Mini-Review

The Role of Kisspeptin in the Onset of Puberty and in the Ovulatory Mechanism: A Mini-review

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A B S T R A C T

The onset of puberty has been a fascinating topic for reproductive endocrinologists for decades; however, its underlying physiological mechanisms have remained elusive until recently. The discovery and understanding of the effects exerted by the peptide hormone kisspeptin have shed light on this research area. This review is aimed to discuss the functions of kisspeptin, with special focus on its role in the onset of puberty and in the ovulatory mechanism. The points under discussion are (1) the characteristics of kisspeptin and its receptor, (2) the relevance of this hormone and its interaction with leptin in the onset of puberty, (3) the role of kisspeptin in the ovulatory mechanism based on its differential expression at hypothalamic nuclei, which is modulated by sex steroid hormones, and (4) the clinical relevance of kisspeptin and its antagonists in new therapeutic strategies for the treatment of various reproductive pathologies. All of this explains the revolution that kisspeptin has caused among researchers working in the field of gynecological endocrinology and reproductive biology.

Key Words: Estradiol, Kisspeptin, Kisspeptinergic nuclei, Leptin, Ovulation, Puberty, Sex dimorphism

Introduction

Puberty, from the Latin word *pubescence*, meaning "the appearance of pubic hair,"[1] is a gradual biological process characterized by several hormonal changes that allows an individual to become sexually mature and acquire the reproductive ability. Puberty also leads the individual to behavioral changes and generally begins at 8-10 years of age. In girls, it culminates in the first ovulation, which leads to menarche at 12-13 years of age.[2] However, the first menses are sometimes anovulatory because they can also be the result of a hemorrhagic shedding of the endometrial lining not preceded by ovulation. In boys, puberty generally begins one year later than in girls and culminates at the completion of spermatogenesis, with the full development of the spermatogenic line.[3] During puberty, hormonal changes lead to the expulsion of mature oocytes from the ovary and of mature spermatozoa from the testicles.[4,5]

Endocrine regulation of the onset of puberty has been a fascinating topic for endocrinologists, who have been working on this area continuously for decades. It is known that at around 6-8 years of age, children experience the physiological process known as adrenarche, corresponding to an increased secretion of androgens, such as androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate, by the cortex of adrenal glands.[6] After this, maturation of the hypothalamic-hypophyseal-gonadal axis occurs, a fact that triggers an increase in the frequency and amplitude of the liberation of gonadotropin-releasing hormone (GnRH),[6] with a consequent increase in the secretion of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[1] As a consequence of this hormonal stimulation, gonads undergo a process of growth, development, and maturation known as gonadarche, and this process leads to a rise in sex steroid secretion from the ovaries and testicles. Until recently, it was thought that the main marker for the onset of puberty was an increase in the frequency and amplitude of pulsatile GnRH secretion.[1,6] However, in the past years, there have been significant advances in this area, and, in particular, the discovery of the hormone kisspeptin and its receptor, which are critical factors stimulating the release of GnRH, has allowed a better understanding of the key events leading to puberty.

In view of this, the objective of this review is to address the main characteristics and functions of kisspeptin, with special focus on its role in the onset of puberty and in the ovulatory mechanism.

Kisspeptin and Its Receptor

Originally discovered in 1996 as a product of a metastasis-suppressor gene,[7] the peptide kisspeptin (abbreviated as KISS) received its name for the site of its discovery, Hershey, Pennsylvania, home of the famous "Hershey Chocolate Kiss," and for its role as a suppressor sequence.[8]

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Due to its role in cancer, the term “metastatin” (or “metastin”) is preferred by oncology researchers, but investigators in the field of endocrinology prefer the name kisspeptin. Even though the name ‘kisspeptins’ was given to the family of neuropeptides encoded by the *KISS1* gene,[9] there is some confusion when naming this peptide. In this mini-review, the nomenclature *KISS1* will be used to name the human gene/mRNA, and the nomenclature “kisspeptin” is appropriate for the peptide product, as suggested by other authors.[8,10]

In the human, the *KISS1* gene is located on chromosome 1q32,[11] and it has been proposed that after transcription, *KISS1* mRNA is translated into prepro-kisspeptin, a 145–amino-acid protein that later is proteolytically cleaved, giving rise to the peptide kisspeptin-54 (metastin), which can be cleaved, producing three shorter peptides: kisspeptin-14, kisspeptin-13, and kisspeptin-10.[12,13] Although all four kisspeptin products are biologically active,[14] the in vivo importance of the three shorter peptides is poorly understood.

In the human, kisspeptin-synthesizing neurons are located in two main sites at the hypothalamus: the preoptic area and the arcuate (infundibular) nucleus.[15] When released, kisspeptin can bind its receptor, termed GPR54 (galanin-like G protein–coupled receptor 54, also known as KISS1R), which has been found in the GnRH-secreting neurons from the hypothalamus of mice and humans; this fact suggests that kisspeptin could directly act on these neurons.[16] In humans, GPR54 is encoded by a gene located at chromosome 19p13.3.[7] Once kisspeptin binds to GPR54, it activates a G protein–activated phospholipase C, which leads to the generation of inositol trisphosphate and diacylglycerol. These second messengers mediate an intracellular Ca^{2+} increase and the activation of protein kinase C, respectively, producing effects on other proteins and ion channels.

It is known that the expression of GPR54 is an absolute requirement for a functional gonadotropic axis. However, Messager et al[16] argued that although kisspeptins have been previously described as high-affinity ligands for the GPR54 receptor, it has not been shown that they are the only ligands or, crucially, that the effects of kisspeptins on gonadotropin secretion act only by means of the GPR54 receptor.

Recent studies suggest that kisspeptin participates in the regulation of metabolism.[17] It has been shown that adult *Kiss1r* KO female mice, compared with their wild-type littermates, possess a significantly higher body mass and higher levels of leptin and fat, as well as an evident impaired glucose tolerance. On the other hand, adult *Kiss1r* KO male mice were shown to possess a normal body mass and adequate glucose regulation.[17] The latter is evidence that kisspeptin signaling exerts an influence on the energetic and metabolic status in a sexually dimorphic way (ie, a sex-specific manner).[18]

Role of Kisspeptin on Puberty

Current evidence shows that an intact kisspeptin-signaling pathway is a requisite for the onset of mammalian puberty, especially in rodents and humans. Thus, some researchers have suggested that “puberty begins with a *Kiss*.”[19,20] Studies on *Kiss1R* knockout mice show that they do not progress toward puberty and that they have severe deficits in their reproductive function in adulthood, such as sexual immaturity, smaller gonads, absence of spermatogenesis, low concentrations of gonadotropins and sex steroids, and impaired ovulation and, therefore, irregular or absent cycling.[18] A number of studies in male and female primates and rodents have shown a remarkable rise in the hypothalamic expression levels of *Kiss1* mRNA during puberty.[21–23] In this respect, it has been proposed that such changes in the expression levels of *KISS1* mRNA possibly reflect not only an increased neuronal activity during puberty but also a possible mediation of kisspeptin on the neuroendocrine events, triggering the onset of puberty.[19] It is currently known that at the beginning of puberty, one of the functions of kisspeptinergic neurons in humans is precisely to constitute the “target” of leptin hormone (Fig. 1). Close to puberty, and as a consequence of the increase of adipose tissue in the body, higher amounts of leptin are released from the adipocytes, leading to higher levels of this hormone in blood.[24]

Recent research[25,26] suggests that leptin surge would promote kisspeptin secretion from kisspeptinergic neurons, and the latter hormone would bind to its GPR54 receptor in the GnRH-releasing neurons. Once stimulated, these would secrete higher amounts of GnRH, enhancing the release of FSH and LH from the adenohypophysis, a fact that constitutes one of the main events associated with gonadarche (Fig. 1). Therefore, kisspeptin is a key factor triggering puberty in humans. This is in line with research in the field of adolescent nutrition and endocrinology: in the past 50 years, the age of onset of puberty and thelarche has decreased (ie, occurring earlier in life) but the time when ovarian cycle regularity is reached has not[27] (ie, after the first menses, the girl's menstrual cycles are not always regular). Some girls are known to menstruate with no prior ovulation.[28,29] The age of ovarian cycle regularity would probably be influenced by the nutrition and metabolic state, leading to the hypothesis that alterations in the proportion of adipose tissue, such as those observed in obesity, can contribute to disorders in the mechanism involved in progression of puberty.[30] Kisspeptin would have a relevant role to exert in this sense because malnutrition and increased body mass cause lower and higher amounts of the hormone, respectively. The latter would be due to altered leptin levels resulting from an imbalance in adipose tissue.

Role of Kisspeptin in the Ovulatory Mechanism

In rodents, the presence of kisspeptin and *Kiss1* mRNA has been reported in 2 regions of the hypothalamus—the arcuate nucleus and the anteroventral periventricular nucleus—hence, the name kisspeptinergic nuclei. Worth pointing out, the anteroventral periventricular nucleus forms a hypothalamic continuum with the rostral periventricular nucleus (where kisspeptin is also found), and this anatomic continuum is also known as the rostral portion of the third ventricle.[31] Several investigations have reported a sexual dimorphism in the kisspeptinergic nuclei in

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