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Role And Significance Of Kisspeptin In The Female Reproductive System

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ABSTRACT

The functioning of the female reproductive system depends on the proper development and regulation of the hypothalamic-pituitary-ovarian axis. It is based on the secretion of GnRH, which stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). There have been many studies investigating the factors that regulate the secretion of gonadotropins. In recent years, the significance and role of kisspeptin and its receptor has aroused interest. This review will provide data from foreign studies and literature on the role of kisspeptin in the regulation of the female reproductive system.

KEYWORDS

Kisspeptin, reproductive system, gonadotropin-releasing hormone, hyperprolactinemia, premature sexual development, polycystic ovary syndrome.

INTRODUCTION

Kisspeptin was first discovered in Pennsylvania (hence its unusual name, coined for the famous confection of this region - Hershey's kisses) in 1996 as a gene that inhibits the metastasis of

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cancer cells. It is a hydrophobic protein and consists of 145 amino acids. The human KISS1 gene is displayed on chromosome 1q32 [1]. In 2001, the expression of kisspeptin receptors KISS1R was found in the placenta, hypothalamus and adenohypophysis. This aroused interest in the role and influence of kisspeptin on the endocrine regulation of the reproductive system. In 2003, the presence of kisspeptin in human blood plasma was first demonstrated, and it was also found that the concentration of kisspeptin in plasma increases significantly during pregnancy [2].

Kisspeptin and gonadotropin-releasing hormonesecretion. As you know, gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus and stimulates the synthesis luteinizing hormone(LH) and follicle stimulating hormone(FSH). These, in turn, affect the production of sex hormones. The key role of gonadotropin-releasing hormone (GnRH) in reproduction is well known, but the mechanisms of regulation require clarification. In recent years, many studies have been carried out on the effect of kisspeptin on the reproductive system. The synthesis of gonadoliberin is influenced not only by sex hormones, but also by kisspeptin. Since there are no receptors for sex hormones in neurons that secrete gonadoliberin, kisspeptin is a mediator substance. Estrogens and progesterone inhibit the secretion of kisspeptin by the hypothalamus (arcuate nucleus) and, according to the principle of negative feedback, the production of gonadoliberins decreases. Studies have shown that estrogens affect the periventricular nuclei and stimulate kisspeptin synthesis. According to the latest information, it was found that kisspeptin affects not only the central regulation of the hypothalamic-pituitary-ovarian axis, but also directly on the regulation of the function of the ovaries, fallopian tubes and placenta [4].

Kisspeptin and hyperprolactinemia. One of the common causes of infertility, hypogonadotropic anovulation is hyperprolactinemia. Prolactin is synthesized by pituitary lactotrophs, often due to adenomas, its level rises. Studies have shown that excess prolactin in the blood affects the synthesis of GnRH in the hypothalamus, and does not directly affect the pituitary gland and gonads. Studies have shown that a number of GnRH neurons express prolactin receptors in mice [5]. This suggests that PRL affects neurons that regulate GnRH neurons. They, in turn, are stimulated by kisspeptin-producing neurons (CPN) expressing prolactin receptors [6]. According to Charlotte Sonigo et al. the lack of gonadotropin-releasing hormone against the background of hyperprolactinemia can be reduced with the introduction of kisspeptin, since it is currently considered important in the regulation of the reproductive system [7]. With the introduction of kisspeptin, the synthesis of gonadotropin-releasing hormone, gonadotropins and the cyclic activity of the ovaries are restored. Based on this, it was suggested that kisspeptin should be used in women with resistance or intolerance to dopamine agonists in infertility [7]. One study analyzed the genes of two families of blood relatives with an isolated deficiency of gonadotropin-releasing hormone. Mutations associated with loss of function in KISS1R have been identified. It has been shown that KISS1R affects the timing of puberty through its effect on the synthesis of gonadotropin-releasing hormone [8]. Despite the importance of the

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regulation of gonadotropin-releasing hormone secretion by kisspeptin, there is also regulation independent of kisspeptin [9]. There is an opinion, that kisspeptin has an effect on the biosynthesis of gonadotropin-releasing hormone, and not on neuronal migration. The administration of kisspeptin is the trigger for GnRH-induced secretion of LH and FSH. Thus, kisspeptin has become one of the main regulators of gonadotropin-releasing hormone activation [9].

Kisspeptin and puberty. Since the deficiency of gonadotropin-releasing hormone leads to delayed sexual development, and due to early activation of hypothalamic gonadotropin-secreting neurons, premature puberty of central origin develops [10]. In 2008, the role of kisspeptin in the development of PPR was identified. The first description of the KISS1R (p.R386P) mutation was in a Brazilian woman with premature sexual development [11]. She was diagnosed with slowly progressing thelarche from birth, accelerated growth and progressive development of the mammary glands at the age of 7 years. Estradiol levels were within puberty, and after stimulation, LH levels were borderline for puberty [11]. An in vitro study revealed that R386P mutations led to a long-term activation of signaling pathways within cells against the background of kisspeptin administration [11]. This shows that the p. R386P reduces the degradation of KISS1R, thus increasing the number of receptors on the plasma membrane [12]. Definitely, KISS1 is one of the mechanisms for the development of premature puberty. Recent studies have shown that the content of kisspeptin is significantly higher in girls with a central form of premature puberty compared to the level of this protein in girls in prepubertal period [13]. These data have a positive correlation with the peak levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) after their stimulation with gonadotropin-releasing hormone [13]. Based on these findings, kisspeptin is suggested to play an important role in the onset of puberty [14]. KISS1 is one of the mechanisms for the development of premature puberty. Recent studies have shown that the content of kisspeptin is significantly higher in girls with a central form of premature puberty compared to the level of this protein in girls in prepubertal period [13]. These findings are positively correlated with peak levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) after their stimulation with gonadotropin-releasing hormone [13]. Based on these findings, kisspeptin is suggested to play an important role in the onset of puberty [14]. KISS1 is one of the mechanisms for the development of premature puberty. Recent studies have shown that the content of kisspeptin is significantly higher in girls with a central form of premature puberty compared to the level of this protein in girls in prepubertal period [13]. These data have a positive correlation with the peak levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) after their stimulation with gonadotropin-releasing hormone [13]. Based on these findings, kisspeptin is suggested to play an important role in the onset of puberty [14]. that the content of kisspeptin is significantly higher in girls with a central form of precocious puberty compared to the level of this protein in girls in the prepubertal period [13]. These findings are positively correlated

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Kisspeptin and polycystic ovary syndrome. `Currently, there is a limited amount of research in the world on the importance of kisseptin in polycystic ovary syndrome. Polycystic ovary syndrome is one of the most common endocrine disorders. Since the description of this syndrome, the mechanism of the pathogenesis of this condition has not yet been developed. It is known that kisspeptin and its receptor play an important role in the hypothalamus-pituitary-ovary system and play a role in adolescence [15]. Determination of the role of the kisspeptin / KISS1R signaling pathway in the functioning of the reproductive system is considered one of the main mechanisms for understanding the regulation of GnRH secretion [15]. Since neurons GnRH secreted by axons can stimulate the secretion of LH and FSH by the anterior pituitary gland. Thus, GnRH forms the last common pathway for fertility control [16]. And they also stimulate sex hormones. The study of kisspeptin (KISS1) and its receptor (KISS1R) in the pathogenesis of this disease aroused interest, since in the classic form of polycystic ovary syndrome, an increase in the basal level of LH compared to the level of FSH is observed. Research examining the level of kisseptin in polycystic ovary syndrome is scarce. In one study [17], three groups were created when studying the content of kisseptin in peripheral blood in patients with PCOS. The first group consisted of 19 adolescent girls with PCOS, the second - 23 adult patients with PCOS, and the third of 20 healthy adolescents as a control group. Blood sampling for the level of kisseptin, LH, FSH, prolactin, free testosterone, DHEA-s, SHBG, insulin, glucose. The research results showed that plasma levels of kisseptin were higher in adolescent girls and women of reproductive age with PCOS than in adolescents in the control group. It was noted that the content of kisseptin positively correlated with the levels of LH, testosterone and glucose, measured 2 hours after the oral glucose tolerance test. The findings suggest that kisseptin may play a role in the development of PCOS [17].

Cotransmitters of the kisspeptinergic system. It is believed that KISS1 neurons in the arcuate nucleus are capable of expressing neurotransmitters, neurokinin B and dynorphin (KND neurons). It is believed that with the help of autosynapses they participate in the regulation of kisspeptin secretion. Dynorphin is an endogenous opioid peptide that binds to the κ opioid receptor and participates in negative feedback between progesterone and GnRH. Such interactions contribute to the inhibition of kisspeptin and GnRH secretion. The rise in dynorphin levels in response to stress and exercise can suppress the secretion

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of GnRH and LH, causing anovulation and even hypogonadotropic amenorrhea. The use of naloxone (an opioid receptor blocker) can normalize the production of GnRH, restore the rhythm of menstruation and ovulation [18]. Neurokinin B, binding to the NK3R receptor, on the contrary, stimulates the secretion of kisspeptin in the hypothalamus. Literature data indicate that administration of neurokinin B or a selective NK3R agonist (senctide) can stimulate the ovulatory peak of LH. As for the expression of the TAC3 gene, which is responsible for the synthesis of neurokinin B, it depends on the levels of sex steroids, presumably through a negative feedback mechanism [19]. It was shown that ovariectomy stimulates the expression of the TAC3 gene in neurons of the arcuate nucleus. In contrast, estrogen therapy suppresses gene expression and LH secretion [20]. It should be noted that similar results were not obtained in KISS1R knockout mice. This may indicate that neurokinin B is an important regulator of the kisspeptinergic signaling system. Mutations that inactivate the neurokinin B gene and its NK3R receptor, associated with extremely low LH levels (with normal FSH levels), with the occurrence of hypothalamic hypogonadism and infertility. Inactivating mutations of the KISS1R gene, responsible for the expression of the kisspeptin receptor, are associated with low concentrations of both LH and FSH [21]. KND neurons are associated with estradiol signaling in the arcuate nucleus of the brain, which regulates heat production. Experiments have shown that ablation of KND neurons reduces vasodilation of skin vessels and partially blocks the effect of estradiol on thermoregulation [21]. It is assumed that KND neurons of the arcuate nucleus control heat transfer and are involved in the pathogenesis of hot flushes in postmenopausal women. are associated with low concentrations of both LH and FSH [20]. KND neurons are associated with estradiol signaling in the arcuate nucleus of the brain, which regulates heat production. Experiments have shown that ablation of KND neurons reduces vasodilation of skin vessels and partially blocks the effect of estradiol on thermoregulation [22]. It is assumed that KND neurons of the arcuate nucleus control heat transfer and are involved in the pathogenesis of hot flushes in postmenopausal women. are associated with low concentrations of both LH and FSH [21]. KND neurons are associated with estradiol signaling in the arcuate nucleus of the brain, which regulates heat production. Experiments have shown that ablation of KND neurons reduces vasodilation of skin vessels and partially blocks the effect of estradiol on thermoregulation [22]. It is assumed that KND neurons of the arcuate nucleus control heat transfer and are involved in the pathogenesis of hot flushes in postmenopausal women.

Effect of stress on the kisspeptinergic system. Suppression of the functioning of the kisspeptinergic system is observed not only in energy deficit, but also in chronic stress and inflammation. The body's response to stress is manifested by the activation of the hypothalamic-pituitary-adrenal system, in particular, increased secretion of corticoliberin and glucocorticoids. The discovery of kisspeptin allowed a new look at the mechanisms of suppression of the reproductive system due to stress. In animal studies, it was found that immobilization of male mice for 10 days, simulating an acute

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stress reaction, led to a significant increase in the content of corticosterone and a sixfold decrease in the level of kisspeptin [23]. It is important to note that the main glucocorticoid produced in response to stress in birds and rodents is is corticosterone, while in other mammals it is cortisol. The results of studies on female mice showed a decrease in the secretion of GnRH and kisspeptin, mainly due to a violation of the feedback mechanism between estrogens and neurons of the arcuate nucleus. It prevented the onset of the LH peak and ovulation [24]. In clinical practice, it is often observed how stress leads to suppression of the reproductive system in the form of anovulation, and sometimes functional hypothalamic amenorrhea. Recent studies have demonstrated that the suppressive effect of psychosocial stress on the hypothalamus and pituitary gland is mediated by cortisol, which binds to type II glucocorticoid receptors localized on the KND neurons of the arcuate nucleus. Disruption of the secretion of dynorphin and neurokinin B by KND neurons leads to inhibition of kisspeptin synthesis.

CONCLUSION

Thus, the data on kisspeptin presented in this review show its undoubted role in the regulation of the reproductive system function, and its further study is necessary for a deeper understanding of the mechanisms of action and the possibility of using it in the diagnosis of various diseases and the development of new therapeutic approaches in clinical practice.

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