IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 3 Ver. IX (March. 2017), PP 122-124
www.iosrjournals.org

Role of Orexin in Reproductive System

Abdinasir Isse[1], Yue-Hong Tao, Waleed Naji, Sami Ullah*
Department Of Pediatrics, Clinical Medical School Of Yangzhou University (Northern Jiangsu People's Hospital), Yangzhou , China

Abstract: *Orexins (OX), OX-A and OX-B, were initially identified as hypothalamic neuropeptides primarily involved in the control of food intake and states of arousal. Thereafter, orexins have been substantiated as putative pleiotropic regulators of a wide diversity of biological systems, including different neuroendocrine axes. Among the latter, compelling experimental evidence has recently been documented that orexins, mainly OX-A, may act at different levels of the hypothalamic-pituitary-gonadal (HPG) axis to modulate reproductive function. However, orexin neurons are "multi-tasking" neurons that regulate sleep/wake states as well as feeding behavior, emotion, and reward processes. Orexin deficiency causes abnormalities in energy homeostasis, stress-related behavior, and reward systems. Male sexual behavior is altered by orexin receptor-1 agonists or antagonists, suggesting a role for orexin-A in this naturally rewarding behavior. However, the specific role of endogenous orexin-A or B in different elements of male sexual behavior is currently unclear. Therefore this review aims to explain the role of orexin in male and female reproductive system.*
Keywords: *orexin; hypocretin; puberty, sexual behavior, reproductive, hypothalamus, pituitary-gonadal*

I. Introduction

Orexin also called hypocretin is a neuropeptide that regulate, arousal wakefulness, and appetite. The orexins bind to two G-protein coupled receptors, orexin receptor 1 (OxR1) and orexin receptor 2 (OxR2), with OxR1 being selective for orexin-A and OxR2 being equally selective for both orexin-A and orexin-B[1]. The previous studies demonstrated that the sleep disorder narcolepsy is caused by orexin deficiency in human and animals[2, 3]. High levels of orexin-A have been reported to be correlated with happiness in human subjects, while low levels reported to be correlated with sadness[4] . High levels of Orexin also reported to be associated with increase the meal size and food intake[5] . Orexin neurons project their axons broadly throughout the brain and spinal cord to regions important for arousal and sleep, feeding behavior, and reward and motivation[6] .Orexin-A is a peptide synthesized mainly by neurons with perikarya located within and around the lateral and posterior hypothalamus, found to modulate the activity of gonadotropin-releasing hormone (GnRH) neurons and gonadotropin-secreting pituitary cells [7]. Orexin-A has also been shown to affect GnRH release. Orexin A is involved in the regulation of sleep/wakefulness, energy homeostasis and locomotor activity[8] The precise role of orexin in reproductive system remains unclear, therefore this review aims to explain the role of orexin in male and female reproductive system.

II. Methods

This study considers a number of documents and studies that need to be considered for the study. 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; puberty, sexual behavior, reproductive, hypothalamus, pituitary-gonadal. Which were formulated to ensure that only relevant sources are obtained. Studies were limited to rats and humans which were published in English language. The first search of literature was conducted as a component of broad orexin and reproductive system. A supplementary study was further conducted as a way of ensuring that the material touching the subject was not misplaced. The analysis included analyzing the significance of the differences in observation and findings, and making an inference. For instance, in each case, the analysis would seek to understand what the number of sources that support certain positions is. Subsequently, the analysis would examine the significance in differences.

Orexins And Orexin Receptors:

Orexin A and orexin B (also known as hypocretin A and B) are neuropeptides derived by proteolytic cleavage from a 130 amino acid precursor, prepro-orexin (PPO), which was isolated from the rat hypothalamus(9) Both are synthesized mainly, but not exclusively, by neurons with their soma located in the lateral hypothalamus and projections throughout the brain. Both peptides are potent agonists for the OX1 and

OX2 G-protein coupled receptors. Orexin A is a more selective ligand for OX1, while OX2 binds both orexins A and B with similar affinity (10) 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 (11) Furthermore, the orexinergic system has been described in several peripheral tissues outside the CNS, with different biological relevance (11, 12, 13, 14) All these aspects are clearly expounded in different sections of the present publication.

Orexin receptor expression in the rat estrous cycle:

For successful reproduction, the hormonal secretion of the estrous cycle must be combined with appropriate nutritional and vigilance states. Though some studies have addressed the impact of orexins on the regulation of pituitary secretion (15, 16), little is known about the inverse relationship, i.e. the impact of the physiological hormonal milieu on the orexinergic system. To address this issue, Silveyra et al, started by determining PPO, OX1 and OX2 expression in hypothalamus and pituitary from Sprague–Dawley female rats at different stages of the estrous cycle and correlated these expressions with the endocrine status, the dark–light cycle and food consumption. The author founded that OX1 and OX2 expression increased in the hypothalamus and pituitary, but not in the front parietal cortex, between 17:00 hours and 23:00 hours of pro estrus, without variations in estrus, diestrus or males. PPO in hypothalamus increased only during pro estrus afternoon. As the increases in OX1, OX2 and PPO observed bear no relationship to the light–dark cycle or to food intake, Silveyra et al, understand that they are cycle-related events associated with the neuroendocrine status of pro estrus (17)

Orexin in Male reproductive System

Several studies (15, 18, 19) have demonstrated a role of orexin in sexual performance, reward, and motivation. Electrical brain stimulation in the anterior dorsolateral hypothalamus produced a marked increase in sexual capacity in some male rats. Several measures of sexual behavior, including the length of the post ejaculatory refractory period, were significantly affected. (18) All males were tested for sexual behavior during 4 mating sessions conducted every second day in the home cage. During each session, males mated with a receptive female to one ejaculation or for 60 minutes, whichever came first. Mating behavior was recorded as described above and copulation efficiency was also calculated [numbers of intromissions [(numbers of mounts + numbers of intromissions). Statistical differences in parameters of sexual performance were compared between lesion and sham groups for each trial using a one way ANOVA with lesion surgery as a factor and Fisher's LSD test with a 95% confidence level, or when appropriate, non-parametric tests were run using a Kruskal Wallis one-way ANOVA with lesion surgery as a factor and Dunn's test with a 95% confidence level. In addition, data for each group were compared to the pre-surgery data using paired t-tests. (19)

Orexin in Female reproductive System

Some previous studies had investigated a possible relationship between the orexinergic system and the hypothalamic-pituitary-gonadal axis. Most works explored the actions of orexins on GnRH neurons and gonadotropin secretions mainly in rodents, though some controversy remained regarding the effects observed (15, 24, 25), In vivo, a dual effect of an intracerebroventricular administration of orexin A has been reported; the peptide was able to stimulate luteinizing hormone (LH) secretion in castrated female rats primed with oestradiol and progesterone but inhibited this gonadotropin secretion in unprimed rats. Thus, a steroid regulation of the orexin receptors was hypothesized (20, 21, 22, 23). Furthermore, an anti-orexin antiserum injection was also reported to inhibit LH and prolactin surges in rats (21). In vitro, when hypothalamic explants from male rats and from females in proestrus were incubated with orexin A, GnRH release was stimulated. However, this effect was not observed in explants obtained at estrus or metestrus. In pituitary cell cultures obtained from proestrous females, orexin A inhibited the GnRH-stimulated LH release (22). The GT1-7 cell line showed an increased GnRH gene expression and secretion in response to orexin A stimulus (25)

III. Conclusion

Orexin neurons provide crucial links between energy balances, emotion, reward systems, and arousal the new data suggest that orexins may act directly on GnRH neurons in the investigated structures. The main intension of this review is that; orexins may affect reproductive functions at the highest level of the hypothalamus-pituitary gonadal axis. In summary, a clear relationship between the mechanisms of the orexinergic system expression and the hormonal situation in the hypothalamus, pituitary and ovary, and its dependence on the time of the day, were described. All together these results suggest that the orexinergic system might be a general link among vigorous functions such as reproduction, food intake, alertness and the inner

biological clock.

References

[1]. Sakurai, T., et al., Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell, 1998. 92(4): p. 573-585.
[2]. Chemelli, R.M., et al., Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell, 1999. 98(4): p. 437-451.
[3]. Lin, L., et al., The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell, 1999. 98(3): p. 365-376.
[4]. Blouin, A.M., et al., Human hypocretin and melanin-concentrating hormone levels are linked to emotion and social interaction. Nature communications, 2013. 4: p. 1547.
[5]. Baird, J.-P., et al., Orexin-A hyperphagia: hindbrain participation in consummatory feeding responses. Endocrinology, 2009. 150(3): p. 1202-1216.
[6]. Peyron, C., et al., Neurons containing hypocretin (orexin) project to multiple neuronal systems. The Journal of Neuroscience, 1998. 18(23): p. 9996-10015.
[7]. Rosati, S., et al., Histrelin for central precocious puberty—a single surgeon experience. Journal of Surgical Research, 2015. 198(2): p. 355-359.
[8]. Abbas, M.G., et al., Comprehensive Behavioral Analysis of Male Ox1r−/− Mice Showed Implication of Orexin Receptor-1 in Mood, Anxiety, and Social Behavior. Frontiers in behavioral neuroscience, 2015. 9.
[9]. De Lecce, L., Kilduff, T.S., Peyron, C., Gao, X., Foye, P.E., Danielson, P.E., Fukuhara, C., Battenberg, E.L., Gautvik, V.T., Bartlett, F.S., 2nd, Frankel, W.N., van den Pol, A.N., Bloom, F.E., Gautvik, K.M. & Sutcliffe, J.G. 1998.
[10]. Sakurai, T., Amemiya, A., Ishii, M., Matsuzaki, I., Chemelli, R.M., Tanaka, H., Williams, S.C., Richarson, J.A., Kozlowski, G.P., Wilson, S. et al. 1998. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 92, 1 page following 696.
[11]. Brogan, R.S., Grove, K.L. & Smith, M.S. 2000. Differential regulation of leptin receptor but not orexin in the hypothalamus of the lactating rat. J Neuroendocrinol 12, 1077–1086.
[12]. Cluderay, J.E., Harrison, D.C. & Hervieu, G.J. 2002. Protein distribution of the orexin-2 receptor in the rat central nervous system. Regul Pept 104, 131–144.
[13]. Hervieu, G.J., Cluderay, J.E., Harrison, D.C., Roberts, J.C. & Leslie, R.A. 2001. Gene expression and protein distribution of the orexin-1 receptor in the rat brain and spinal cord. Neuroscience 103, 777–797.
[14]. Peyron, C., Tighe, D.K., van den Pol, A.N., de Lecea, L., Heller, H.C., Sutcliffe, J.G. & Kilduff, T.S. 1998. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 18, 9996–10015.
[15]. Pu, S., Jain, M.R., Kalra, P.S. & Kalra, S.P. 1998. Orexins, a novel family of hypothalamic neuropeptides, modulate pituitary luteinizing hormone secretion in an ovarian steroiddependent manner. Regul Pept 78, 133–136.
[16]. Jaszberenyi, M., Bujdoso, E., Pataki, I. & Telegdy, G. 2000. Effects of orexins on the hypothalamic-pituitary-adrenal system. J Neuroendocrinol 12, 1174–1178.
[17]. Silveyra, P., Catalano, P.N., Lux-Lantos, V. & Libertun, C. 2007a. Impact of proestrous milieu on expression of orexin receptors and prepro-orexin in rat hypothalamus and hypophysis: actions of Cetrorelix and Nembutal. Am J Physiol Endocrinol Metab 292, E820–E828
[18]. Vaughan, E. and A.E. Fisher, Male sexual behavior induced by intracranial electrical stimulation. Science, 1962. 137(3532): p. 758-760.
[19]. Andrea R. Di Sebastiano1, Sabrina Yong-Yow etal Horm Behav. 2010 August ; 58(3): 397–404. doi:10.1016/j.yhbeh.2010.06.004.
[20]. Furuta, M., Funabashi, T. & Kimura, F. 2002. Suppressive action of orexin A on pulsatile luteinizing hormone secretion is potentiated by a low dose of estrogen in ovariectomized rats. Neuroendocrinology 75, 151–157.
[21]. Kohsaka, A., Watanobe, H., Kakizaki, Y., Suda, T. & Schioth, H.B. 2001. A significant participation of orexin-A, a potent orexigenic peptide, in the preovulatory luteinizing hormone and prolactin surges in the rat. Brain Res 898, 166–170.
[22]. Russell, S.H., Small, C.J., Kennedy, A.R., Stanley, S.A., Seth, A., Murphy, K.G., Taheri, S., Ghatei, M.A. & Bloom, S.R. 2001. Orexin A interactions in the hypothalamo-pituitary gonadal axis. Endocrinology 142, 5294–5302.
[23]. Irahara, M., Tamura, T., Matuzaki, T., Saito, S., Yasui, T., Yamano, S., Kamada, M. & Aono, T. 2001. Orexin-A suppresses the pulsatile secretion of luteinizing hormone via beta-endorphin. Biochem Biophys Res Commun 281, 232– 236
[24]. Tamura, T., Irahara, M., Tezuka, M., Kiyokawa, M. & Aono, T. 1999. Orexins, orexigenic hypothalamic neuropeptides, suppress the pulsatile secretion of luteinizing hormone in ovariectomized female rats. Biochem Biophys Res Commun 264, 759–762.
[25]. Sasson, R., Dearth, R.K., White, R.S., Chappell, P.E. & Mellon, P.L. 2006. Orexin A induces GnRH gene expression and secretion from GT1-7 hypothalamic GnRH neurons. Neuroendocrinology 84, 353–363.