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Orexin A and Central Precocious Puberty

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ABSTRACT

Orexin A and orexin B are neuropeptides that control appetite and play an important role in energy homeostasis. Central precocious puberty (CPP) is an energy consuming process, which characterized as GnRH neurons activated in advance. Kisspeptin is a trigger of GnRH neurons activation, known as a milestone of puberty initiating. Maternally expressed gene 3 (MEG3) is an imprinted long non-coding RNAs (LncRNAs), which is highly expressed in the brain and pituitary gland, may involve in pituitary hyperplasia of CPP. In this review, we searched literature to clarify the possible relationship between orexin A and CPP.

Keywords: Orexin A, Central precocious puberty, Kisspeptin, Maternally expressed gene 3

INTRODUCTION

Data sources

This review was conducted under PRISMA-P guidance. A search of literature was performed using Pub Med (MEDLINE) and EMBASE databases. Literature search was informed by the use of key words: orexin; hypocretin; precocious puberty, hypothalamus, pituitary, kisspeptin, MEG3. Which were formulated to ensure that only relevant sources are obtained. Studies were published in English language. The first search of literature was conducted as a component of broad orexin and precocious puberty. A supplementary study was further conducted as a way of ensuring that the material touching the subject was not misplaced.

Orexin

Orexin A and orexin B, also known as hypocretin A and B, are neuropeptides that control body arousal wakefulness and appetite [1,2]. Orexins are highly suppressive neuropeptides which was first found in the brain of rats [3]. Thereafter the neuropeptide is shaped in very small population of cells in the lateral and posterior hypothalamus. By affecting dopamine, norepinephrine, histamine and acetylcholine systems, Orexins strongly excite various brain neurons to influence an organism's wakefulness [4]. Orexin A and orexin B are potent agonists for the OX1 and OX2 G-protein coupled receptors. Orexin A is a more selective ligand for OX1, while OX2 binds with orexins A and B with similar affinity. These receptors will recognize molecules outside the cell and will therefore activates an inside signal pathways to elicit cellular response eventually [5]. The structure of orexins and their receptors is highly conserved in mammals including rodents and humans. Both receptor genes are widely expressed within the rat brain, but with some differences in the OX1 and OX2 distribution; furthermore, differential roles for OX1 and OX2 receptors have been suggested [6]. Moreover, the orexinergic system has been described in several peripheral tissues outside the CNS, with different biological relevance [7-9]. Orexin neurons are specially localized in the lateral hypothalamus and perifornical areas, and display arousal-promoting peptides. Immunoelectron microscopy indicated that glutamate was localized with orexins in the same synapses in tuber mammillary nucleus (TMN) [10] and orexin-B have a role in increasing presynaptic release of glutamate in ventral tegmental region VTR) [11]. Equally, orexin neurons in the lateral hypothalamus also produce dynorphin [12]. Co-regulation of neuronal impulsiveness in TMN by orexin and dynorphin was established in 2004 by Eriksson, et al. [13]. Dynorphin repressed the spontaneous inhibitory postsynaptic potentials but orexins enhanced them by presynaptic OX2 receptors in TMN neurons. After they were simultaneously administrated, these two peptides created a comparable effect to application of dynorphin alone, suggesting a more challenging mechanism of orexin regulation in neuronal impulsiveness. The two orexin peptides

are derived from the same precursor pro-orexin, and share about 46% of series identity of primary structure. Orexin-A has 33 amino acids with two disulfide bonds within the peptide chain while orexin-B is made up of 28 amino acids. Both of these two peptides are highly preserved in, rats, dogs, mouse, pigs, zebrafish, humans and other vertebrates [3]. Originated from lateral hypothalamus and perifornical areas, orexinergic characters are broadly spread over different brain areas. Although exact rules of receptors sharing can barely be highlighted, some neuronal cell types act to favor specific orexin or orexin receptors [14]. For instance, neurons in locus coeruleus express generous OX1 receptor whereas large amounts of OX2 receptors are detected in neurons in TMN [10]. The hypothalamus, cerebral cortex, and other brain structures show mixed circulation of an equally receptors.

Orexin-induced signal pathways

Several studies have demonstrated the facts from producing cells indicate that both OX1 and OX2 receptors can couple to Gq, Gs, and Gi [15]. However, results from these recombinant cells do not provide details about how orexin receptors respond to the ligands and agonists in neurons. Another study has been proposed that *in vitro* administration of orexins can easily increases activation of inhibitory G proteins in brain stem nucleus [16]. In additionally other studies show that Gq proteins can be triggered by orexin in medial and lateral hypothalamic neurons and nucleus tractus solitarius neurons [17]. In sympathetic of pertussis toxin-insensitive G proteins and phospholipase C (PLC) are triggered to rise intracellular Ca^{2+} levels in TMN neurons when stimulation of orexin-A or orexin-B [18]. In contrast, orexins initiate Gi proteins through OX2 receptors, and decrease intracellular Ca^{2+} levels in propiomelanocortin neurons [19]. A kind preganglionic neurons, activation of Gi proteins was followed by inhibition of K^{+} channels [20].

Precocious puberty

Puberty is a time of immense developmental change. From the earlier work as demonstrated by Marshall and Tanner, we know that the process occurs in a predictable sequence of events in both girls and boys. The first sign of puberty in girls is usually breast development, followed by growth of pubic hair, a linear growth spurt, and lastly menarche. In boys, the first sign of puberty is enlarged testicular, which is followed by thinning of the scrotum, penile growth, pubic hair development, and at last, a linear growth spurt. When comparing genders, peak height velocity and secondary sexual development occur later in boys than in girls. On average, both girls and boy complete secondary sexual development in three to five years.

Precocious puberty is defined as the onset of secondary sexual characteristics before the age of 8 y in girls and 9 y in boys and is associated with an increase in linear growth velocity, acceleration of bone maturation, and can result in early epiphyseal closure if untreated [21]. Furthermore, if left untreated, the impact of early maturation because of central precocious puberty (CPP) places children at risk for developing psychological problems, deviant behaviors, and early pregnancy and childbirth when compared with their on-time and late maturing peers. Children can experience such hostile feelings and marginalization from their peers that psychosocial and behavioral difficulties can be considered as possible reasons to treat [22].

The most common cause of precocious puberty is idiopathic CPP, which occurs much more commonly in girls [23]. Goals of therapy involve the restoration of a prepubertal state, and therefore, attenuating the multitude of deleterious effects of early sex steroid exposure on the developing young female or male's body [24]. CPP has traditionally been treated with monthly injections of depot parenteral preparations of gonadotropin-releasing hormone agonists [25,26]. Although effective in suppression of the hypothalamic-pituitary-gonadal axis and offers very few technical adverse effects (the most common of which is an abscess), monthly injections for children are painful, require multiple trips to the doctor, which can be inconvenient for parents and can lead to decreased compliance. In order to enhance the clinical compliance, 3-month leuprolide acetate formulation has been used. Although it is possible to undergo less frequent injections, and therefore theoretically have better compliance, with 3-mo depot leuprolide formulations, comparative studies have found more effective and sustained gonadotropin suppression with monthly injections [27]. Another alternative treatment is a subcutaneous implant that contains Histrelin acetate, which is continuously released for more than 1 y; then it is removed or replaced with a new implant. From the time of the development of the Histrelin implant, several studies have described the efficacy of these Histrelin implants and the resumption of puberty after its removal [28]. Multicenter Trial has proved Long-term Histrelin implant therapy can provide sustained safe and effective gonadotropin suppression and improve predicted adult height in children with CPP [29].

Kisspeptins and the metabolic control of puberty

Knowledge of the neurobiological basis of puberty in general, and of the mechanisms for its metabolic regulation

has substantially enlarged in recent years. Probably, the most important development in this front was the recognition of the essential roles of kisspeptins in the central control of different aspects of reproductive function, especially puberty onset [30]. Due to the high rapid progress of this field, a detailed review of major features of the physiology of kisspeptins shall not be considered here but can found in the works of Clarke, et al. [31]. However, in order to introduce later sections of this review, a brief account of the proposed roles of kisspeptins as putative gatekeepers of puberty has been presented here. Kisspeptins, encoded by the Kiss1 gene, are a family of structurally-related peptides with the ability to activate the G protein-coupled receptor, Gpr54 or Kiss1R [32,33]. A growing number of studies, conducted in different model species as well as in humans, have set the contention that kisspeptins are key transmitters involved in the reproductive brain. These originate from discrete neuronal populations in the hypothalamus and are able to stimulate the secretory activity of GnRH neurons. The neuro-anatomy of such populations has been well characterized in rodents, where two major sets of Kiss1 neurons, located in the arcuate nucleus (ARC) and the rostral periventricular area of the 3rd ventricle (RP3V), have been described [34]. The importance of kisspeptins in reproductive function is not only illustrated by the HH phenotypes of humans and mice with inactivating mutations of the Kiss1 or Gpr54 genes, but also by solid neuroanatomical, electrophysiological, pharmacological and hormonal data [35]. Convergently these data have documented the involvement of the so-called Kiss1 system in the regulation of virtually all aspects of reproductive maturation and function, from brain sex differentiation to the neuroendocrine control of ovulation and sex steroid feedback [36]. In such a scenario, the possibility that the Kiss1 system plays a physiological role in the control of puberty has attracted considerable attention and has been the subject of thorough analyses in numerous (mammalian and no mammalian) species [37]. The findings of the lack of pubertal maturations in patients or mice with null mutations in Gpr54 or Kiss1 genes suggest a prominent, indispensable role of kisspeptin signaling in the control of puberty. However due to the fact that congenital inactivation of Gpr54 or Kiss1 perturbs puberty does not necessarily imply an activation role of the Kiss1 system in puberty itself, as the above phenotype (lack of puberty) may derive from the alteration of early developmental phenomena in the absence of kisspeptin signaling, in any case the available experimental evidence does suggest that kisspeptins participate in the activation program responsible for puberty as documented by a combination of neuroanatomical and functional analyses, conducted mainly in rodent species, especially in the female [38]. Expression studies documented an increase in the hypothalamic expression of the Kiss1 gene during pubertal maturation in the rat and monkey, therefore suggesting a rise of the kisspeptin tone at the hypothalamus during puberty [39]. Pharmacological analyses demonstrated the functional relevance of such a phenomenon, since repeated administration of kisspeptin was sufficient to advance the occurrence of different indices of puberty onset in immature female rat.

Considering the important roles of kisspeptin signaling in the control of puberty and reproduction, and relevance of energy homeostasis and metabolic cues in pubertal regulation, especially in females, it is not surprising that the possibility of specific functions of Kiss1 neurons in the metabolic control of puberty and the gonadotropic axis have been thoroughly analyzed in recent years using a number of experimental trials [40]. As a potential call of caution, the majority of those studies have focused on the consequences in terms of Kiss1 expression and/or function of conditions of negative energy balance that causes some degree of pubertal suppression and hypogonadism, and hence have addressed rather extreme experimental conditions [41]. Apart from this limitation the available evidence does suggest that Kiss1 neurons are sensitive to the metabolic energy state of the organism and likely participate in the modulation of the reproductive axis by metabolic cues, at least under certain circumstances. As side comment, most of the supportive data has been obtained in adult models hence, extrapolation of adult results to puberty must be made with caution. Experimental data has documented that extreme conditions of negative energy balance induce a suppression of the hypothalamic Kiss1 system. This has been well characterized at the mRNA and protein levels in pubertal rats, in which fasting decreased hypothalamic Kiss1 expression and kisspeptin immunoreactivity in association with a significant lowering of circulating LH levels [42]. A similar response to fasting has been also reported in adult female rats, and adult male mice, in which a decrease in hypothalamic Kiss1 mRNA was detectable as earlier as 12-hour post food deprivation [43].

MEG3 in central nerves system

Maternally expressed gene 3 (MEG3) is an imprinted long non-coding RNAs (LncRNAs), which is highly expressed in the brain and pituitary gland [44]. Normally, in pituitary, it is co-localized in gonadotroph-producing cells. But human pituitary tumors of gonadotroph cell linage do not express MEG3 [44]. In addition, MEG3 can suppress numerous human cancer cell lines including brain cancer derived lines [45-49]. Low expression of MEG3 is associated with increased risk of metastasis and with a poor prognosis. A newest meta-analysis indicated that long non-coding MEG3

might serve as a potential novel biomarker to indicate the clinical outcomes of human cancers [50]. These studies suggest that the MEG3 gene play a vital role in tumor suppression. Predominantly, the known tumor suppressors are protein-coding genes. However, recent studies have proved that another class of genes, whose products are lncRNAs with sizes >200 nucleotides, also play an important role in tumor suppression [51]. MEG3 is located on human chromosome 14q32.2 [52] and located on mouse distal chromosome 12 [53]. The gene expression in this area is tightly guided by at least two differentially methylated regions (DMRs): the MEG3-DMR and the intergenic DMR (IG-DMR). The imprinted expression of these non-coding RNAs also plays an important role in development and growth [54].

Pituitary adenomas are the most common intracranial tumor in human with diverse endocrine and neurological effects, accounting for about 10% of all diagnosed brain neoplasms [55]. Secretory adenomas can produce one or more pituitary hormones such as GH, TSH, ACTH, and prolactin, causing various clinical syndromes. Pituitary adenomas are typically monoclonal origin tumors and a somatic mutation is a necessary event in tumor formation [56]. However, mechanisms of selective clonal proliferation remain unclear. None of commonly known oncogenes and tumor suppressor genes, such as MEN-1, c-myc, ras, Rb, p53, gsp, and nm23, are involved in the pathogenesis of the majority of human pituitary tumors [57]. Nonfunctioning pituitary adenomas (NFAs) account for approximately 40% of diagnosed human pituitary tumors in clinical. Recently, it is revealed that MEG3 is a lncRNA tumor suppressor in the pituitary and its inactivation contributes to NFA development [58]. The pituitary of children with CPP often underlie a status of hyperplasia which is similar to pituitary adenomas, make it difficult to be identified. So, it is hypothesized that MEG3 may also inhibit the pituitary hyperplasia of CPP.

CONCLUSION

In summary, CPP is characterized as premature activation of GnRH neurons. Kisspeptin is a trigger of GnRH neurons activation and known as a milestone of puberty starting. Puberty is process of energy-consuming, and Orexin A is involved in energy balance. Pituitary hyperplasia of patients with CPP usually look like pituitary adenoma, whose pathogenesis is related to MEG3. So, Orexin A/ Kisspeptin/MEGE may interact as a network.

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