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Review

A review of the role of orexin system in pain modulation

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ABSTRACT

The roles of orexinergic system (orexin-A, orexin-B) and their receptors (orexin receptor type-1, orexin receptor type-2) in various physiological processes such as arousal, reward seeking behavior, energy homeostasis, sensory modulation, stress processing, cognition, endocrine functions, visceral functions and pain modulation have been established. This review summarizes the studies investigating orexin antinociceptive effects and their cellular mechanisms in various types of pain including neuropathic pain, migraine and cluster headache, visceral and orofacial pains. Moreover, the role of orexins in stress induced analgesia and on the development of morphine analgesic tolerance has been discussed. The antinociceptive effects of orexins have been shown in several pain models including thermal, mechanical and chemical induced nociception. Orexins modulate pain perception at both spinal and supraspinal levels. The periaqueductal gray (PAG) is one important supraspinal sites of orexin pain modulation. A possible involvement of endocannabinoids in supraspinal orexin-induced analgesia has been proposed. This review suggests a potential role of orexins in the management of pain.

Contents

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1. Introduction

The orexin (hypocretin) system contains two G-protein coupled receptors (GPCR) including orexin-1 (Ox_1) and the orexin-2 (Ox_2) receptors and two neuropeptides including orexin-A and orexin-B that produced from prepro-orexin in the lateral hypothalamus by enzymatic reactions. Orexin-A is a 33 amino-acid neuropeptide which activates both Ox_1 and Ox_2 receptors with similar affinity. Orexin-B is a 28 amino-acid neuropeptide, which activates Ox_2 receptors. The Ox_1 receptor signals are generally coupled through Gq while Ox_2 receptors are able to couple to Gq or Gi/o proteins [1].

Orexin-containing cell bodies are located in the lateral and perifornical regions of the hypothalamus, but their fibers project widely throughout the central nervous system [2]. Orexin receptors are also broadly distributed in the brain and spinal cord. These receptors were expressed abundantly in the cerebral cortex, basal ganglia, ventral tagmental area (VTA), nucleus accumbens, hippocampus, hypothalamic and thalamic nuclei, dorsal and medial raphe, locus coeruleus (LC), preoptic area, periaqueductal gray (PAG) and reticular formation [3–5]. The different functions of orexin receptors could be due to the fact that many areas express both Ox_1 and Ox_2 receptors, while others express mainly one out of the two orexin receptors [1]. The orexin system is also involved in a variety of physiological processes such as arousal, reward seeking behavior, energy homeostasis, sensory modulation, stress processing, or locomotion, cognition, endocrine functions, visceral functions and pain modulation [6].

There is emerging evidence that orexins have antinociceptive effects in the brain and spinal cord in different types of pains including thermal (hot-plate, tail-flick, paw-withdrawal), mechanical (tail-pressure), chemical (formalin, capsaicin and abdominal stretch) induced nociceptions and nociceptin-induced behavioral responses [7].

Orexin receptors have been found in many brain structures which are known to be involved in pain processing [8]. Orexin-A is reported to exert antinociceptive effects in the brain and spinal cord, whereas, orexin-B has shown little or no antinociceptive effects [9].

Due to the involvement of orexin in several functions, it is an attractive target for neuroscience research all over the world.

2. Literature search methods

This review summarized the studies investigating orexin antinociceptive effects and their cellular mechanisms in various types of pain including neuropathic pain, migraine and cluster headache, visceral and orofacial pains. Moreover the role of orexins in stress induced analgesia and on the development of morphine analgesic tolerance has been discussed. Scientific databases including Scopus, MEDLINE and Web of Science databases and local references were used. The keywords for the search were: orexin; hypocretin; pain; antinociceptive and analgesic.

3. Results

3.1. Antinociceptive effect of orexins at spinal and supraspinal levels

Orexins have antinociceptive effects at supraspinal levels in different animal models of pain.

It is suggested that the orexinergic system from hypothalamus to rostral ventromedial medulla (RVM) may have a potential role in modulation of nociceptive transmission [10]. In this study, orexin-A directly injected into rats' intracerebroventricular (ICV) and tail flick test was used as a nociceptive test. Increased firing rate of on-cells and decreased firing rate of off-cells were observed in response to noxious stimuli on the tail, and in neutral cells the firing rate was unchanged prior to tail flick. Results indicated that orexin-A via ICV injection reduced the spontaneous firing rate of on-cells (the type of RVM neurons believed to have facilitatory action on nociception) and increased the firing rate of off-cells (the type of RVM neurons believed to have an inhibitory action on nociception) [10]. In another study, the formalin test was used to evaluate the effect of orexin-A microinjection into the RVM on nociceptive behaviors. The microinjection of orexin-A into the RVM, but not adjacent reticularis gigantocellularis nucleus, decreased formalin induced nociceptive behaviors. Pretreatment with SB-334867 (orexin receptor type 1 antagonist) inhibited the antinociception produced by orexin-A, while the administration of SB-334867 alone had no effect. These data demonstrate that orexin-A-induced antinociception in the formalin test is mediated in part through orexin receptor type-1 in the RVM [11]. According to a study, intra-periaqueductal gray (PAG) matter microinjection of orexin-A could reduce formalin-induced nociceptive behaviors in adult male rats. In this study, intra-PAG injection of orexin-A had no effect on tail-flick test as thermal and acute model. However, in the formalin test, intra-PAG injection of orexin-A reduced the formalin-induced nociception in the interphase and phase 2, but not in phase 1. Injections of orexin-A into the sites near the PAG caused less or no reduction of pain. Therefore, orexin-A induced analgesia is possibly due to a site of action within the PAG rather than at surrounding neural structures. To compare the antinociceptive effect of orexin-A with morphine, morphine was injected via intra-PAG 5 min before the formalin injection. Data showed that morphine could reduce the formalin-induced nociceptive behaviors in all phases. Results also indicated that orexin possesses a specific action on the early part of the second phase of formalin test. Because the results of orexin-A intra-PAG injections 5 and 10 min before the formalin injection were similar, so its delayed effects are not related to its pharmacokinetics. Moreover, intra-PAG injection of SB-334867 inhibited the antinociceptive effect of orexin-A, indicating the involvement of orexin receptor type-1 in antinociception induced by intra-PAG injection of orexin-A [12]. According to the documents, antinociception induced by orexin-A in formalin and hot plate tests could be attributed to the orexin receptor type-1 in paragigantocellularis lateralis nucleus that may play a pivotal role in processing the pain information associated with descending pain modulation [13]. Moreover, another study reported that orexin-A may activate H1 and H2 receptors at the supraspinal levels through the release of histamine from neurons, which can reduce the antinociceptive effects of orexin-A. Thus, blocking of the histamine H1 or H2 receptor may induce antinociception and it also increases the orexin-A-induced antinociception [7].

According to the several scientific documents, the analgesic effect of orexins, mainly attributed to the orexin-A in several animal models by various routes of administration and tests. However, orexin-B has shown little or no antinociceptive effects. Only one study revealed the analgesic effect of orexin-B via injection into vl-PAG [14].

In addition to supraspinal mechanisms, spinal mechanisms appear to contribute to the role of orexin in nociception [15]. A probable mechanism of the orexinergic modulation of spinal nociceptive transmission is direct effect of orexinA on dorsal root ganglion (DRG) neurons [16]. In the spinal cord, DRG neurons are primary afferent neurons which are responsible for transmitting of peripheral stimuli to the pain-processing areas [17]. According to a study, orexin-A could induce excitability and intracellular calcium concentration elevation in the isolated rat DRG neurons, which was due to the activation of spinal orexin-1 receptor [16]. Another study indicated that intrathecal injection of orexin-A, but not orexin-B, reduced the sum of flinches in phases 1 and 2 in the formalin test. Pre-treatment with SB-334867, completely reversed