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Research Paper

The Role of Orexin-A in Water Intake in Water-deprived Rats

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ABSTRACT

Background: The lateral hypothalamus (LH), which produces orexin, is vital for body solution homeostasis. Lateral hypothalamus (LH) lesion causes adipsia and its stimulation increases water intake.

Objective: This study aimed to investigate the effect of an intracerebroventricular (ICV) injection of orexin-A (OXA) on water-drinking behavior in water-deprived rats.

Metods: A total of 32 male Wistar rats (220–250 g) were used and divided into 4 groups, control (no injection), vehicle (Normal saline, 5 µL), OXA (30 µg/rat), SB-334867 (OXA receptor selective antagonist, 30 µg/rat). After the microinjection of drugs or vehicles in the right lateral ventricle, each rat was placed individually into the metabolic cage and the amount of water intake, the delay time for the first water intake, and the referral number for water intake were recorded for 4 h.

Findings: This study showed that ICV administration of OXA increased both water intake and the referral number for water intake in water-deprived animals ($P<0.05$). On the other hand, ICV administration of SB-334867 decreased water intake compared to vehicle and control groups.

Conclusion: It can be concluded that OXA has a regulatory role in water drinking behavior in water-depriving states.

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1. Introduction

The amount of body fluids is physiologically balanced, mainly by thirst and diuresis. The brain receives neural and hormonal messages that adjust the amount of drinking water [1-3]. Few substances have been discovered to affect water intake so far. For example, angiotensin II rapidly stimulates water intake and nesfatin-1, a post-translational product of the nucleobindin-2 gene, can inhibit water intake [4-6]. Moreover, secretin, obestatin, apelin, histamine, and glucagon-like peptide-1, morphine, N-methyl-D-aspartate (NMDA) receptors, and sex hormones can have regulatory effects on drinking behavior [7-14]. Recent studies show that orexin is also vital in the homeostasis of body fluids [13]. Orexin (hypocretin) is a neuropeptide that was simultaneously discovered by two independent research teams [15, 16]. Two different orexin neuropeptides, orexin-A (OXA) and Orexin-B, have been identified up to now. Widespread projections of orexinergic neurons in the central nervous system (CNS) are concerned with the regulation of various brain functions, such as feeding [16-19], wakefulness [20, 21], analgesia after stress [18, 22-25], reward and addiction [26-31]. Sakurai et al. described two different orexin receptors coupled to G proteins, known as OX1 and OX2 [16]. These receptors are differently localized in the CNS, especially in the nuclei involved in critical physiological processes [32-35]. The lateral hypothalamus (LH) is involved in the regulation of water and food intake [16, 36, 37]. Numerous studies have shown that LH lesion causes adipsia, that electrical stimulation of the LH increases water intake, such as intraventricular administration of OXA or orexin-B, and that fasting increases prepro-orexin mRNA levels in the LH [37]. It also seems OXA is involved in food and water intake through OX1 receptors [27]. Despite all the studies conducted so far, the effect of intracerebroventricular (ICV) injection of OXA on water-drinking behavior in water-deprived rats is unclear. For this purpose, in the current study, we evaluated the effects of ICV injection of OXA and its antagonist on water intake behavior in water-deprived male rats.

2. Materials and Methods

Animals

Adult Sprague-Dawley rats (220–250 g) were purchased from the Razi institute (Karaj City, Iran). Animals were housed in a controlled temperature room under a 12 hour light-dark cycle with lights on from 7_{AM} to 7_{PM}. Food and water were provided except 12 hours before the experiments. All processes involving animals are conducted according to the policy of the Iranian convention for the protection of vertebrate animals used for experimental purposes, and the protocol was approved by the Ethics Committee of the Qazvin University of Medical Sciences, Qazvin City, Iran.

Drugs

The drugs used in the present study were OXA and SB-334867 (OX1 receptor selective antagonist) and were purchased from Tocris Bioscience (Bristol, UK). The drugs were dissolved in dimethyl sulfoxide (DMSO) and sterile 0.9% saline (up to 1% v/v).

Stereotaxic surgery and microinjection

Rats were initially anesthetized with ketamine and xylazine (100/10 mg/kg). A 23-gauge, stainless steel guide cannula was stereotaxically (Narishige, Japan) lowered 2 mm above the lateral right ventricle by applying coordinates from the Paxinos and Watson atlas [38], incisor bar -3.3 mm, 0.9 mm posterior to the bergma, -1.8 mm lateral to the sagittal suture, and 3.8 mm below the top of the skull. The cannula was anchored with dental cement to stainless steel screws in the skull. After a week of recovery, each rat was transferred to the test room 12 hours before the test and was deprived of water. ICV administration of drugs or respective vehicles was conducted with a stainless steel cannula (30-gauge; 0.3 mm outer diameter) connected to a 5 µL Hamilton syringe via a polyethylene tube. A volume of 5 µl of drug solution or vehicle was injected into the ventricle in 60 s (30 µg/rat) and the injection cannula was gently removed 1 minute later.

Experimental protocols

In the present study, four water-deprived groups of animals were considered as follows, control (cannulated/no injection), vehicle (normal saline; 5 µL/rat), OXA (30 µg/rat), and SB-334867 (30 µg/rat). The doses for the drugs were selected according to the previous studies [39-41].

Behavioral studies

After microinjections, each rat was individually placed in a metabolic cage, and the amount of water intake, the delay time for water intake, and the referral number for water bottles were recorded for 4 hours [16].

Histology

At the end of the experiments, rats were deeply anesthetized with an overdose of ketamine, and then pontamine sky blue (0.2%, 0.5 µL) was injected into the right ventricle 10–20 minutes before sacrificing the animals. Then the rats were transcardially perfused with 100 mL of 4% formalin solution, and the brains were removed and sectioned. Only those rats whose microinjection and diffusion of dye were located within the ventricle were included in the results.

Statistical analysis

Values are expressed as the Mean±SEM for eight animals in each group. The data were analyzed using SPSS software, version 19. Changes in all groups were subjected to a one-way analysis of variance (ANOVA) followed by Turkey's tests. The results are considered significant at $P<0.05$.

3. Results

Water intake

The findings showed that ICV injections of OXA (3.61±0.87) increased and SB-334867 (1.58±0.41) decreased water intake significantly in water-deprived rats compared to the control group (2.26±0.15), respectively ($P<0.05$) (Figure 1).

Referral number of water intake

The findings showed that ICV injection of OXA significantly increased the referral number of water intake in water-deprived rats during 4-hour intervals (23.5±3.61) compared to the control group (15±2.46; $P<0.05$). However, ICV injection of SB-334867 (17±3.77) had no significant effect on the referral number for water intake induced by water deprivation (Figure 2).

Delay time for first water intake

The rats started to drink within a few seconds after the administration of drugs or vehicles. ICV injection of OXA (901.12±74.33) or SB-334867 (782.11±79.53) compared to the control group (726.25±66.75) had no significant effect on the delay time of water intake in water-deprived rats (Figure 3).

4. Discussion

In this study, the role of orexin on water consumption in the state of water deprivation was evaluated. Our findings showed that central injection of orexin increased water consumption in water-deprived rats, and this effect was attenuated by the injection of orexin-1 receptor antagonist. Consistent with our results, recent studies have shown that central OXA injection increases water consumption in non-deprived rats [33]. It has also been reported that in thirsty rats, the level of prepro-orexin

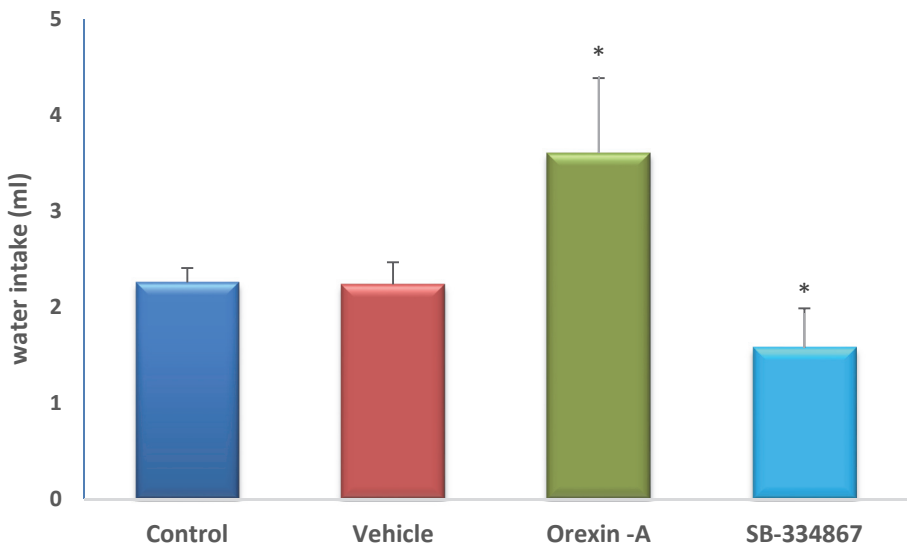

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Figure 1. Comparison of water intake for 4 hours after drugs administration

ICV injection of OXA increased and SB-334867 decreased water intake. Data are presented as Mean±SEM (n=8).

*$P<0.05$, compared to vehicle and control groups.

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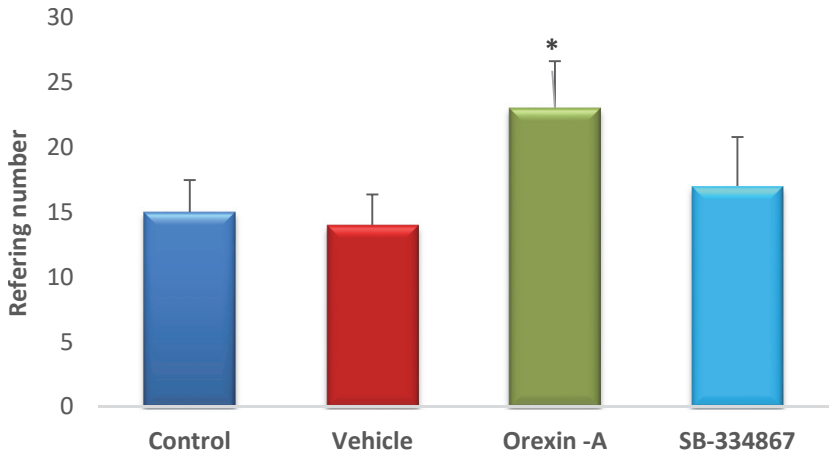

Figure 2. The number of referrals for water intake for 4 hours after drug ICV administration

OXA increased the referral number for water intake. The data are shown as Mean±SEM (n=8).

*P<0.05, compared to control and vehicle groups.

mRNA increases in regions related to the regulation of water intake, including LH. Moreover, the level of orexin mRNA increases in water-deprived rats for up to 3 hours and increases the axonal varicosity of orexin neurons in different areas involved in the control of drinking water [37, 42]. LH has a crucial role in the regulation of water and food intake [35-37]. Animals with LH lesions only drink enough to allow mastication while eating. In addition, it has been observed that LH stimulation, chemically and electrically, increases water consumption [37].

These findings are consistent with our results and highlight the physiological role of OXA in the control of water intake and body fluid homeostasis. Water is a vital substance for living and has numerous roles in the human body. It acts as a building material, solvent, reaction medium, reactant, and carrier for nutrients and waste products, as well as a lubricant and shock absorber. The homeostasis of water enables different biochemical reactions and metabolic processes [1-3]. Both deficit and excess water intakes are counterbalanced by fine hormonal (anti-diuretic hormone [ADH], aldosterone, and atrial

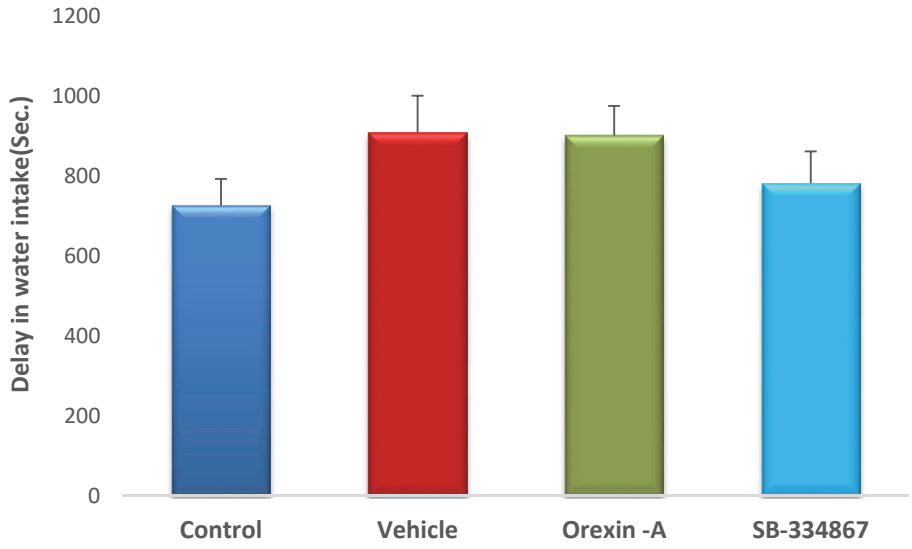

Figure 3. Comparison of water intake delays in experimental groups

No difference was observed between OXA and SB-334867 ICV injection on the start time for water drinking compared to the control group. Data are presented as Mean±SEM (n=8).

natriuretic peptide) changes that contribute to buffering the deleterious effects of these abnormal conditions. Therefore, voluntary drinking of water is a key behavior to maintaining water balance. Consequently, drinking water before being thirsty is a good habit to maintain a good body hydration status [43]. The intake of water is partially determined by thirst. When water losses exceed water intake, the osmotic pressure of the extracellular fluid increases and, by activation of hypothalamic osmoreceptors, ADH is released from the posterior pituitary gland. Both increased extracellular fluid osmotic pressure and ADH release elicit the feeling of thirst. ADH can act on the kidneys to increase water reabsorption before thirst is elicited. Previous studies demonstrated that orexinergic fibers innervate magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus. Furthermore, OX1 receptor immunoreactivity has been detected in vasopressinergic neurons in these nuclei, indicating that orexin may influence the secretion of vasopressin, which has a vital role in water homeostasis in the body. In this sense, it has been reported that OXA activates magnocellular and parvocellular neurons in the rat hypothalamic paraventricular nucleus in vitro [44- 46]. It seems that the OX1 receptors have more importance than orexin-2 in this effect [37]. The inhibitory effect of SB-334867 on the amount of water intake in the present study implies that OXA has a baseline stimulatory effect on water intake. Our finding highlights the role of the OX1 receptor in water homeostasis in water-deprivation conditions. The inhibitory effect of SB-334867 on water intake is similar to its effect on food intake [47]. The exact molecular mechanism by which orexin induces drinking is not clear and needs to be explored in future studies. However, vasopressin is vital in body water balance and water consumption, and previous research has shown that orexinergic fibers innervate the neurons of the hypothalamic paraventricular and supraoptic nuclei, where vasopressin is produced, and the OX1 receptor is present in vasopressinergic neurons [48]. Therefore, it seems that orexin, in addition to directly activating the thirst center neurons, probably exerts part of its effects by increasing the production and secretion of vasopressin and thus increases water consumption.

5. Conclusion

In summary, our findings showed that OXA has a stimulator effect on water consumption and OXA in the CNS has a basic role in water-drinking behaviors in water-deprived rats, possibly by activation of OX1 receptors.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Qazvin University of Medical Sciences (Code: IR.QUMS.REC.1400.040).

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Authors' contributions

Conceptualization and finalization, data analysis and interpretation: Mohammad Sofiabadi and Hasan Azhdari-Zarmehri; Methodology, project supervision and management: Mohammad Sofiabadi; Data collection: Mohammad Sofiabadi and Ali Tishuri; Preparation of draft article: Mohammad Hossain Esmaeili, Hashem Haghdost–Yazdi; Critical editing and review of the text and content of the draft: Mohammad Hossain Esmaeili, Hashem Haghdost–Yazdi and Mohammad Sofiabadi.

Conflict of interest

The authors declared no conflict of interest.

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References

[1] Zhou Y, Zhu X, Qin Y, Li Y, Zhang M, Liu W, et al. Association between total water intake and dietary intake of pregnant and breastfeeding women in China: A cross-sectional survey. BMC Pregnancy Childbirth. 2019; 19(1):172. [DOI:10.1186/s12884-019-2301-z] [PMID] [PMCID]

[2] Jequier E, Constant F. Water as an essential nutrient: The physiological basis of hydration. Eur J Clin Nutr. 2010; 64:115-23. [DOI:10.1038/ejcn.2009.111] [PMID]

[3] Popkin BM, D'Anci KE, Rosenberg IH. Water, hydration, and health. Nutr Rev. 2010; 68(8):439-58. [DOI:10.1111/j.1753-4887.2010.00304.x] [PMID] [PMCID]

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Inflammatory Diseases
(Previous Title: The Journal of Qazvin University of Medical Sciences)

[4] Nakano-Tateno T, Shichiri M, Suzuki-Kemuriyama N, Tani Y, Izumiyama H, Hirata Y. Prolonged effects of intracerebroventricular angiotensin II on drinking, eating and locomotor behavior in mice. Regul Pept. 2012; 173(1-3):86-92. [DOI:10.1016/j.regpep.2011.09.011] [PMID]

[5] Davern P, Mckinley M. Brain regions influenced by the lateral parabrachial nucleus in angiotensin II-induced water intake. Neuroscience. 2013; 252:410-9. [DOI:10.1016/j.neuroscience.2013.08.027] [PMID]

[6] Yosten GL, Redlinger L, Samson WK. Evidence for a role of endogenous nesfatin-1 in the control of water drinking. J Neuroendocrinol. 2012; 24(7):1078-84. [DOI:10.1111/j.1365-2826.2012.02304.x] [PMID]

[7] Lazartigues E, Sinnayah P, Augoyard G, Gharib C, Johnson AK, Davisson RL. Enhanced water and salt intake in transgenic mice with brain-restricted overexpression of angiotensin (AT1) receptors. Am J Physiol Regul Integr Comp Physiol. 2008; 295(5):R1539-45. [DOI:10.1152/ajpregu.00751.2007] [PMID] [PMCID]

[8] Samson WK, Yosten G, Chang J, Ferguson A, White M. Obestatin inhibits vasopressin secretion: Evidence for a physiological action in the control of fluid homeostasis. J Endocrinol. 2008; 196(3):559-64. [DOI:10.1677/JOE-07-0364] [PMID]

[9] Neubauer G, Mletzko I. [24-hour rhythm of feed and water consumption by BD IX rats in relation to pregnancy and lactation (German)]. Zeitschrift für Versuchstierkunde.1990; 33(3):115-9. [PMID]

[10] Lv SY, Yang YJ, Chen Q. Regulation of feeding behavior, gastrointestinal function and fluid homeostasis by apelin. Peptides. 2013; 44:87-92. [DOI:10.1016/j.peptides.2013.03.024] [PMID]

[11] Kraly FS, Tribuzio RA, Keefe ME, Kim YM, Lowrance R. Endogenous histamine contributes to drinking initiated without postprandial challenges to fluid homeostasis in rats. Physiol Behav. 1995; 58(6):1137-43. [DOI:10.1016/0031-9384(95)02056-X] [PMID]

[12] Gutzwiller JP, Hruz P, Huber AR, Hamel C, Zehnder C, Drewe J, et al. Glucagon-like peptide-1 is involved in sodium and water homeostasis in humans. Digestion. 2006; 73(2-3):142-50. [DOI:10.1159/000094334] [PMID]

[13] Solati J, Hajikhani R. Microinjection of NMDA receptor agents into the central nucleus of the amygdale alters water intake in rats. Iran J Basic Med Sci. 2010; 13(1):238-41. [DOI:0.22038/IJBMS.2010.5069]

[14] Hosseini M, Alaei HA, Eslamizade MJ, Saffarzade F. Effect of morphine self-administration on water and food intake in rat. Iran J Basic Med Sci. 2007; 10(3):169-75. [DOI:10.22038/IJBMS.2007.5291]

[15] de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, et al. The hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA. 1998; 95(1):322-7. [DOI:10.1073/pnas.95.1.322] [PMID] [PMCID]

[16] Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, et al. Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell. 1998; 92(4):573-85. [DOI:10.1016/S0092-8674(00)80949-6] [PMID]

[17] Shabani M, Mohammad-Zadeh M, Azhdari-Zarmehri H. [Orexin (hypocretin): A multi-functional hypothalamic peptide (Persian)]. Koomesh. 2014; 15(3):275-81. [Link]

[18] Sofiabadi M, Nazemi S, Erami E, Azhdari-Zarmehri H. [Role of orexinergic system in the effects of morphine on food and water intake in male rat (Persian)]. Koomesh. 2014; 15(3):380-7. [Link]

[19] Azhdari-Zarmehri H, Sofiabadi M. [Effects of endogenous opioidergic system interaction with orexin on eating in rats (Persian)]. J Inflamm Dis. 2014; 18(2):46-52. [Link]

[20] Bourgin P, Huitrón-Résendiz S, Spier AD, Fabre V, Morte B, Criado JR, et al. Hypocretin-1 modulates rapid eye movement sleep through activation of locus coeruleus neurons. J Neurosci. 2000; 20(20):7760-5. [DOI:10.1523/JNEUROSCI.20-20-07760.2000] [PMID] [PMCID]

[21] Jones BE. From waking to sleeping: Neuronal and chemical substrates. Trends Pharmacol Sci. 2005; 26(11):578-86. [DOI:10.1016/j.tips.2005.09.009] [PMID]

[22] Sofiabad M, Heidari N, Ghasemi E, Esmaeili MH, Haghdoost-Yazdi H, Erami E, et al. [Assesment of orexin receptor 1 in stress attenuated nociceptive behaviours in formalin test (Persian)]. Physiol Pharmacol. 2011; 15(3):395-402. [Link]

[23] Azhdari-Zarmehri H, Mohammad-Zadeh M, Shabani M. [The role of hypocretin/orexin in stress-induced analgesia (Persian)]. J Kerman Univ Med Sci. 2015; 22(2):205-17. [Link]

[24] Esmaeili M, Haghdoost-Yazdy H, Sofiabadi M, Ajdari Zarmehri H. [The effect of magnesium on on morphine withdrawal signs in rats (Persian)]. J Sabzevar Univ Med Sci. 2010; 17(1):6-12. [Link]

[25] Heidari-Oranjaghi N, Azhdari-Zarmehri H, Erami E, Haghparast A. Antagonism of orexin-1 receptors attenuates swim- and restraint stress-induced antinociceptive behaviors in formalin test. Pharmacol Biochem Behav. 2012; 103(2):299-307. [DOI:10.1016/j.pbb.2012.08.007] [PMID]

[26] Azhdari-Zarmehri H, Esmaeili MH, Sofiabadi M, Haghdoost-Yazdi H. Orexin receptor type-1 antagonist SB-334867 decreases morphine-induced antinociceptive effect in formalin test. Pharmacol Biochem Behav. 2013; 112:64-70. [DOI:10.1016/j.pbb.2013.09.018] [PMID]

[27] Karasawa H, Yakabi S, Wang L, Taché Y. Orexin-1 receptor mediates the increased food and water intake induced by Intracerebroventricular injection of the stable somatostatin pan-agonist, ODT8-SST in rats. Neurosci Lett. 2014; 576:88-92. [DOI:10.1016/j.neulet.2014.05.063] [PMID] [PMCID]

[28] Nazemi S, Azhdari-Zarmehri H, Haghdoost-Yazdi H. [Role of orexin in the tolerance and physical dependence to morphine (Persian)]. J Babol Univ Med Sci. 2014; 16:54-61. [Link]

[29] Erami E, Azhdari-Zarmehri H, Rahmani A, Ghasemi-Dashkhasan E, Semnanian S, Haghparast A. Blockade of orexin receptor 1 attenuates the development of morphine tolerance and physical dependence in rats. Pharmacol Biochem Behav. 2012; 103(2):212-9. [DOI:10.1016/j.pbb.2012.08.010] [PMID]

[30] Harris GC, Wimmer M, Aston-Jones G. A role for lateral hypothalamic orexin neurons in reward seeking. Nature. 2005; 437(7058):556-9. [DOI:10.1038/nature04071] [PMID]

[31] Georgescu D, Zachariou V, Barrot M, Mieda M, Willie JT, Eisch AJ, et al. Involvement of the lateral hypothalamic peptide orexin in morphine dependence and withdrawal. J Neurosci. 2003; 23(8):3106-11. [DOI:10.1523/JNEUROSCI.23-08-03106.2003] [PMID] [PMCID]

[32] Marcus JN, Aschkenasi CJ, Lee CE, Chemelli RM, Saper CB, Yanagisawa M, et al. Differential expression of orexin receptors 1 and 2 in the rat brain. J Comp Neurol. 2001; 435(1):6-25. [DOI:10.1002/cne.1190] [PMID]

[33] Kunii K, Yamanaka A, Nambu T, Matsuzaki I, Goto K, Sakurai T. Orexins/hypocretins regulate drinking behaviour. Brain Res. 1999; 842(1):256-61. [DOI:10.1016/S0006-8993(99)01884-3] [PMID]

[34] Trivedi P, Yu H, MacNeil DJ, Van der Ploeg LH, Guan XM. Distribution of orexin receptor mRNA in the rat brain. FEBS Lett. 1998; 438(1-2):71-5. [DOI:10.1016/S0014-5793(98)01266-6] [PMID]

[35] Lu XY, Bagnol D, Burke S, Akil H, Watson SJ. Differential distribution and regulation of OX1 and OX2 orexin/hypocretin receptor messenger RNA in the brain upon fasting. Horm Behav. 2000; 37(4):335-44. [DOI:10.1006/hbeh.2000.1584] [PMID]

[36] Sakurai T. Roles of orexins in regulation of feeding and wakefulness. Neuroreport. 2002; 13(8):987-95. [DOI:10.1097/00001756-200206120-00001] [PMID]

[37] Rowland N. Recovery of regulatory drinking following lateral hypothalamic lesions: Nature of residual deficits analyzed by NaCl and water infusions. Exp Neurol. 1976; 53(2):488-507. [DOI:10.1016/0014-4886(76)90088-1] [PMID]

[38] Paxinos G, Watson C. The rat brain in stereotaxic coordinates. Amsterdam: Elsevier; 2006. [Link]

[39] Hagan JJ, Leslie RA, Patel S, Evans ML, Wattam TA, Holmes S, et al. Orexin A activates locus coeruleus cell firing and increases arousal in the rat. Proc Natl Acad Sci. 1999; 96(19):10911-6. [DOI:10.1073/pnas.96.19.10911] [PMID] [PMCID]

[40] Date Y, Ueta Y, Yamashita H, Yamaguchi H, Matsukura S, Kangawa K, et al. Orexins, orexigenic hypothalamic peptides, interact with autonomic, neuroendocrine and neuroregulatory systems. Proc Natl Acad Sci. 1999; 96(2):748-53. [DOI:10.1073/pnas.96.2.748] [PMID] [PMCID]

[41] Dong H, Niu J, Su B, Zhu Z, Lv Y, Li Y, et al. Activation of orexin signal in basal forebrain facilitates the emergence from sevoflurane anesthesia in rat. Neuropeptides. 2009; 43(3):179-85. [DOI:10.1016/j.npep.2009.04.006] [PMID]

[42] Villano I, La Marra M, Di Maio G, Monda V, Chieffi S, Guatteo E, et al. Physiological role of orexinergic system for health. Int J Environ Res Public Health. 2022; 19(14):8353. [DOI:10.3390/ijerph19148353] [PMID] [PMCID]

[43] Rush EC, Chhichhia P, Kilding AE, Plank LD. Water turnover in children and young adults. Eur J Appl Physiol. 2010; 110(6):1209-14. [DOI:10.1007/s00421-010-1621-5] [PMID]

[44] Follwell MJ, Ferguson AV. Cellular mechanisms of orexin actions on paraventricular nucleus neurones in rat hypothalamus. J Physiol. 2002; 545(Pt 3):855-67. [DOI:10.1113/jphysiol.2002.030049] [PMID] [PMCID]

[45] Backberg M, Hervieu G, Wilson S, Meister B. Orexin receptor-1 (OX-R1) immunoreactivity in chemically identified neurons of the hypothalamus: Focus on orexin targets involved in control of food and water intake. Eur J Neurosci. 2002; 15(2):315-28. [DOI:10.1046/j.0953-816x.2001.01859.x] [PMID]

[46] Olson VG, Green TA, Neve RL, Nestler EJ. Regulation of morphine reward and feeding by CREB in the lateral hypothalamus. Synapse. 2007; 61(2):110-3. [DOI:10.1002/syn.20344] [PMID]

[47] Haynes AC, Jackson B, Chapman H, Tadayyon M, Johns A, Porter RA, et al. A selective orexin-1 receptor antagonist reduces food consumption in male and female rats. Regul Pept. 2000; 96(1-2):45-51. [DOI:10.1016/S0167-0115(00)00199-3] [PMID]

[48] Fakhoury M, Salman I, Najjar W, Merhej G, Lawand N. The lateral hypothalamus: An uncharted territory for processing peripheral neurogenic inflammation. Front Neurosci. 2020; 14:101. [DOI:10.3389/fnins.2020.00101] [PMID] [PMCID]

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