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Endogeneous Signals and Mammalian Puberty Onset: A Review

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Abstract

One of the most important events in the life of mammals is the onset of puberty during which the secondary sexual characters appear, the growth increase until the final height is reached and fertility is achieved. The timing of puberty is precisely controlled by a plethora of endogenous signals and environmental cues that affect hypothalamic–pituitary–gonadal (HPG or

reproductive) axis at different levels. This phenomenon, which ensures that the tempo of puberty is adjusted to the internal and external conditions of the body, is also responsible for perturbations of its timing when such conditions are not optimal. Accordingly, puberty has been regarded not only as a fundamental developmental event, but also as sensor of the proper interplay between genes and environment along development.

Keywords: Puberty, HPG-axis, Fertility

1. Introduction

In mammals puberty is one of the most complex and mysterious phenomenon that results from complex neuroendocrine alterations. This is not only the chronological age on which pubertal onset depends. Beside this, environmental factors, psychological factors, weight and nutritional status also affects pubertal onset (Herbison, 2007; Buck *et al.,* 2008; Kaplowitz, 2008; Ghulam et *al.,* 2014). In children especially in girls, increased incidence of precocious puberty has been reported during the last decades (Parent *et al.,* 2003). Precocious puberty has a negative impact on health such as, cardiovascular diseases, reproductive cancers and obesity. These children are also susceptible to engage in alcohol abuse, smoking and sexual activities (Ghulam *et al.,* 2014). This review article focuses on the recent discovered endogenous factors that are involved in pubertal onset either directly or indirectly. The endogenous factors which play an important role in pubertal signalling are kisspeptin, leptin, melatonin, growth hormone, ghrelin and nesfatin-I. These are discussed one by one below.

2. Kisspeptin

Kisspeptin is a neurohormone, synthesized by the hypothalamic nuclei especially arcuate (ARC). It is also called metastin and is encoded by *KISS1* gene (Lee *et al.,* 1996). Kisspeptin is a member of RF-amide family (Graham, 2004). Kisspeptin cells, fibers and mRNA are found in preoptic, median eminence, ARC, dorsal medial nucleus of hypothalamus (DMH) and ventro medial hypothalamus (VMH) (Hrabovszky *et al.,* 2010). This is also found in the small intestine, liver, testis, ovary and pancreas (Castellano *et al.,* 2005). Kisspeptin receptor, KISS1R also called GPR-54 is expressed in ARC, preoptic, hypothalamus and anterior pituitary (Kotani *et al.,* 2001). Most of the kisspeptin neurons especially ARC has Neurokinin B and dynorphin. Their reciprocal interaction has a role in the control of GnRH pulses and sex steroid negative feedback (Navaro *et al.,* 2011). Kisspeptin play a key role in fertility and reproductions. This has been confirmed by several studies that, pubertal failure results when there is inactivating mutation in *KISS1* or *KISS1R*. Similarly activating mutations in these genes can cause precocious puberty (Teles *et al.,* 2008). Kisspeptin is a very important GnRH secretagogue. It causes the release of GnRH. During infancy the kisspeptin pulsatility is very high, so is GnRH. However kisspeptin pulsatility is reduced during juvenile period. This directly reduces GnRH secretion, resulting into hypogonadotropic condition (Kauffman and Smith, 2013). But at the end of juvenile period kisspeptin pulsatility is restored as a result, resurgence of GnRH pulsatility occurs and so puberty accomplished (Seminara *et al.,* 2003). In juvenile period, this is gamma amino butyric acid (GABA) that inhibits the expression of ARC kisspeptin neurons. It has been explored that GABA levels are higher and GnRH is lower in prepubertal monkeys (Terasawa and Fernandez, 2001). But after pubertal onset, GABA is

lower while GnRH is high (Mitsushima *et al.,* 1994). Infusion of GABA in adult monkeys suppresses GnRH release but not in prepubertal monkeys. Similarly infusion of bicuculine ($GABA_A$ receptor antagonist) induces secretion of GnRH to a greater extent in prepubertal as compared to pubertal monkeys. Long term use of bicuculine in prepubertal monkeys can cause precocious puberty and first ovulation (Mitsushima *et al.,* 1994; Keen *et al.,* 1999). Bicuculine in prepubertal monkeys stimulate GnRH release. This release was blocked by simultaneous infusion of peptide 234 (kisspeptin antagonist). These results confirmed that GABA regulates GnRH pulsatility but, this is not cleared that what factors regulate GABA during infancy, juvenile and pubertal stage. Thus the most basic things that actually induce puberty remain a mystery (Plant *et al.,* 1989; Terasawa *et al.,* 2012).

3. Leptin

Leptin is an adipocyte-derived hormone that has been implicated to serve as a metabolic signal to the reproductive axis (Campfield *et al.,* 1995). Leptin and melanocortin signaling control ingestive behavior, energy balance, and substrate utilization, but only leptin signaling defects cause hypothalamic hypogonadism and infertility. Although GnRH neurons do not express leptin receptors, leptin influences GnRH neuron activity via regulation of immediate downstream mediators including the neuropeptides NPY and the melanocortin agonist and antagonist, MSH, agouti-related peptide, respectively (Barash *et al.,* 1996; Ahima *et al.,* 1997).

Leptin signaling appears to be more important in the onset of puberty in the female, since more energy consumption is required for the reproductive functions in the female. It informs the brain about whether there are sufficient energy stores to initiate reproductive functions (Kiess *et al.,* 2000). Increases in serum leptin levels have been observed around the beginning of the menarche (Gruaz *et al.,* 1998) or the estrous cycle (Zeinoaldini *et al.,* 2006). These results indicated that leptin in female is very crucial in the induction of puberty. It has been suggested that intra-cerebroventricular infusion of leptin into the brain accelerated the onset of puberty; however, peripheral administration of this hormone only prevented delayed puberty caused by insufficient feeding in rats (Zeinoaldini *et al.,* 2006). It has been reported that leptin caused early onset of puberty in mice fed with a normal diet (Ahima *et al.,* 1997). All these findings suggest that leptin directly triggers pubertal onset as well as acting as a permissive metabolic signal in this process. In one of the study (Emine *et al.,* 2013) leptin administration was started before weaning and animals were continuously given leptin for 28 days. In order to examine melatonin modulation of leptin's effects on pubertal maturation, pinealectomies (PNX) were performed on a group of rats to minimize melatonin secretion in the present study. Thus, increased release of leptin and reduced secretion of melatonin were induced, similar to the physiological profiles of these hormones around the onset of puberty. Vaginal opening (VO), one of the morphological signs of puberty, was observed early in rats receiving leptin, with or without pinealectomy. It is thus shown that peripheral administration of leptin may accelerate the onset of puberty in young female rats with access to normal unrestricted food intake. The onset of puberty was determined to be on days 29 and 30 in the sham leptin and PNX leptin groups, respectively, and on day 33 in the intact control group. Body weight in the sham leptin and PNX leptin groups was lower than in the intact control group when vaginal opening was observed. Exogenous leptin infusion was presumed by the brain to show that the adipose tissue

was developed enough to provide the energy needed to initiate puberty, although body weight, and thus fat tissue, was not at a level critical enough to release leptin in these animals. Another interesting finding observed in this study was that removal of the pineal gland did not cause any significant change in leptin's action. The onset of puberty already occurred in a physiologically early phase; therefore, it would be biologically difficult to expect an even earlier onset of puberty as a result of removal of the pineal gland. In addition, melatonin is known to be secreted by extra pineal tissues (Sanchez-Hidalgo *et al.*, 2009) such that melatonin may still be able to prevent early onset of puberty despite the pinealectomy. In this study, serum estradiol values and uterine and ovarian weights did not significantly change among the groups. Since all animals were sacrificed on the day of estrus, no change would be expected in terms of serum estradiol levels. It has been reported by others (Ahima *et al.*, 1997) that leptin did not significantly affect the weights of the uterus or ovaries. From the above discussion it can be concluded that, before weaning peripheral administration of leptin leads to early induction of puberty and pienalectomy does not alter leptin actions on pubertal onset.

4. Melatonin

The role of melatonin in animal reproduction was confirmed in experiments with its exogenous infusion, which successfully mimics the seasonal effects of changing photoperiod (Badura and Goldman, 1992).Melatonin probably regulates production at three levels: the hypothalamic GnRH neurons, pituitary and gonads and reproductive tissues. Melatonin micro- implants in to the area of preoptic and mediobasal hypothalamus of mice (areas that contain GnRH neurons) elicit complete gonadal involution, whereas its injection in other areas was ineffective (Glass and Knotts, 1987). It has been hypothesized that melatonin acts directly on synapses of hypothalamic neurons and inhibits reproduction by decreasing GnRH synthesis and release (Glass and Knotts, 1987; Kennaway and Rowe, 1995). The extracellular messenger functions of melatonin are mediated by its high-affinity membrane receptors expressed in target tissues. In mammals, melatonin receptors are expressed in high density in the hypothalamic neurons localized in the SCN and gonadotropin- releasing hormone (GnRH)-secreting neurons within the preoptic area and/ or the mediobasal hypothalamus, depending on the species. Melatonin receptors are also present in pars tuberalis and pars distalis regions of anterior pituitary (Vaněček *et al.*, 1987; Reppert *et al.*, 1988; Williams and Morgan, 1988; Williams *et al.*, 1991, 1997).

Melatonin receptors are of two subtypes, MT1 and MT2. These receptors are expressed in neonatal pituitary cells. These receptors are also coupled to pertussis toxin. Melatonin activates these receptors (Vaněček and Klein, 1992; Reppert *et al.*, 1994, 1995; Zemková and Vaněček, 1997). This activation decreases the activity of protein kinase A, production of cAMP, and attenuation of gonadotropin-releasing hormone (GnRH)-induced gonadotropin secretion (White *et al.*, 1987; Carlson *et al.*, 1989). This has been confirmed by electrophysiological recordings and single cell calcium that, melatonin causes inhibition of GnRH-stimulated calcium signaling leading to reduction in gonadotropin release (Glass and Knotts, 1987; Kennaway and Rowe, 1995). Melatonin inhibits mobilization of calcium from intracellular stores and also through voltage-dependent calcium channels inhibits calcium influx. Calcium influx inhibition via cAMP/protein kinase C-dependent manner and the associated

calcium-induced calcium release from ryanodine-sensitive intracellular pools by melatonin results in a delay of GnRH-induced calcium signaling (Bezprozvanny *et al.*,1991). Melatonin-induced attenuation of GnRH-induced an inositol (1,4,5)- trisphosphate-mediated calcium release from intracellular pools attenuates the amplitude of calcium signal. As the age advances, the expression of functional melatonin receptors decreases. As a result melatonin tonic inhibitory action on GnRH decreases. In adult organism, melatonin does not affect pituitary functions directly. However, this connection between hypothalamic functions, GnRH release and melatonin release persists and are very crucial in synchronizing reproductive functions and external photoperiod through a mechanisms not well elucidated (Slanař *et al.,* 1997; Zemkov á and Vaněček, 1997, 2000). From the above studies it can be concluded that, melatonin inhibit precocious puberty in individuals by inhibiting gonadotropin secretions during infancy and juvenile period.

5. Role of growth hormone in puberty

This has been confirmed by Sara DiVall and his team at Johns Hopkins University, Baltimore, that IGF-1 in mice has a very important role in synchronizing the timing of puberty onset. The team for studying this issue produced mice that in GnRH-producing nerve cells either lack receptors for IGF-1 or insulin. Normal fertility and pubertal timing were observed in female and male mice with deleted insulin receptors, but normal fertility and delay pubertal development were reported in female and male mice lacking receptors for IGF-1. Furthermore, in normal female mice administration of IGF-1 induced pubertal onset (Luna *et al.,* 1983; Handelsman *et al.,* 1987; Crawford *et al.,* 1993; Sara *et al.,* 2010).

Pubertal onset, initiated by pulsatile gonadotropin-releasing hormone (GnRH), only occurs in a favorable, anabolic hormonal milieu. Anabolic factors that may signal nutritional status to the hypothalamus include the growth factors insulin and IGF-1. It is unclear which hypothalamic neuronal subpopulation these factors affect to ultimately regulate GnRH neuron function in puberty and reproduction. We examined the direct role of the GnRH neuron in growth factor regulation of reproduction using the Cre/lox system. Mice with the IR or IGF-1R deleted specifically in GnRH neurons were generated. Male and female mice with the IR deleted in GnRH neurons displayed normal pubertal timing and fertility, but male and female mice with the IGF-1R deleted in GnRH neurons experienced delayed pubertal development with normal fertility. With IGF-1 administration, puberty was advanced in control females, but not in females with the IGF-1R deleted in GnRH neurons, in control males, or in knockout males. These mice exhibited developmental differences in GnRH neuronal morphology but normal number and distribution of neurons. These studies define the role of IGF-1R signaling in the coordination of somatic development with reproductive maturation and provide insight into the mechanisms regulating pubertal timing in anabolic states.

Pubertal onset is trigger by the release of pulsatile gonadotropin-releasing hormone (GnRH). This only occurs in a favourable, anabolic hormonal milieu. Anabolic factors such as IGF-1 and growth factors insulin may signal nutritional status to the hypothalamus. This is not fully clear that which neuronal subpopulation of the hypothalamus these factors affect, that eventually control GnRH neuron function in reproduction and puberty. GnRH neurons deleted

with IR or IGF-1Rwas generated. Normal fertility and pubertal timing were reported in male and female mice with IR deleted in GnRH neurons. On the other hand normal fertility with delay pubertal development was observed in male and female mice with IGF-1R deleted in GnRH neurons. In control females puberty was advanced with IGF-1 administration, but no pubertal advancement was reported in females with the IGF-1R deleted in GnRH neurons, in control males, or in knockout males. These mice in GnRH neuronal morphology showed developmental differences but normal distribution and number of neurons (Danilovich *et al.*, 1999; Sara *et al*., 2010; Palmert and Boepple, 2001; Keene *et al.*, 2002). Pubertal onset, initiated by pulsatile gonadotropin-releasing hormone (GnRH), only occurs in a favourable, anabolic hormonal milieu. Anabolic factors that may signal nutritional status to the hypothalamus include the growth factors insulin and IGF-1. It is unclear which hypothalamic neuronal subpopulation these factors affect to ultimately regulate GnRH neuron function in puberty and reproduction. We examined the direct role of the GnRH neuron in growth factor regulation of reproduction using the Cre/lox system. Mice with the IR or IGF-1R deleted specifically in GnRH neurons were generated. Male and female mice with the IR deleted in GnRH neurons displayed normal pubertal timing and fertility, but male and female mice with the IGF-1R deleted in GnRH neurons experienced delayed pubertal development with normal fertility. With IGF-1 administration, puberty was advanced in control females, but not in females with the IGF-1R deleted in GnRH neurons, in control males, or in knockout males. These mice exhibited developmental differences in GnRH neuronal morphology but normal number and distribution of neurons. These studies define the role of IGF-1R signalling in the coordination of somatic development with reproductive maturation and provide insight into the mechanisms regulating pubertal timing in anabolic states. Pubertal onset, initiated by pulsatile gonadotropin-releasing hormone (GnRH), only occurs in a favourable, anabolic hormonal milieu. Anabolic factors that may signal nutritional status to the hypothalamus include the growth factors insulin and IGF-1. It is unclear which hypothalamic neuronal subpopulation these factors affect to ultimately regulate GnRH neuron function in puberty and reproduction. We examined the direct role of the GnRH neuron in growth factor regulation of reproduction using the Cre/lox system. Mice with the IR or IGF-1R deleted specifically in GnRH neurons were generated. Male and female mice with the IR deleted in GnRH neurons displayed normal pubertal timing and fertility, but male and female mice with the IGF-1R deleted in GnRH neurons experienced delayed pubertal development with normal fertility. With IGF-1 administration, puberty was advanced in control females, but not in females with the IGF-1R deleted in GnRH neurons, in control males, or in knockout males. These mice exhibited developmental differences in GnRH neuronal morphology but normal number and distribution of neurons. These studies define the role of IGF-1R signalling in the coordination of somatic development with reproductive maturation and provide insight into the mechanisms regulating pubertal timing in anabolic states. Simultaneous increases in GH and IGF-1, and the concomitant changes in the hormonal milieu (i.e. reproductive hormones, testosterone and estrogen, and insulin)are the major contributors to anabolic effects seen throughout the pubertal transition, and are affected by various factors including (but not limited to) energy status and body composition. Effects of cytokines, many of which may be considered catabolic, extend beyond their traditionally viewed role involving the immune system, accompanying

reproductive maturity further regulating aspects of energy and bone metabolism (Casazza *et al.*, 2010).These studies define that, at puberty IGF-1 signalling is very important for inducing timely pulsatile GnRH production. IGF-1 also aid to coordinate puberty with a specific stage of body development.

6. Nesfatin-1

Nesfatin-1 is a hypothalamic peptide. The precursor, NEFA/nucleobindin2 (NUCB2) transformed into Nesfatin-1 (Oh-I *et al.*, 2006).Nesfatin-1 acts *via* leptin-independent manner and is recently recognized as anorexigenic (Colmers, 2007).The role of Nesfatin-1 in the control of other body functions gated by the energy status of the body remains a mystery (Yosten and Samson, 2009). In females it is the NUCB2/nesfatin-1, involved in controlling puberty. In female pubertal rat protein and mRNA of NUCB2/nesfatin were reported along with conspicuous signals at supraoptic (SON), Para ventricular (PVN) and lateral hypothalamus (LHA) nuclei. During pubertal transition, the expression of hypothalamic NUCB2 is raised. The level of its mRNA is elevated at SON, PVN and LHA. Between per pubertal and late infantile periods about a total of three fold rise in its total protein occurs. In pubertal females during persistent sub-nutrition or fasting for 48 h results into diminish hypothalamic NUCB2 mRNA and/or protein levels. Nesfatin-1 central administration at this age brought modest but significant increase in circulating gonadotropins. The magnitude of this increase was conspicuously amplified in a state of food deprivation. During pubertal maturation in female rats, Continuous intra cerebroventricular administration of morpholino oligonucleotides (as-MONs) against NUCB2, significantly deceased serum luteinizing hormone (LH) levels, reduced hypothalamic NUCB2 protein content, decreased ovarian weights and delayed vaginal opening. In contrast, in adult female rats, intra cerebroventricular injection of nesfatin did not stimulate LH or follicle stimulating hormone secretion; neither did central as-MON infusion alter preovulatory gonadotropin surges, despite suppression of hypothalamic NUCB (Oh-I *et al.*, 2006;David *et al.*, 2010). In sum, Nesfatin-1in female rate is a very important regulator of HPG-axis at puberty.

7. Ghrelin

Experimental evidences from different species, including rodents and primates, have accumulated in recent years to strongly suggest that the gut hormone, ghrelin, which operates as signal of energy insufficiency and functional antagonist of leptin, may play a physiological and eventual patho-physiological role in the regulation of puberty onset and gonadal function. Such a 'reproductive' dimension of ghrelin is likely to include, among others, its ability to modulate gonadotropin secretion, to influence the timing of puberty and to directly regulate gonadal (both testicular and ovarian) functions. In keeping with its proposed role as signal for energy deficit, most of the reported actions of ghrelin upon the reproductive axis appear to be inhibitory, thus suggesting that ghrelin may convey at least part of the suppressive effects of low body fuel stores and energy insufficiency on puberty and fertility (Fernandez-Fernandez *et al.*, 2007; Tena-Sempere, 2013).

Ghrelin, mainly produced by the stomach, can act through its functional receptor GHS-R1a in endocrine or/and local manner in all male and female reproductive tissues including

hypothalamus, pituitary, ovary, and testis. It is well known that ovarian steroid production (oestradiol and progesterone) can modulate pituitary and hypothalamus secretions. Furthermore, GnRH produced by the hypothalamus controls LH, and FSH secretion that is known to regulate gonad functions. In mammalian species, ghrelin treatment inhibits GnRH, LH and FSH secretion at the hypothalamic and pituitary levels. Opposite effects have been describing in several species of fish. In the gonads, ghrelin exerts also inhibitory effects by altering steroidogenesis and germ cells production or viability in ovary and testis. In contrast, ghrelin treatment reduces proliferation of leydig cells whereas it increases those of granulosa cells (Sirotkin *et al.*, 2009; Gaytan *et al.*, 2004; Dupont *et al.*, 2010). In another study in ewe, Ghrelin treatment attenuated GnRH-induced a preovulatory surge of both gonadotropins, with the effect being greater for LH. No difference was detected for insulin, estradiol, and progesterone concentrations, and insulin-like growth factor-I levels were increased in the GH group. It is suggested that in sheep, ghrelin conducts specific regulatory effects on the GnRH/LH axis, and provide for the first time strong evidence that besides its central action, ghrelin might regulate gonadotropins release acting at the pituitary level (Dovolou *et al.*, 2013).Consistent with its role in modulating gonadotropin secretion, ghrelin delays pubertal onset both in male and female rats but males appear to be more sensitive than females (Roa *et al*., 2010). A similar inhibitory action of ghrelin has been suggested in humans, which show a progressive decline in circulating ghrelin levels along puberty. Of note, preclinical studies have demonstrated that the inhibitory actions of ghrelin on LH secretion in vivo and ghrelin's ability to delay puberty onset can be mimicked by administration of des-acyl ghrelin suggesting the involvement of an independent GHS-R1a pathway in both effects (Muccioli *et al.*, 2011).

8. Conclusion

During puberty various endogenous factors play an important role in the resurgence of gonadotropin-releasing hormone secretion from the hypothalamus, which triggers a cascade of hormone-dependent processes. It is concluded that leptin causes early induction of puberty and sexual maturation. Melatonin and leptin do not interact in the initiation or progression of the human pubertal development, although they probably act as permissive factors for the onset of puberty. Melatonin plays an important role in calcium signaling to the GnRH neuron through MT_1 and MT_2 receptors. Besides these, growth hormone is the major player in the control of ovarian functions conjunction with gonadotropin. Ghrelin play inhibitory role in the onset of puberty because there is progressive decline in the circulating ghrelin level along puberty.Nesfatin-1 act as a modulator of different element of HPG axis from the central pathway involved in the onset of (female) puberty to the key testicular cell populations. Kisspeptin triggers puberty, by increasing its amplitude and frequency at the end of juvenile period. GABA regulates kisspeptin pulsatility in infancy, juvenile and pubertal stage but, what regulates GABA is unknown. Thus the most key endogenous factor that causes puberty remains a mystery. Various environmental cues affect these endogenous signaling, resulting into alter pubertal timing. Further studies are needed to explore the molecular mechanism, of how these environmental cues affect puberty onset.

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