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Evolution of Hormonal Mechanisms

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Abstract

Hormones are key chemical messengers that regulate major physiological and developmental processes. They are extremely diverse and encompass peptides or small proteins encoded by genes as well as small molecules that are the products of complex metabolic pathways. Their receptors are also diverse from membrane receptors acting via second messengers to nuclear hormone receptors that are ligand-activated transcription factors regulating directly target gene expression. If the mode of action of hormones is better and better known, the question of their origin and evolution is still nimbed in mystery. It is however possible now to draw some common principles underlying their evolution. At the heart of this question is the hormone / receptor couple that controls the hormonal response and whose evolution will be different depending on the nature of the ligand. Whatever this nature, the couple did evolve and recent results suggest that even small molecules such as steroids or thyroid hormones can change during evolution. Another important layer of evolutionary changes are all the mechanisms that exquisitely control hormone levels in peripheral organs. Lastly we can start to ask the question of the origins of some hormonal systems that are much more ancient than anticipated.

Keywords

Hormone evolution, Receptor evolution, Hormone/receptor couple, Ligand metabolism, Coevolution Nuclear Hormone Receptors, GPCR, Steroids, Thyroid Hormones.

Glossary

Endocrine signalling: distant intercellular signalling through a body fluid.

Exocrine secretion: secretion of molecules (independent of their physiological role) outside the body cavity, mainly through the digestive system.

Paracrine signalling: local intercellular signalling that does not involves a transport by a body fluid.

Nomenclature

3,5-T2 : 3,5-diiodothyronine

AR : Androgen Receptor

CO : Carbon monoxide

ER : Estrogen Receptor

FSH : Follicle-Stimulating Hormone

FXR : Farnesoid X Receptor

GR : Glucocorticoid Receptor

LH : Luteinizing Hormone

LXR : Liver Xenobiotic Receptor

MR : Mineralocorticoid Receptor

NO : Nitric Oxide
PR : Progesterone Receptor
Rev-erb, E75 : nuclear heme-binding receptors
TH: Thyroid Hormones
TRIAC : Triiodothyroacetic acid
TSH : Thyroid-Stimulating Hormone

Body Text

Introduction: the evolution of hormonal systems in the context of animal evolution.

Hormones are biologically active molecules that are secreted in the blood by a gland, acting remotely and transported until target cells that express specific receptors. Hormones are therefore key in transmitting a message in chemical form. The endocrine system, with a wide range of hormones, is the body's second-largest regulatory system, and it works in synergy with the nervous system, which acts very quickly, in a few milliseconds, and whose action does not last much longer. Typically, the endocrine system is much slower, it can take a few seconds or even days to react, but its action can be felt also over a period of several days or even weeks.

The endocrine system fulfils the need for cells and organs to communicate with each other within the body to organise growth, differentiation and cell division in the adult but also during development. The term "hormone" (from a Greek term meaning "set in motion") was adopted by the British physiologist Ernest Starling in 1905 to designate the substances that provide the link between the various organs (Starling, 1905). They are effectively key in the coordination of physiological responses in different organs.

There are thousands of different hormones that control virtually all biological processes. Some cause emergency reactions (i.e. adrenaline), others play a regulating role (i.e., insulin, which regulates the glucose level in our blood), still others play a role in the management energy, adaptation to the external environment (temperature for example), the amount of water in the body, salt and ion concentrations, growth, reproduction (the estrogens and androgens that determine female and male sexual characters respectively), blood pressure, digestion etc. Also, some hormones like ecdysone that controls molting in insects or thyroid hormones that control the metamorphosis of a tadpole into a frog, are key regulators of life cycle transitions in animals. Very often, a hormone has several simultaneous effects, and interacts with other substances or hormones and it is more and more important to realise that hormone action is exquisitely regulated at the tissue level by extraordinarily complex and finely tuned mechanisms (Tata, 2005). It is now well demonstrated that controlling the amount of hormone or hormone signalling levels is of critical importance, hence the worries about the widespread presence in the environment of pollutants acting as endocrine disruptors (Denver et al., 2009).

Given the variety of hormones and of mode of action, discussing their evolution in general is a challenge. There are, however, a number of general principles that seem valid for all hormones. The first is that at the heart of hormonal systems and their evolution is the hormone/receptor couple. To understand the evolution of this couple we must separate protein or peptide hormones from hormones that are small molecules produced through complex biosynthesis pathways. The second is that the peripheral mechanisms that control the availability of ligands and their activation are extraordinarily important and have been far too neglected. But before we get to the heart of the matter, we need to look at the history of animals in order to have a framework in which we can discuss the evolution of hormonal systems.

More than a century ago, biologists have been interested in the origin of animals, which in zoological terms are called the metazoans. They first ask when and how multicellular animals appeared. Paleontology provides some answers and suggests that animals are at least 650 million years old.

But it is impossible to know how the first metazoans were built, because the oldest fossils attest a rather long earlier evolution giving almost no clues on the very first metazoans. These fossils are remains of already diversified animals, presenting several modes of organisation. They belong to the so-called Ediacara fauna, exhumed initially in Australia and, subsequently, in other continents. Their burial goes back to 600 million years ago. Therefore there is a deep and partly hidden history of metazoans and we mostly rely to molecular phylogeny, the reconstruction of the history of living Metazoans, to get some information on what could have been the first metazoans (Budd and Jensen, 2017).

The formation of metazoans required many innovations. It was necessary to join together cells, allow them to communicate with each other and to specialise. It was also necessary to build with each generation a new organism from a single cell; therefore to invent an embryogenesis. Given the major role of hormonal systems in controlling cell differentiation, embryonic development, homeostasis and long-range communications in the body, it is evident that the establishment of the very first hormonal systems have been somehow concomitant with the establishment of the first metazoans.

This is why it would be interesting to study in more detail the mechanisms of cellular communication in choanoflagellates, the sister group of metazoans. These are flagellated protists that sometimes exhibit a colonial way of life and live in either open water or fixed on benthic substrates. There are more than 125 widely distributed and often abundant species and the inventory is certainly not exhaustive. As, they are considered to be the closest living relatives of early animals they are used by evolutionary biologists as a model for reconstructions of the last ancestor of metazoans (Brunet and King, 2017).

It would be important also to have informations about the very first phyla of metazoans. However this question is very controversial because the phylogeny of basal metazoans is not completely resolved (Simion et al., 2017, Whelan et al., 2017). Depending whether sponges (sessile multicellular organisms with a simple body without obvious symmetry) or ctenophora, also known as comb jellies, (ciliated transparent carnivorous marine organisms with a rotational symmetry) are considered as the most basal metazoan group, the most ancient metazoan organism inferred would be very different. In one case it would be a relatively simple sponge-like inactive animal whereas in the other it would be more active and organised, with a primitive symmetry. We cannot further discuss here the implications of these two visions that are still unresolved but we can however insist on the fact that the resolution of this question will have implication for the level of complexity of global communication devices existing in the first metazoans. Clearly, in both cases, because they lack an internal circulating body fluid, these animals cannot have a classical hormonal system in which hormones are transported in the blood. However this does not mean that there is no intercellular signalling in those animals. Indeed the classical view of hormones defined as internal circulating molecules is changing and the frontier between hormones and growth factors and other paracrine signalling molecules is becoming more and more blurry with the acknowledgment of many short-range functional roles of hormones.

1. The evolution of the Hormone/Receptor couple

At the heart of the hormonal systems is the hormone/receptor couple. According to the classical vision, highlighted in numerous textbooks, hormones specifically turn on their receptors by fitting into a hormone-binding site (also called ligand binding pocket or LBP) as a key fills a lock. However it is becoming increasingly clear that this view is by far too schematic and that in real the situation is much more plastic. This should be emphasised as it may have implications at the evolutionary level. This plasticity is well exemplified in the case of nuclear receptors that are ligand-activated transcription factors mediating the effects of numerous hydrophobic hormones such as steroids or

thyroid hormones. First, this family of well-conserved receptors illustrates very well that the strong difference we often make between hormones (signalling molecules acting at distance from their origin and transported by blood) and growth factors (signalling molecule acting close to its origin and even sometimes on neighbouring cells) do not correspond to a biological reality. Indeed, the nuclear receptors cluster receptors for hormones (e.g. estrogens) but also to growth factors (e.g. retinoic acid) and even active molecules directly derived from food (e.g. fatty acids), and some compounds, such as steroids, can act both as distant hormones and local paracrine signalling factors. All these different classes of compounds act in a very similar fashion by regulating a gene regulatory cascade through a well-conserved superfamily of receptors. Second, the structural variety of ligands acting through nuclear receptors is really impressive and question the distinction between ligands, that is molecules capable of binding and activating a receptor and prosthetic group defined as organic molecule maintained permanently in a protein structure and essential for its activity. This is shown by the Rev-erb/E75 receptors that are able to bind heme, the well-known prosthetic group of haemoglobin. In Rev-erb, heme, a large molecule, is also permanently bound in the structure and its redox status control the activity of the receptor. It is a gas, nitric oxide or carbon monoxide, that controls the redox status and heme and therefore the activity of the receptor. Therefore E75 in *Drosophila*, but also Rev-erbs in vertebrates are biological sensors for diatomic gasses such as NO and CO (Marvin et al., 2009). This example illustrates very well that hormone receptors can have a much diverse set of ligands than anticipated. Third, and lastly, it is now clear that a given receptor can bind, sometimes with different affinities, a diverse set of ligands that all have clear biological activities. This is well exemplified by the case of vitamin D receptor whose natural ligand is 1,25-dihydroxycholecalciferol which regulates calcium metabolism, in particular in the bones. But the same receptor can also be activated in the liver and intestine by a bile acid, lithocholic acid that in fact controls its own degradation as it is a carcinogenic compound (Makishima et al., 2002). Many other nuclear receptors are no longer viewed as highly specific for a small set of ligands that they bound with high affinity but are rather sensors that can be activated by many different compounds on which they bind with a much lower affinity (Sladek, 2010). This is the case for many nuclear receptors implicated in the control of metabolism (e.g. LXR, FXR etc...). Therefore the key-lock model although not wrong is an oversimplification and we should have that in mind when discussing the evolution of hormone-receptor couple.

Being nuclear receptors that activate a set of target genes or membrane receptors acting through second messengers, the hormonal receptors should of course control a specific response in order to fulfil their physiological need. Insulin must promote the absorption of glucose present in the blood, whereas glucagon, on the contrary causes an increase of the amount of glucose in the blood. Therefore, even if more complex than the key-lock model, specificity is a key concept for the hormone-receptor couple. And this specificity could rely on quite tiny differences. Let's compare the structure of 17β -estradiol and 5α -dihydrotestosterone, the respective ligands of estrogens and androgen receptors responsible of female, and male sex features respectively: one carbon and two hydrogen atoms differs between the two molecules that both harbour the classical steroid skeleton. Therefore, even if somehow plastic, the receptors must recognise their ligands and not others. This question of specificity is key in our understanding of the evolution of hormone-receptor couple.

For discussing how the hormone-receptor couple can evolve it is necessary to clearly separate two cases: the receptors for peptidic or protein hormones in which both the hormone and the receptors are encoded by genes and the case of receptors for small molecules which are derived from a metabolic pathway that is a series of chemical reactions modifying a precursor compound.

When both hormone and receptors are encoded by genes, the situation is conceptually simple: when a mutation occurs on one of the partners, let say the ligand, a compensatory reaction must occur in the other partner, here the receptor to allow the binding to be maintained. In case of gene duplication it is therefore quite simple to see how a ligand and a receptor couple can diverge from

another one. This has been beautifully illustrated in the 90's by the case of FSH and LH and their respective receptors (Moyle et al., 1994). It has been shown in that case that precise regions of the ligands act as determinants that restrict ligand-receptor interaction, therefore enabling selectivity and explaining binding specificities in family of homologous ligands and their receptors. This model applies easily in cases when the respective members of the couple belongs to the same families and render more easily tractable the structural basis of the selectivity (see Jiang et al., 2014 for glycoprotein hormones). But this is not always the case and in other ligand-receptor pairs (e.g., cytokines) the receptors are in a same family but their ligands belong to distinct families (Liongue et al., 2016). However this model has well resisted across time (Szkudlinski, 2015) and has been extended to some other ligand-receptor couples such as ghrelin (Tine et al., 2016), oxytocin (Yamashita and Kitano, 2013; Ren et al., 2015) and even outside the endocrinology field in the context of protein-protein interactions (Lovell and Robertson, 2010).

The situation is different when the ligand is not encoded by a gene but is a small molecule whose synthesis is controlled by a series of enzymatically-controlled biochemical reactions. This aspect has been studied in more details in the case of steroid receptors. The case is effectively interesting as the 5 steroid hormone receptors and their respective ligands in humans and other mammals (ER/estrogens, PR/progesterone, AR/androgen, as well as MR and GR/corticoids) arise from the same common ancestor. This raises the question: how did these receptors acquire their specificity with respect to their hormone molecule? As a simple coevolution mechanism obviously cannot operate, alternative models such as the ligand exploitation model (Thornton, 2001) have been proposed to explain how changes of specificity can take place during evolution. According to this model, the terminal ligand in a metabolic pathway has to be the primordial ligand for which a receptor should exist. The existence of this ligand implies the existence of intermediate molecules in the metabolic pathway since however the terminal ligand will not be maintained. In case of duplication of the gene encoding the receptor some duplicated copies can therefore exploit (hence the name of the model) these intermediate compounds. This may explain how novel hormone-receptor pairs can be created.

The ligand exploitation model has been proposed in the case of the estrogen receptors that was considered with its ligand 17 β -estradiol to be the primordial steroid-receptor couple (Thornton, 2001). However this model has a fundamental limitation as it considers that the receptors are evolving but that the ligand remains the same across time. We know that this can't be true and indeed in the case of estrogens this is not true. Detailed comparative genomics have shown that estrogens are a vertebrate specific compound and that the estrogen receptor in invertebrates should therefore have a different endogenous ligand. The fact that some invertebrate ER effectively bind 17 β -estradiol is therefore a pharmacological effect, unrelated to their endogenous ligand and physiological function that remains unclear.

Even if one cannot speak about direct co-evolution, when the receptor is considered, the evolution of the ligand-binding pocket can occur by the slow accumulation of mutations that gradually change the structure of the pocket and its specificity. This has been exquisitely shown for the steroid receptors (Bridgham et al., 2009), but also for retinoid receptors (Gutierrez-Mazariegos et al., 2016) as well as for membrane receptors, in the case of cannabinoid receptors. Here the enzyme implicated in the metabolism of anandamide and 2-arachidonyl glycerol, the two endogenous ligands of cannabinoid receptors, have been shown to follow the evolution of the receptor suggesting some sort of coevolution (McPartland et al., 2007).

Clearly the evolution of small molecules and their receptor should now be scrutinized in greater detail and this is becoming possible. Indeed by scrutinizing on steroidogenesis it has been possible to reconstruct an ancestral receptor-ligand couple (Markov et al., 2017). For this the authors have retraced the history of steroidogenesis using an approach developed for the analysis of universal

metabolism (Cunchillos and Lecointre, 2007). The originality of the approach was to use comparative anatomy methods to study evolution at a biochemical level. It's a simple principle: as with animal anatomical features, metabolic pathways are the product of evolution and are modified over the course of time. Using phylogenetic tree construction methods it is therefore possible to infer the evolution of the steroidogenic pathways and to show that, as suggested by comparative genomics approach the 5 steroid hormones share a unique common ancestor at the basis of vertebrates and are therefore specific to vertebrates. Interestingly, such an evolutionary tree makes it possible to predict the molecules that were present at each evolutionary stage, so it was possible to determine the structure of the ancestral steroid. This molecule called "paraestrol A" was chemically synthesised and shown to bind and activate an ancestral receptor that was also predicted by molecular phylogeny. This interaction was confirmed by structural modelling, allowing to explain how the receptor specificity to its ligand was reinforced over the course of evolution. This "resurrection" of an ancestral hormone/receptor couple opens the way to the study of small molecule evolution and is therefore opening a new era, as it will undoubtedly be reproduced in the case of other receptor-ligand couples.

2. Evolution of peripheral control of hormone response

Whatever the receptor system, the hormonal response must be carefully regulated both in time and space. The transport of hormones, their entry into target cells when needed, their activation in target tissues, or their degradation after use allows to precisely controlling the duration and magnitude of hormone response. Every step is regulated and therefore every step can be used by natural selection in order to allow the organisms to be in register with their environment, ultimately leading these organisms to be adapted.

The importance of a tight regulation of peripheral hormonal regulation is well exemplified by the case of the early metamorphosis of desert frogs (Buchholz and Hayes, 2005). Living in ephemeral desert pools, the spadefoot toad *Scaphiopus couchii* has the shortest larval period known among frogs, as it must complete its metamorphosis before complete drying of the pool. In this species differences, in TH physiology correlating with larval period differences were identified and are consistent with the notion that selection favouring rapid metamorphosis to avoid desiccation acted, at least in part, through TH physiology that occurred on a tissue-by-tissue level. This suggests that an increase in tissue thyroid hormone content and/or increased tissue sensitivity occurred in the ancestors of *Scaphiopus couchii*. Such a higher tissue response to higher TH levels led to more rapid transformation of metamorphic tissues and therefore to the adaptation to the ephemeral nature of the pond. This example shows very well how an important, and even vital change in larval period duration can be obtained by altered endocrine signalling and beautifully illustrates how change in hormonal response can play an important role. Other recent similar examples, among others also include the central regulation of TH level by TSH in freshwater vs. marine sticklebacks (Kitano et al., 2010) or the variation in tooth number controlled by the local production of retinoic acid in cypriniform fishes (Gibert et al., 2015).

Even if given the wide diversity of hormonal systems it is difficult to generalize, it is interesting to note that the enzymes used to regulate in space and time the level of hormone signalling are effectively variable during evolution. Clearly the various enzymes controlling hormone availability vary often in number in different species and are therefore likely contribute to evolutionary innovations in the control of hormone response. For example the 3β -hydroxysteroid dehydrogenase, an essential enzyme involved in the biosynthesis of all classes of steroid hormones, is present in at least 6 genes in mouse, 4 in rats, 3 in hamster and 2 in humans, all coming from species-specific gene duplications (Simard et al., 2005). Similarly, but in a different scale, the number of deiodinases, essential enzymes that control the tissue availability of triiodothyronine, the active thyroid hormone, is also changing in chordates: there are 3 deiodinase genes in most vertebrates, but at least 5 in the

cephalochordate amphioxus and only one in sea squirt (Paris et al., 2008). We could multiply the examples: the proteins controlling hormone production and availability in tissues are much more variable than those of the receptors. In addition detailed analysis of their sequence evolution often reveal strong evolutionary pressures in action.

Given these observations, the notion that the ligands are evolving should not come as a surprise. Of course this has been widely accepted since a long time for protein hormones but for obscure reasons this has remained virtually unexplored for small molecules. Strikingly, this was known since a long time for specific cases but never generalised. Indeed rodents and primate do not have the same major corticosteroid: cortisol is the major corticoid in human as well as most other mammals whereas corticosterone is the active compound in rodents. Similarly, in teleost fish the active androgen is 11keto-testosterone a derivative of testosterone. These cases clearly show that hormones are evolving in different species but still; the generalisation of this observation is barely recognised by comparative endocrinologists. Because triiodothyronine is the *bona fide* ligand of thyroid hormone receptors in mammals it should be the same in all animals: but this is not the case! In invertebrates, all suggests that the active ligand is not triiodothyronine but TRIAC, a deaminated derivative that is known since a long time but have not been seriously investigated, and the physiological importance of 3,5-T₂ in teleost fishes is also gaining increasing recognition (Orozco et al., 2017). The same is true for retinoids or, as discussed above, for estrogens. This is most probably the case in much other systems: it is not because a hormone is present in human that it must be also active in other animals. If there is an area where it is necessary to avoid any anthropomorphism it is indeed the one of hormonal ligands and their receptors!

3. The origins of hormones

If there is one mysterious question, it is the question of the origin of hormonal systems. That the very early metazoans need a system to allow efficient transfer of information from organs to organs in order to synchronise central and peripheral response is accepted since a long time. But how such a system emerges? This vexing question has not yet received sufficient attention. One reason is that because of anthropomorphism, many people have tried to trace back the origin of human compounds rather to consider animal evolution in an unbiased manner. There is a strong need to biochemically characterise the hormones present in diverging metazoans. The effort that has been done in some systems (e.g. the nematode *Caenorhabditis elegans*) has revealed a wide variety of compounds, some related to steroids, but none of them being simplified version of human hormones, as many would have anticipated. Complexity and diversity are everywhere even in the apparently simplest animals. The analysis of complete genomes has shown that even the most basal metazoans may have surprising sophistication in signalling systems. Clearly, "basal" does not mean "primitive" and even a placozoan or a hydra have the same amount of years of evolution than us and therefore can be quite elaborated. For sure the unbiased characterisation of active compounds (steroids, leukotrienes, prostaglandines etc..) present in early metazoans will undoubtedly shed light on this important question.

However even in the present paucity of information one can make some interesting observations. Among the many types of hormones, some, as the steroids but also the numerous derivatives of fatty acids are particularly interesting because their chemical structures are conserved outside metazoans (Kushiro et al., 2003). The fact that in such divergent systems similar active molecules are used may be revealing of a deep analogy between the hormonal systems. One reason could be that the biochemical pathways allowing the metabolism of these molecules predates the divergence between, say, animals, fungi and plants (Baker, 1995). This would therefore suggest that evolution has simply used again and again similar enzymatic systems and pathways to diversify an existing class of active molecules. This may explain for example the existence of vertebrate steroids, ecdysteroids of insects and brassinosteroids in plants. Another poorly explored, but quite exciting idea, could be

that some structural or chemical property render these molecules particularly apt to fulfil a hormonal function (Kushiro et al., 2003). Being their hydrophobicity, size, ability to cross membranes, to be buried in protein cores or to be transported in biological fluids, steroids and fatty acid derivatives are apparently more suitable than others to serve as efficient molecules to transport, at long range, a specific information. This must be further explored.

Lastly, there is now accumulating evidence that hormones may derive from food related compounds. This is obvious for leukotrienes and prostaglandins that are fatty-acid derivatives but this probably also true for steroids or thyroid hormones. The cladistic analysis of steroid hormones discussed above reveals that sex steroids are in fact, biochemically speaking, degradation products of cholesterol, a molecule directly linked to diet. In addition, the phylogenetic analysis of the 4 main families of steroidogenic enzymes has revealed that many of these enzymes are coming from detoxifying enzymes that hydroxylate toxic compounds targeting them towards degradation pathways. Thyroid hormones are clearly derived from iodinated molecules that were produced in the pharynx of filter-feeding organisms. Indeed many marine organisms filter planktonic particles by gluing them in mucus and it is known that in basal chordates such as amphioxus and sea squirt mucus contains iodinated proteins that help in this process (Holzer et al. 2017). From this an endocrine secretion of iodinated thyroid hormones evolved and it came therefore as no surprise that thyroid hormones promote energy expenditure as their basal exocrine function was probably linked to the signalling of the presence of food. Clearly all these indications reveal a deep, ancient, relationship between nutrition and hormonal signalling. As many hormones are regulating reproduction, one can posit that hormone signalling derived from signalling pathways that were primitively involved in the regulation of the reproductive maturation according to nutritional conditions (Della Torre et al., 2014). This has some important implications on the way we have to look at endocrinology. Classically, as we pointed out in the introduction, hormonal signalling is viewed as a bottom-up cascade from the nervous centres to the target cells, and hormones such as steroids, occupy an intermediary position in the middle of this cascade (see Fig 1A). But our quick journey through metazoan signalling physiology reminds that a significant part of the environmental input is integrated not through the nervous system, but through the digestive system. This is consistent with the recent proposal that the liver may be act as an integrative centre complementary to the brain (DellaTorre et al., 2011), and with the now well acknowledged importance of the gut microbiome on the nervous system (Vuong et al., 2017). Therefore we should perhaps now conceptualise a more "pluralistic view", in which not only the brain, but also the liver, the intestine and possibly the gonad too, are all partial and complementary integration centers (Fig 1B). Probably due to the special status of the brain as a "noble organ", being considered as the supreme integrator of body signals, the nervous system has benefitted from many studies from evolutionary biologists, with many ramifications even out of the strict biological field. Let us hope that the interest in hormones origins will stimulate next generations of scientists to dedicate the same attention to the digestive apparatus and to its functional connections with hormonal signalling.

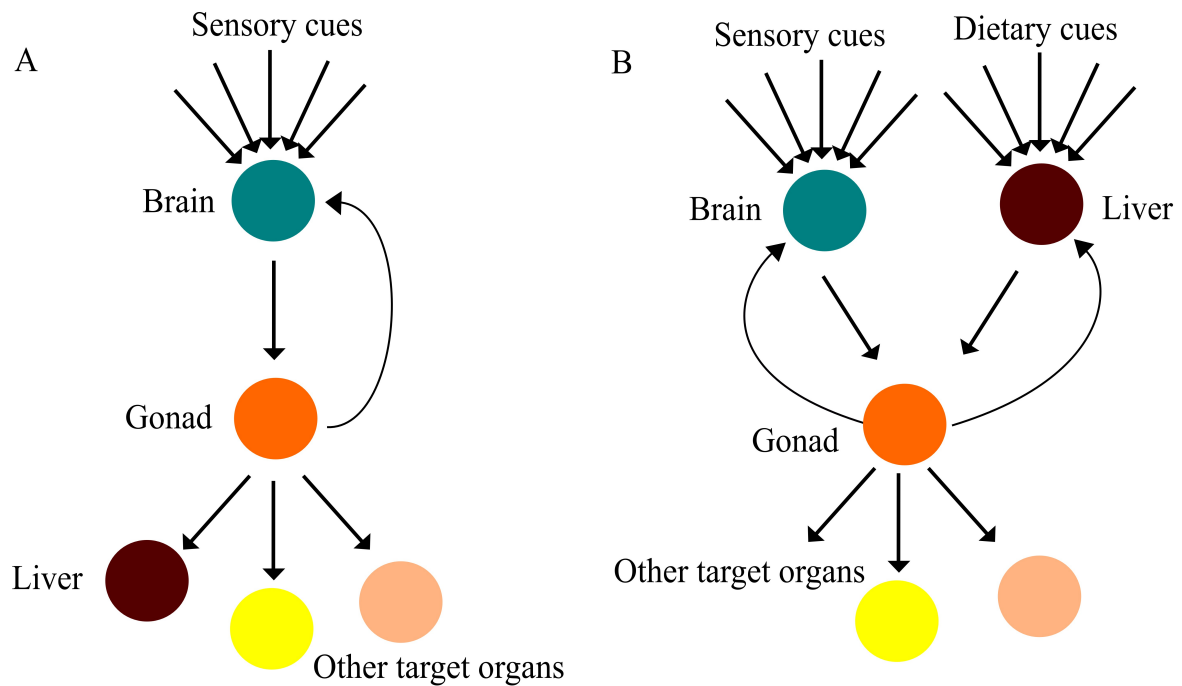


Fig. 1 For a reappraisal of the integrative role of the digestive system. (A) A classical textbook hierarchical regulatory model, where the signal goes upside-down—even if retroactions are acknowledged—from the nervous centers to the target organs, among which is the liver. (B) A “pluralistic view,” where not only the brain, but also the liver, and possibly the gonad too, are all partial and complementary integration centers.

Take-Home Message for Clinicians

An evolutionary perspective tells us that whatever their chemical nature, both partners in hormone-receptor couples are constantly evolving, as do the fine-tuned mechanisms controlling their availability in time and space. This explains why those systems are so plastic and so difficult to classify. The origin of the hormonal system is deeply rooted into the perception of external nutritional cues, which also explains why it is so sensitive to disruption by environmental chemicals.

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Relevant Websites

IUPHAR Nomenclature: <http://www.guidetopharmacology.org/>

NURSA: <https://www.nursa.org/nursa/index.jsf>