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1 REPRODUCTION REVIEW

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3 **Adiponectin and resistin: potential metabolic signals affecting hypothalamo-pituitary**  
4 **gonadal axis in females and males of different species**

5

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19 **Short title:** Adiponectin and resistin in reproduction

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21

## 22 Abstract

23 Adipokines, including adiponectin and resistin, are cytokines produced mainly by adipose  
24 tissue. They play a significant role in the metabolic functions that regulate insulin sensitivity  
25 and inflammation. Alteration of adiponectin and resistin plasma levels, or their expression in  
26 metabolic and gonadal tissue, are observed in some metabolic pathologies, such as obesity.  
27 Several studies have shown that these two hormones and the receptors for adiponectin,  
28 AdipoR1 and AdipoR2, are present in various reproductive tissues in both sexes of different  
29 species. Thus, these adipokines could be metabolic signals that partially explain infertility  
30 related to obesity, such as polycystic ovary syndrome (PCOS). Species and gender differences  
31 in plasma levels, tissue or cell distribution and hormonal regulation have been reported for  
32 resistin and adiponectin. Furthermore, until now, it has been unclear whether adiponectin and  
33 resistin act directly or indirectly on the hypothalamo-pituitary-gonadal axis. The objective of  
34 this review was to summarize the latest findings and particularly the species and gender  
35 differences known to date of adiponectin and resistin on female and male reproduction, based  
36 on the hypothalamo-pituitary-gonadal axis.

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40 **Key words:** adipose tissue, fertility, signalling pathways, reproductive tracts

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## 46 **Introduction**

47 Many authors have observed relationships between energy metabolism and fertility or  
48 infertility in various species, including sheep, cattle, pigs, rodents and primates. For example,  
49 in cattle selected for high milk production, high negative energy balance in the post-partum  
50 period is associated with reduced fertility (Wathes *et al.* 2007). In sheep, it is well known that  
51 an increase in availability of energy substrates is associated with an increase in prolificacy  
52 (Teleni *et al.* 1989). In pigs, it is also known that a negative energy balance and a decrease in  
53 body fat results in a reduction in litter size and viability of piglets (Quesnel *et al.* 2007).  
54 Clinical studies have also established some links between insulin resistance and polycystic  
55 ovarian syndrome (PCOS) (Gambineri *et al.* 2002). This syndrome is often associated with  
56 obesity, metabolic disorders, and an imbalance of reproductive hormones in women (Dunaif  
57 & Thomas 2001). White adipose tissue (WAT) is one of the main tissues involved in the  
58 regulation of energy balance. For a long time, this organ was considered as a simple tissue for  
59 the storage of triglycerides. However, it is now well established that white adipose tissue  
60 synthesizes and secretes numerous cytokines, termed adipokines that participate in several  
61 physiological and pathological processes, such as food intake and metabolic control, diabetes,  
62 atherosclerosis, immunity, and also reproductive functions (Reverchon *et al.* 2014). In the  
63 present review, we describe and analyse the role of two of these adipokines, adiponectin and  
64 resistin, in the female and male hypothalamo-pituitary-gonadal axis.

65

## 66 **Structure, expression and role in metabolic functions of adiponectin and resistin**

67 Adiponectin, also known as Acrp30, is mainly secreted by mature adipocytes. It is the  
68 most abundant adipokine in plasma (approximately 1–50 µg/ml) in various species including  
69 human, rat, birds (chicken and turkey), pig and dairy cows (Nishizawa *et al.* 2012, Chabrolle  
70 *et al.* 2007, Diot *et al.* 2015, Hendricks *et al.* 2009, Maleszka *et al.* 2014a, De Koster *et al.*

71 2016). Plasma adiponectin concentrations are inversely correlated with the adipose tissue  
72 reservoir (Kadowaki & Yamauchi 2005, Yamauchi *et al.* 2014). In addition, levels of  
73 adiponectin in plasma were significantly lower in males than in females in humans and  
74 rodents (Nishizawa *et al.* 2002). One explanation is that sexual hormones such oestradiol (E2)  
75 and testosterone (T) could regulate the plasma adiponectin concentration (Nishizawa *et al.*  
76 2002). The adiponectin gene encodes a protein (full-length adiponectin; full AdipoQ)  
77 composed of four domains: an N-terminal signal peptide, a variable region, a collagenous  
78 domain and a globular domain at the C-terminal end (Figure 1A). Mammalian adiponectin  
79 genes, which contain three exons and two introns, are highly conserved between species (Hu  
80 *et al.* 1996). For example, the homology between pig and mouse, rat, and dog was 83, 82 and  
81 90%, respectively (Wang *et al.* 2004). The shorter globular adiponectin (g AdipoQ) possesses  
82 potent biological activities that have similar properties to full AdipoQ. The circulating  
83 adiponectin is found in trimer, hexamer and high molecular weight (HMW) forms, the latter is  
84 considered the metabolically bioactive form. Two distinct main receptors (AdipoRs) have  
85 been described in the literature, namely AdipoR1 (almost ubiquitously expressed, and  
86 abundantly so in skeletal muscle; binds the globular form) and AdipoR2 (predominantly  
87 expressed in the liver and WAT; binds the full-length protein) (Kadowaki & Yamauchi 2005,  
88 Yamauchi *et al.* 2014). Unlike G-coupled protein receptors, AdipoRs are seven-  
89 transmembrane domain receptors with an extracellular carboxyl terminus and an intracellular  
90 amino terminus. The homology between AdipoR1 and AdipoR2 is 67% amino acid identity.  
91 Furthermore, they are structurally conserved from yeast to humans (Yamauchi *et al.* 2014).  
92 AdipoR signalling can be modulated by an interaction with two adaptor proteins named  
93 APPL1 (Adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1)  
94 and APPL2 (Adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper  
95 2) (Yamauchi *et al.* 2014). Once adiponectin binds to AdipoR1, APPL1 activates various

96 downstream signalling events associated with adiponectin function. When AdipoR1 is  
97 inactive, APPL2 binds and inhibits APPL1 function. However, APPL2 binding is displaced  
98 upon AdipoR1 activation. It is well known that adiponectin activates different main signalling  
99 pathways in various tissues: AMPK (AMP-activated protein kinase), MAPK (mitogen-  
100 activated protein kinase: p38, ERK1/2 (Extracellular signal-regulated kinases 1/2)), Akt  
101 (serine/threonine protein kinase), and PPAR  $\alpha$  (Peroxisome proliferator-activated receptor  
102 alpha) (Kadowaki & Yamauchi 2005, Yamauchi *et al.* 2014) (Figure 1B). Many functions  
103 have been described for adiponectin: this hormone can control energy homeostasis and insulin  
104 sensitivity, and it affects lipid metabolism, vasodilatation, atherogenic activity and  
105 reproductive functions (Kadowaki & Yamauchi 2005, Yamauchi *et al.* 2014, Brochu-  
106 Gaudreau *et al.* 2010).

107 Resistin is a cysteine-rich, secretory protein, which is also known as found in  
108 inflammatory zones (FIZZ) or adipocyte secreted factor (ADSF) (Steppan *et al.* 2001) (Figure  
109 1A). It is produced by white and brown adipose tissue, but has also been identified in several  
110 other peripheral tissues. In adipose tissue, the production of resistin is dependent on the  
111 species. Indeed, resistin is produced by the adipocytes in mice whereas it is predominantly  
112 expressed in macrophages in humans (Steppan *et al.* 2001). Human resistin is a 12.5 kDa  
113 cysteine-rich peptide with a mature sequence consisting of 108 amino acid, while rat and  
114 mouse resistin has 114 amino acids. There is 55 % amino acid identity within the mature  
115 segment of human and mouse resistin. The resistin gene is located on chromosome 19 in  
116 human whereas it is located on chromosome 8 and 2 in mouse and pig, respectively (Yang *et al.*  
117 *al.* 2003, Adeghate 2004). Furthermore, the human and mouse resistin genes have markedly  
118 divergent promoter regions, suggesting different mechanisms of regulation, tissue distribution  
119 and functions (Steppan *et al.* 2001). The comparison of amino acid sequence of bovine  
120 resistin with that of human, pig, rat, mouse showed 73%, 80%, 58% and 57% identity,

121 respectively (Kang *et al.* 2006). Plasma and follicular fluid resistin concentration in humans is  
122 from 5 to 50 ng/ml (Munir *et al.* 2005). In pig, the resistin level in follicular fluid is around  
123 0.32 ng/ $\mu$ g protein, dependent on the stage of the oestrous cycle (Rak-Mardyła *et al.* 2013).  
124 Resistin plasma levels are significantly higher in females when compared with males (Lee *et*  
125 *al.* 2003). It has not been described receptor of resistin and the molecular mechanism of  
126 resistin action is unclear. However, recent reports have suggested potential receptors for  
127 resistin like an isoform of decorin (DCN) (Daquinag *et al.* 2011), mouse receptor tyrosine  
128 kinase-like orphan receptor 1 (ROR1) (Sanchez-Solana *et al.* 2012), toll-like receptor 4  
129 (TLR4) (Benomar *et al.* 2013) or adenylyl cyclase-associated protein 1 (CAP1) (Lee *et al.*  
130 2014). Furthermore, it is well known that resistin activates signalling pathways in different  
131 tissues (Figure 1B) like Akt, MAPK (ERK1/2 and p38), Stat-3 (signal transducer and  
132 activator of transcription 3) and PPAR type gamma (PPAR $\gamma$ ). Several studies have identified  
133 positive correlations between resistin levels and the pathogenesis of obesity, adipogenesis and  
134 insulin resistance (Steppan *et al.* 2001).

135

### 136 **Adiponectin and resistin expression and action at hypothalamus-pituitary levels**

137 Despite the conflicting evidence as to whether adiponectin can cross the blood-brain  
138 barrier, some studies have reported adiponectin and AdipoR expression in the brain and  
139 pituitary of various species, including humans, rats, pigs, rodents, and chickens (Rodriguez-  
140 Pacheco *et al.* 2007, Wilkinson *et al.* 2007), suggesting that adiponectin may be a factor  
141 modulating the reproductive functions. AdipoRs have been identified in the hypothalamic  
142 GnRH neuron cells (GT1-7) and in human and rodent hypothalami, including in the  
143 paraventricular nucleus and in the periventricular areas. Adiponectin inhibits kisspeptin  
144 (KISS-1) gene transcription (Wen *et al.* 2012) and gonadatropin-releasing hormone (GnRH)  
145 secretion (Wen *et al.* 2008) (Figure 2) in GT1-7 cells.

146 In pigs, pituitary adiponectin levels depend on the phase of the oestrous cycle, and *in*  
147 *vitro* experiments in primary pituitary cells showed that treatment with adiponectin increases  
148 follicle-stimulating hormone (FSH) release (Kiezun *et al.* 2014). Conversely, exposure of  
149 rodent pituitary cell cultures to adiponectin resulted in a reduction in luteinizing hormone  
150 (LH) secretion and GnRH-induced LH release (Rodriguez-Pacheco *et al.* 2007, Lu *et al.* 2008).  
151 Moreover, in primary rat pituitary cells, GnRH treatment suppressed pituitary adiponectin  
152 expression (Kim *et al.* 2013). AdipoRs have been identified in gonadotropins producing cells  
153 in the pars distalis but not in the pars tuberalis in the human pituitary (Wilkinson *et al.* 2007).  
154 To our knowledge a sexual dimorphism has been described in the levels of circulating plasma  
155 adiponectin, with males having lower adiponectin levels than females (Arita *et al.* 1999).  
156 However, adiponectin levels in human cerebrospinal fluid (CSF) showed no gender difference  
157 (Kos *et al.* 2007).

158 Expression of resistin has been reported in the hypothalamus of rodents (Morash *et al.*  
159 2002). Resistin was identified in human CSF with levels 100-fold lower than in serum (Kos *et*  
160 *al.* 2007). However, its role in GnRH neurons remains to be determined. In the pituitary,  
161 gender differences of resistin are evident (male > female at postnatal day 28 and 42) and this  
162 was not modified by neonatal treatment of female pups with T (Morash *et al.* 2004).  
163 Moreover, expression of resistin mRNA in the pituitary is significantly higher in pre-pubertal  
164 mice (Morash *et al.* 2002, Morash *et al.* 2004), while in the rat increases until the age of 28  
165 days, suggesting that pituitary resistin expression is age-dependent. Moreover, corticosteroids  
166 significantly increased pituitary mRNA resistin levels. It was demonstrated that the AdipoRs  
167 expression are decreased, while GH secretion is increased after resistin treatment in *in vitro*  
168 rat pituitary cells in culture (Nogueiras *et al.* 2004), but there is a lack of data describing the  
169 effect of resistin on gonadotropin secretion. However, Singh *et al.* (2014) showed that serum  
170 resistin levels correlated negatively with changes in serum LH level in bats. In addition to the

171 effects of adiponectin and resistin on GnRH neurons in the hypothalamus and/or on the  
172 gonadotrophs of the anterior pituitary (Figure 2), they also affect, in a direct manner, both  
173 female and male gonads (Figures 3 and 4).

174

#### 175 **Adiponectin, AdipoRs and resistin expression in the ovary**

176 As described in Table 1, adiponectin is not only present in the follicular fluid, but also  
177 in ovarian cells of various species. In granulosa cells, adiponectin expression is low and  
178 almost undetectable in humans, rodents and chickens, suggesting species-specific differences  
179 in ovarian expression of the adiponectin gene (Chabrolle *et al.* 2007, Chabrolle *et al.* 2009,  
180 Richards *et al.* 2012). Adiponectin and its receptors are present in the corpus luteum (CL) of  
181 mammalian species (rat, cow, sows), including women. In bovine species, the physiological  
182 status of the ovary influences the expression pattern of adiponectin and its receptors in  
183 follicular and luteal cells (Tabandeh *et al.* 2010). In these species, a positive correlation is also  
184 observed between the adiponectin transcript in the ovarian cells of the dominant follicle and  
185 follicular fluid oestradiol (E2) levels, indicating an association between adiponectin and  
186 follicular dominance and oocyte competence (Tabandeh *et al.* 2012). In humans, ovarian  
187 adiponectin and AdipoRs expression are hormonally controlled *in vivo*, as suggested by an  
188 increase in adiponectin concentrations in the ovarian follicular fluid of women in response to  
189 LH treatment in the *in vitro* fertilization procedure (Gutman *et al.* 2009). Gonadotrophins  
190 modify the expression levels of AdipoR2, but not AdipoR1 and eventually contribute to  
191 enhanced 3  $\beta$ -hydroxysteroid dehydrogenase (3 $\beta$ HSD) activity and increased progesterone  
192 (P4) secretion in human granulosa cells (Wickham *et al.* 2013). Furthermore, following  
193 pregnant mare serum gonadotropin (PMSG) pre-treatment, an injection of human chorionic  
194 gonadotropin (hCG) increases the expression of adiponectin and AdipoR1 (but not AdipoR2)  
195 genes in rat ovaries (Chabrolle *et al.* 2007). Also, in bovine theca interna cells, LH increases

196 the concentrations of AdipoR2 mRNAs, whereas insulin-like growth factor type 1 (IGF1)  
197 suppresses the expression of AdipoR2 (Lagaly *et al.* 2008). Steroids could also affect  
198 adiponectin expression. Indeed, in swine, adiponectin serum concentrations are higher during  
199 the luteal phase than the follicular phase, which suggests that ovarian steroids influence  
200 plasma adiponectin levels (Maleszka *et al.* 2014 b). However, it remains to be demonstrated  
201 whether steroids can locally affect ovarian adiponectin production. Adiponectin can also  
202 influence the expression of its receptors differently according to the ovarian cell type. For  
203 example, AdipoRs expression are increased in the complex-oocyte-cumulus, but not in  
204 granulosa cells (Richards *et al.* 2012).

205 Like adiponectin, resistin is expressed in the ovarian cells of various species (Table 1).  
206 Niles *et al.* (2012) demonstrated resistin expression in human granulosa cells derived from the  
207 preovulatory follicles of females undergoing oocyte retrieval during *in vitro* fertilization,  
208 suggesting its role in follicular development (Niles *et al.* 2012). Resistin is also present in  
209 human granulosa cells, cumulus cells and human ovarian granulosa tumor-derived cell line  
210 (KGN), as well as in theca cells in large follicles and oocytes in the primary follicles  
211 (Reverchon *et al.* 2013). In bovine species, resistin is widely expressed in different sized  
212 follicles (small < 6 mm and large > 6 mm) where it is localized in oocytes, cumulus, theca,  
213 and granulosa cells. In addition, it is present in the CL (Maillard *et al.* 2011). Interestingly,  
214 resistin mRNA was undetectable in rat granulosa cell cultures (Maillard *et al.* 2011). ‘Species’  
215 specific ovarian resistin expression could contribute to different effects on ovarian follicle  
216 functions, such as steroidogenesis and proliferation, as described for adiponectin. In pig  
217 ovaries, resistin levels and expression depend on the stage of the animal reproductive status;  
218 differences were observed in the expression and concentration of resistin in follicular fluid  
219 collected from small (SFs), medium (MFs), and large (LFs) follicles (Rak-Mardyła *et al.*  
220 2013). Interestingly, in contrast to prepubertal animals, resistin expression and concentration

221 in adult oestrous cycling pigs was independent of follicular size and/or development (Rak-  
222 Mardyła *et al.* 2014). Moreover, several hormones can influence ovarian resistin expression.  
223 For example, Rak *et al.* (2015) reported that gonadotropin and steroid hormone increased, but  
224 IGF1 dose-dependently significantly decreased ovarian resistin mRNA and protein expression  
225 in pig (Rak *et al.* 2015a). In addition, resistin ovarian expression was decreased by  
226 rosiglitazone – a PPAR $\gamma$  agonist (Rak-Mardyła & Drwal 2016).

227

### 228 **Adiponectin and resistin *in vitro* effects on ovarian steroidogenesis and cell survival**

229 The ovarian follicles synthesize steroid hormones, which control and maintain female  
230 sexual development, behaviour and pregnancy, as well as having important local effects  
231 within the ovary. The role of adiponectin has been studied *in vitro* in the steroidogenesis of  
232 granulosa and theca cells in several species (Figure 3). In rats and in women, recombinant  
233 adiponectin at physiological doses (5 or 10  $\mu\text{g/ml}$ ) increases the secretion of steroids in IGF1-  
234 stimulated cells (Chabrolle *et al.* 2007, Chabrolle *et al.* 2009). In rats, this increase is due to  
235 increased signalling of the IGF1 receptor and, in women, it is due to an increase in the  
236 expression of the CYP19A1 (cytochrome P450 aromatase) enzyme responsible for estrogen  
237 biosynthesis. In bats, an adiponectin at physiological doses (5 and 10  $\mu\text{g/ml}$ ) treatment *in vivo*  
238 during the period of delayed development causes a significant increase in circulating P4 and  
239 E2 levels, together with an increased expression of AdipoR1 in the ovary. In this species, the  
240 effects of adiponectin on ovarian steroidogenesis are mediated through increased expression  
241 of luteinizing hormone-receptor, steroidogenic acute regulatory protein and 3 $\beta$ -HSD  
242 (Anuradha & Krishna 2014). In KGN cell lines, specific inactivation of AdipoRs shows that  
243 AdipoR1 regulated cell survival, while AdipoR2 is preferentially involved in steroidogenesis  
244 (Pierre *et al.* 2009). In cows, adiponectin at dose 3  $\mu\text{g/ml}$  *in vitro* decreases the production of  
245 androstenedione (A4) by theca cells by reducing the expression of LH receptors and

246 CYP11A1 (cytochrome P450, family 11, subfamily a, polypeptide 1) and CYP17 $\alpha$ 1  
247 (cytochrome P450, family 17, subfamily a, polypeptide 1) enzymes mediated by both  
248 AdipoR1 and AdipoR2 (Lagaly *et al.* 2008). These data were confirmed by Comim *et al.*  
249 (2013), showing that knockdown of AdipoRs or the downstream effector protein APPL1 leads  
250 to an increase in secretion of androstenedione (Comim *et al.* 2013). Thus, adiponectin  
251 differentially regulates the expression of steroidogenic enzymes in ovarian cells in various  
252 species.

253         The first study showed that resistin at 10 ng/ml treatment increased androgen production  
254 by stimulation of CYP17 mRNA expression in human theca cells *in vitro* (Munir *et al.* 2005)  
255 (Figure 3). Spicer *et al.* (2011) demonstrated that resistin at 30 ng/ml weakly stimulated FSH  
256 plus IGF1-induced E2 production, but had no effect on IGF1- or insulin-induced P4 and A4  
257 production by theca cells or P4 production by granulosa cells of large follicles (Spicer *et al.*  
258 2011). However, in granulosa cells from small follicles, resistin attenuated the stimulatory  
259 effect of IGF1 on P4 and E2 secretion. *In vitro* treatment with resistin on bovine granulosa  
260 cells showed a decreased basal, but not IGF1-induced P4 and E2 production. While in  
261 cultured rat granulosa cells, basal and IGF1-induced P4 secretion increased following  
262 treatment with a physiological dose (10 ng/ml) of resistin, with no effects on E2 release  
263 (Maillard *et al.* 2011). Similarly, studies on human granulosa cells treated with resistin have  
264 also shown reduced steroid hormone secretion in response to IGF1 (Reverchon *et al.* 2013).  
265 However, in human theca cells in normal cycling premenopausal women (Munir *et al.* 2005),  
266 pig ovary (Rak-Mardyła *et al.* 2013, Rak-Mardyła *et al.* 2014) and bats (Singh *et al.* 2015), a  
267 stimulatory effect of resistin at physiological doses on androgen production was observed.  
268 Conversely, in porcine ovarian follicles, resistin decreased gonadotropin- and IGF1-induced  
269 steroid hormone secretion by inhibition of 3 $\beta$ HSD, 17 $\beta$ HSD and CYP19A1 protein  
270 expression (Rak *et al.* 2015a). These contradictory findings may be explained by the presence

271 of various isoforms of resistin, which may explain the functional diversity of resistin in  
272 different species. Thus, the resistin receptor has still unknown, and resistin action in ovarian  
273 steroidogenesis mechanism remains unclear. However, Rak-Mardyła and Drwal (2016)  
274 demonstrated that in cultured porcine ovarian follicles PPAR $\gamma$  is a key regulator of resistin  
275 expression and steroidogenic function (Rak-Mardyła & Drwal 2016). Maillard *et al.* (2011)  
276 clearly documented that in cultured bovine and rat granulosa cells resistin at 10 ng/ml  
277 stimulated phosphorylation of different kinases such as Akt, MAPKs P38 and ERK1/2.  
278 Furthermore, Reverchon *et al.* (2013) demonstrated that resistin decreased the IGF1-induced  
279 tyrosine phosphorylation of the IGF1R $\beta$  subunit and phosphorylation of MAPK ERK1/2 and  
280 suggested that the MAPK ERK1/2 signalling pathway regulated *in vitro* steroidogenesis in  
281 primary human granulosa cells (Reverchon *et al.* 2013). Recently, Singh *et al.* (2014) showed  
282 that resistin injection in bats (6.5  $\mu$ g/100 g body weight/day for 12 days) increased Stat-3  
283 phosphorylation in the ovaries. Similarly, in cultured porcine ovarian cells, resistin (10 ng/ml)  
284 also activated the phosphorylation of Stat-3 but also MAPK ERK1/2 and Akt (Rak *et al.*  
285 2015b).

286 Apoptosis is critically important for the survival of multicellular organisms by getting  
287 rid of damaged or infected cells that may interfere with normal ovarian function such as  
288 oogenesis, folliculogenesis, oocyte loss/selection and atresia. Several pro-survival and pro-  
289 apoptotic molecules are involved in ovarian apoptosis with the delicate balance between them  
290 being the determinant for the final destiny of the follicular cells. In bovine species,  
291 adiponectin at 10  $\mu$ g/ml increases *in vitro* IGF1-induced granulosa cell proliferation but not  
292 basal or insulin-induced proliferation (Maillard *et al.* 2010). In the basal state, similar effects  
293 of adiponectin have been described on the proliferation of large-follicle theca cells. In primary  
294 human granulosa cells, adiponectin at 5  $\mu$ g/ml treatment does not affect IGF1-induced cell  
295 proliferation (Chabrolle *et al.* 2009). Published *in vitro* data concerning ovarian cell

296 proliferation showed some effects dependent on the resistin doses; no effect at the lower,  
297 physiological doses (1 and 10 ng/ml) in pig (Rak *et al.* 2015b) and rat (Maillard *et al.* 2011),  
298 while at higher doses (100; 333 and 667 ng/ml) stimulated effects were observed. Similarly,  
299 *in vivo*, resistin induced a stimulatory effect on the expression of proliferating cell nuclear  
300 antigen (PCNA) in the ovaries of seasonally monoestrous bats (Singh *et al.* 2014). However,  
301 *in vitro*, resistin reduced [<sup>3</sup>H]thymidine incorporation in response to IGF-I in rat granulosa  
302 cells (Maillard *et al.* 2011). The above observations indicate that resistin, depending on doses  
303 and animal models, has different actions on ovarian cell proliferation, which is an important  
304 process in ovarian function.

305 In the *in vivo* ovaries of bats, resistin decreased protein levels but stimulated caspase-3  
306 activity. Similarly, in pig ovary resistin by direct effects on protein involved in both death  
307 receptor- and mitochondria-mediated apoptosis, was described as an anti-apoptotic factor in  
308 the ovary (Rak *et al.* 2015b). As a molecular mechanism of resistin action on cell survival,  
309 authors have proposed activation of several signal transduction pathways such  
310 MAPK/ERK1/2, JAK/STAT and PI3K (Rak *et al.* 2015b). These results show that resistin is  
311 involved in ovarian apoptosis regulation and could regulate follicular development or atresia.

312

### 313 **Adiponectin and resistin effect on oocytes**

314 As described above, adiponectin and AdipoRs are present in the oocytes of different  
315 species (Table 1). In *in vitro* fertilization protocols in women, mice and pigs, but not in cows,  
316 adiponectin at physiological doses improves oocyte maturation and early embryo  
317 development (Chappaz *et al.* 2008, Maillard *et al.* 2010, Richards *et al.* 2012) (Figure 3). In  
318 adiponectin-deficient mice, the number of ovulated oocytes is drastically decreased as  
319 compared to controls with similar body weight (Table 2). However, no experiments to date  
320 have inhibited adiponectin and AdipoRs expression in different ovarian cells to determine the

321 involvement of systemic and ovarian adiponectin. In addition, there are no data about the role  
322 of resistin in oocyte maturation. These should form the basis of future studies.

323

#### 324 **Adiponectin, AdipoRs and resistin expression in testis**

325 In humans, adiponectin concentration in seminal plasma is around 66-fold lower than in  
326 serum, and a positive correlation with sperm concentration, sperm count, and total  
327 normomorphoic spermatozoa has been reported (Thomas *et al.* 2013). In cattle, Heinz *et al.*  
328 (2015) concluded that adiponectin concentration in seminal plasma is likely blood borne and  
329 originates from adipose tissue. Therefore, the potential contribution of local secretion from  
330 the testes, if any, is only marginal. In rats, adiponectin is mainly present in Leydig interstitial  
331 cells, while AdipoR1 is expressed in the seminiferous tubules (Caminos *et al.* 2008).

332 Nogueiras *et al.* (2004) showed that in rat testis mRNA expression of resistin was higher  
333 in interstitial Leydig cells than in Sertoli cells within seminiferous tubules and this expression  
334 was regulated by gonadotropins, leptin, and nutritional status. Resistin is also expressed in  
335 mouse Leydig cell lines (MA-10 and TM3) and exposure to 8-Br-cAMP (8-Bromoadenosine  
336 3',5'-cyclic monophosphate) increased its mRNA expression in MA-10 Leydig cells (Jean *et*  
337 *al.* 2012). In humans, Moretti *et al.* (2014) showed that the resistin level was higher in semen  
338 than in serum, and that semen resistin correlated with sperm quality.

339

#### 340 **Adiponectin and resistin *in vitro* effects on testis function**

341 Adiponectin treatment decreases the production of T in the presence or absence of hCG  
342 in rat testicular tissue, while it has no effect on the expression of the genes encoding AMH  
343 (anti-mullerian hormone) and SCF (stem cell factor), that are specific to the Sertoli cells  
344 (Caminos *et al.* 2008) (Figure 4). However, in MA-10 mouse Leydig cells, adiponectin  
345 treatment improves P4 production through an increase in the cholesterol carrier StAR and the

346 CYP11A1 steroidogenesis enzyme, suggesting that high doses of adiponectin (50, 500, or  
347 5,000 ng/ml) could promote T production from Leydig cells (Landry *et al.* 2015). In mice,  
348 AdipoR2 deficiency results in atrophy of seminiferous tubules and aspermia without a change  
349 in T concentration (Bjursell *et al.* 2007) (Table 2). In chickens, studies show an increase in  
350 testicular adiponectin receptors during sexual maturation, and suggest a role for adiponectin in  
351 steroidogenesis, spermatogenesis, Sertoli cell function, and sperm motility (Ocon-Grove *et al.*  
352 2008). In rams, adiponectin and AdipoR1 mRNA expressions are positively correlated with  
353 sperm motility (Kadivar *et al.* 2016). In bulls, adiponectin and its receptors also play vital  
354 roles in structural and functional sperm traits by regulating sperm capacitation  
355 (Kasimanickam *et al.* 2013).

356 To our knowledge there are limited data on resistin action on testicular cells function.  
357 Resistin significantly increased basal and hCG – stimulated T secretion in rat incubated  
358 testicular tissue (Nogueiras *et al.* 2004). Exposure to low concentrations of resistin (10  
359 ng/ml), corresponding to a normal physiological condition, contributes to increased  
360 proliferation of MA-10 Leydig cells (Jean *et al.* 2012). In addition, Sertoli cells may also  
361 contribute to Leydig cells proliferation by secreting resistin (Nogueiras *et al.* 2004). Thus,  
362 adiponectin and resistin signalling appear to be present in male gonadal tissues, but the extent  
363 to which these hormones contribute to normal human testicular function and fertility potential  
364 remains to be determined. In addition to their role in steroidogenesis, adiponectin and resistin  
365 could be involved in sperm capacitation, sperm-egg fusion and fertilization.

366

### 367 **The role of adiponectin and resistin *in vivo* in mice fertility**

368 Though many studies have reported *in vitro* effects of adiponectin and resistin on  
369 ovarian and testicular cell functions, the involvement of these two adipokines *in vivo* in the  
370 control of fertility remains unclear. Several studies showed that adiponectin-null mice are

371 viable and, in studies where fertility outcomes are mentioned, appear to exhibit normal  
372 fertility (Ma *et al.* 2002, Nawrocki *et al.* 2006) (Table 2). However, over-expression of  
373 adiponectin leads to increased insulin sensitivity and infertility or subfertility (Combs *et al.*  
374 2004), and a recent study demonstrated that disruption of adiponectin can cause subfertility in  
375 female mice (Cheng *et al.* 2016). Indeed, female adiponectin-null mice displayed reduced  
376 retrieval of oocytes, a disrupted oestrous cycle, an elevated number of atretic follicles and  
377 impaired late folliculogenesis (Table 2). Their serum also has lower levels of P4 at dioestrus  
378 that can be explained by a lower expression of CYP11A1 and a significant reduction in E2  
379 and FSH at pro-oestrus. Adiponectin deficiency also altered the hypothalamo-pituitary axis,  
380 since the plasma peak concentrations of LH surged and the number of GnRH immunoreactive  
381 neurons were significantly reduced. Concerning AdipoRs, their genetic deletion was not  
382 associated with subfertility in one study (Yamauchi *et al.* 2007), but a loss of AdipoR2 was  
383 associated with male subfertility in other studies (Bjursell *et al.* 2007, Lindgren *et al.* 2013).  
384 Disruption of AdipoR2 in males leads to an seminiferous tubules atrophy and aspermia  
385 associated with reduced testes weight. Various studies where resistin protein levels were  
386 increased in different peripheral tissues (such as adipose tissue or liver) did not report any  
387 effect on fertility (Pravenec *et al.* 2003, Banerjee *et al.* 2004).

388 Thus, these data indicate that adiponectin signalling is important to normal mouse  
389 female and male reproduction. However, the role of this adipokine specifically in each  
390 gonadal cell remains to be determined. Concerning resistin, however, much less is known  
391 about its involvement in *in vivo* reproductive function and, therefore, this remains to be  
392 investigated.

393

394 **Potential involvement of adiponectin and resistin in some pathologies associated with**  
395 **gonadal dysfunctions such as PCOS**

396 PCOS is a metabolic disorder in humans that is linked to insulin resistance and obesity.  
397 It is characterized by anovulation, hyperandrogenism and hyperinsulinaemia (Dunaif &  
398 Thomas 2001). Excessive production of insulin in PCOS women, with its subsequent  
399 induction of theca cell steroidogenesis, is thought to be the primary cause of  
400 hyperandrogenism.

401 Adipokines such as adiponectin and resistin could act as a link between obesity and  
402 PCOS (Spritzer *et al.* 2015). Many studies have investigated the concentration of adiponectin  
403 and resistin in both plasma and follicular fluid in PCOS and control patients. However, data  
404 are still controversial (Spritzer *et al.* 2015). Several studies have documented a lack of any  
405 difference in resistin concentration in serum or follicular fluid of PCOS patients, compared to  
406 control groups, even though serum adiponectin was significantly lower in obese than in  
407 normal-weight women. However, Munir *et al.* (2005) suggested that resistin is involved in  
408 PCOS because the concentration of resistin was significantly increased in PCOS patients and  
409 was positively correlated with body mass index and T levels. Concerning adiponectin, some  
410 authors have also analysed the different forms of adiponectin in PCOS patients and they  
411 observed that there were low levels of HMW adiponectin in both serum and follicular fluid of  
412 PCOS patients with controlled ovarian hyperstimulation compared to controls (Artimani *et al.*  
413 2016). Furthermore, the expression pattern of the adiponectin system (adiponectin, AdipoRs  
414 and APPL1) has been studied in PCOS patients, and a reduction of APPL1 and the  
415 adiponectin system was observed in human granulosa cells (Dehghan *et al.* 2016).  
416 Furthermore, recently Yuan *et al.* (2016) showed that brown adipose tissue (BAT)  
417 transplantation activated endogenous BAT and increased the circulating level of adiponectin  
418 in a dehydroepiandrosterone (DHEA)-induced PCOS rat. Comim *et al.* (2013) also showed  
419 that a lower proportion of theca cells expressed AdipoRs in polycystic ovaries than in normal  
420 ovaries (Comim *et al.* 2013). Many studies have also described the association of PCOS with

421 polymorphisms of the adiponectin or adiponectin receptor genes. The resistin gene  
422 polymorphism is associated with body mass index in women with PCOS, suggesting that  
423 resistin might be related to adiposity in PCOS.

#### 424 **Conclusions**

425 In conclusion, resistin, adiponectin, and AdipoRs are present and active in the  
426 hypothalamo-pituitary-gonadal axis. Their expression can be regulated by various factors  
427 (such as gender, age, nutritional and hormonal status). Many *in vitro* studies showed that these  
428 two adipokines can regulate gonadal steroidogenesis and gametogenesis. Adiponectin can also  
429 exert effects on GnRH synthesis and the pituitary secretory functions that could then  
430 indirectly affect gonadal functions. The *in vitro* effects of resistin on GnRH and gonadotropin  
431 secretion are still unknown. In mice, adiponectin deficiency leads to female subfertility  
432 associated with ovarian and hypothalamo-pituitary dysfunction and AdipoR2 deficiency leads  
433 to male subfertility with aspermia and atrophy of tubules, suggesting an important role of the  
434 adiponectin system in normal reproduction. If these data are confirmed in human and other  
435 species, adiponectin or its analogues (recombinant adiponectin, adiponectin receptor agonist)  
436 could be used in the treatment of certain infertilities, similar to how they are used in metabolic  
437 syndrome. Furthermore, it remains to be determine whether these *in vivo* adipokine effects act  
438 directly on the hypothalamo-pituitary-gonadal axis. For example, mice with targeted  
439 disruption of the adiponectin system or resistin in ovarian and testicular cells could be  
440 developed in order to analyse the metabolic and reproductive phenotypes. Finally, the role of  
441 other adipokines (visfatin, chemerin, omentin, etc.) in reproductive diseases related to insulin  
442 resistance and obesity should be investigated.

443

#### 444 **Conflict of interests**

445 None declared.

446

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451

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1 **Figure legends**

2

3 **Figure 1:** A. Structure of adiponectin and resistin. B. Signalling pathways of adiponectin  
4 receptors (AdipoR1 and AdipoR2) and resistin.

5 AdipoQ - adiponectin, AdipoR1 and AdipoR2 - adiponectin receptors), APPL1 and APPL2 -  
6 adaptor proteins, PPAR $\alpha$  - peroxisome proliferator-activated receptor alpha, PPAR $\gamma$  -  
7 peroxisome proliferator-activated receptor gamma, AMPK - AMP-activated protein kinase,  
8 MAPK - mitogen-activated protein kinase p38, ERK1/2 - extracellular signal-regulated  
9 kinases 1/2), Akt - phosphatidyl inositol 3' kinase/Akt, Stat3 - signal transducer and activator  
10 of transcription 3, TLR4 - toll-like receptor, ROR1 - tyrosine kinase-like orphan receptor,  
11 CAP1 - cyclase-associated protein 1, DCN – decorin.

12

13 **Figure 2:** Effects of adiponectin and resistin on GnRH and LH/FSH expression and/or  
14 secretion.

15 GnRH- gonadotropin-releasing hormone, FSH - follicle-stimulating hormone, LH -  
16 luteinizing hormone, AMPK - AMP-activated protein kinase, KISS-1 – kisspeptin, GT1 – 7 -  
17 hypothalamic GnRH neuron cells, POMC - pro-opiomelanocortin, NPY – neuropeptide Y,  
18 AgRP – agouti related peptide, CART - cocaine- and amphetamine-regulated transcript,  
19 AdipoR1/R2 – adiponectin receptors, GH – growth hormone.

20  : activation ——— : inhibition

21 (a) : Wen *et al.* 2008, (b) : Vazquez *et al.* 2008, (c) : Rodriguez-Pacheco *et al.* 2007; Lu *et al.*

22 2008, (d) : Kiezun *et al.* 2014, (e) : Nogueiras *et al.* 2014, (f) : Rodriguez-Pacheco *et al.* 2007

23

24 **Figure 3:** Effects of adiponectin and resistin on granulosa, theca and oocyte function  
25 (steroidogenesis, proliferation and apoptosis, oocyte maturation) in different species.

26 P4 – progesterone, T – testosterone, E2 – estradiol, SF – small follicles, LF – large follicles.

27 ↑ : increase ↓ : decrease

28 (a) : Richards *et al.* 2012, (b) : Maillard *et al.* 2010, (c) : Chabrolle *et al.* 2007, 2009, (d) :  
 29 Maleszka *et al.* 2014, (e) : Anuradha *et al.* 2014, (f) : Lagaly *et al.* 2008, (g) : Spicer *et al.*  
 30 2011, (h) : Reverchon *et al.* 2013, (i) : Rak *et al.* 2015, (j) : Maillard *et al.* 2011, (k) : Munir *et*  
 31 *al.* 2005, (l) : Rak-Mardyła *et al.* 2013, 2014 (m) : Singh *et al.* 2015

32

33 **Figure 4:** Effects of adiponectin and resistin on testicular cell functions (steroidogenesis,  
 34 proliferation, apoptosis, sperm motility) in different species.

35 P4 – progesterone, T – testosterone, AMH – anti-mullerian hormone, SCF - stem cell factor.

36 (a) : Caminos *et al.* 2008, (b) : Landry *et al.* 2015, (c) : Nogueiras *et al.* 2004, (d) : Kadivar *et*  
 37 *al.* 2016, (e) : Thomas *et al.* 2013

38

39 **Table 1:** Expression of resistin, adiponectin, AdipoR1 and AdipoR2 in ovarian and testicular  
 40 cells in different species (+: presence; ns: no study)

41

42 **Table 2:** Consequences of targeted or non-targeted disruption or overexpression of resistin,  
 43 Adiponectin, AdipoR1 and AdipoR2 on the fertility and reproductive axis in mice.

44

45

46

**Table 1: Expression of resistin, adiponectin, AdipoR1 and AdipoR2 in ovarian and testicular cells in different species (+: presence; and ns: no study)**

Adipokine or receptor	Species	Ovarian cells			Testicular cells			Reference
		Granulosa	Theca	Oocyte	Sertoli	Leydig	Germinal	
<b>Resistin</b>	Human	+	+	+	ns	ns	ns	Niles <i>et al.</i> 2012, Reverchon <i>et al.</i> 2013, Maillard <i>et al.</i> 2011, Rak-Mardyla <i>et al.</i> 2014, Singh <i>et al.</i> 2015, Nogueiras <i>et al.</i> 2004
	Cattle	+	+	+	ns	ns	ns	
	Rodents	+	+	+	+	+	ns	
	Pig	+	+	ns	ns	ns	ns	
	Birds	ns	ns	ns	ns	ns	ns	
	Fish	ns	ns	ns	ns	ns	ns	
	Bat	+	+	+	ns	ns	ns	
<b>Adiponectin</b>	Human	+	ns	ns	ns	ns	ns	Maillard <i>et al.</i> 2010, Maleszka <i>et al.</i> 2014, Chabrolle <i>et al.</i> 2007, 2009, Gregoraszczuk <i>et al.</i> 2016, Caminos <i>et al.</i> 2007, Ocón-Grove <i>et al.</i> 2008, Nishio <i>et al.</i> 2008,
	Cattle	+	+	+	ns	ns	ns	
	Rodents	+	+	+	+	+	+	
	Pig	+	+	ns	ns	ns	ns	
	Birds	+	+	ns	+	+	+	
	Fish	whole ovary: +			ns	ns	ns	
	Bat	ns	ns	ns	ns	ns	ns	
<b>AdipoR1</b>	Human	+	+	ns	ns	ns	ns	Comim <i>et al.</i> 2013, Maillard <i>et al.</i> 2010, Maleszka <i>et al.</i> 2014, Chabrolle <i>et al.</i> 2007, 2009, Gregoraszczuk <i>et al.</i> 2016, Ocón-Grove <i>et al.</i> 2008, Nishio <i>et al.</i> 2008
	Cattle	+	+	+	ns	ns	ns	
	Rodents	+	+	+	+	+	+	
	Pig	+	+	ns	ns	ns	ns	
	Birds	+	+	ns	+	+	+	
	Fish	whole ovary: +			ns	ns	ns	
	Bat	ns	ns	ns	ns	ns	ns	
<b>AdipoR2</b>	Human	+	+	ns	ns	ns	ns	Comim <i>et al.</i> 2013, Maillard <i>et al.</i> 2010, Maleszka <i>et al.</i> 2014, Chabrolle <i>et al.</i> 2007, 2009, Gregoraszczuk <i>et al.</i> 2016, Ocón-Grove <i>et al.</i> 2008, Nishio <i>et al.</i> 2008.
	Cattle	+	+	+	ns	ns	ns	
	Rodents	+	+	+	+	+	+	
	Pig	+	+	ns	ns	ns	ns	
	Birds	+	+	ns	+	+	+	
	Fish	whole ovary: +			ns	ns	ns	
	Bat	ns	ns	ns	ns	ns	ns	

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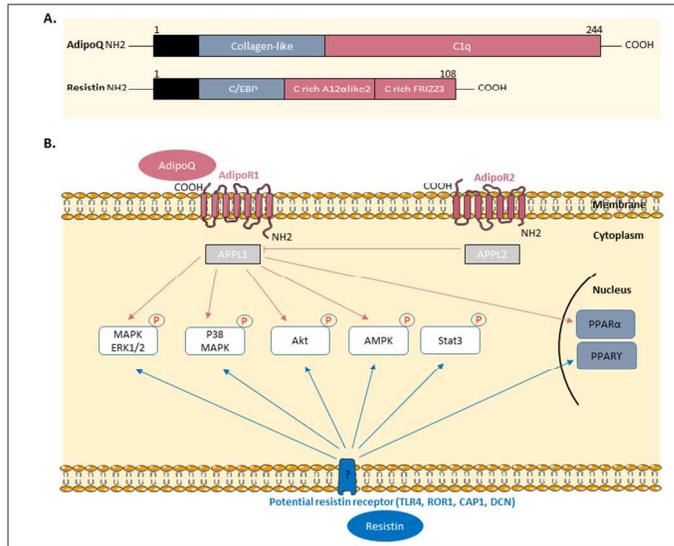
Rak, A., Mellouk, N., Froment, P., Dupont, J. (2017). Adiponectin and resistin: potential metabolic signals affecting hypothalamo-pituitary gonadal axis in females and males of different species. *Reproduction*, 153 (6), R215-R226. DOI : 10.1530/REP-17-0002

**Table 2: The consequences of targeted or non targeted disruption or overexpression of resistin, Adiponectin, AdipoR1 and AdipoR2 on the fertility and the reproductive axis in mice.**

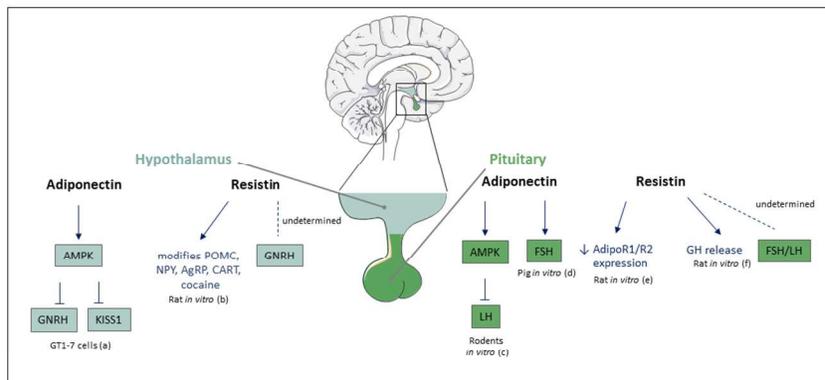
Components	Tissue/cell type	Effect on fertility	Reproductive axis consequences	References
<b>Resistin</b>	All	Fertile		Banerjee <i>et al.</i> 2004 ; Pravenec <i>et al.</i> 2003
<b>Adiponectin</b>	All	Female subfertility	Reduction in retrieval of oocytes, disruption of the estrous cycle, elevated number of atretic follicles, reduction in progesterone, oestradiol and FSH plasma levels,, in concentration of LH surge, and in GnRH immunoreactive neurons.	Cheng <i>et al.</i> 2016
<b>Adiponectin</b>	Overexpression dominant negative lacking collagen domain using promoter ap2 (adipose tissue)	Infertile	One of the line displayed 3-fold increased serum adiponectin levels, and was unfertile	Combs <i>et al.</i> 2004
<b>Adiponectin</b>	All	Fertile		Nawrocki AR <i>et al.</i> 2006, Ma <i>et al.</i> 2002
<b>AdipoR1</b>	All	Fertile (male and female)		Yamauchi T <i>et al.</i> 2007
<b>AdipoR1 and AdipoR2</b>	All	Fertile (male and female)		Yamauchi T <i>et al.</i> 2007
<b>AdipoR2</b>	All	Male subfertility	An atrophy of the seminiferous tubules and aspermia associated with reduced testes weight	Bjursell M <i>et al.</i> 2007 ; Lindgren <i>et al.</i> 2013
<b>AdipoR2</b>	All	Fertile (male and female)		Yamauchi T <i>et al.</i> 2007

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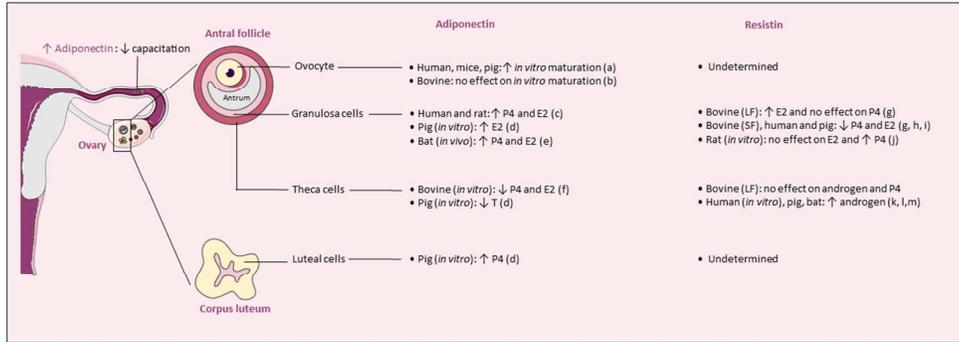
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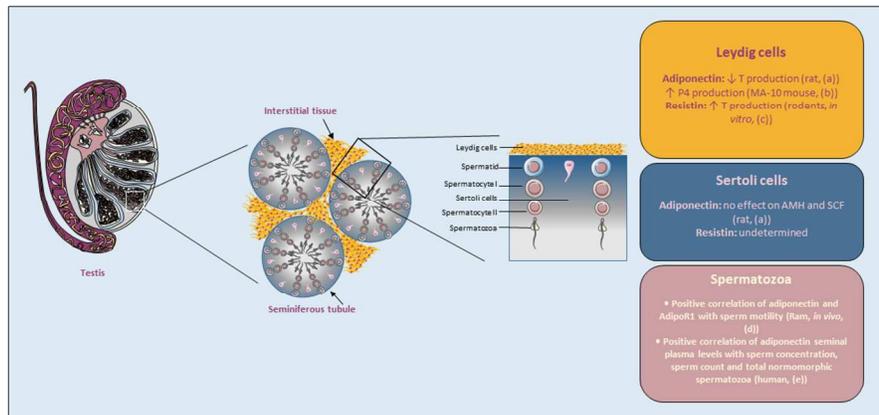
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