholamine terminals, including DA ones (106), but the participation of the
2477 dopaminergic system in the control of FSH and LH release remains controversial in adults
2478 since raising brain DA activity can either inhibit (41, 130, 222, 432) or stimulate (412, 444)
2479 gonadotropin release. By contrast, in the developing rat, DA clearly exerts an inhibitory
2480 control on both LH and FSH secretion during the second and third weeks of female life, by
2481 influencing GnRH release into the portal blood (384). In some other species, a direct
2482 inhibitory effects of DA on LH release at the pituitary level has been reported: for instance, in
2483 rabbits, DA injected intravenously inhibits GnRH- stimulated LH secretion in normal and also
2484 in stalk-sectioned animals (138). Finally, in humans, several observations suggest that a
2485 direct inhibition by DA on LH release may occur under physiological and pathological
2486 conditions. For instance in men, infusion of DA (which does not cross the blood-brain barrier)
2487 significantly decreases circulating LH levels and attenuates the LH release in response to a

2488 bolus of GnRH (299). This DA-induced inhibition of LH secretion is associated with a
2489 reduction in both pulse frequency and amplitude of LH secretion. Further, the observation that
2490 partial inhibition of LH secretion occurs even in the presence of constant GnRH and DA
2491 infusion suggests that DA may also modulate the gonadotrope response to GnRH. In women
2492 with functional hypothalamic amenorrhea (FHA), a reduction of LH pulse frequency (and of
2493 PRL concentrations) has been documented, which can be reversed by a DA receptor blocker.
2494 In this case, however, a hypothalamic site of DA action was inferred, through inhibition of
2495 GnRH pulse frequency (52).

2496 Recently, in male and female mouse, DA has been shown as the most potent inhibitor of
2497 GnRH neuron excitability: using a variety of electrophysiological approaches, the authors
2498 demonstrated that approximately around half of all GnRH neurons are inhibited by DA
2499 through D1 and D2 receptors, and that the inhibition exerted by DA on GnRH neurons is
2500 independent on gonadal steroid status (430).

2501

2502 In summary, DA acts as an inhibitor of reproduction in representatives of all classes of
2503 vertebrates, but this role has been differentially conserved throughout vertebrate evolution.
2504 This may either reflect an ancient regulatory pathway, common to actynopterygian
2505 (chondrosts and teleosts) and sarcopterygian (tetrapods) species, or result from convergent
2506 recruitments of DA neurons for the inhibition of reproduction in various vertebrate taxa (167).
2507 The recruitment of DA neurons for exerting similar functions in different vertebrates suggests
2508 that DA neurotransmission may be especially suitable for the neuroendocrine inhibitory
2509 control of reproduction.

2510

2511 6.2.6. Dopamine as an inhibitor of reproduction in other metazoan

2512 The inhibitory role of DA in the control of reproduction may be more ancient than the origin
2513 of vertebrates. Indeed, a few studies have reported an inhibitory action of DA on reproductive
2514 function in some non-vertebrate species. For example, DA inhibits the growth and maturation
2515 of oocytes in an echinoderm, the sea urchin *Strongylocentrotus nudus* (358). It is thus likely
2516 that this control was present in the ancestor of deuterostomes. In protostomes, an inhibitory
2517 effect of DA on reproduction has been reported both in some ecdysozoans (such as insects,
2518 crustaceans, nematodes) and lophotrochozoans (such as mollusks). In insects, DA levels are
2519 constantly maintained at a high level in the hemolymph during diapause (308, 537, 538), and
2520 change with the photoperiod (115). In particular, DA is clearly a key factor for the induction
2521 of egg diapause of the silkworm, *Bombyx mori* (537). In crustaceans, there is evidence for a
2522 dopaminergic inhibition of testicular maturation in the fiddler crab, *Uca pugilator* (666) and
2523 in the red swamp crayfish, *Procambarus clarkii* (668). Similarly, in the giant freshwater
2524 prawn, *Macrobrachium rosenbergii*, DA inhibits testicular maturation (711) and inhibits
2525 vitellogenin synthesis and ovarian maturation by inhibiting the release of vitellogenesis-
2526 stimulating hormone (VHS) from the thoracic ganglia (107, 787). In a nematode,
2527 *Caenorhabditis elegans*, genetic and pharmacological analyses reveal that a dopaminergic
2528 pathway, acting through a D2-like DA receptor (755), inhibits egg laying (865). In a mollusk,
2529 zebra mussel, DA has been shown to reduce the intensity of 5-HT-induced spawning (199).
2530 It is thus likely that inhibitory actions of DA on reproductive functions occurred in the
2531 bilaterian ancestor and even possibly predate the emergence of bilateria, since even in a
2532 cnidarian, the coral *Acropora tenuis*, DA was reported to have an inhibitory effect on
2533 spawning (310).
2534 Therefore, although its physiological functions appear to differ among species, DA plays
2535 multiple roles in suppressing the reproductive events in a number of non-vertebrate species
2536 (Figure 12).

2537

2538 **6.3. Many other neuromediators involved in the control of reproduction**

2539 A variety of actors in mammals: Among neurotransmitters, that have been reported to also
2540 influence LH release and play a role in the control of reproduction, are found NE, 5-HT, HA
2541 as well as GABA.

2542

2543 6.3.1. Norepinephrine (NE)

2544 a- In mammals

2545 Sawyer and colleagues gave the first evidence that noradrenergic neurons may participate in
2546 the control of the gonadotropic axis, by demonstrating that α -adrenergic receptor antagonist
2547 blocks ovulation in rabbits (676). Further studies by various laboratories reported that NE
2548 may modulate plasma LH levels by regulating the activity of GnRH neurons (for review (34)).
2549 However, the idea that NE was essential for triggering of the preovulatory release of LH (34)
2550 has been challenged by experiments in rodents (120, 675), and in primates (369, 376),
2551 showing that chronic interruption of the noradrenergic afferents to the hypothalamus does not
2552 impair normal ovulation. This strongly suggests that the noradrenergic system, far from being
2553 essential, exerts a modulatory action on gonadotropin secretion. It is now accepted that NE
2554 has a permissive action within the network of afferences to GnRH neurons, which may be
2555 modulated by sex steroid levels (275).

2556 b- In other vertebrates

2557 The role of NE in the control of reproduction has also been investigated in other vertebrates.
2558 In birds, existing evidence suggests a role for NE in the neuroendocrine control of LH release.
2559 The avian median eminence is known to be well supplied with NE fibers and terminals (81,
2560 701), and the α -adrenoreceptor blocking drug, dibenamine, has been early shown to
2561 suppresses ovulation in the hen (786). Specific blockade of NE synthesis prevents ovulation

2562 in the laying hen (867) and causes a decline in plasma concentrations of LH in young and
2563 adult male domestic fowl (75, 76). *In vitro*, GnRH secretion from chicken hypothalamus-
2564 preoptic area slices (410) or from Japanese quail hypothalamus explants (486) is significantly
2565 elevated in the presence of NE or β adrenergic agonists. However, icv administration of NE in
2566 laying and non-laying turkeys has no effect on LH secretion (262). In non-laying geese,
2567 noradrenergic stimulation is involved in the control of LH secretion, probably through GnRH
2568 neurons (897). In the Chinese geese (*Anas cygnoides*), the expression of DBH (the enzyme
2569 catalyzing the transformation of DA into NE) undergoes marked periodic variations in
2570 reproductive and endocrine tissues during the reproductive cycle (890). In the Japanese quail,
2571 a noradrenergic pathway is involved in the control of LH release through a modulation of
2572 GnRH gene expression in the hypothalamus (789).

2573 In teleosts, NE appears to play only a slight stimulatory role on gonadotropin secretion, by
2574 acting either directly on gonadotrope cells, via α_1 -like adrenergic receptors (98) or on
2575 hypothalamic GnRH neurons to stimulate the release of GnRH (607, 902). In fish, as in
2576 mammals, the effectiveness of NE is dependent on the stage of gonadal development: *e.g.* in
2577 goldfish, NE stimulates LH release mainly during gonadal regression (98, 603).

2578 c- In other metazoa

2579 Few data are available on the role of NE in the reproductive function in other metazoa. In
2580 mollusks, cyclic variations of NE strongly support its participation in the reproductive cycle
2581 of bivalve species. Notably, marked variations in NE content occur in the gonads and pedal
2582 ganglia of mussels, with a 3 to 4-fold increase during gametogenesis and a decline during
2583 spawning (368). Similarly, increased NE levels are measured in gonad of the female Pacific
2584 lion's paw Scallop during gametogenesis stages (developing and maturing stages) while NE
2585 concentrations drop after spawning, suggesting that NE exerts a direct control over
2586 gametogenesis (433).

2587 Collectively, data reveal the recruitment of NE signalling in the control of reproduction both
2588 in protostomes in deuterostomes, as well as in cnidaria, before the emergence of bilateria.
2589 (Figure 12).

2590

2591 6.3.2. Serotonin (5-HT)

2592 a- In mammals

2593 There is strong pharmacological evidence for a role of 5-HT in the regulation of
2594 hypothalamo-pituitary-gonadal axis, through an action either on GnRH neurons or on
2595 gonadotrope cells. Actually, 5-HT neurons located in the raphe region may play inhibitory
2596 roles in gonadotropin secretion: the pharmacological elevation of hypothalamic 5-HT levels
2597 with monoamine oxidase inhibitors suppress spontaneous ovulation in rats (383) and *in vitro*,
2598 5-HT significantly inhibits the release of GnRH from the mediobasal hypothalamus of male
2599 rats (Charli et al, 1978). In sheep (155) and rabbits (624), infusion of 5-HT into the
2600 mediobasal hypothalamus blocks the ovulatory discharge of LH and ovulation. On the other
2601 hand, several lines of evidence support a permissive or facilitatory role for 5-HT in ovulation:
2602 inhibition of 5-HT synthesis with PCPA, suppresses ovulation in rats (383) and several 5-HT
2603 antagonists inhibit spontaneous ovulation (457).

2604 Actually, the hormonal environment of the animal appears to be critical to the expression of
2605 5-HT actions on gonadotropin secretion and ovulation. Indeed, 5-HT system can be
2606 modulated by gonadal steroids (222, 515, 598) and in several mammalian species, 5-HT
2607 receptors are colocalized with estrogen receptors beta (250), indicating that 5-HT and
2608 reproductive endocrine signaling pathways are closely associated. Accordingly, differential
2609 effects are observed in male and female rats: neonatal exposure to androgen is responsible for
2610 the sex difference in the LH response to 5-HTP, a 5-HT precursor, a difference which may be
2611 associated with a regulatory action of 5-HT on the cyclic hypothalamic control of

2612 gonadotropin secretion (501). 5-HTP has been shown to stimulate FSH release in normal rats
2613 and to inhibit it in castrated rats, testosterone concentration being a relevant factor in
2614 determining the 'type' of effect produced (331).

2615 The functional interactions between 5-HT and reproductive functions have also been
2616 demonstrated in other vertebrates:

2617 b- In other vertebrates

2618 In birds, 5-HT synthesized in the hypothalamus exerts an inhibitory influence on
2619 reproduction: elevation of 5-HT levels directly inhibits GnRH synthesis and LH secretion in
2620 female turkey (256) or hen (657) and male domestic fowl (257). Conversely, blockade of the
2621 serotonergic system generally stimulates gonadotropin secretion and enhances gonadal
2622 development, as shown in young female turkeys (256), or in aging male roosters (27).

2623 In teleosts, by contrast to what is observed in birds, hypothalamic 5-HT neurons exert a
2624 positive stimulatory influence on reproductive neuroendocrine function and gonadotropin
2625 secretion (for review (621)). Specifically, 5-HT stimulates GnRH release, LH release and
2626 socio-sexual behaviors, acting at different levels. At the hypothalamic level, a close
2627 association of 5-HT fibers with GnRH neurons has been observed in the Atlantic croaker
2628 (354). However, central administration of 5-HT has no effect on preoptic GnRH1 mRNA
2629 levels (782), indicating that 5-HT may stimulate GnRH release but not synthesis. As a matter
2630 of fact, 5-HT stimulates GnRH release from the hypothalamus of the goldfish and seabream
2631 (696, 902). In the zebrafish, 5-HT receptors are present in several regions containing GnRH
2632 neurons (539) suggesting possible expression of 5-HT receptors in GnRH neurons, as in
2633 mammals (56).

2634 At the pituitary level, in several teleost species, 5-HT stimulates gonadotropin release *in vivo*
2635 and *in vitro* (goldfish (730, 731, 878); Atlantic croaker (353, 355)). In some other teleost
2636 species, 5-HT alone has no influence on spontaneous LH release, but potentiates GnRH

2637 analog-induced LH secretion when co-administered (Atlantic croaker (878); Prussian carp
2638 (729)). Interestingly, the stimulatory action of 5-HT on GnRH release is time- and season-
2639 dependent (355), and the mode of action of 5-HT on gonadotropin release also changes as a
2640 function of the reproductive stage: in the Atlantic croaker, the effect of 5-HT is more
2641 pronounced in mature than in sexually regressed fish (353).

2642 Therefore, as in mammals, the stimulatory action of 5-HT on gonadotropin secretion in teleost
2643 appears to be modulated by various factors such as gonadal steroids, environmental
2644 conditions and social cues (for review (621)).

2645 c- In other metazoans

2646 Together with DA and NE, 5-HT represents a possible endocrine and neuronal link between
2647 endogenous and exogenous signals allowing non-vertebrates to modulate reproductive
2648 functions in conjunction with environmental constraints (368). In non-vertebrates, the
2649 function and location of 5-HT have been studied mainly in arthropods, mollusks and annelids.
2650 In crustaceans, 5-HT is involved in various physiological processes including sexual behavior
2651 and reproduction (191, 666, 668, 669, 711). Specifically, 5-HT stimulates release of gonad
2652 stimulating hormone (GSH) in the crayfish *Procambarus clarkia* (668) and in the fresh water
2653 crab (620) and also accelerates testicular maturation in the fiddler crab (666, 667) and the red
2654 swamp crayfish (668) as well as ovarian maturation and spawning in the white shrimp (827).

2655 In several species of mollusks, 5-HT and its receptors play an important role in reproduction,
2656 through stimulation of biosynthesis and release of active egg-laying peptide precursor
2657 proteins, *i.e.* control and initiation of gamete release, and gamete maturation. For instance,
2658 studies on bivalves show that 5-HT levels change during the different stages of the sexual
2659 cycle (resting, developing, maturing and egg-laying) in the gonads and cerebroid ganglia of
2660 mussels, and that the endocrine function of gonads in marine bivalves is regulated through
2661 monoamine neurosecretions arising from the cerebroid ganglia (368). Moreover,

2662 administration of 5-HT induces oocyte maturation and spawning (282, 466, 766). The
2663 endogenous 5-HT signal is transmitted to the oocyte through 5-HT receptors (33, 857).
2664 In annelids such as Nereidae, immunopositive staining for 5-HT is observed in neurons of the
2665 brain of *Nereis diversicolor* (278) and 5-HT exerts a positive effect on oocyte development,
2666 probably by stimulating a gonadotrophic hormone, present in mature females (392).
2667 Altogether these studies indicate a conserved or convergent role of 5-HT in the control of
2668 reproduction in various bilateria, protostomes and deuterostomes (Figure 12). The presence of
2669 5-HT receptors has been demonstrated in cnidarian, thus before the emergence of bilateria
2670 (for review (860)), but to our knowledge the effect of 5-HT on reproduction in this phylum
2671 has not yet been addressed.

2672

2673 6.3.3. Histamine (HA)

2674 The possible stimulatory effect of histamine (HA) on LH secretion was first evidenced in the
2675 rabbit by Sawyer (674) who reported that icv injection of HA induces ovulation and increases
2676 plasma LH levels in animals lightly anesthetized with pentobarbital but not awake or ether-
2677 anesthetized. Subsequent studies, however, provided inconsistent results, likely depending on
2678 sex steroid environment: icv injection of HA increases plasma LH levels in proestrous or
2679 ovariectomized estrogen and progesterone-primed female rats (157, 160, 418), but has no
2680 effect in males (156, 158). Actually, HA participates in the neuroendocrine regulation of
2681 pituitary hormone secretion by an indirect action at a hypothalamic level: In mammalian
2682 brain, HA cell bodies are located exclusively in the tuberomammillary nucleus (TMN) of the
2683 posterior hypothalamus (253) and send their axons all over the central nervous system. In the
2684 hypothalamus they arborize extensively and may thereby influence the release and function of
2685 various hypothalamic neuropeptides and hormones (254), including GnRH (368, 395):

2686 GnRH-induced secretion of LH in female rats (497). By contrast, it does not affect LH release
2687 from isolated rat pituitary cells (57) or pituitary fragments (497).

2688 Considering the ancient origin of HA, investigation on its potential role on reproductive
2689 function in other vertebrates and other metazoa would deserve to be launched.

2690

2691 6.3.4. GABA

2692 GABA is an inhibitory neurotransmitter extremely abundant in the brain of all vertebrates,
2693 that plays a role in the control of reproduction in various vertebrate classes.

2694 a- In mammals, the influence of GABA on LH secretion has long been demonstrated (21,
2695 159, 388, 560, 839). The distribution of hypothalamic GABAergic neurons and their
2696 involvement in the neural control of reproductive processes are now well documented (451).

2697 Although both GABA_A and GABA_B receptors have been identified in rat pituitary
2698 gonadotrope cells (21) and that evidence exists for a possible direct stimulatory effect of
2699 GABA on the LH cells (842), the vast majority of studies support a key inhibitory role of
2700 GABA on gonadotropin release, predominantly at the central level, through modulation of the
2701 GnRH neuron activity and secretion. Notably, increasing endogenous GABA concentration
2702 by drugs, GABA or GABA agonist administration, in rats and non-human primates, prevents
2703 ovulation and pulsatile LH release, and blunts the LH surge induced by estrogen or an
2704 estrogen-progesterone combination (162). GABA infusion into the preoptic area or
2705 intraperitoneal injection of muscimol, a GABA_A receptor agonist, blocks the LH surge (7,
2706 277), while the GABA_A receptor antagonist, bicuculline, advances the timing of the LH surge
2707 (363). Moreover, GABA release in the preoptic area decreases prior to and during the time of
2708 the LH surge (317).

2709 GABAergic activity is known to be sensitive to environmental conditions (183) and the
2710 alteration of GABAergic neuronal activity is likely associated with the season-dependent

2711 reproductive cyclicity in seasonal mammals (235). GABAergic activity may also depend on
2712 the stage of reproductive development: in female mice, at puberty, the effect of GABA on
2713 GnRH neurons switches from depolarization to hyperpolarization ((259). Both
2714 autoradiographic and immunohistochemical studies show that a large proportion of GABA
2715 neurons in the diencephalon represents targets for estrogens (197, 277, 388, 471), and it has
2716 been postulated that these neurons may mediate estrogen feedback on GnRH neurons, (388,
2717 752), as suggested by the existence of synaptic contacts between GABAergic terminals and
2718 GnRH neurons (405, 733). Interestingly, it appeared recently that a subpopulation of GnRH
2719 neurons in the adult mouse forebrain is GABAergic and thus that GnRH neurons could
2720 secrete GABA to regulate their own activity (917).

2721 GABA exerts its regulatory effects via two main receptors, the GABA_A and GABA_B
2722 subtypes. The origin and evolution of the GABA receptors is highly complex. As some
2723 publications exist, focusing on the phylogeny of the multiple GABA_A receptor (458, 650,
2724 803), this topic will not be addressed in the present review.

2725 *In vivo* experiments undertaken in adult rats, sheep and monkeys all indicate that the
2726 inhibitory effect of GABA on LH secretion is mediated through the GABA_A receptors located
2727 on the soma of GnRH neurons (276, 277, 495, 683). Furthermore, GnRH neurons express
2728 functional GABA_A receptors that may inhibit GnRH neuronal excitability (260, 717, 743).
2729 Much less is known about the possible involvement of GABA_B receptors. Functional GABA_B
2730 receptors are present in various hypothalamic neurons (11, 12, 387, 846) but studies
2731 examining their role suggest that major species differences exist. In the ewe, GABA_B
2732 receptors mediate inhibition of GnRH secretion during the non-breeding season, but not
2733 during the breeding season, this change being possibly part of the mechanism for the seasonal
2734 shift in the negative-feedback effect of estradiol on LH secretion (683). In the adult rat,
2735 GABA_B receptors play an important role in controlling the excitability of GnRH neurons

2736 especially in females (429). Interestingly, GABA stimulates GnRH secretion in the adult rat
2737 (59, 161). Yet, the precise physiological role of the excitatory action of GABA on GnRH
2738 neurons remains elusive (861).

2739 b- In other vertebrates

2740 In birds: The domestic turkey is a seasonally breeding bird with a reproductive cycle
2741 regulated by photoperiod and terminated by the state of photorefractoriness (720). In this bird,
2742 GABAergic neurotransmission in the hypothalamic premammillary nucleus regulates
2743 reproductive seasonality and the onset of photorefractoriness (374) through GABA_A receptors
2744 (374).

2745 In teleost fish, there is also good evidence for the involvement of GABA in the control of LH
2746 release (451, 799, 921). Following the discovery of a heavy GABAergic innervation of the
2747 anterior pituitary in goldfish, (334, 335), the effects of GABA have been explored, mainly in
2748 goldfish (for review (616)), and to a lesser extent in trout *Oncorhynchus mykiss*. By contrast
2749 to its inhibitory effect in mammals, GABA predominantly stimulates LH secretion in adult
2750 goldfish and trout, although inhibitory actions have been described in two other species, the
2751 Atlantic croacker (356) and the common carp (116).

2752 In goldfish, intraperitoneal injection of GABA increases serum gonadotropin levels (338).
2753 Injection of a GABA transaminase inhibitor, that augments GABA levels within the
2754 hypothalamus and pituitary, also induces an increase in serum gonadotropin levels (723). This
2755 stimulatory effect of GABA on gonadotropins can be accounted for by two major
2756 mechanisms: stimulation of GnRH secretion (338, 723) and inhibition of DA release (723,
2757 797, 798) at the brain level. *In vitro*, GABA also induces a dose-related stimulation of GnRH
2758 release from pituitary slices, which in teleosts contain GnRH nerve terminals (797). By
2759 contrast, GABA does not directly stimulate LH release from dispersed goldfish pituitary cells
2760 *in vitro* (338). The *in vivo* stimulatory effect of GABA varies seasonally and is modulated by

2761 sex steroids (338, 356, 459, 798). Both muscimol (a GABA_A receptor agonist) and baclofen (a
2762 GABA_B receptor agonist) stimulate LH secretion in females, indicating that both receptor
2763 subtypes may mediate the effect of GABA (459, 799).

2764 In rainbow trout, GABA exerts an overall stimulatory effect on basal and GnRH-induced LH,
2765 but also on FSH secretion, both *in vivo* and *in vitro*, and these effects are also highly
2766 dependent on the sex and the reproductive stage of the fish (451). As in mammals and
2767 goldfish, a role for GABAergic neurons as target cells for oestrogen feedback on LH release
2768 has been hypothesized in rainbow trout because oestrogen receptors are present in
2769 GABAergic, but not in GnRH neurons. In addition, the stimulatory action of GABA may also
2770 be exerted directly onto the gonadotrope cells of the pituitary, as GABA stimulates basal and
2771 GnRH-induced FSH and LH secretion from dispersed pituitary cells (451).

2772 In the zebrafish brain, the connection between GABAergic and GnRH neurons has been
2773 recently evidenced: GnRH3 neurons are directly contacted by GABAergic neurons in the
2774 ventral telencephalon and hypothalamus (733). Moreover, as shown also in mouse (917),
2775 some GnRH neurons in the anterior part of the telencephalon coexpress GAD67, thus being
2776 also GABAergic. Administration of GABA_B receptor agonists and antagonists support the
2777 implication of GABA_B receptors in the regulation of GnRH neurons (733).

2778 In agnaths, studies in sea lamprey also indicate that GABA may directly affect GnRH release
2779 in the brain: dual-label *in situ* hybridization shows that GABA cells are closely apposed to
2780 GnRH cells in the rostral hypothalamus and preoptic region (647). *In vitro* perfusion or *in*
2781 *vivo* injection of GABA and its analogs both significantly increase GnRH in the brain (647),
2782 suggesting that GABAergic control of GnRH is phylogenetically ancient.

2783 c- In other metazoa

2784 GABA may also play some role in the control of reproduction in other metazoa: for instance,
2785 GABA induces spawning in non-chordate deuterostomes, echinoderms (764). GABA also

2786 enhances reproduction in protostomes such as rotifers (220), indicating a role of GABA in the
2787 control of reproduction in both deuterostomes and protostomes. The presence of GABA
2788 receptors demonstrated in cnidaria, attests the early origin of GABA receptors before the
2789 emergence of bilateria (for review (346)), and should inspire future investigation on the
2790 possible role of GABA in reproduction of basal metazoa (Figure 12).

2791

2792 **6.4. Neuromediators and reproduction: from conservation to disruption**

2793 6.4.1. Ancient origin of neuromediators and receptors in metazoan

2794 The neurotransmitter function of DA, NE, 5-HT, HA and GABA in adult organisms is their
2795 more recently developed function. Cell communication through secreted, diffusible signals is
2796 phylogenetically older than neural transmission (223), and the substances known as
2797 neurotransmitters appeared long before the development of the most primitive nervous system
2798 and even multicellular organisms (79): Organisms like protists and animals devoid of nervous
2799 system, as sponges and placozoans, produce a wide array of molecules, which are in some
2800 cases identical to the corresponding compounds found in higher taxa (223). Monoamines
2801 (catecholamines, indoleamines and HA) are found in many protozoans and in almost all
2802 metazoans (811). Non-bilaterian metazoans, with or without neurons, exhibit many
2803 components of the molecular toolkits for synapse function. GABA, catecholamines, and
2804 indoleamines as well as a large number of G protein-coupled receptors for monoamines, and
2805 biogenic amine-synthesizing enzymes can be found in prebilaterian animals such as
2806 cnidarians (69). GABA is used as a signal molecule by non nervous cells of vertebrates (224)
2807 and also in sponges (173) and in plants (71).

2808 The catecholaminergic signalling has an old phylogenetic history and the enzymatic pathway
2809 for the biosynthesis and degradation of monoamine transmitters and the β -adrenergic-
2810 mediated mechanisms were conserved throughout evolution from early metazoans to

2811 mammals (223). Alpha-adrenergic receptors are found in representatives of two major clades
2812 of bilateria, the protostomes and the deuterostomes (40).

2813 If we take the example of monoamines, according to Turlejski hypothesis (811): their
2814 “*earliest role has been as intracellular regulators of cell activity*”. Produced either inside the
2815 cell or entering it from its environment, they act directly on some of the intracellular signaling
2816 systems, and “*cause long-lasting changes in the cell functional state, that allow the organism*
2817 *to adapt to its environment*”. “*However, very early in evolution, they acquired functions of*
2818 *hormones*”, *i.e.* molecules of external origin acting on specific receptors localized in the cell
2819 membrane and stimulating specific intracellular second messengers to cause long-term
2820 changes in the functional state of cells. “*Later on in evolution, biogenic amines acquired*
2821 *functions of neuromodulators*”, thus produced and released by specific neurons, and able to
2822 modulate the activity of other neurons, through specific receptors placed within synaptic
2823 contacts. “*Finally, preserving some of the evolutionary older functions, monoamines took the*
2824 *function of neurotransmitters conveying fast changes*”, through receptors activating ion
2825 channels (811).

2826 The development of a signaling system requires the evolution of a mechanism for producing
2827 signals, receptors and adaptive reactions to the signal. Various data now support the
2828 evolutionary model proposed by Harris and Zahavi (263) to explain the selection of these
2829 precise molecules for intercellular communication: « Classical neurotransmitters » are small
2830 molecules that are catabolic products of biological molecules involved in basal cell
2831 metabolism: DA and NE are produced from tyrosine, 5-HT from tryptophan, HA from
2832 histidine, GABA from glutamate,... and the extracellular release of these molecules reflects
2833 the metabolic activity of the secretory cell. Their (i) physico-chemical characteristics, which
2834 are best suited to display reliably the levels of specific metabolic activities, and (ii) toxicity
2835 which induced the selection by neighboring cells of membrane proteins to bind them, may

2836 explain why they have been selected for paracrine communication and then for nervous
2837 communication (263).

2838

2839 6.4.2. Non-peptidic neuromediators as potential targets for neuroendocrine disruption of
2840 reproduction: a phylogenetic approach

2841 Neuroendocrine disruptors (NEDs) are defined as “*pollutants in the environment that are*
2842 *capable of acting as agonists/antagonists- or altering the synthesis and/or metabolism- of*
2843 *neuropeptides, neurotransmitters or neurohormones, which subsequently alter diverse*
2844 *physiological, behavioral or hormonal processes to affect an animal's capacity to reproduce,*
2845 *develop and grow, or deal with stress and other challenges*” (863).

2846 While NEDs are now well known to adversely affect reproduction through binding to steroid
2847 receptors (mimicking or antagonizing the activity of steroid hormones), it is important to
2848 mention that they may also affect reproductive functions by acting upon neurotransmitter
2849 systems (such as DA, GABA, NE and 5-HT) that modulate GnRH output (150, 400). To take
2850 only a few examples in mammals: (1) bisphenol A (BPA): When pregnant rats are orally
2851 administered BPA, the turnover of DA and 5-HT in the forebrain are accelerated in both the
2852 mother and the offspring, suggesting an increase in the release of both monoamines from
2853 nerve endings (288). BPA exposure, at even lower doses than environmentally relevant levels,
2854 was shown to have a great impact on monoamine levels in neonatal rat brain over 28 d after
2855 its disappearance (463). In male mice, an increase in anxiety-like behavior induced by
2856 perinatal exposure to BPA seems to be related to decreases in DA metabolites and in the
2857 activity of monoamine oxidase (MAO)-B in the brain. (462). (2) Polychlorinated biphenyls
2858 (PCBs), that are industrial chemical products, also affect DA and 5-HT levels in the brain:
2859 they have been shown to bind to 5-HT, DA, and NE receptors (689). Decreased brain levels of
2860 DA, DOPAC and HVA are observed in the brain of pregnant rats treated with PCBs, but also

2861 in the brain of their offspring (289). PCBs and brominated flame retardants (BFRs) decrease
2862 DA turnover, primarily via inhibition of DA transporters DAT and VMAT, and also decrease
2863 the uptake of glutamate and GABA, inhibiting GABA signaling, and decreasing 5-HT levels.
2864 Several epidemiological studies have shown that PCBs and BFRs may be responsible for
2865 similar effects in humans (for review (200)). (3) GABAergic neurons in the preoptic area of
2866 the rat brain are known targets of TCDD, a dioxin, and may mediate developmental effects of
2867 this contaminant on reproductive function (270).

2868 In birds also, several hypothalamic neural systems proved to be responsive to NEDs (571–
2869 573): for instance, there is evidence in the quail that the catecholamine and indoleamine
2870 systems may be altered by perinatal exposure to NEDs (571).

2871 In fish (for review (863)) various pollutants have been shown to impact neurotransmitters
2872 involved in the neuroendocrine control of reproduction. For example, (a) the antidepressant
2873 fluoxetine (FLU), one of the most prevalent environmental pharmaceutical contaminant in
2874 North American and European aquatic ecosystems, that is a selective 5-HT reuptake inhibitor
2875 (SSRI), was reported to affect multiple neuroendocrine pathways and behavioral circuits in
2876 teleost fishes including disruptive effects on reproduction (481). Recently, in zebrafish
2877 embryos, in very much the same as in mammals, FLU was shown to impair the serotonergic,
2878 dopaminergic and adrenergic neurotransmission systems at environmentally relevant
2879 concentrations, by down-regulating transcription patterns of monoamine receptors and
2880 transporters (134). (b) PCBs disrupt the stimulatory 5-HT/GnRH pathway controlling LH
2881 secretion activity by inhibiting hypothalamic TPH and decreasing 5-HT availability in
2882 croakers (357). (c) Mercury, both in its inorganic and organic forms, is capable of impairing
2883 the monoaminergic neurotransmitters involved in the regulation of GnRH and gonadotropins:
2884 after mercury exposure, 5-HT concentrations are decreased in the brains of several fish
2885 species, whereas levels of NE and DA are increased (for review (133)). (d) Pulp and paper

2886 mill effluents contain compounds that interact with key enzymes and receptors that regulate
2887 the GABAergic, glutamatergic and dopaminergic modulation of GnRH and LH, thereby
2888 impairing reproduction in the goldfish (39). (e) Bifenthrin (BF), a pyrethroid insecticide,
2889 alters dopaminergic function in zebrafish embryos and juveniles (54).

2890 While most investigations on NEDs are carried out with vertebrate models, research on non
2891 vertebrate species led to similar results: For instance, (i) in insects, azadirachtin (AZA), an
2892 insecticidal limonoid with antifeeding and sterilizing properties, blocks neurosecretion from
2893 the corpus cardiaca, interacting with the cholinergic, GABAergic and 5-HT systems (504). (ii)
2894 In crustaceans, cadmium and mercury have inhibitory effects on ovarian maturation in the red
2895 swamp crayfish, partly by inhibiting 5-HT-stimulated gonad-stimulating hormone release, and
2896 preventing the ovaries from responding to this hormone (633). Antidepressants, by interfering
2897 with 5-HT, DA or NE neurotransmission, affect freshwater amphipod activity patterns,
2898 marine amphipod photo- and geotactic behavior, and daphnid reproduction and development
2899 (for review (198)). (iii) In mollusks, in the freshwater mussel, exposure to estrogenic
2900 chemicals present in municipal effluents alters the normal metabolism of 5-HT and DA, both
2901 of which are involved in sexual differentiation (217). Antidepressants affect spawning and
2902 larval release in bivalves and reduce fecundity in snails. Exposure to the environmental
2903 contaminant, serotonergic antidepressant fluoxetine, induces spawning in estuarine and
2904 freshwater bivalves (for review (198)).

2905

2906 6.4.3. The “One Health concept”

2907 The neuroendocrine systems, as the links between the brain and peripheral endocrine systems,
2908 play key roles in the ability of an organism to respond to its environment. They are thus
2909 highly vulnerable to disruption by environmental contaminants such as industrial chemicals,
2910 pesticides, pharmaceuticals..., the worldwide presence of which is now demonstrated. NEDs

2911 are known to exert some of their adverse effects acting directly upon neurotransmitter
2912 pathways that regulate the neuroendocrine systems.

2913 As most neurotransmitter molecules, as well as some of their receptors and transporters are
2914 phylogenetically ancient and conserved within the animal phyla, NEDs may interact with
2915 them and affect the neurotransmission systems of all metazoan. Chemical disruption of
2916 neuromediator signaling may therefore adversely affect health and reproduction in human but
2917 also in a diversity of wildlife thus encompassing the whole ecosystem.

2918

2919 In conclusion, molecular families of neuromediators, hormones, their biosynthesis enzymes
2920 and their receptors, involved in the neuroendocrine control of vertebrate reproduction, have an
2921 ancient origin in metazoa, pre-existing the emergence of vertebrates and the innovation of the
2922 brain-pituitary axis (Figure 13). Evolutionary scenarios, based on phylogeny approaches,
2923 enable retracing the origin and evolution of these molecular families, highlighting the impacts
2924 of gene and genome duplications, as well as gene loss events. Combined with physiological
2925 data they allow inferring evolutionary constraints and mechanisms leading to functional
2926 conservation and diversification of the actors of the neuroendocrine control of reproduction.

2927

2928 **Call Out Box**

2929 • Reproduction is the essential biological process of living organisms and is therefore
2930 submitted to strong evolutionary constraints.

2931 • In human as in other vertebrates, reproduction is controlled by the brain-pituitary
2932 gonadotropic (BPG) axis. Evolutionary endocrinology contributes to a better understanding of
2933 the neuro-endocrine control of reproduction in living organisms including human, by
2934 providing new insights on the origin, conservation and variations of the key actors of the BPG
2935 axis.

- 2936 • As revealed by molecular phylogeny analyses, many actors that have been recruited
2937 for the BPG axis in vertebrates (neuromediators, neurohormones, hormones, biosynthesis
2938 enzymes, and receptors) belong to large molecular families of an ancient origin in metazoa.
- 2939 • The number of actors of the BPG axis has expanded *via* the two rounds of whole
2940 genome duplication that occurred at the basis of the vertebrate lineage, which is at the origin
2941 for instance of the two gonadotropins LH and FSH and their sister hormone the thyrotropin
2942 TSH. Local gene duplications have also contributed to an increase of actor numbers, and
2943 such is the origin of human chorionic gonadotropin.
- 2944 • An additional round of whole genome duplication has occurred at the basis of the
2945 teleost fish lineage, so that some “fish models” currently used for biomedical research, such
2946 as zebrafish or medaka, may present a larger number of actors as compared to human.
- 2947 • Conversely to gene increase via duplications, gene loss events have also marked the
2948 evolutionary history of some BPG actor families, as is the case for kisspeptin receptors, with a
2949 single gene left in human, as compared to four in basal vertebrate representatives.
- 2950 • The synthesis and function of the BPG axis actors (neuromediators, neurohormones
2951 and hormones) are the targets of disruption by environmental pollutants from industrial,
2952 agricultural and pharmaceutical activities. The ancient origin of the BPG actor families
2953 makes a variety of living organisms both targets and sentinels of neuro-endocrine disruption.
2954 This highlights some of the strong links between ecosystems, biodiversity health and human
2955 health, within the framework of the “OneHealth” concept.

2956

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2959

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5718 teleost fish. *Gen Comp Endocrinol* 165: 438–455, 2010.

5719
5720

5721 **Figure Legends**

5722 **Figure 1. Neuroendocrine control of reproduction in mammals: the brain-pituitary-**
5723 **gonad axis.** Internal and environmental factors are integrated at the brain level and modulate
5724 the activity of gonadotropin-releasing hormone (GnRH) neurons. GnRH is released in the
5725 hypophyseal portal vessel system and controls the production of pituitary gonadotropins,
5726 follicle stimulating hormone (FSH) and luteinizing hormone (LH), which in turn control
5727 gonad activity. A variety of neuromediators, peptidic and non-peptidic, are also involved in
5728 the control of GnRH and gonadotropins, such as Kisspeptin (Kiss), gonadotropin-inhibiting
5729 hormone (GnIH), dopamine (DA), norepinephrine (NE), serotonin (or 5-hydroxytryptamine
5730 5-HT), Histamine (HA), gamma-aminobutyric acid (GABA). The pituitary gland, as a relay
5731 between brain neurons and peripheral glands is considered as a vertebrate innovation.

5732

5733 **Figure 2. Vertebrate phylogeny with a special focus on whole genome duplications.**

5734 Two rounds (1R and 2R) of whole genome duplication (WGD) occurred at the basis of the
5735 vertebrate lineage. Whether the 2nd round occurred before or after (dotted line) the emergence

5736 of the cyclostome lineage is still under debate. A third round (3R) of WGD occurred
5737 specifically in the teleost lineage, and is also referred to as TWGD (teleost-specific whole
5738 genome duplication). Human belong to mammalian, amniote, tetrapod, sarcopterygian
5739 lineages. Coelacanth is a representative species of basal sarcopterygians. Actinopterygians are
5740 the sister clade of sarcopterygians.

5741

5742 **Figure 3. Metazoan phylogeny.**

5743 Human belong to the vertebrate, chordate, deuterostome, bilateria lineages. Urochordates are
5744 considered as the sister clade of vertebrates. Among bilateria, protostomes are the sister clade
5745 of deuterostomes. The most consensual classifications of protostomes distinguish two sister
5746 clades, lophotrochozoa and ecdysozoa. Cnidaria represent one of the basic groups of metazoa.

5747

5748 **Figure 4. Schematic representation of the glycoprotein hormone (GpH) α and β subunits
5749 and comparison with predicted GPA2 and GPB5 structures.**

5750 Amino acids are represented by circles. Glycosylation chains are represented by Y shape sign.
5751 Position of intron splicing sites is indicated by V shape sign. The disulfide bonds are
5752 symbolized by bars, red bars between red circles for those responsible for the cystine-knot
5753 structure and in grey for the additional ones. The conserved cysteine residues are numbered.
5754 Location of the β strands (β 1- β 4) and loops (L1-L3) is indicated.

5755

5756 **Figure 5. Schematic representation of the gene duplication, genome duplication and
5757 gene loss events leading to the extant repertoire of glycoprotein hormone subunit related
5758 genes in vertebrates.**

5759 1R, 2R: first and second rounds of whole genome duplication in early vertebrates; 3R: third
5760 round of whole genome duplication in early teleosts. 1* The GPA2-GPB5(a) tandem was

5761 maintained in teleosts and basal sarcopterygian (coelacanth). GPB5a was lost in tetrapods. 2*
5762 Thyrotropin β 2 subunit (TSH β 2) was maintained in basal sarcopterygians (coelacanth,
5763 lungfish) and chondrichthyes but lost in teleosts and tetrapods. 3* The LH β subunit encoding
5764 gene was duplicated in primates to generate several copies of the chorionic gonadotropin β
5765 (CG β) subunit genes. 4* After 3R, except for the TSH β 1 subunit, only one of the duplicated
5766 glycoprotein hormone related genes was conserved. 5* Some teleosts may have two copies of
5767 the GPH α subunit resulting from recent, specific tetraploidization events.

5768

5769 **Figure 6. Evolutionary scenario of the GnRH family in vertebrates** (adapted from (219)).

5770 Anc GnRH: ancestral gonadotropin-releasing hormone gene. 1R, 2R: first and second rounds
5771 of whole genome duplication in early vertebrates; 3R: third round of whole genome
5772 duplication in early teleosts. Black cross: gene loss. Red arrow: local gene duplication.

5773

5774 **Figure 7. Evolutionary scenario of the GnRH receptor family in vertebrates** (adapted
5775 from (644)).

5776 Anc GnRHR: ancestral gonadotropin-releasing hormone receptor gene. 1R, 2R: first and
5777 second rounds of whole genome duplication in early vertebrates; 3R: third round of whole
5778 genome duplication in early teleosts. Black cross: gene loss. Red arrow: local gene
5779 duplication.

5780

5781 **Figure 8. Two evolutionary scenarios of the GnRH-like systems in bilaterians** (adapted
5782 from (654)).

5783 Anc: ancestral; GnRH: Gonadotropin-releasing hormone; CRZ: corazonin. AKH:
5784 adipokinetic hormone; ACP: AKH/corazonin-related peptide. Black cross: gene loss. Red
5785 arrow: local gene duplication.

5786

5787 **Figure 9. Evolutionary relationships between RF-amide and non RF-amide peptide**
5788 **families.**

5789 RF-amide peptides are encoded by 5 distinct genes in mammals, which have been named by
5790 Dockray (153) *farp-1* to 5, based on the chronology of their discoveries. Various
5791 nomenclatures are used according to authors and phyla such as: Neuropeptide F (NPFF) or
5792 PQRF for *farp-1*; Prolactin-releasing peptide (PrRP) for *farp-2*; Gonadotropin-inhibiting
5793 hormone (GnIH) or Neuropeptide VF (NPVF) or LPXFR for *farp-3*; Kiss for *farp-4*; QRFP or
5794 26RF for *farp-5*.

5795 The figure displays some current hypotheses on their evolutionary relationships (for reviews:
5796 (359, 567, 807, 904)):

5797 NPFF (*farp-1*) and GnIH (*farp-3*) would be the closest related RF-amide peptide families,
5798 likely having a common PQRF ancestor and resulting from one of the two rounds of whole
5799 genome duplication (1R/2R WGD) that occurred in early vertebrates.

5800 QRFP (*farp-5*) would be related to NPFF (*farp-1*) and GnIH (*farp-3*) families *via* a local gene
5801 duplication of their common ancestor, before the WGD duplication of NPFF and GnIH.

5802 PrRP (*farp-2*) and Kiss (*farp-4*) would be more related to non RF-amide peptide families than
5803 to the other RF-amide peptide families: PrRP to neuropeptide Y (NPY) and QRFP to galanin
5804 and spexin, *via* local gene duplications, respectively.

5805

5806 **Figure 10. Evolutionary scenario of the Kiss family in vertebrates** (adapted from (587)).

5807 Anc Kiss: ancestral Kisseptin gene. 1R, 2R: first and second rounds of whole genome
5808 duplication in early vertebrates; 3R: third round of whole genome duplication in early
5809 teleosts. Black cross: gene loss.

5810

5811 **Figure 11. Evolutionary scenario of the Kiss receptor family in vertebrates** (adapted from
5812 (587)).

5813 Anc KissR: ancestral Kisseptin receptor gene. 1R, 2R: first and second rounds of whole
5814 genome duplication in early vertebrates; 3R: third round of whole genome duplication in early
5815 teleosts. Black cross: gene loss.

5816

5817 **Figure 12. Ancient origin of neuromediators involved in the neuroendocrine control of**
5818 **reproduction.**

5819 Various neuromediators such as Dopamine (DA), norepinephrine (NE), serotonin (or 5-
5820 hydrotryptamine, 5-HT), histamine (HA), gamma-aminobutyric acid (GABA) are involved in
5821 the brain control of reproduction in mammals. Their presence in other vertebrates, in other
5822 deuterostomes, in protosomes and in cnidaria (non-bilateria), suggests an ancient origin in
5823 metazoa. They may also have exerted an early role in reproduction in metazoa. Straight
5824 letters: neuromediator with a reported role in the control of reproduction. Italic letters with
5825 question mark: neuromediator present but no information on its putative role in reproduction.

5826

5827 **Figure 13. Schematic drawing of the origin of some major actors of the brain-pituitary**
5828 **control of mammalian reproduction.**

5829 The pituitary gland is a vertebrate innovation ensuring the relay between the brain and
5830 peripheral glands and target organs. Molecular families of the various actors of the vertebrate
5831 brain-pituitary reproductive neuroendocrine axis have an ancient origin, largely preceding the
5832 emergence of the vertebrate lineage. Local and whole genome duplications in vertebrates
5833 contributed to the diversification of the Kiss and GnRH (Gonadotropin-releasing hormone)
5834 systems and of the glycoprotein (GP) hormones, pituitary gonadotropins FSH and LH, and
5835 chorionic gonadotropin CG. 1R, 2R: first and second rounds of whole genome duplication in

5836 early vertebrates; 3R: third round of whole genome duplication in early teleosts. Red bar:

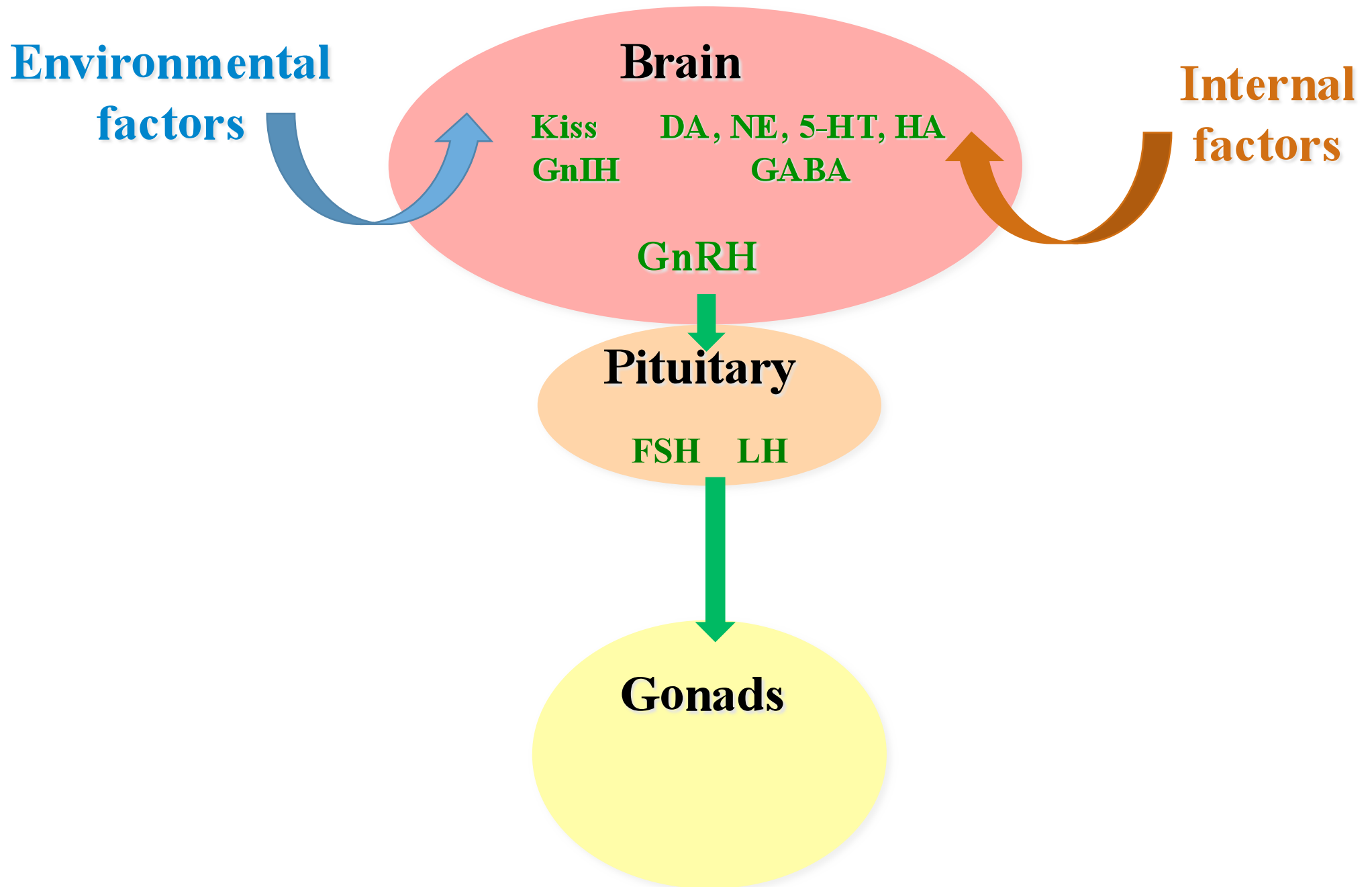
5837 local gene duplication.

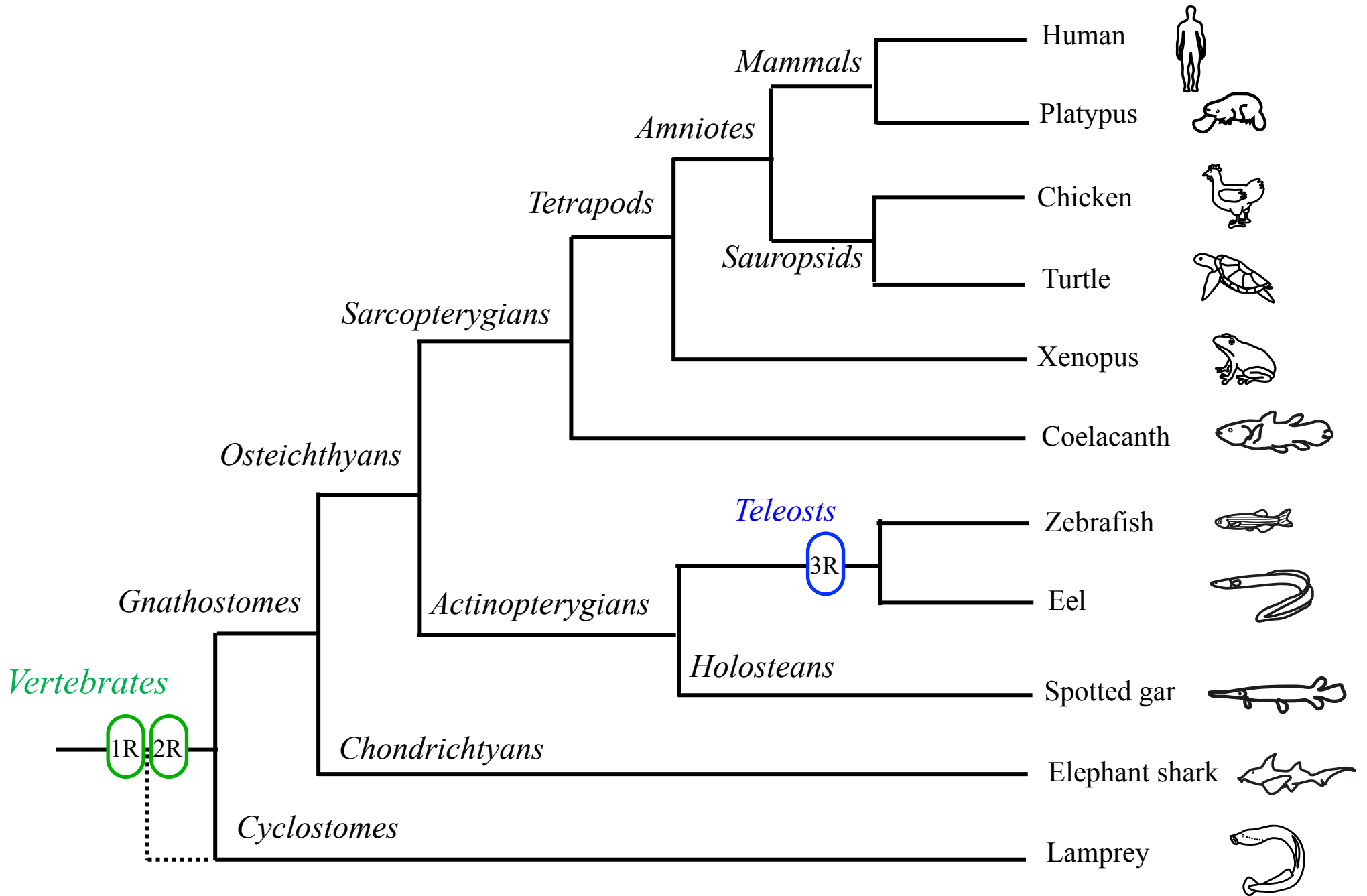
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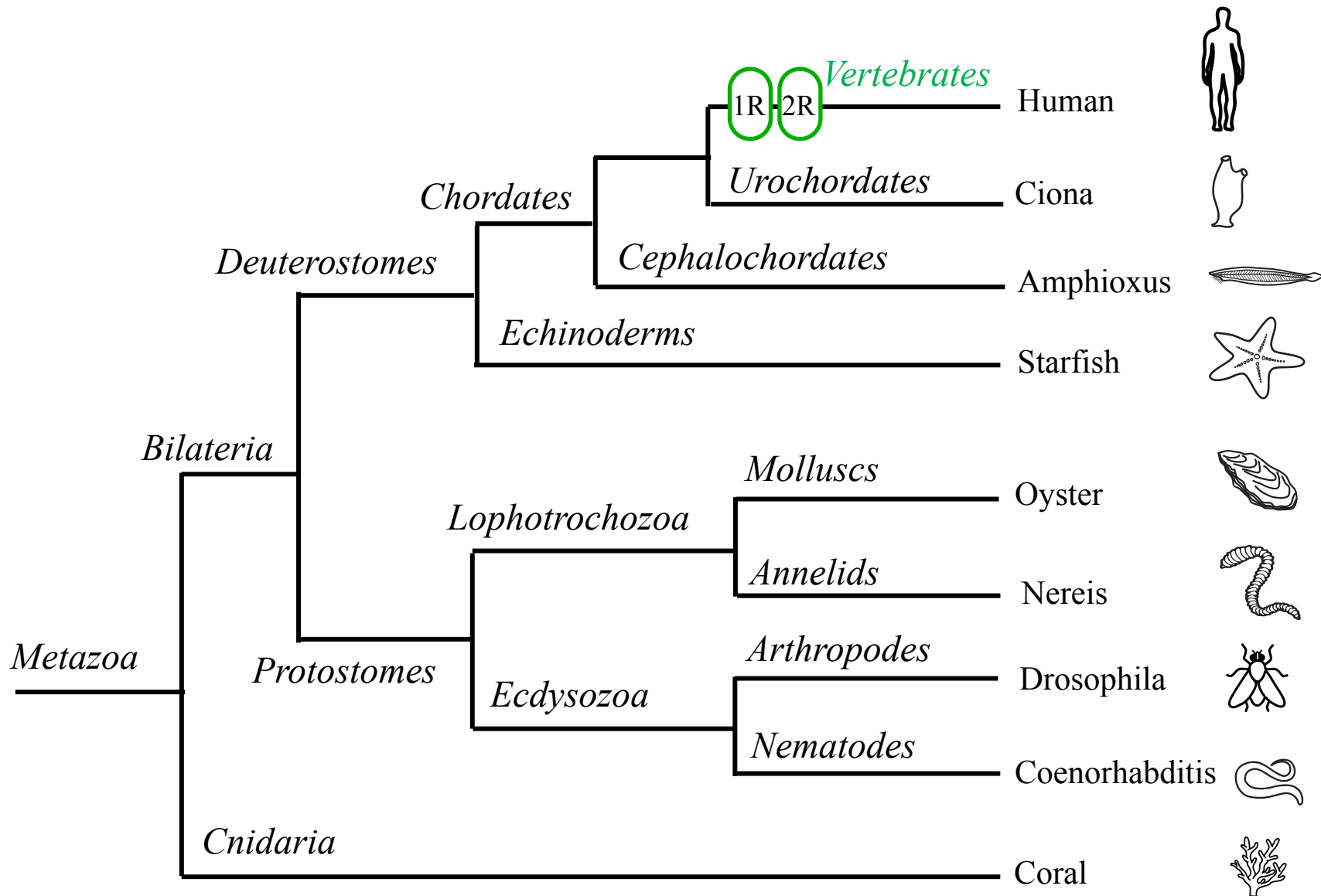
5839 **Table legends**

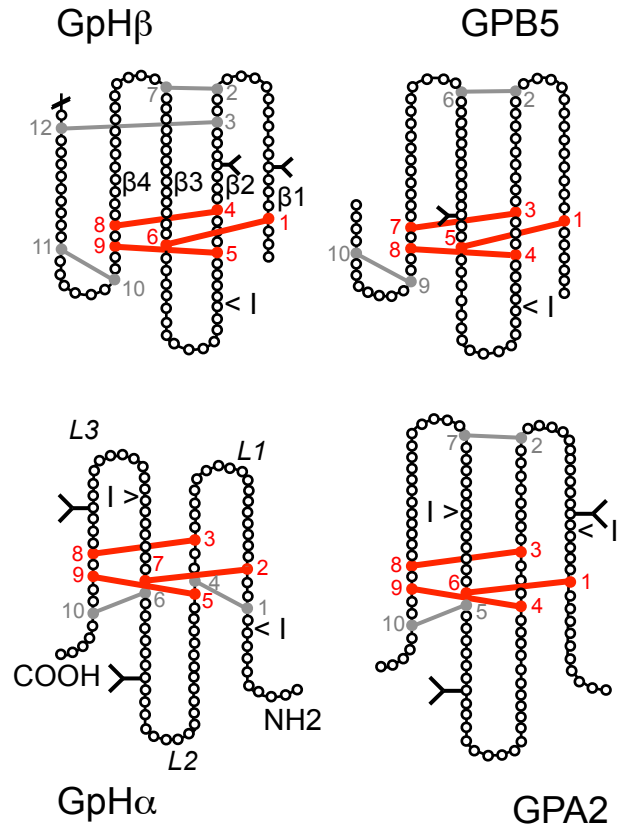
5840 **Table 1. Sequences of GnRH-like peptides**

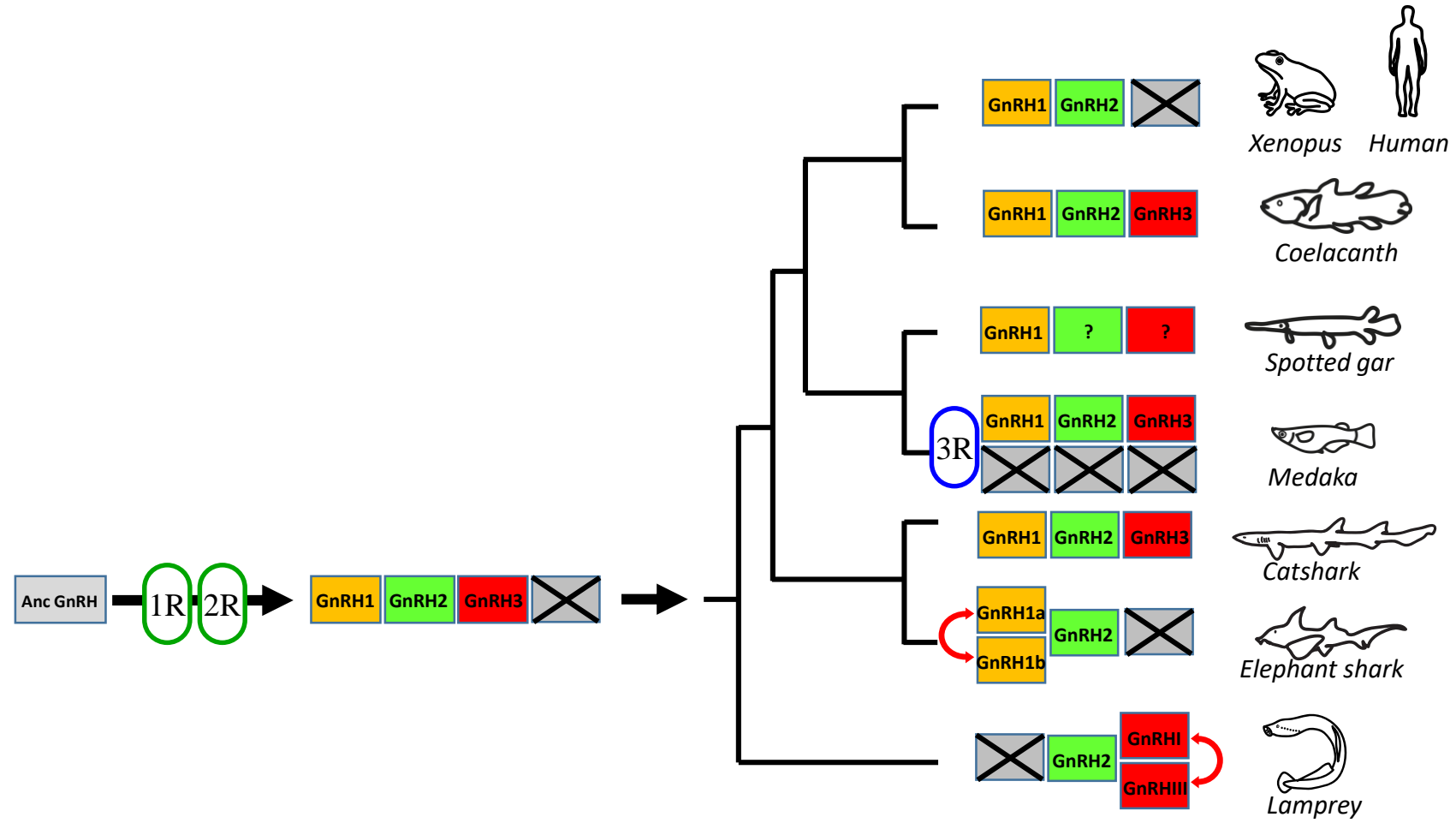
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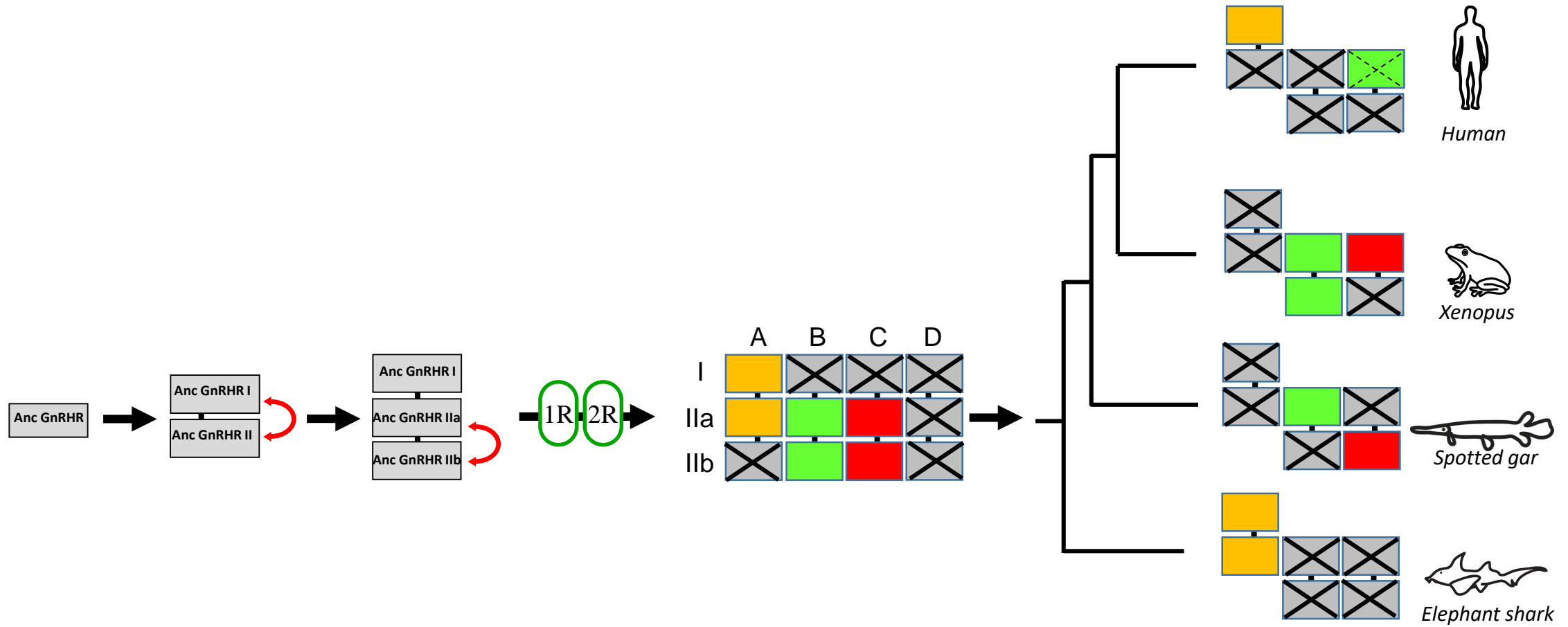


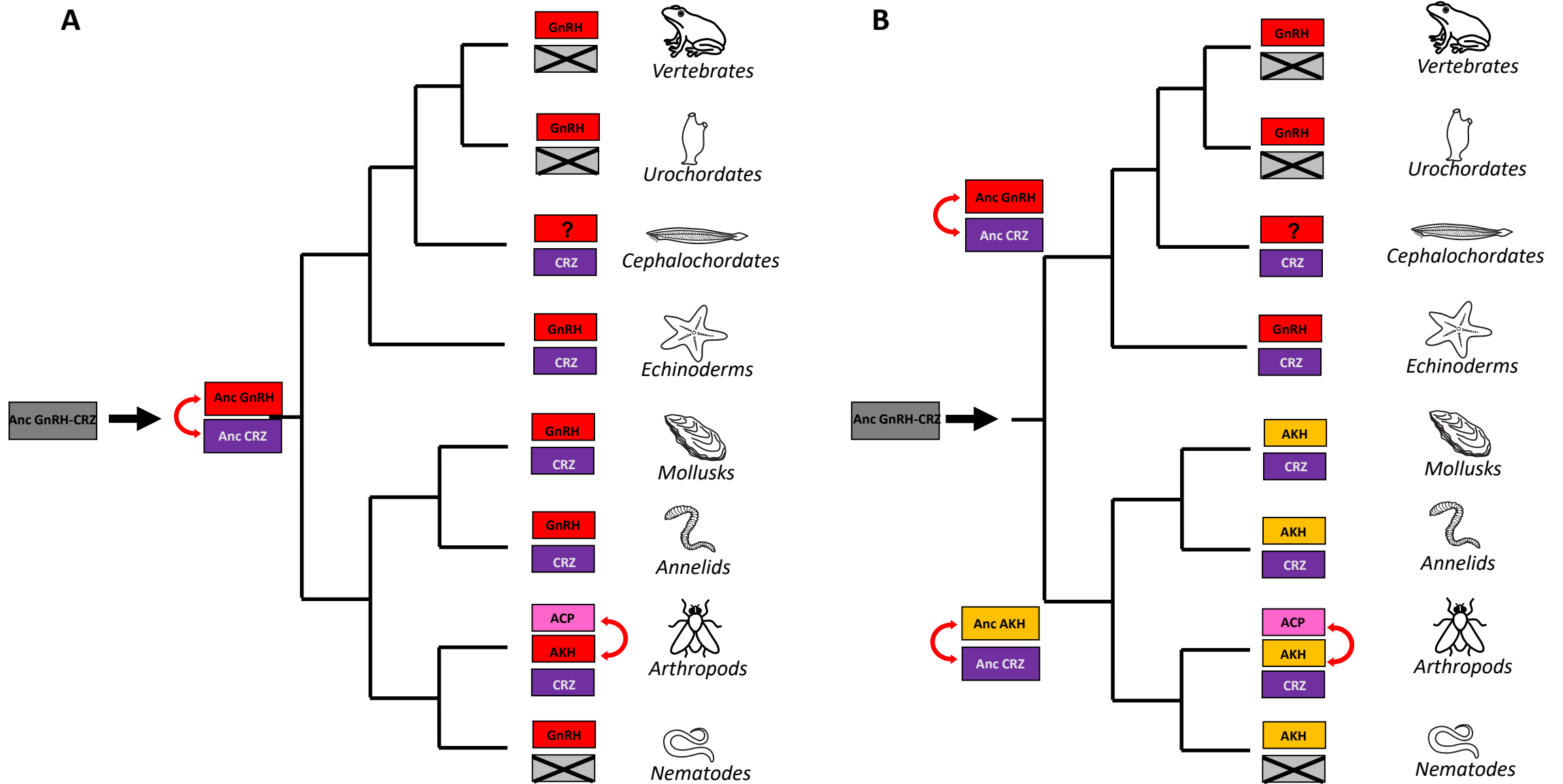






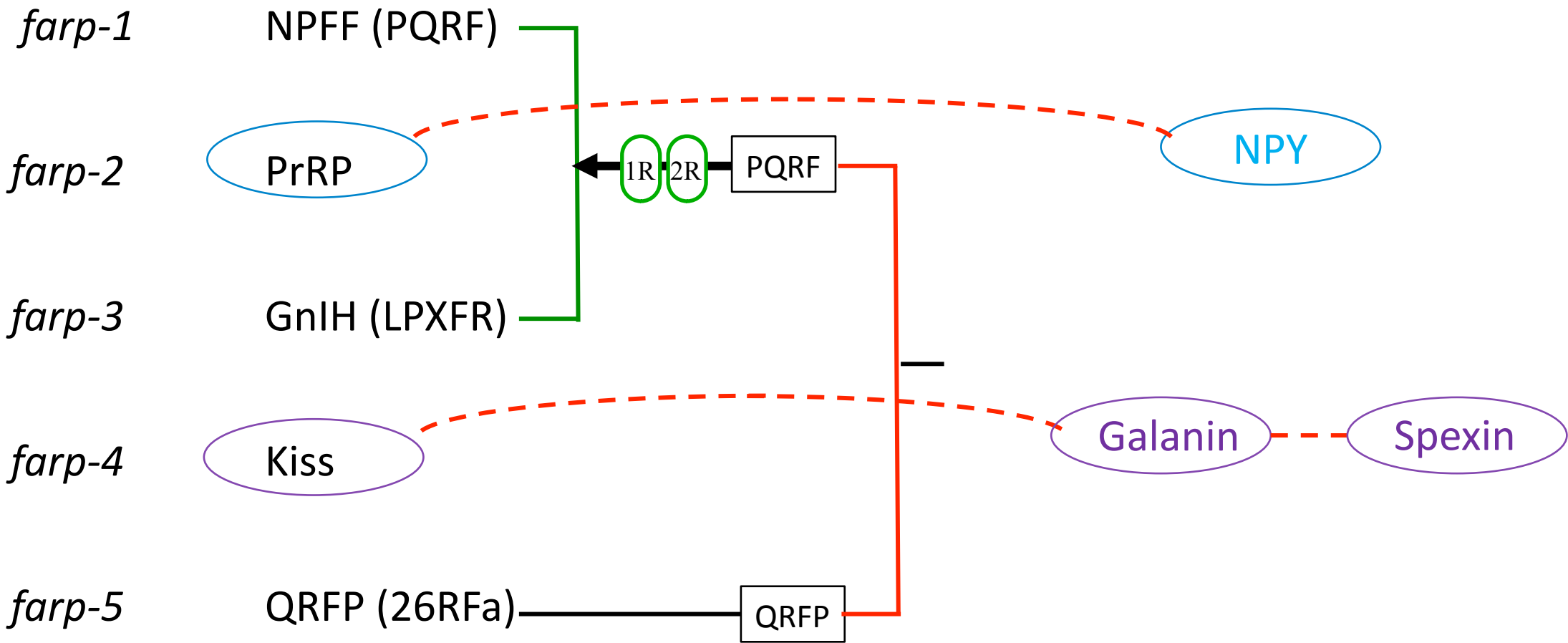


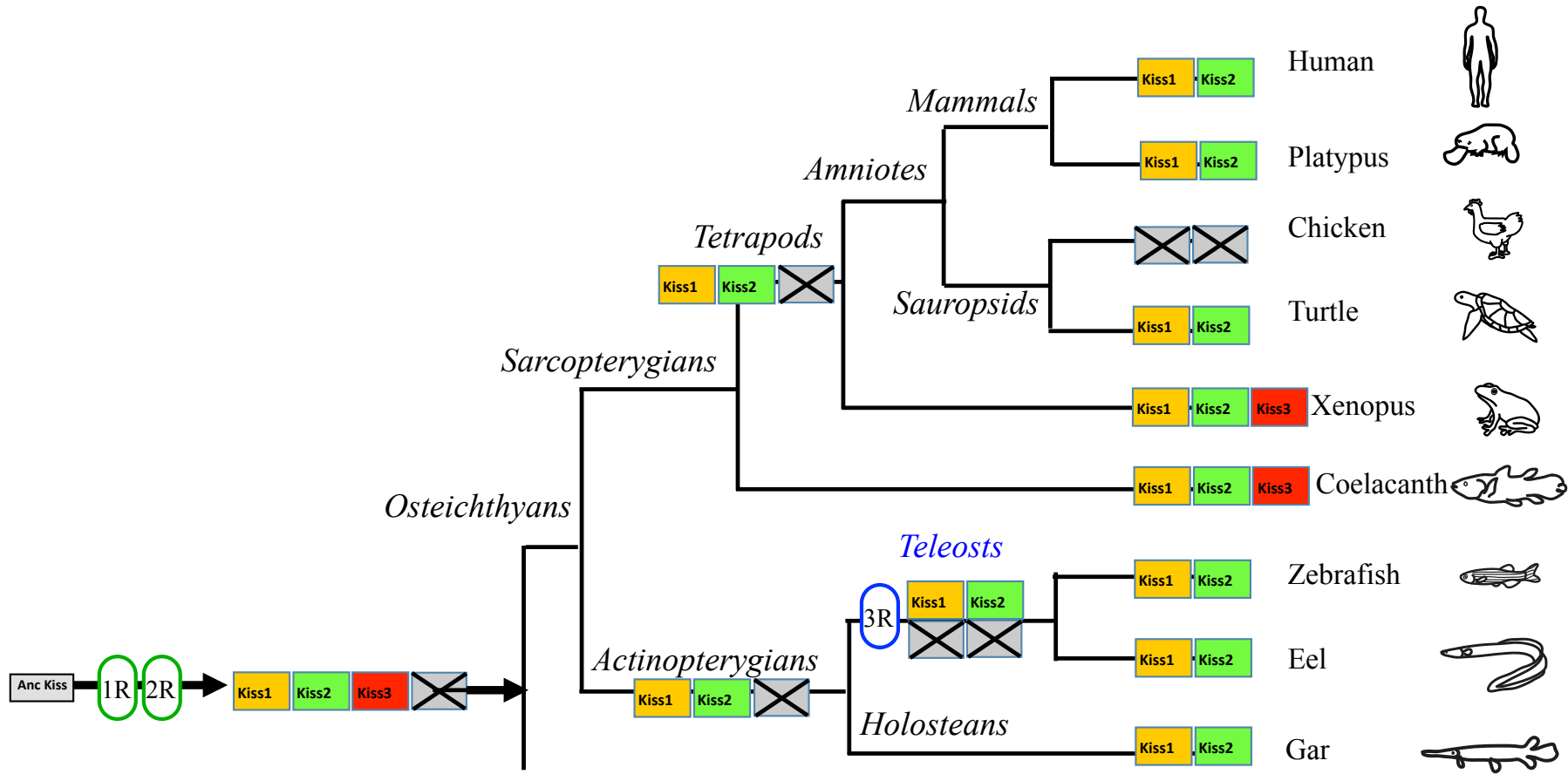


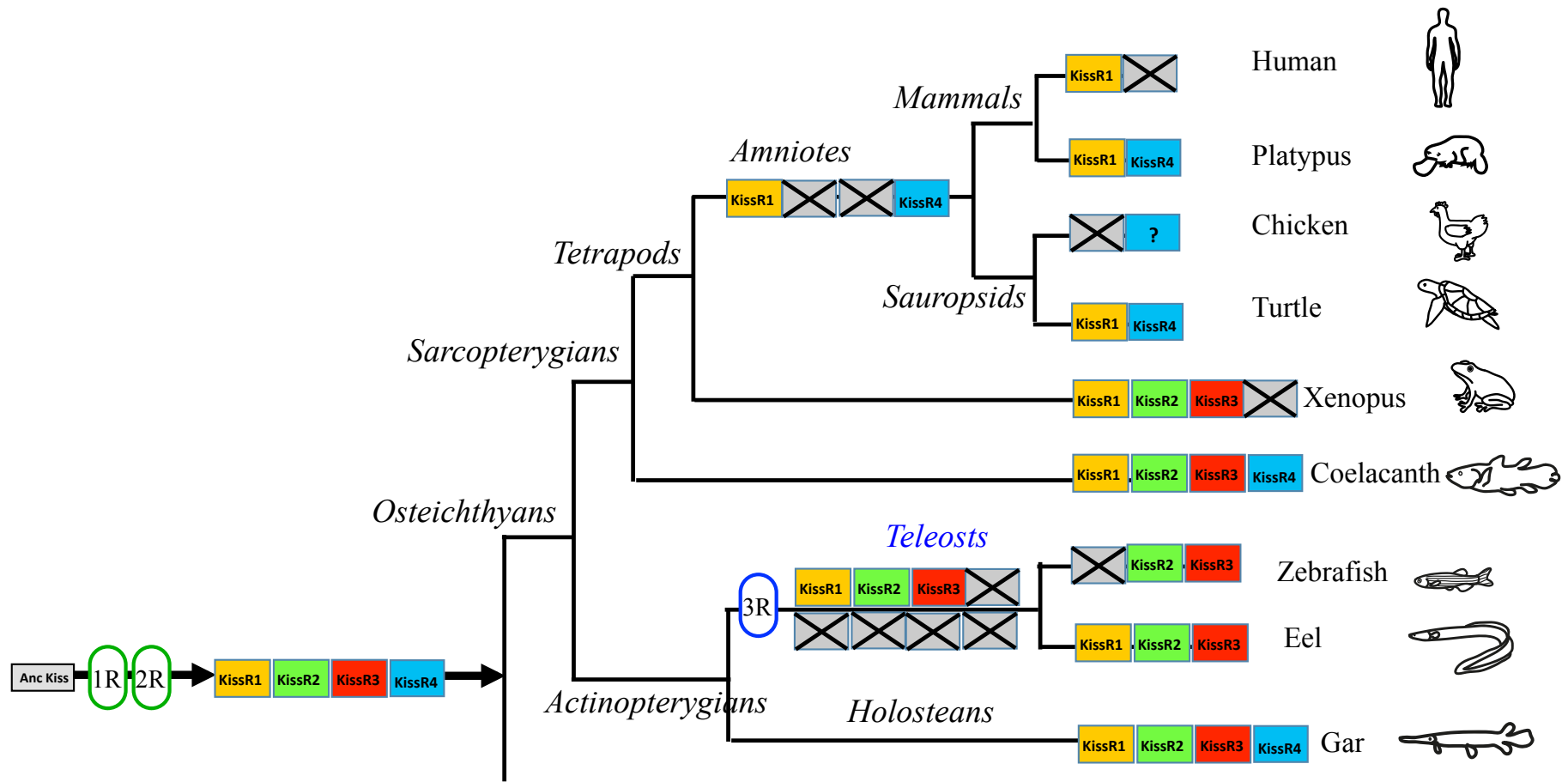


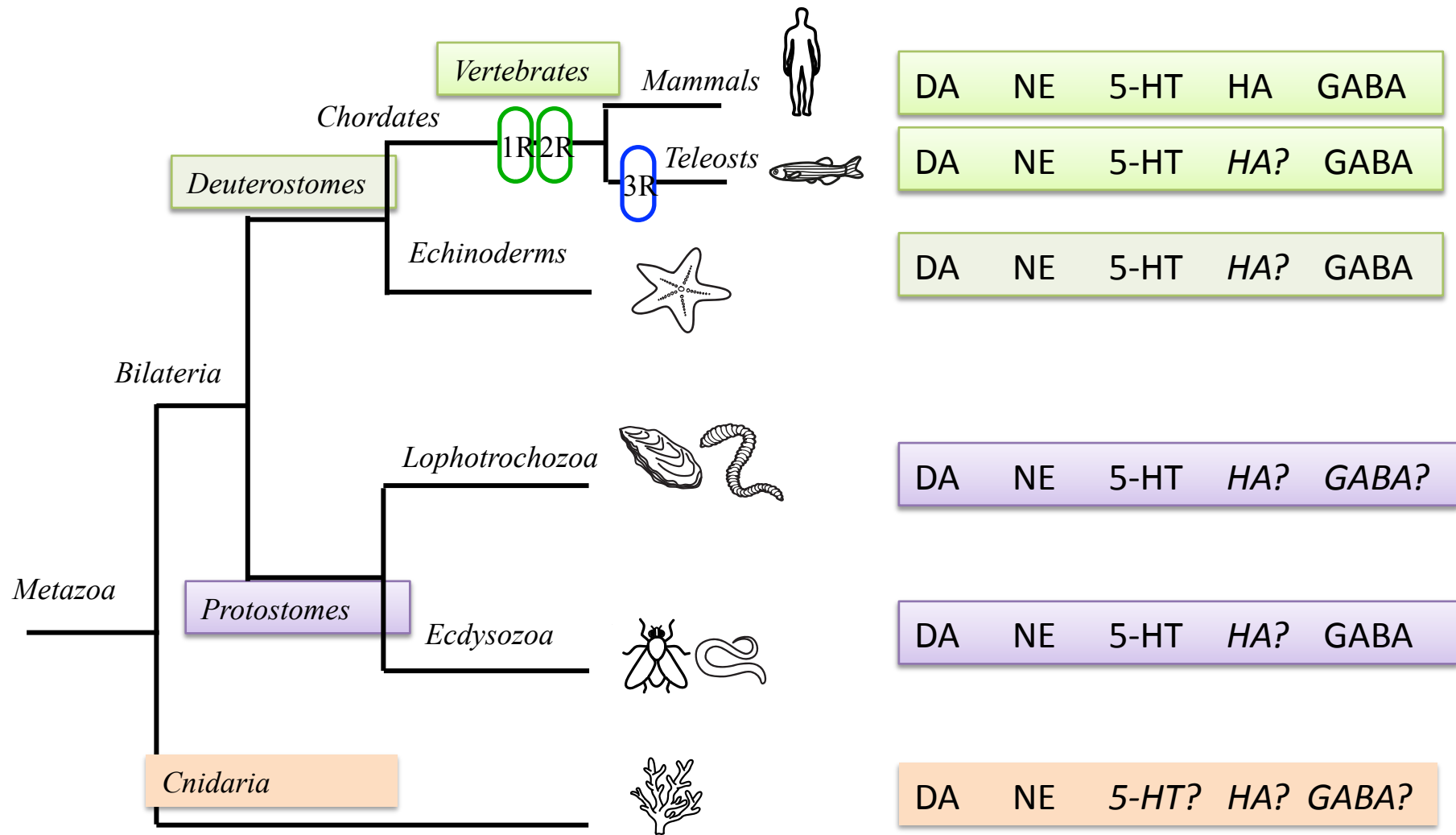
RF-amide peptide families

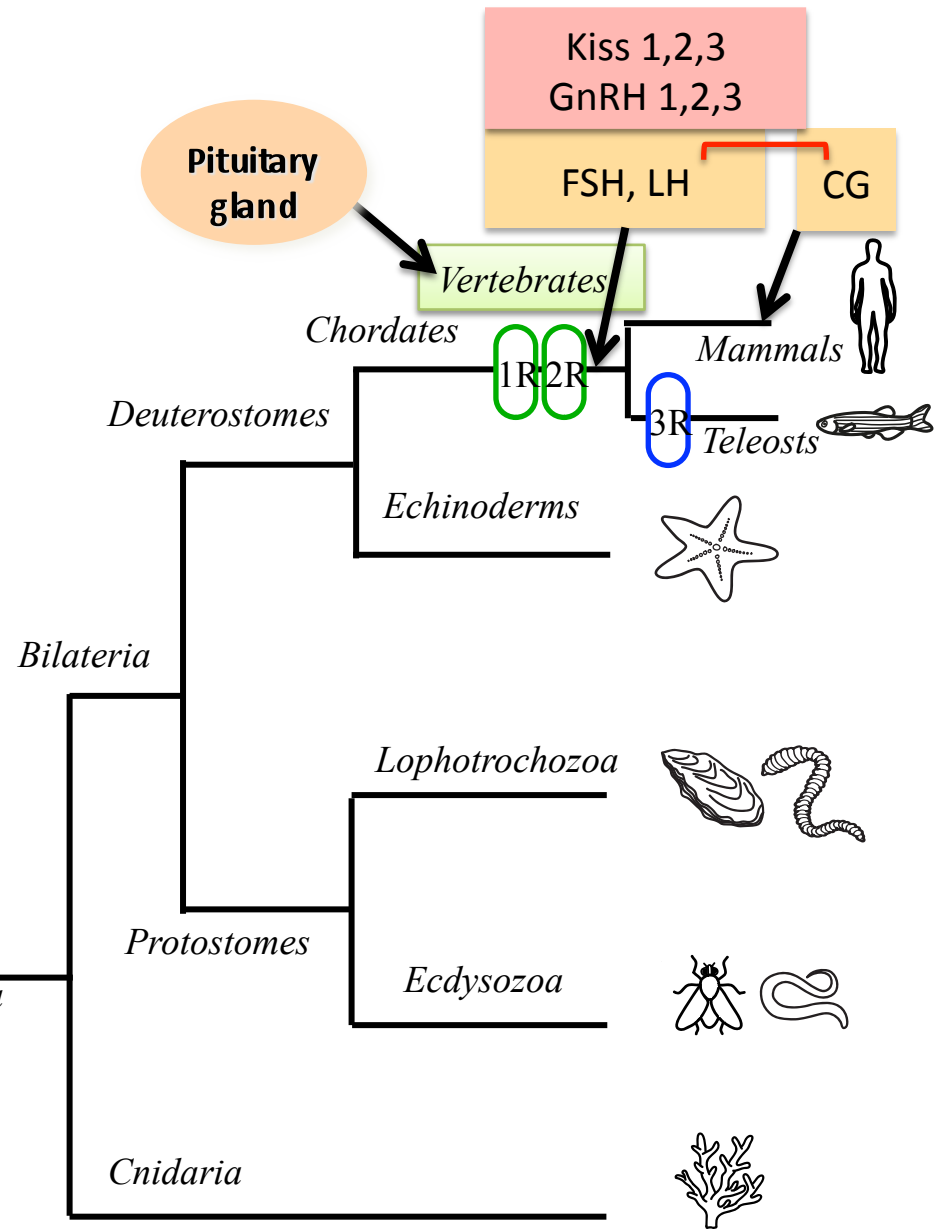
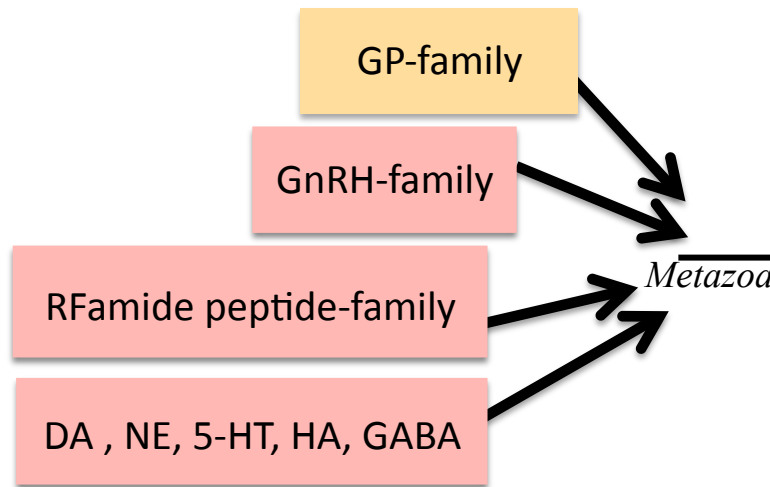
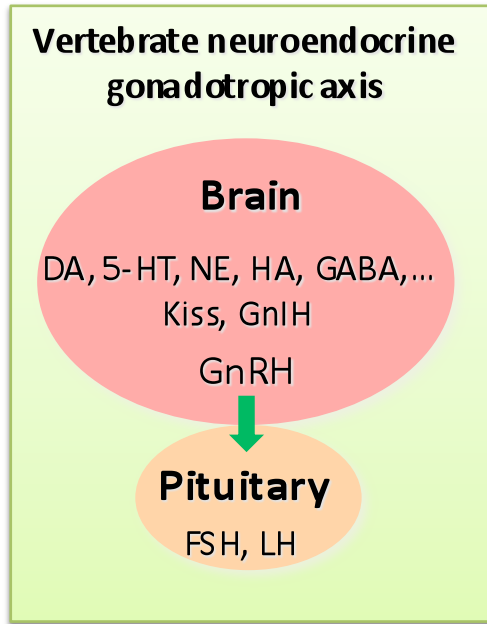
non RF-amide peptide families











	Sequences	Species	Original name	Revised name according to 905
Vertebrate GnRHs				
GnRH1	pQHWSYGLRPGa	most mammals	mGnRH	
	pQHWSYGVVPPGa	Guinea pig	gpGnRH	
	pQHWSYGLQPPGa	Chicken	cGnRH-I	
	pQHWSYGLWPPGa	Frog	frGnRH	
	pQHWSYGLSPGa	Sea bream	sbGnRH	
	pQHWSFGLSPGa	Medaka	mdGnRH	
	pQHWSHGLSPGa	Herring	hgGnRH	
	pQHWSHGLNPPGa	Catfish	cfGnRH	
	pQHWSYGMNPPGa	Whitefish	whGnRH	
GnRH2	pQHWSHGWPYPGa	Chicken	cGnRH-II	
	pQHWSHGWFPPGa	Lamprey	lGnRH-II	
GnRH3	pQHWSYGWLPGa	Salmon	sGnRH	
	pQHWSHGWLPPGa	dogfish (catshark)	df-GnRH	
	pQHYSLEWKPPGa	Lamprey	lGnRH-I	
	pQHWSHDWKPPGa	Lamprey	lGnRH-III	
Tunicate GnRHs				
	pQHWSDYFKPPGa	<i>Chelysoma</i>	tGnRH-1	
	pQHWSLCHAPPa	<i>Chelysoma</i>	tGnRH-2	
	pQHWSYEFMPGa	<i>Ciona</i>	tGnRH-3	
	pQHWSNQLTPGa	<i>Ciona</i>	tGnRH-4	
	pQHWSYEYMPGa	<i>Ciona</i>	tGnRH-5	
	pQHWSKGYSPGa	<i>Ciona</i>	tGnRH-6	
	pQHWSYALSPGa	<i>Ciona</i>	tGnRH-7	
	pQHWSLALSPGa	<i>Ciona</i>	tGnRH-8	
	pQHWSNKLAPPa	<i>Ciona</i>	tGnRH-9	
	pQHWSYGFSPGa	<i>Halocynthia</i>	tGnRH-10	
	pQHWSYGFLPPa	<i>Halocynthia</i>	tGnRH-11	
Cephalochordate GnRHs				
	pQILCARAFTYTHTWa	Amphioxus	AmphGnRH	CRZ
	pQEHWQYGHWYa	Amphioxus	AmphGnRH-v	?

Hemichordate CRZ

pQPHFSLKDRYRWKPa	Acorn worm	skCRZ-like
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Echinoderm GnRHs

pQVHHRFSGWRPGa	Sea urchin	SpGnRH
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pQIHYNPFGWGPga	Starfish	ArGnRH
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Echinoderm CRZs

HNTFSFKGRSRYFPa	Sea urchin	SpCRZ
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HNTFTMGQNRWKAGa	Starfish	ArCRZ
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Nematode AKH-GnRH

pQ MTFDQWa	<i>Caenorhabditis</i>	CeAHK-GnRH
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Arthropod AKHs

pQINFSPGWGQa	Centipede	SmarAKH
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pQLTFSPDWa	Fruit fly	DmAKH
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pQLTFTSSWGa	Silk worm	BmAKH1
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pQLNFTPWWa	Locust	LmAKH
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Arthropod ACPs

pQVTFSRDWTPa	Centipede	SmarACP
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pQVTFSRDWNaa	Mosquito	AgamACP
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pQVTFSRDWNPa	Flour beetle	TcACP
--------------	--------------	-------

pQITFSRSWVPQa	Prawn	MroACP
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Arthropod GnRH

pQQHFRTSHFRPDNVa	Prawn	MroGnRH	?
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Arthropod CRZs

pQTFQYSKGWEPa	Centipede	SmarCRZ
---------------	-----------	---------

pQTFQYSRGWTNa	most insects	CRZ
---------------	--------------	-----

pQTFQYSHGWTNa	Locust	LmCRZ
---------------	--------	-------

Mollusk AKHs

pQVSFSTNWGSa	Oyster	CgAKH	GnRH
pQIHFSPTWGSa	Owl limpet	LgAKH	GnRH
pQHFSPDWGTa	<i>Aplysia</i>	ApAKH	GnRH

Mollusk GnRHs

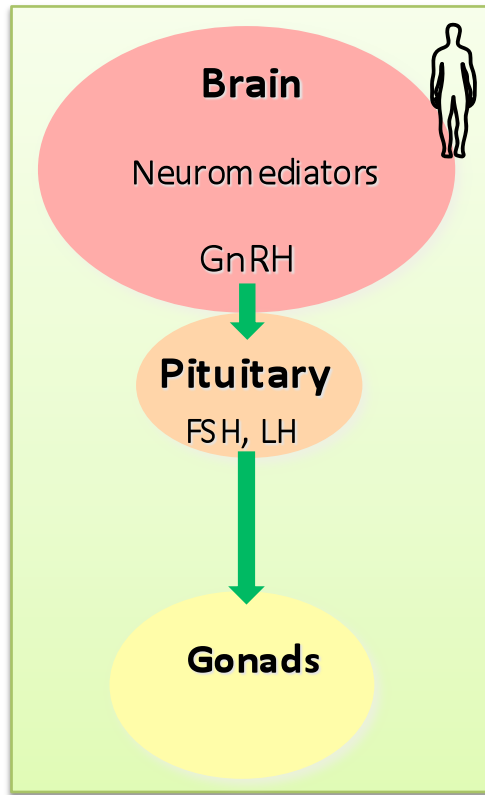
pQNYHFSNGWHPGa	<i>Octopus</i>	OctGnRH	CRZ
pQNYHFSNGWQPa	Oyster	CgGnRH	CRZ
pQNFHFSNGWQPa	Yessi scallop	PwGnRH	CRZ
pQNYHFSNGWYaa	<i>Aplysia</i>	ApGnRH	CRZ
pQNYHFSNGWKSa	Owl limpet	LgGnRH	CRZ

Annelid GnRHs

pQAYHFSHGWFPa	<i>Capitella</i>	CpGnRH	CRZ
pQAYHFSNGWMPa	<i>Platynereis</i>	PmGnRH-1	CRZ
pQHAHFSTGWTGFGIa	<i>Platynereis</i>	PmGnRH-2	?
pQSIHFSRSWQPa	Leech	HrGnRH	CRZ

Annelid AKHs

pQFSFSLPGKWNa	<i>Platynereis</i>	PmAKH-1	GnRH
pQLTQSLGWGSAGSSa	<i>Platynereis</i>	PmAKH-2	?



Ancient origin of molecular families of the brain-pituitary actors

