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Kisspeptin and Neuroendocrine Pubertal Transition in Boys[A Review]

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Abstract: In recent decades, a progressive decline in the age of puberty has been occurred due to secular trends, food insecurity, children social hardship, immigration, socio-economic status, father absence and neighborhood environment. The initiation of neuroendocrine pubertal transition in human biology is a great mystery as very little information is available on this regard. In this review, role of kisspeptin in the neuroendocrine pubertal transition has been focused.

Key words: Kisspeptin · Neuroendocrine · Puberty

INTRODUCTION

Kisspeptin triggers puberty [1]. The earliest identified neuroendocrine manifestation of puberty is the production of kisspeptin from arcuate neurons that alters release of GnRH from the hypothalamus [2]. In the early stages of puberty, GnRH pulse amplitude increases and pulse frequency increases to every 1–2 h, primarily at night. As maturation progresses, these changes extend into the daytime hours. In response to GnRH secretion, LH and FSH production also increase, initially during the night and then during the day in later pubertal stages [3]. In boys, the first sign of pubertal development is usually testicular enlargement. The degree of pubertal maturation is usually described using Tanner stages (I-V) of sexual maturation [4]. In Tanner stage I testicular length is <2.5cm, Tanner II >2.5cm, Tanner III >3.0cm, Tanner IV >4.0cm and Tanner V >5.0cm [5]. Penile length in Tanner stage I is 3 cm or less, in stage II length unchanged, in stage III begin to lengthen to about 6 cm, in stage IV penis increases in circumference and length to 10 cm and in stage V penis is approximately 15 cm in length [6]. In both sexes, however, pubic hair may be the first manifestation of puberty [7]. The secretion of adrenal androgens causes pubarche (the onset of pubic hairs), the initiation of which is termed as adrenarche [7]. In Tanner stage I there are no testosterone sensitive pubic hairs but only vellos hairs over the pubes. In stage II very little hairs are present at the base of penis. In stage III hairs are darker and spread over the junction of pubes. In stage IV hairs distribution is of adult type but not spread to the medial surface of thigh. In stage V hairs spread to the medial surface of thigh and both in type and quantity are of adult type. The term "gonadarche" is often used to indicate the initiation of sex hormone production from the ovary or testis [8].

Throughout the past century, a progressive decline in the age of puberty has been occurring. The reasons for this relate to the availability of better nutritional and health facilities to the general population. All these facilities in turn are the result of improvement in socioeconomic conditions and medical care [9,10]. Environmental factors, nutritional factors, ethnics and genetics, affect sexual maturation in normal individuals living in the same area [11]. Exposure to environmental factors such as, food insecurity, children social hardship, immigration, socio-economic status, father absence and neighborhood environment during pre-pubertal period alter the timing of puberty onset [12]. It has been reported in USA that, puberty timing in girls occurred earlier now than in the mid-1900s [13,14]. But in boys as compared to girls very little data are available on sexual maturation [15].

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Due to inconsistent findings and few studies it is still not clear in boys whether there has been secular trend towards later or earlier pubertal timing [15,16]. For secular trends in USA, data from 1940 to 1994 for pubertal timing showed that pubic hair development and genital development are not sufficient to suggest a trend towards an earlier puberty in boys [14]. To asses Asians, National Health and Nutrition Examination survey (NHANES) did not include enough population of Asians, so in Asian population very few studies regarding puberty timing are available [17,18]. To predict puberty in children, blood samples were obtained from individuals after stimulation with GnRH or at frequent intervals during sleep for determination of LH concentration [19-21]. But the overlap between hypogonadotropic, prepubertal and early pubertal responses limits their values in individual cases [22]. To improve this discrimination, more sustained stimulations were given by GnRH agonist [23]. In boys it has been reported that, puberty in individuals can be predicted by measuring single morning plasma testosterone concentration, which is the reflection of alterations in the LH pulsatility that occurs with the onset of puberty. However, still for the detection of pubertal onset a precise marker is lacking [24].

Kisspeptin and Puberty: In human biology, initiation of puberty is one of the greatest mysteries because, very little is known about the maturation and physiology of gonadotropin releasing hormone (GnRH) neurons, secretion of GnRH and key elements involved in pubertal transition. In recent years a role of GPR-54 and kisspeptin in the control of GnRH physiology and pubertal transitions, has been increasingly indicated. A condition called, idiopathic hypogonadotropichypogonadism (IHH) were reported in patients having loss of function mutations in GPR-54. Similarly, pubertal failure, immature reproductive organs and low concentration of gonadotropic and sex steroids hormones were noticed in mice lacking GPR-54 [25-27]. The central initiator of reproductive hormone cascade GnRH is secreted in pulsatile manner enters into the hypophyseal portal circulation and stimulates the synthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [28]. LH and FSH are then responsible for stimulating gonadal functions such as, steroid hormone synthesis and gametogenesis. For the episodic release of GnRH, various inhibitory and excitatory signals are acting at the level of hypothalamus in the form of neurotransmitters and neurohormones [29]. In human, hypothalamus releases GnRH pulses during fetal and neonatal stage. GnRHpulsatility during early childhood, also called juvenile pause is suppressed until adolescence, when resurgence of GnRHpulsatility occurred, stimulating pubertal development and reproductive maturations[29,30]. During juvenile pause, gonads are relative quiescence, developing a condition of hypogonadotropic. During juvenile period, the pause in GnRHpulsatility may be considered as a result of a, hypothetical neurobiological brake that keeps the GnRHpulsatility suppressed until the initiation of puberty onset [31]. This conceptual brake may be accounted for by either the imposition of the loss of a stimulatory input and/or inhibitory input to GnRH neurons. In primates during pubertal initiation, resurgence of robust GnRHpulsatility occurred, suggesting release from hypothetical brake during juvenile pause [31,32]. This has been confirmed by various studies that, in primates during juvenile pause, the restrain on GnRHpulsatility is independent of testicular or ovarian steroids because same conditions were reported in agonadal humans [33,34] and neonatally castrated monkeys [35,36]. Terasawa and Fernandez [30], proposed the hypothesis that, in female rhesus monkey central inhibition is due to the inhibitory action of gamma amino butyric acid (GABA). This finding is supported by the observations such as, (1) in pre-pubertal monkeys GABA levels are higher when GnRH secretion is diminish but, after pubertal onset GABA levels are lowered while GnRH secretion is elevated [37]. (2) In pre-pubertal monkeys, infusion of bicuculline, a $GABA_A$ receptor antagonist into the stalk-median eminence (S-ME) causes the release of GnRH to a much greater extent as compared to pubertal monkeys. Similarly infusion of GABA in pubertal monkeys effectively suppressed GnRH release as compared to pre-pubertal monkeys [37]. (3) In juvenile female primates, first ovulation and precocious puberty can be induced by long term infusion of bicuclline into S-ME [38]. According to Plant and his colleagues, in male monkeys during juvenile development, neuropeptides Y (NPY) neurons are responsible for central inhibition of pulsatile gonadotropin releasing hormone (GnRH) secretion. This finding is supported by observations such as, (1) in the medio basal hypothalamus (MBH) during neonatal period mRNA and peptides levels of NPY are significantly lowered as compared to juvenile period. (2) In the MBH of pubertal male monkeys, mRNA and peptides levels of NPY decreases while mRNA of GnRH increases [39]. Work in Terasawa's lab found that, in pre-pubertal female

monkey's infusion of bicuculine into the S-ME stimulates the release of kisspeptin-54 and GnRH and that simultaneous infusion of peptide 234, a kisspeptin antagonist blocks the bicuculline induced GnRH secretion [40]. These findings confirmed the important role of GABA in the central inhibition of GnRH secretion during juvenile period in primates. But prior to puberty, what exactly reduces GABA inhibition and whether alternative or additional somatic cues and neuronal substrates are involved in the upstream control of GnRH pulse generation remained unclear. Thus, in primates what exactly triggers puberty remains a mystery [41].

Kisspeptin regulates hypothalamic- pituitary-gonadal (HPG) axis by stimulating GnRH secretion that acts on the pituitary gonadotrops to secrete LH and FSH. Kisspeptin is a fundamental regulator of GnRH both in puberty and adulthood [42]. The hypothalamic expression of *kiss1* in rats and monkeys increases during the progression of puberty [43,44] while high GPR54 mRNA level was observed in female monkeys during pubertal progression [44]. *Kiss1r* expression in both sexes of rats and female mice was found to be higher at adulthood as compared to juvenile period [43, 45]. The sensitivity of kisspeptin receptor on hypothalamic GnRH neuronal populations also increases during the progression of puberty [45]. Kisspeptin release during puberty in human increases because, serum kisspeptin level in Korean girls with central precocious puberty was found significantly higher as compared to age matched pre-pubertal control group [46] suggesting increase expression of hypothalamic *KISS1*. No studies in humans are available regarding kisspeptin receptor signaling that, whether expression of kisspeptin and its receptor or KISS1R sensitivity increases during pubertal transition. In humans, how puberty is initiated is still a mystery.

CONCLUSION

In summary, kisspeptin signaling has a role in neuroendocrine pubertal transition in human, rats, mice and monkeys. In these animal models either the expression of kiss1, kiss1r or the sensitivity of kiss1r on GnRH neuron to kisspeptin increases during pubertal transition. But how kisspeptin stimulate the HPG-axis and triggers pubertal onset is still unknown in human. Whether, during pubertal transition either the number of KISS1R on GnRH neuron increases or the sensitivity of KISS1R on GnRH neuron increases is still not understood.

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