Chapter 2

The Regulation of the Male Hypothalamic-Pituitary-Gonadal Axis and Testosterone Production by Adipokines

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Abstract

There is evidence that the mass and metabolic status of the adipose tissue that produces adipokines significantly affect the activity of the hypothalamic-pituitary-gonadal (HPG) axis and the synthesis of testosterone. This is due to the fact that adipokines, such as leptin, adiponectin, visfatin and resistin have an important role in the regulation of the male HPG axis and steroidogenesis in the testes. The regulation of the HPG axis by adipokines can be carried out both through the changes the plasma levels of adipokines (a systemic regulation) and through the changes in the expression and activity of adipokines in the pituitary and testes, the components of the HPG axis (an autonomous regulation). This review presents the comprehensive analysis of the involvement of leptin, adiponectin, resistin and visfatin in the regulation of the male HPG axis and the testosterone production, as well as of the possible mechanisms of this regulation. The role of adipokines in the dysregulation of the male reproductive system and the impaired steroidogenic activity in the testes in obesity and type 2 diabetes mellitus are also discussed.

Keywords: adipokines, testosterone, leptin, hypothalamic-pituitary-gonadal axis, obesity

1. Introduction

There is much evidence that significant changes in the body and fat weight in men with metabolic disorders, such as severe obesity and type 2 diabetes mellitus (DM2), and with long-term fasting can lead to the alteration in the hypothalamic-pituitary-gonadal (HPG) axis, as

illustrated by the changed secretion of gonadotropin-releasing hormone (GnRH) and gonadotropins, the reduced testosterone (T) production by Leydig cells and the impaired spermatogenesis. The alterations in the HPG axis, as a result, lead to infertility [1–3]. The relationship between the fat content and androgens level has been demonstrated in animals with obesity and DM2, as well as in fasting conditions [4–6]. All this indicates that adipocyte-produced factors can play an important role in controlling the HPG axis and in regulating the steroidogenesis in Leydig cells. Among these factors, the most interesting are adipokines, such as leptin, adiponectin, resistin and visfatin [3, 7, 8]. It is well known that in metabolic disorders, the plasma levels of these adipokines and the functional activity of adipokines-regulated signaling systems in the target tissues undergo significant changes, which can be considered to be one of the key causes of abnormalities in the HPG axis and androgen deficiency [9–11].

There is evidence that adipokines affect the different components of the male HPG axis. Transferred to the brain through the blood-brain barrier (BBB), adipokines act on the activity of hypothalamic GnRH-expressing neurons, thus changing the GnRH-stimulated production of luteinizing hormone (LH), the main regulator of T synthesis, by pituitary gonadotrophs [12, 13]. The adipokines can directly affect the gonadotrophs producing LH, and in this regulation both the adipokines circulating in the bloodstream and the adipokines synthesized within the pituitary can be involved [14, 15]. Some adipokines can also directly affect the functions of Leydig cells, as indicated by a high level of adipokines expression in the testes, as well as detection of the main components of the adipokine signaling, including adipokine-specific receptors, in testicular cells, including Leydig cells [16–19]. The study of the effects of leptin, adiponectin and other adipokines on the male HPG axis and their role in the regulation of steroidogenesis is a major problem of clinical endocrinology and reproductive medicine. The solution of this problem will allow developing the new approaches for restoring the reproductive functions and androgen status in men with endocrine and metabolic disorders, which is based on the normalization of the adipokine signaling in the CNS and at the periphery.

This review presents the comprehensive analysis of the involvement of leptin, adiponectin, resistin and visfatin in the regulation of the male HPG axis and steroidogenesis, as well as of the possible mechanisms of this regulation. The role of adipokines in the dysregulation of the male reproductive system and the impaired steroidogenic activity in the testes in obesity and DM2 are also discussed.

2. Leptin

2.1. Leptin and its signaling system

Leptin, a 167-amino acid polypeptide hormone encoded by the *ob* gene, is produced preferably by the adipose tissue and is involved in the regulation of eating behavior, energy expenditure and endocrine functions [20–22]. Fasting reduces the plasma leptin level, while food intake, on the contrary, leads to its elevation. A prolonged increase in the plasma leptin level leads to leptin resistance, resulting in the impaired metabolism and eating behavior [23, 24]. Along with the adipose tissue, the *ob* gene expression is detected in other tissues, including the pituitary and testes [25].

The regulatory effects of leptin are realized due to its specific interaction with leptin receptors (Ob-R) that are generated by alternative splicing and include at least six isoforms [26]. The full-length isoform Ob-Rb is active and expressed in the hypothalamus with high intensity [27, 28]. The truncated isoforms, Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf are inactive, but retain the ability to bind to leptin at its excess. It is assumed that they carry out the receptor-mediated transport of leptin through the BBB and, possibly, through other tissue barriers [29, 30]. In the arcuate nuclei (ARC) of hypothalamus, leptin binds to Ob-Rb receptor, which leads to the phosphorylation of JAK2, a non-receptor tyrosine kinase, that phosphorylates the Tyr^{985}, Tyr^{1077} and Tyr^{1138} residues located within the intracellular domain of Ob-Rb, each responsible for the activation of certain signaling cascade [23]. It has been shown that the phospho-Tyr^{985} is responsible for activation of Src Homology 2 domain-containing protein tyrosine phosphatase 2 (SHP-2) and the mitogen-activated protein kinases (MAPK), such as extracellular signal-related kinases-1/2 (ERK1/2), c-Jun amino-terminal kinases (JNK) and p38-MAPK, which are involved in the regulation of cell growth and differentiation. The targets of MAPK are different transcription factors, including c-Fos, c-Jun and cAMP response element-binding protein (CREB), which control the expression of a large number of genes [3, 31]. The phospho-Tyr^{1138} is responsible for activation of the transcription factor STAT3 (signal transducer and activator of transcription-3) regulating the expression of genes involved in metabolic and growth processes. In turn, phospho-Tyr^{1077} induces the activation of the transcription factor STAT5, responsible for the regulation of energy metabolism and endocrine system [23, 32].

Another mechanism of leptin action is the activation of 3-phosphoinositide pathway, which involves phosphatidylinositol-3-kinase (PI3K) and Akt kinase controlling the activity of the multi-component kinase mTOR complex 1. Since Akt-mediated inhibition of this complex in the hypothalamic ARC leads to a decrease in the expression of the *Kiss1* gene encoding polypeptide kisspeptin, there is reason to believe that the mTOR complex 1 is involved in the regulation of hypothalamic kisspeptin signaling [33]. The leptin-induced activation of the kisspeptin/neurokinin B/dynorphin (KNDy)-neurons leads to the secretion of kisspeptin that triggers the GnRH secretion by the GnRH-expressing neurons, the main target of kisspeptin [34, 35]. The other targets of Akt kinase are the transcription factors Nur77 and CREB that are involved in the regulation of the reproduction. Along with the 3-phosphoinositide pathway, leptin activates AMP-activated protein kinase (AMPK), the most important energy sensor of the cells, and stimulates protein phosphotyrosine phosphatase 1B and the suppressor of cytokine signaling 3 (SOCS3), the negative regulators of the leptin signaling that are responsible for leptin resistance [23, 36].

2.2. The mechanisms of leptin action on the male reproductive system and testosterone synthesis

In the recent years, the evidence has been obtained that leptin plays a very important role in the control of male reproductive functions and puberty, which is based on leptin-mediated regulation of the HPG axis [8, 37]. The *ob*/*ob* double knockout male mice had severe obesity, metabolic and hormonal abnormalities, and were infertile. A low-fat diet led to a decrease in the body and fat weight, but did not allow recovery of fertility in the *ob*/*ob* mice [38, 39]. The administration of leptin to *ob*/*ob* male mice, along with the improved energy expenditure and metabolic processes, led to the onset of puberty and partially restored reproductive functions, which was due to the normalization of the GnRH and gonadotropins secretion [4, 8, 37]. In

the prepubertal period, the mutations in the *ob* gene, along with the early obesity, lead to the reduced levels of LH and follicle-stimulating hormone (FSH) and induce the signs of hypogonadotropic hypogonadism and the impaired reproductive functions [40–43].

A survey of men from Slovenia, Macedonia and Serbia with three different mononucleotide mutations within the *ob* gene showed that infertility was characteristic for men with only a polymorphism rs10244329 [42]. The polymorphism 2548G/A (genotype AA) in the *ob* gene in Iranian men was also associated with reproductive dysfunctions. However, the polymorphism with the genotype AG was much more common in men with normal fertility, which can indicate its protective effect on the male reproductive system [43].

The mutations within the *Ob-R* gene had a less pronounced effect on the male reproduction, which was illustrated by the experimental and clinical studies. The polymorphisms in this gene, as a rule, had a little influence on the male reproductive system and did not cause infertility [42, 43]. As in the *ob*/*ob* mice, the delayed puberty was shown in the *db*/*db* double knockout male mice lacking a functionally active receptor Ob-Rb, but the animals retained fertility [37]. Unlike men, women with inactivating mutations in the *Ob-R* gene had the pronounced reproductive dysfunctions and the decreased levels of estradiol, gonadotropins and GnRH [44, 45].

The effects of leptin on the male HPG axis can be carried out at the level of hypothalamic neurons, pituitary gonadotrophs and testicular cells. It is important to note that the response of the HPG axis to leptin depends on the dose of this adipokine and the duration of treatment, the metabolic and hormonal status, as well as the functional state of the leptin signaling system in the target tissues. This is well illustrated by the data on the influence of leptin on the hypothalamic structures. It is shown that a single i.c.v. administration of leptin to ovariectomized female rats under starvation conditions, when the leptin level was reduced, led to a rapid increase in the plasma LH level, which demonstrates leptin-mediated stimulation of secretory activity of the GnRH-neurons [12, 46]. At the same time, under conditions of prolonged administration of leptin, an increase in LH level [47] or lack of leptin effect on LH secretion [48] were detected, which may be assumed to be due to varying degrees of leptin resistance in the case of long-term action of leptin on hypothalamic neurons. This was supported by the fact that the action of low, nanomolar concentrations of leptin on the ARC and the ventromedial nuclei of the hypothalamus led to an increase in the GnRH secretion, while high, micromolar leptin concentrations did not cause this effect [5, 37]. The i.c.v. administration of leptin to fasting cows led to an increase of both basal and GnRH-stimulated LH secretion, while the administration of leptin to fed animals with the increased leptin level did not induce significant changes in LH level [49, 50]. Thus, the stimulating effect of leptin on the HPG axis at the hypothalamic level was largely dependent on eating behavior, and was the main mechanism that mediates the relationship between the satiety and metabolic status, on the one hand, and the gonadotropins levels and activity of the steroidogenesis system, on the other.

2.2.1. Hypothalamus

The central effects of leptin on the HPG axis are mediated through its interaction with leptin receptors located on hypothalamic ARC neurons expressing either pro-opiomelanocortin

(POMC) or agouti-related peptide (AgRP) and neuropeptide Y (NPY). Due to activation of these neurons by leptin, the positive (POMC-neurons) or negative (AgRP/NPY-neurons) regulation of GnRH-neurons occurs, especially since these neurons themselves do not contain the receptor Ob-Rb and, therefore, can not be target for leptin (**Figure 1**).

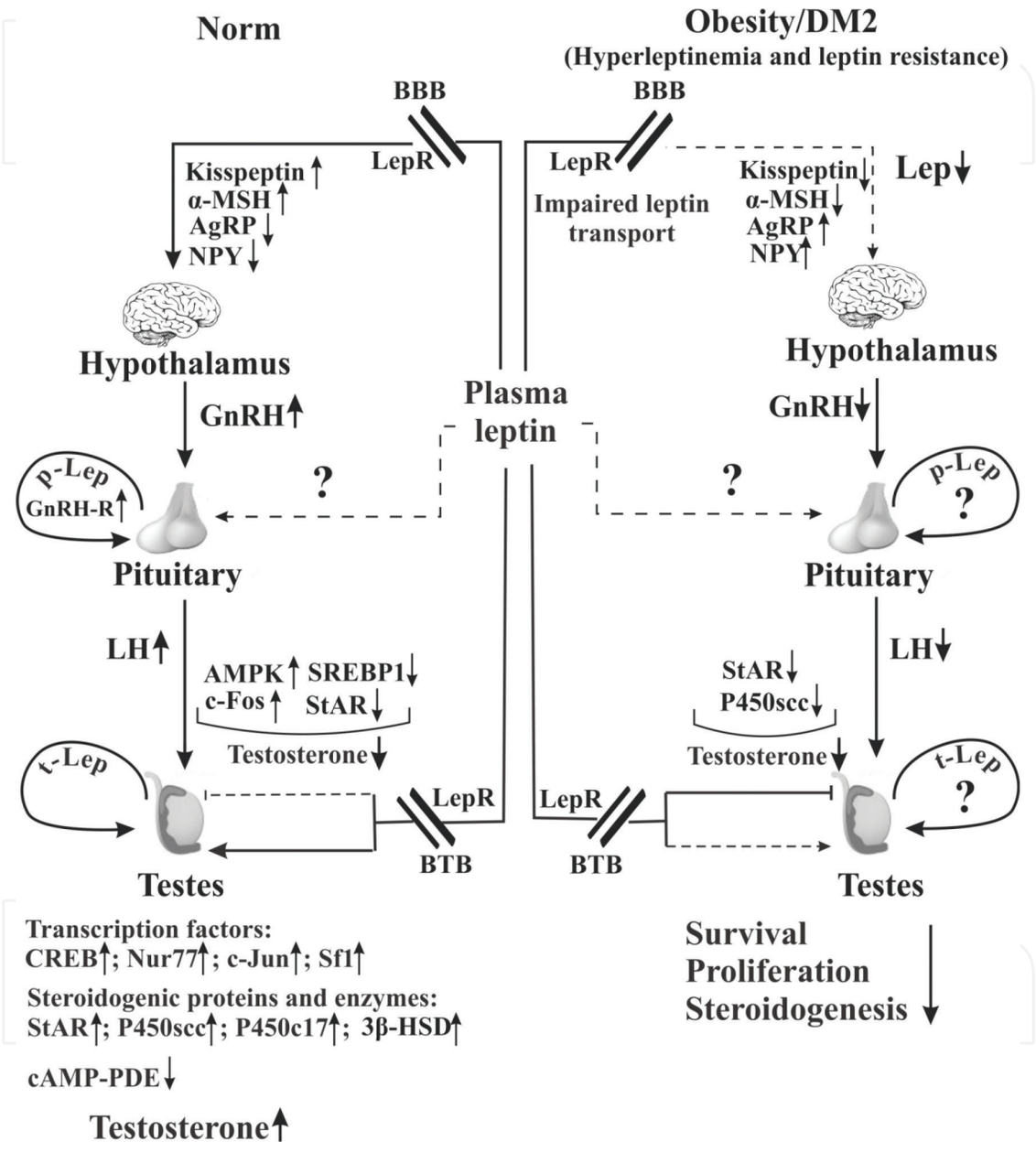

Figure 1. The regulatory effects of the plasma, pituitary and testicular leptin on the male HPG axis and the testosterone synthesis in the testes in the norm and in the metabolic disorders. Abbreviations: p-Lep and t-Lep, the pituitary and testicular leptin; LepR, leptin receptor; GnRH, gonadotropin-releasing hormone; GnRH-R, receptor of GnRH; LH, luteinizing hormone; T, testosterone; AMPK, AMP-activated protein kinase; CREB, cAMP response element-binding protein; Nur77, c-Jun, c-Fos and Sf1, transcription factors Nur77, c-Jun, c-Fos and Sf1; SREBP1, sterol regulatory element-binding protein-1; cAMP-PDE, cAMP-specific phosphodiesterase; StAR, steroidogenic acute regulatory protein; P450scc and P450c17, cytochromes $P450_{scc}$ (P450 cholesterol side chain cleavage enzyme) and P450c17; 3β-HSD, 3β-hydroxysteroid dehydrogenase; α-MSH, α-melanocyte-stimulating hormone; AgRP, agouti-related peptide; NPY, neuropeptide Y; BBB, blood-brain barrier; BTB, blood-testicular barrier.

Leptin-induced activation of ObRb located on the POMC-neurons leads to an increase in the production of POMC-derived melanocortin peptides, primarily α-melanocyte-stimulating hormone (α-MSH), an agonist of types 3 and 4 melanocortin receptors (MC_3R and MC_4R) [51]. The α-MSH binds to $MC_{3/4}R$ located on GnRH-neurons, and stimulates the GnRH secretion by them. In favor of this mechanism, there is evidence that the administration of leptin to the preoptic area of the hypothalamus leads simultaneously to an increase in α-MSH level and a stimulation of GnRH secretion [52]. The $MC_{3/4}R$ agonists, such as α-MSH and its analogue melanotan-II are also effective, increasing GnRH release [53, 54]. It should be noted that at least 70% of GnRH-neurons are activated by α-MSH [53]. Both MC_3R and MC_4R are involved in the effects of melanocortin peptides on GnRH-neurons, since mice lacking only one type of MCR remain capable of reproduction [55, 56].

Another mechanism for leptin regulation of GnRH secretion, in which the melanocortin peptides also participate, is more complex. In accordance with this, in the first stage the melanocortin peptides secreted by POMC-neurons interact with MCR located on the KNDy-neurons. Kisspeptin released from KNDy-neurons binds to the kisspeptin receptors located on GnRH-neurons and stimulates GnRH secretion [57]. In the hypothalamic ARC, the outgrowths of POMC-neurons form the contacts with the bodies of KNDy-neurons, and a release of α-MSH by POMC-neurons causes a rapid depolarization of KNDy-neurons. Pharmacological inhibition of MC_3R and MC_4R by the antagonist SHU9119 decreases the expression of kisspeptin by 45%. The stimulating effect of melanotan-II on LH production in mice lacking the kisspeptin receptor GPR54 was reduced significantly [57].

The AgRP, the endogenous $MC_{3/4}R$ antagonist, and NPY, both produced by the AgRP/NPY-neurons, mediate the inhibitory effect of leptin on LH production by pituitary gonadotrophs. However, the degradation of AgRP/NPY-neurons and the knockout of the *Ob-R* gene in them, making these neurons insensitive to leptin, lead to a delay in puberty in mice and reduce their fertility [58, 59]. The most important in the regulation of reproductive functions is NPY, which, by binding to the receptors Y1 and Y5 on the GnRH-neurons [60], suppresses GnRH expression and lowers the plasma LH levels [61, 62]. A prolonged treatment of animals with NPY suppresses the production of gonadotropins and terminates the puberty [63, 64]. Leptin suppresses NPY expression, preventing its inhibitory effect on the HPG axis. Insulin also inhibits NPY expression [63]. The similarity of the leptin and insulin effects on NPY expression is due to the fact that the main target for leptin and insulin is the 3-phosphoinositide cascade, which is believed to be involved in positive regulation of POMC production and in negative regulation of NPY and AgRP production within the ARC [65, 66].

2.2.2. Pituitary

Leptin can stimulate LH production, acting directly on gonadotrophs (**Figure 1**). Unlike the hypothalamus, where leptin is mainly transferred from the bloodstream, its source in gonadotrophs can be either the plasma leptin or pituitary leptin synthesized by gonadotrophs [67, 68]. There is a good reason to believe that pituitary leptin functions as a paracrine and autocrine regulator controlling the survival and functional activity of gonadotrophs, since the plasma leptin can not mediate the complex pattern of pituitary hormone secretion [69]. This assumption is supported by the data obtained in mice with tissue-specific knockout of the *ob* gene, either in

the adipose tissue or in the pituitary. Mice lacking the *ob* gene in the adipose tissue did not have leptin circulating in the bloodstream. At the same time, they had functionally active somatotrophs, which, like gonadotrophs, are targets for leptin and contain Ob-Rb, as well as normal expression of growth hormone in them. Meanwhile, the plasma level of growth hormone and the expression of growth hormone receptors in the hypothalamus were decreased, which indicates an impairment of the somatotropic axis. The production of leptin in the pituitary cells did not lead to its transfer from the pituitary to the bloodstream, indicating the autonomous function of leptin in the pituitary [70]. These data suggest that for normal hypothalamic-pituitary regulation, both the levels of plasma leptin and the pituitary production of leptin are important, and pituitary leptin is mainly involved in the regulation of survival and secretory activity of pituitary cells, but does not influence significantly the other leptin targets in organism.

The functions of the autonomous leptin system in the pituitary, its participation in gonadotropins production and the relationship between the activity of this system and the physiological state of the HPG axis are supported by the following facts. The *ob* gene is expressed in gonadotrophs, although the data on the number of pituitary cells that produce leptin and on the co-expression of leptin and pituitary hormones differ significantly [15, 71, 72]. In adult males and females, the *ob* gene is expressed in 30% of gonadotrophs [72]. In rats the pituitary leptin level varies significantly during the postnatal development, and in female rats it changes at the different stages of the estrous cycle and during pregnancy [15]. It is shown that leptin influences the production of gonadotropins, changing the GnRH receptor activity and, thereby, controlling the sensitivity of gonadotrophs to hypothalamic regulation [73]. The gene *Ob-R* encoding leptin receptor is expressed in a large number of gonadotrophs, and this suggests that these cells are the main target for leptin [8, 37, 67, 68, 74]. The sensitivity of gonadotrophs to leptin is indicated by the fact that this adipokine at relatively low concentrations, 10^{-9} and 10^{-11} M, stimulates the LH and FSH secretion in the hemi-anterior pituitaries of adult male rats. At the same time, in the *in vivo* conditions, leptin increases LH level, but does not affect the secretion of FSH [46]. The expression of pituitary leptin is controlled by steroid hormones, GnRH and other factors. GnRH and NPY increase the leptin expression by pituitary gonadotrophs, while the gastrointestinal hormone ghrelin, the regulator of food intake and the functional antagonist of leptin, on the contrary, suppresses the *ob* gene expression [69, 72].

2.2.3. Testes

Currently, there is evidence that leptin not only indirectly affects the steroidogenesis in Leydig cells through the regulation of the HPG axis but is also capable of directly affecting the activity of steroidogenesis system [3, 8]. The following facts support this: (1) the transport of leptin circulating in the bloodstream through the blood-testicular barrier (BTB) and the synthesis of leptin in the testicular cells; (2) the expression of leptin receptors and the presence of effector components of the leptin signaling in Leydig cells and (3) the results of the *in vitro* experiments demonstrating the leptin effect on steroidogenesis in the cultured Leydig cells.

In 1999, Banks and coauthors showed that leptin circulating in the blood was transported through the BTB, and the permeability was higher than in the case of the BBB [75]. Based on high rate of leptin transport through the BTB and high permeability of this barrier to other proteins, it was concluded that the mechanisms of leptin transport through the BBB and BTB

differ significantly. However, taking into account the high density of the truncated isoform Ob-Ra of leptin receptor on the surface of endothelial cells forming the BTB, there is reason to believe that, like the BBB, leptin transport through the BTB is also a receptor-dependent [37]. In this case, one should expect its dependence on the activity of the leptin signaling system at the periphery and its decrease in the conditions of leptin resistance. Another source of intratesticular leptin was its synthesis in the testes of adult men and animals. The highest level of the *ob* gene expression was shown in the seminiferous tubules, spermatocytes and spermatozoa [18, 76–79]. In Leydig cells, leptin expression was demonstrated only in pigs [18]. Along with the truncated isoform Ob-Ra, which may be involved in leptin transport through the BTB, a functionally active isoform Ob-Rb was detected in the plasma membrane of testicular cells, preferably Leydig cells, which convincingly demonstrates that activity of these cells is regulated by leptin [37, 80]. It should be noted that in adult men, Ob-Rb is expressed only in Leydig cells [78]. The leptin receptors, although to varying degrees, are expressed in the testes throughout the ontogenesis, including the late embryogenesis [76, 77, 80]. The maximal expression of leptin receptors is observed during the puberty of rats at the age of 1–3 months, which positively correlates with the increased T production.

The effectors, whose activity is regulated by leptin through the activated forms of Ob-Rb and JAK2, control the activity of the transcription factors regulating the expression of steroidogenesis genes in different ways [3]. Leptin-induced stimulation of Akt-kinase and MAPK results in the phosphorylation and activation of the transcription factor CREB that is also activated by gonadotropins via cAMP-dependent pathways [81]. The activation of p38-MAPK and JNK leads to the stimulation of the transcription factors Nur77 and c-Jun [82, 83]. The main targets for these factors are the genes encoding StAR protein responsible for transport of cholesterol into the mitochondria and P450 cholesterol side chain cleavage enzyme (cytochrome $P450_{scc}$) converting cholesterol to pregnenolone [84] (**Figure 1**). Along with this, the activation of MAPK cascade results in an increase in the expression of Sf-1 factor, the coactivator of expression of the gene encoding StAR and the genes *Cyp11a1*, *Cyp17a1* and *Hsd3b1* encoding the steroidogenesis enzymes, cytochromes $P450_{scc}$ and P450c17 and 3β-hydroxysteroid dehydrogenase (3β-HSD) [85–88]. Since the transcription factors Sf-1, CREB, Nur77 and c-Jun are able to enhance steroidogenesis in Leydig cells, the leptin pathways that stimulate their activity are the positive regulators of T production [3].

Leptin activation of the STAT3 and STAT5, as well as leptin-induced ERK1/2-dependent activation of the factor c-Fos lead to the opposite effect and suppress steroidogenesis in Leydig cells. An increase in ERK1/2 activity may be due to the prolonged leptin effect on the system Ob-Rb/JAK2 and, as a result, the activation of SHP-2 phosphatase, which affects the activity of MAPK cascade [89]. A decrease in T production by Leydig cells can be the result of AMPK activation, which suppresses the activity of sterol regulatory element-binding protein-1 (SREBP1) [90]. As is well known, SREBP1 positively regulates the *Star* gene expression [91, 92].

In addition to direct leptin effect on the expression of steroidogenesis genes, this adipokine can modulate the gonadotropin signaling pathways in Leydig cells, inducing an increase in gonadotropin-stimulated T production. It is well known that LH and human chorionic gonadotropin (hCG) specifically bind to LH/hCG receptors located on Leydig cells and stimulate

the activity of adenylyl cyclase catalyzing cAMP synthesis, which leads to the activation of protein kinase A and CREB. Further, the level of intracellular cAMP is reduced due to its hydrolysis by cAMP-specific phosphodiesterases (cAMP-PDE), which leads to the attenuation of signal transduction generated by gonadotropins and inhibits their stimulating effect on steroidogenesis. Leptin suppresses the cAMP-PDE activity, maintaining the increased level of intracellular cAMP and thereby potentiates steroidogenic effect of gonadotropins (**Figure 1**). This is supported by the data that leptin enhances the stimulating effect of hCG on the cAMP level in rat Leydig cells [77].

Along with the regulation of T synthesis in Leydig cells, leptin controls the mass and size of the testes, diameter of the seminiferous tubules and spermatogenesis and affects the survival of Leydig cells and other testicular cells [26, 93]. Leptin also regulates steroidogenesis in the ovaries and adrenal glands, and the mechanisms of its regulatory effect are believed to be similar to those in Leydig cells [37, 94].

2.3. Leptin regulation of the male gonadal axis and steroidogenesis in metabolic disorders

In men with obesity, metabolic syndrome and DM2, the activity of the male HPG axis and the T production are decreased, which lead to androgen deficiency [95–97]. Along with this, in diabetic men the plasma level of estrogens and the ratio of estrogen/T are significantly increased, which due to the increased activity of aromatase and the altered production of sex hormone-binding globulin [98–101]. The elevated concentrations of reactive oxygen species and inflammatory factors lead to the damage in Leydig cells and reduce their steroidogenic activity [97, 102].

In obesity and DM2, the plasma leptin level is significantly increased [103, 104], which leads to leptin resistance. As a result, the receptor-mediated transport of leptin through the BBB is reduced, which leads to a decrease in the intrahypothalamic leptin level and to a weakening of the regulatory effects of leptin on hypothalamic neurons and GnRH secretion (**Figure 1**). It is also not possible to exclude the possibility of reducing leptin transport through the BTB, although such data have not yet been obtained.

The detailed study of the relationships between the leptin signaling and androgen deficiency in men with obesity and DM2 are not currently available. In rats with diet-induced obesity, severe hyperleptinemia and leptin resistance was associated with a decrease in the number of Leydig cells by 30%. This can be caused by the reduced intratesticular levels of leptin or the decreased sensitivity of testicular cells to this adipokine that participates in the regulation of survival and proliferation of Leydig cells (**Figure 1**). Although the plasma T level in obese male rats did not change, in the testes of animals it decreased by 25%, which was associated with a decrease in the expression of the *Star* and *Cyp11a1* genes encoding StAR and cytochrome $P450_{scc}$ [105].

The deterioration of reproductive functions was found in mice with a knockout of the gene encoding the catalytic p110α-subunit of PI3K in the adipose tissue [106]. In the testes of 30-day knockout mice with severe hyperleptinemia, the expression of the gene encoding leptin was increased, while the expression of the genes encoding StAR and $P450_{scc}$ was reduced. Adult

knockout mice had a severe form of hyperleptinemia, obesity, hepatic steatosis and the impaired glucose tolerance, and were infertile. It was quite unexpected that in the testes of knockout animals the expression of the *ob* gene and the *Hsd17b3* gene encoding 17β-hydroxysteroid dehydrogenase 3 (17β-HSD) was significantly increased, and the plasma level of T was also increased, indicating a pronounced hyperandrogenemia [106]. A possible cause for this was the reduced activity of estrogen receptor-α (Esr1), since in animals lacking the *Esr1* gene a similar phenotype with hyperandrogenemia and infertility was described [107, 108].

3. Adiponectin

3.1. Adiponectin and its signaling system

Polypeptide hormone adiponectin is produced mainly by the adipose tissue [109, 110], but despite this, the plasma adiponectin level is negatively correlated with the body mass index and the reserves of adipose tissue [111]. The plasma level of adiponectin is characterized by gender specificity and significantly lowers in males, which is true for humans and rodents [112]. Adiponectin can be synthesized not only by the adipose tissue but also by the brain, pituitary, testes and others [17, 113]. Adiponectin is consists of a variable N-terminal domain, a large globular C-terminal domain and a collagenous domain located between them, containing 22 collagenous Gly-XY repeats [114–116]. Using the collagenous repeats, adiponectin molecules interact with each other to form the homotrimeric complexes that aggregate into the hexamers and high-molecular complexes similar to those in the case of tumor necrosis factor-α (TNF-α) [117]. To form the trimeric complex, hydroxylation of the proline and lysine residues in the collagenous repeats is necessary, since the lack of this modification does not allow the formation of such complex and leads to a loss in the adiponectin activity [118, 119]. High-molecular complexes of adiponectin are stabilized by disulfide bonds formed between the trimers [120]. The trimeric, hexameric and high-molecular complexes are present in the bloodstream, while the monomeric forms are found in trace amounts [115, 121–123]. Post-translational modifications of adiponectin and its oligomerization significantly affect the bioavailability, binding characteristics and pattern of specific activity of adiponectin [115, 120, 123–125].

The tissues, the targets of adiponectin, express the adiponectin receptors AdipoR1 and AdipoR2, which bind specifically to various forms of adiponectin with different affinity [111, 125–127]. Despite the fact that both these receptors seven times penetrate the plasma membrane, like classical G protein-coupled receptors, they differ significantly from them in membrane topology, having the extracellular C-terminal domain and the intracellular N-terminal domain. In addition, the adiponectin receptors interact with APPL proteins (adaptor protein, phosphotyrosine interacting with plekstrin-homologous domain and leucine zipper), but not with heterotrimeric G-proteins. The AdipoR1 binds with a high affinity to the truncated globular form of adiponectin and with a low affinity with the oligomeric and high-molecular forms of full-length adiponectin, while AdipoR2 binds with an intermediate affinity to both the full-length and globular forms. The both receptors interact with two isoforms of the APPL proteins, APPL-1 and APPL-2 [128, 129]. The interaction of adiponectin-activated AdipoR1 with APPL-1 leads to the activation of AMPK and the 3-phosphoinositide and MAPK cascades. The APPL-2 forms a complex with APPL-1 and prevents APPL-1-mediated regulations.

When adiponectin binds to AdipoR1, the APPL-1/APPL-2 complex dissociates, resulting in the release of APPL-1 to interact with the downstream effector proteins [116, 130].

3.2. The effect of adiponectin on hypothalamic neurons

Adiponectin is able to control steroidogenic function in the testes directly, acting on Leydig cells, and indirectly, acting on the HPG axis at the hypothalamic and pituitary levels. To interact with hypothalamic neurons, the main target of adiponectin in the CNS, it is necessary to transport adiponectin into the brain through the BBB. It is suggested that the receptor-mediated transport of adiponectin through the BBB can be carried out through the AdipoR1 and AdipoR2 receptors located on the endothelium of cerebral vessels (**Figure 2**). In addition, a large number of adiponectin receptors and the components of adiponectin-regulated signaling pathways have been identified in the ARC and paraventricular nuclei of the hypothalamus [131–134] and in other brain areas [13]. Adiponectin is easily transferred from the bloodstream to the brain and cerebrospinal fluid (CSF), although its concentration in the CSF is low, being only 0.1% of that in the blood [132–135]. In obesity, which was characterized by the reduced plasma level

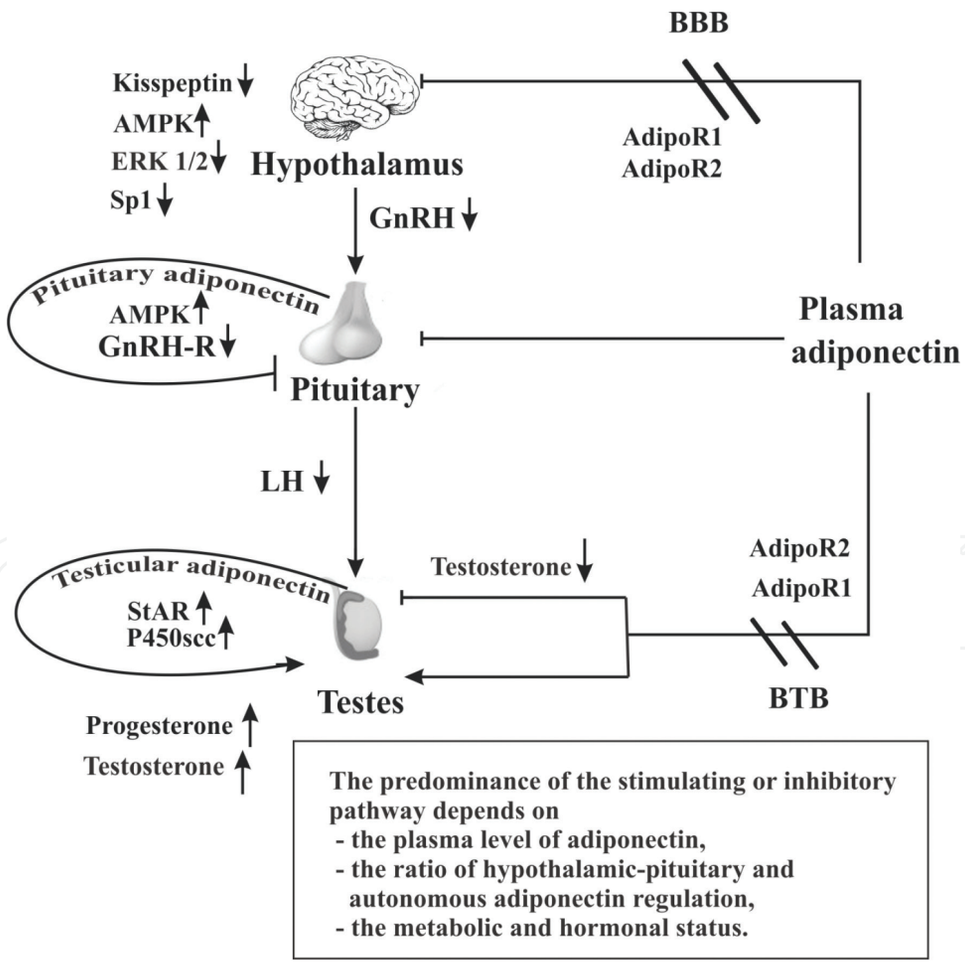

Figure 2. The regulatory effects of adiponectin circulating in the blood and adiponectin synthesized in the pituitary and testes on the activity of the male HPG axis and the testosterone production. Abbreviations: AdipoR1 and AdipoR2, adiponectin receptors of the types 1 and 2; ERK1/2, extracellular signal-regulated kinases 1/2; Sp1, transcription factor Sp1. The other abbreviations are the same as in **Figure 1**.

of adiponectin [134, 136, 137], its concentration in the brain areas was also decreased [134]. It should be noted that, as in the case of circulating adiponectin, a negative correlation was found between the adiponectin level in the CSF and the body mass [133, 134]. Thus, unlike leptin, intracerebral adiponectin deficiency in obesity is caused by a reduced level of this adipokine in the blood. Although there is evidence that adiponectin can be synthesized in the CNS [17, 113], the greatest, if not all, amount of this adipokine comes from the periphery, and the intracerebral level of adiponectin depends on the activity of adiponectin-transporting system of the brain.

Upon binding to adiponectin receptors in neurons of the paraventricular nuclei and the periventricular region of the hypothalamus, adiponectin activates AMPK [13, 138], decreases the activity of ERK1/2 [13], causes a weakening of the calcium-dependent signaling pathways and inhibits the hyperpolarization-activated cationic currents responsible for pacemaker activity of GnRH-neurons [139]. It is important to note that the inhibition of ERK1/2 activity is due to an increase in AMPK activity [13]. The main result of adiponectin action on GnRH-neurons is a decrease in the synthesis and secretion of GnRH and, as a consequence, a decreased LH production by gonadotrophs [13, 139] (**Figure 2**).

Adiponectin also interacts with the KNDy-neurons expressing kisspeptin. Adiponectin-induced increase in AMPK activity in these neurons results in the inhibition of AMPK-dependent transport of the transcription factor SP1 into the nucleus, which is illustrated by SP1 accumulation in the cytoplasm. As a result, the expression of the *KISS1* gene is reduced, which leads to a decrease of the stimulating effect of kisspeptin on the activity of GnRH-neurons [140]. There is reason to believe that a decrease in the SP1 activity may be due to adiponectin-induced inhibition of ERK1/2 activity in the KNDy-neurons [141].

3.3. The effect of adiponectin on pituitary gonadotrophs

The inhibitory effect of adiponectin on LH production can be carried out at the pituitary level, since both adiponectin receptors were detected in the LH-expressing gonadotrophs of human and rats [14, 142, 143]. In addition, the expression of the *Adiponectin* gene was detected in the pituitary gland [142–144], whereby the regulators of the adiponectin receptors in gonadotrophs can be both plasma and pituitary adiponectin (**Figure 2**). A long-term treatment of the primary culture of gonadotrophs with adiponectin results in a decrease in the AdipoR1 expression, but has a little effect on the expression of AdipoR2, indicating the development of receptor-specific resistance of gonadotrophs to adiponectin [144]. Adiponectin inhibits both the basal and GnRH-stimulated LH secretion, and its effect is detected even after a short exposure with gonadotrophs [14, 144]. This is largely due to adiponectin-induced decrease in the expression of GnRH receptors in gonadotrophs [144]. As in the hypothalamic GnRH- and KNDy-neurons, regulatory effects of adiponectin on gonadotrophs are mediated by its ability to activate AMPK [14]. Although adiponectin inhibits LH secretion [14, 138, 144], it has very little effect on FSH secretion [14]. This indicates that the targets of adiponectin in the pituitary are preferably gonadotrophs that produce LH.

3.4. The effect of adiponectin on the testes

As noted above, the expression of the *Adiponectin* gene was found in the testes, which demonstrates the intratesticular production of adiponectin, and the main source of this adipokine is

Leydig cells [17]. Three transcripts of the *Adiponectin* gene, 2.5, 1.8 and 1.2 kb, were detected in the adipose tissue, while in Leydig cells were only two transcripts, 1.2 and <1.0 kb, and in both cases the adiponectin isoform with a molecular weight of 30 kDa was dominant [17]. However, the contribution of the adiponectin synthesized in the testes to total pool of intratesticular adiponectin is difficult to assess, especially since the plasma adiponectin level is significantly higher than in the testes and seminal fluid. The concentration of adiponectin in the seminal fluid of healthy men is 100 times lower than in the bloodstream. The adiponectin level in the semen of men and bulls is positively correlated with its plasma level [145, 146]. Furthermore, adiponectin level in the seminal fluid positively correlates with the number of spermatozoa, their mobility and normal morphology [145]. In men with a vasectomy that excludes the intratesticular sources of adiponectin, this level in the seminal fluid does not change. These facts suggest that the main, if not the only, source of adiponectin in the semen is adiponectin, coming from the bloodstream. On the other hand, the source of adiponectin in Leydig cells can be both plasma and intratesticular adiponectin [116, 123].

The main regulators of the *Adiponectin* gene expression in the testes are gonadotropins with LH activity. The production of adiponectin in the testes of hypophysectomized rats is significantly reduced, but is completely restored after their treatment with hCG. In rats, during the neonatal period, when LH level is low, the content of adiponectin in the testes is also very low. During puberty, when plasma LH concentration and the proliferation of Leydig cells are increased, the expression of adiponectin also increased rapidly, reaching a maximum in rats at 2 months of age [17]. There is a positive correlation between the adiponectin levels and the T production, because the T synthesis also depends on gonadotropins with LH activity [147]. Unlike LH and hCG, FSH has a little effect on the adiponectin content in the testes, which is due to the fact that the expression of adiponectin in the Sertoli cells, the main target for FSH, has not been identified. The expression of adiponectin in the testes is also controlled by thyroid hormones and corticosteroids. An increase in thyroid hormone levels due to therapy with L-thyroxine causes an increase in the *Adiponectin* gene expression, while the treatment with dexamethasone leads to opposite effect [17].

The AdipoR2 was located on the surface of Leydig cells, while AdipoR1 was found in the epithelium of the seminiferous tubules. In spermatozoa there are both types of the adiponectin receptors [17, 148, 149]. The *AdipoR2*$^{-/-}$ mice had the reduced mass and size of testicles, the atrophy of the seminiferous tubules and the impaired spermatogenesis [150]. The expression of AdipoR2 in Leydig cells is controlled by gonadotropins with LH activity, and is almost independent of FSH. The expression of the *AdipoR2* gene in the testes is strongly reduced in hypophysectomized rats, and the treatment of animals with hCG completely restores it [17]. Studying the male rats, it was shown that during puberty with an increase in plasma LH level the expression of AdipoR2 in the testes also increases, which positively correlates with an increase in the adiponectin expression. With regard to the adiponectin signaling in spermatozoa, it is shown that, in addition to adiponectin, both types of adiponectin receptors are expressed in them. The expression of the *Adiponectin*, *AdipoR1* and *AdipoR2* genes in the high-mobility spermatozoa fractions is 3.5, 3.6 and 2.5 times higher in comparison with the low-mobility fraction [149]. The most pronounced correlation was found between the mobility and the expression of the *Adiponectin* and *AdipoR1* genes. These data indicate that AdipoR1 plays an important role in the regulation of spermatogenesis, while AdipoR2 is very important for the T synthesis by Leydig cells.

All of the above indicates that adiponectin positively regulates the T synthesis (**Figure 2**). Indeed, treatment of the MA-10 Leydig cells with adiponectin at the concentrations of 50–5000 ng/mL resulted in an increase in the production of progesterone, a precursor of T, which was associated with cAMP-dependent activation of StAR and cytochrome $P450_{scc}$ [151]. In the earlier studies, it was shown that adiponectin, acting on the testes, suppressed both the basal and hCG-stimulated T production, although the expression of the steroidogenesis enzymes, such as cytochrome $P450_{scc}$ and dehydrogenases 3β-HSD and 17β-HSD3, did not change [17, 148]. The mechanisms of adiponectin action on Leydig cells include the stimulation of PI3K and Akt kinase, which results in the changed expression of Akt-dependent genes, as well as the regulation of ERK1/2, whose activity decreases at low concentrations of adiponectin and increases at its high concentrations [148]. It can be assumed that the dependence of adiponectin effect on ERK1/2 on its concentration, as well as a set of the effector components of MAPK cascade regulated by adiponectin are responsible for the different mode of the regulation of steroidogenesis by this adipokine. The treatment of Leydig cells with adiponectin did not affect the expression of LH receptor, and this indicates the preservation of the sensitivity of these cells to gonadotropins [148].

4. Visfatin

Visfatin produced by the adipose tissue is a multifunctional protein that functions as a signal molecule and as a nicotinamide phosphoribosyltransferase (NAMPT) catalyzing the synthesis of nicotinamide adenine mononucleotide from nicotinamide and 5-phosphoribosyl-1-pyrophosphate [152–154]. In humans, visfatin includes 491 amino acids and forms a functionally active homodimer complex [10, 155, 156]. Paradoxically, the receptor for visfatin has not yet been found. It is known that the main targets of visfatin, as in the case of most other adipokines, are the MAPK and PI3K/Akt pathway, and the activation of Akt kinase occurs 5 min after treatment of cells with visfatin [156–158].

The highest concentration of visfatin is detected in the white adipose tissue. In obesity and DM2, the plasma visfatin level is steadily increased, and the degree of this increase varies greatly, due to both the individual characteristics of patients and the various approaches to measure the visfatin concentration [2, 155]. The visfatin level is also increases in women with a polycystic ovary syndrome, for which obesity and insulin resistance are characteristic [155]. Despite an increase in the plasma level of visfatin, its concentration in the CSF decreases, and this is probably due to the impaired transport of visfatin through the BBB. These data suggest that, as in the case of leptin and insulin, the transport of visfatin into the brain can be receptor-mediated, and decreases in the conditions of visfatin resistance.

The data on the involvement of visfatin in regulation of the reproductive system are mainly related to the female HPG axis, folliculogenesis and steroidogenesis in the ovaries [7]. There is a positive correlation between the visfatin level in follicular fluid and the quantity and quality of the follicles [159]. It is assumed that the effect of visfatin on the ovarian steroidogenesis system can be realized via the mechanisms that lead to an increase in the production of insulin-like growth factor-1 (IGF-1), a stimulator of steroidogenesis [138]. In this case, the

effects of visfatin are characterized by species specificity. The introduction of recombinant human visfatin into chicken did not stimulate, but, on the contrary, suppressed the basal and IGF-1-stimulated expression of the *Star* and *Hsd3b1* genes, which led to a decrease in estrogens production by follicular cells [7].

In the case of the male reproductive axis, the targets for visfatin may be all of its components. Information on the central mechanisms of action of visfatin is limited to its effect on the hypothalamic neurons responsible for control of glucose homeostasis [160]. However, the fact that visfatin, like leptin, affects the activity of 3-phosphoinositide pathway, supports its possible participation in the regulation of GnRH-neurons activity. The evidences were obtained in favor of the regulation of LH-expressing pituitary gonadotrophs by visfatin. Firstly, the mRNA for visfatin was detected in gonadotrophs, which indicates its synthesis in them and the role of visfatin in the autocrine and paracrine regulation of the anterior pituitary. Secondly, visfatin stimulates the AMPK activity in the cultured murine gonadotroph-like cells LβT2, resulting in a decrease in LH secretion [161].

The ability of visfatin to influence the testicular functions and the T synthesis is supported by the following data. Visfatin is expressed in Leydig cells, spermatocytes and spermatozoa [19], and its level in the seminal fluid is much higher than in the blood [162]. When exposed to Leydig cells, visfatin increases the T production, and the maximal effect of visfatin is achieved at its concentration of 10^{-6} M [163]. The inhibitor of Raf-1 kinase reduces the stimulating effect of visfatin on steroidogenesis, while the inhibitors of the protein kinases A and C have a little influence on this effect. It is assumed that the effects of visfatin on steroidogenesis may be due to activation of insulin receptors [163], which are widely represented in Leydig cells, especially since previously it has been reported that insulin receptor can interact with visfatin [154, 164]. However, despite the similarity of regulatory effects of insulin and visfatin, in the recent years the ability of visfatin specifically binds to insulin receptor has been questioned [157].

5. Resistin

Resistin is a polypeptide with a molecular mass of 12.5 kDa, which forms a homodimer stabilized by disulfide bonds [138]. Although resistin is mainly secreted by adipocytes of the white and brown adipose tissues and macrophages [165, 166], its expression is also shown in the testes in the Sertoli and Leydig cells, which indicates the participation of resistin in the autocrine and paracrine regulation of testicular cells [16]. The expression of the *Resistin* gene was detected in the different lines of mouse Leydig cells, and it increased with increasing intracellular level of cAMP, which indicates the involvement of cAMP-dependent transcription factors in the regulation of the *Resistin* gene expression [3]. Currently, a specific receptor for resistin is not established, but the most acceptable candidate for this is Toll-like receptor 4 (TLR4) [167]. The functions of receptor proteins for resistin can also be performed by tyrosine kinase-like orphan receptor 1 (ROR1), adenylyl cyclase-associated protein-1 (CAP-1) and δ-decorin. The TLR4 receptor mediates the regulatory effects of resistin on the 3-phosphoinositide and MAPK pathways, AMPK and the transcription factors of the STAT family [3].

The level of resistin in the bloodstream, from which it is able to be transported to the testes, varies greatly depending on the metabolic status, gender and species. Fasting leads to a decrease in the plasma resistin level and the *Resistin* gene expression in the adipose tissue, while food intake increases these indices [9, 16]. In women, the resistin level in the blood is higher than in men [168, 169]. In male rats, the expression of the *Resistin* gene in the adipose tissue exceeds that in female rats [170]. This is believed to be due to the stimulating effect of T and the inhibitory effect of estrogens on adipocytes [171]. There is evidence that resistin is expressed in adenohypophysis cells [172, 173]. In the pituitary of rhesus monkeys and baboons, the ratio of the mRNA for resistin, leptin and adiponectin was 1:13:4 and 1:7:3, respectively [174]. The *Resistin* expression in the pituitary strongly depends on the age and gender, and was higher in males as compared to females and increased at the prepubertal stage [172, 173].

Using the primary culture of pituitary cells of rhesus monkey it was shown that resistin activates a number of signaling pathways, including cAMP-dependent and 3-phosphoinositide cascades regulating the cell survival and secretory activity. Resistin affects the secretion of growth hormone and adrenocorticotropic hormone, although LH secretion remains unchanged. It should be noted, however, that the treatment of pituitary cells with leptin and adiponectin also did not affect LH secretion, which is probably due to the peculiarities of cultured cells used in the experiment [174].

Resistin was found in the brain and CSF, and although its concentration was much lower than in the bloodstream, it can be assumed that resistin affects the activity of hypothalamic neurons controlling GnRH secretion [116, 133]. One of the mechanisms of this may be the influence of resistin on the adiponectin signaling in hypothalamic neurons. A prolonged i.c.v. administration of resistin into rats and mice results in a decrease in the expression of both types of adiponectin receptors, AdipoR1 and AdipoR2, and also reduces the functional activity of APPL-1 protein, thereby weakening the APPL-1-mediated adiponectin signaling. There is reason to believe that this effect of resistin is implemented through the receptor TLR4, since the inhibiting effect of resistin on the adiponectin signaling was not detected in mice lacking TLR4 [175].

The *Resistin* gene is expressed in Leydig cells, and the intratesticular expression of resistin was identified throughout postnatal development with a maximum in adult animals [16]. Resistin is also expressed in Sertoli cells, but its level in them is significantly lower than in Leydig cells. Fasting and i.c.v. administration of leptin lead to a significant decrease in the intratesticular level of resistin, while in diet-induced obesity the expression of resistin in the testes remained unchanged [16]. These data indicate a positive correlation between the levels of resistin in the blood and in the testes. This gives reason to believe that, along with intratesticular synthesis of resistin, the plasma adipokine can be transferred through BTB into the testes, and the receptor TLR4, which are capable of binding to resistin and widely presented in testicular cells may be involved in this process.

6. Conclusion and future perspectives

The regulation of the male gonadal axis by adipokines can be carried out both through the changes in the plasma level and bioavailability of adipokines produced (a systemic regulation) and through the changes in the expression and specific activity of adipokines in the target

tissues, the components of the HPG axis, such as the hypothalamus, pituitary and testes (an autonomous regulation). In the case of systemic adipokines regulation, the changes in the plasma level of adipokines that are associated with feeding behavior, physiological conditions, and also with an imbalance of adipokines and a resistance to them in obesity, DM2 and other metabolic disorders directly affect the functional activity of the male HPG axis and T production. Of great importance is the activity of the adipokine-transporting system, which transfers the adipokines through the BBB into the brain, where they regulate the GnRH- and KNDy-neurons involved in GnRH secretion, and also through the BTB into the testes, where they control the steroidogenesis system and the synthesis of T, the main effector hormone of the male HPG axis. In the case of autonomous regulation, the adipokines synthesized in the pituitary and testes function as the autocrine and paracrine factors and to a large extent determine functional activity of the components of the HPG axis. On the one hand, they regulate proliferation and survival of gonadotrophs and testicular cells, primarily Leydig cells, and on the other, affect their ability to produce gonadotropins and steroid hormones. It is important to note that between the systemic and autonomous adipokine-mediated regulation of the male HPG axis there are the complex integrative relationships and interactions that are realized at different levels of this axis. As a consequence, the changes in the pattern and levels of adipokines in the bloodstream can be differently associated with activity of the hypothalamic, pituitary and testicular components of the HPG axis, since in this case it is necessary to take into account the functional state of autonomous adipokine systems. The ratio of different adipokines in the blood and in the tissues, the components of the HPG axis, contributes significantly to the resulting effects of adipokines on the reproductive system, since their effects on the male HPG axis, including the testicular steroidogenesis system, may be synergistic or antagonistic.

The study of the role of adipokines in the regulation of the male HPG axis is of great interest, since it will allow in the future to develop the effective approaches for monitoring functional activity of the male reproductive system and correcting the dysfunctions in this system in metabolic and endocrine disorders, including obesity and DM2. The adipokines and their analogues, as well as regulators and modulators of their signaling cascades in the hypothalamic neurons and testes, can be used as potential drugs to improve the reproductive functions and to normalize the steroidogenesis in men. It is also important how the treatment of men with GnRH analogous, gonadotropins with LH-like activity and androgens will affect the systemic and autonomic regulation of the GPH axis by adipokines. This should be taken into account when developing the approaches to improve metabolic status in obese and diabetic patients and in elderly men with an androgen deficiency using the activators of the HPG axis and androgens. The study of the interaction between the male HPG axis and the adipokine system will allow us to decipher the fundamental mechanisms that determine the relationships between the eating behavior, hunger and satiety, on the one hand, and the sexual behavior and aggression, on the other.

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Disclosure

Conflicts of interest are absent.

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