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Invited review

Role of orexin type-1 receptors in paragiganto-coerulear modulation of opioid withdrawal and tolerance: A site specific focus

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ABSTRACT

Orexin-A and -B neuropeptides are exclusively synthesized in hypothalamic neurons. These have been implicated to play critical roles in the expression of various behavioral manifestations such as feeding, arousal, wakefulness, drug dependence and tolerance. Orexin ligands activate orexin type-1 and orexin type-2 receptors each displaying a distinct selectivity and distribution profile. Orexinergic neurons innervate various brain structures among which the locus coeruleus (LC) and the lateral paragigantocellularis (LPGi) nuclei are well established as the two key mediators of opiate dependence and tolerance. Both nuclei express OX1Rs and the LC receives excitatory and inhibitory inputs from LPGi. Interestingly, the expression of opiate withdrawal signs is temporally associated with the enhanced activity of LC neurons. Numerous studies support the involvement of the orexin system in mediating opiate effects via affecting OX1Rs within the LC and LPGi. Extensive research has long been focused on the role of the ventral tegmental area (VTA) as a critical center in mediating orexin effects as well as reward processing and addiction. However, a growing amount of evidence supports the involvement of some other brain nuclei (such as LC and LPGi) in these phenomena. The mutual contribution of these structures has not been previously addressed in the literature. The present review aims to discuss and piece together the recent findings on the role of OX1Rs in modulating opiate withdrawal and tolerance with an emphasis on the involvement of the putative paragiganto-coerulear pathway. We conclude with a discussion about possible mechanisms of orexin actions within this pathway and its interaction with other neurotransmitter/modulator systems.

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1. Introduction

1.1. Orexin background: origin, functions, projections and receptor distribution

Orexin neuropeptides (orexin A and orexin B), also known as hypocretin-1 and hypocretin-2, are synthesized by proteolytic processing of their precursor peptide prepro-orexin (de Lecea et al., 1998; Sakurai et al., 1998). The source of orexinergic neurons are exclusively restricted to the dorsal medial hypothalamus (DMH), perifornical area (PFA) and lateral parts of the lateral hypothalamus (LLH) (de Lecea et al., 1998; Peyron et al., 1998; Sakurai et al., 1998). These peptides have been shown to mediate a wide variety of physiological functions such as feeding (Sakurai et al., 1998), arousal (Chemelli et al., 1999), neuroendocrine processes (Taylor and Samson, 2003), autonomic control (Date et al., 1999), reward and drugs of abuse-related manifestations (Georgescu et al., 2003). Up to now, two types of G-protein coupled receptors have been identified for orexin ligands throughout the CNS with different selectivity and distribution patterns (Marcus et al., 2001). These include orexin type-1 and orexin type-2 receptors (OX1Rs and OX2Rs respectively). The OX1R is selective for orexin-A while the OX2R binds both orexin neuropeptides (Sakurai et al., 1998). Interestingly, both receptor subtypes have been shown to couple to the three families of heterotrimeric G-proteins including Gq, Gi/o and Gs. Studies performed on expression systems support the ability of either receptor to interact with any of these effector proteins (Kukkonen and Leonard, 2014; Leonard and Kukkonen, 2014).

Orexin receptors display a differential distribution pattern throughout the brain and this explains the multifaceted contribution of the endogenous orexinergic system in homeostatic regulation within the central nervous system (Marcus et al., 2001). Reports indicate that both receptors are expressed on pre- and post-synaptic terminals as well as on soma within the medial and lateral hypothalamic areas (Van den Pol et al., 1998). OX1R mRNA is mainly expressed in the hippocampus, prefrontal and infralimbic cortex, ventromedial hypothalamic nucleus, paraventricular thalamic nucleus, dorsal raphe nucleus, locus coeruleus (LC) and lateral paragigantocellularis (LPGi) neurons (Ciriello et al., 2003; Hervieu et al., 2001; Marcus et al., 2001; Trivedi et al., 1998). The LC has been shown to display the strongest density of OX1R protein-like immunoreactivity (Hervieu et al., 2001). In a complementary manner, OX2Rs mRNA are primarily found in cerebral cortex, septal structures, medial thalamic neurons, raphe and hypothalamic nuclei (Marcus et al., 2001). Orexinergic fibers send widespread projections to various brain regions, particularly structures known for their critical role in opiate dependence and tolerance such as LC and lateral paragigantocellularis (LPGi) nuclei (Mondal et al., 1999; Nambu et al., 1999; Peyron et al., 1998).

2. Locus coeruleus and paragigantocellularis nuclei: mutual modulation of opiate dependence and tolerance

Long-term opiate administration results in development of dependence and tolerance to the effects of these drugs. Opiate dependence is defined as the need for continuing drug use to prevent the expression of withdrawal signs which may occur spontaneously or following pharmacologic induction, while tolerance refers to the diminished drug effect following repeated administration and is characterized by the need for dose escalation in order to obtain the initially observed response (Dumas and Pollack, 2008; Freye and Latasch, 2003; Jage, 2005; Martini and Whistler, 2007; Williams et al., 2001). The euphoria obtained from the activation of brain reward systems by opioids promotes repeated drug taking during the initial stages. However, long-term opioid exposure triggers the activation of some specific brain mechanisms resulting in opioid dependence which is characterized by compulsive drug seeking (Williams et al., 2001). If a dependent person suddenly stops drug-taking, he/she will exhibit predictable and measurable physical signs which is known as withdrawal syndrome.

The measurement of somatic withdrawal symptoms gives a reliable picture over the severity of dependence to opioid effects (Jacobsen and Kosten, 1989; Koob et al., 1992; Kosten et al., 1989; Lyvers and Yakimoff, 2003). This approach has widely been used in experimental models for investigation of various brain systems modulating opiate dependence (Ahmadi-Soleimani et al., 2014; Azizi et al., 2010; Georgescu et al., 2003; Gold et al., 1978; Mousavi et al., 2014).

It is worthwhile to mention that behavioral methods involving opioid-induced positive or negative reinforcement (such as “self-administration” or “preference methods”) do not necessarily evaluate neuroadaptations occurring during the development of opioid dependence. This is because brain regions involved in induction of dependence to opiates are anatomically distinct from those mediating the rewarding effects of opiates (Bozarth and Wise, 1984).

Various brain regions have been demonstrated to mediate the development of opiate dependence and tolerance (Abdollahi et al., 2016; Ahmadi-Soleimani et al., 2014; Al-Hasani and Bruchas, 2011; Ghaemi-Jandabi et al., 2014; Gupta and Kulhara, 2007; Ranjbar-Slamloo et al., 2012). Among these, the LC, located in the ventrolateral margin of the 4th ventricle, and the LPGi, located in the rostral ventrolateral medulla (RVLM), have recently received attention specifically with regard to the role of the endogenous orexin system in mediating opiate effects (Abdollahi et al., 2016; Ahmadi-Soleimani et al., 2014; Azizi et al., 2010; Davoudi et al., 2016; Ghaemi-Jandabi et al., 2014; Hooshmand et al., 2017; Mohammad Ahmadi Soleimani et al., 2015; Mousavi et al., 2014; Ranjbar-Slamloo et al., 2012). The LC is known as the largest cluster of brain noradrenergic neurons (Dahlstroem and Fuxe, 1964; Foote et al., 1983) which expresses a high level of opioid receptors, particularly μ and κ (Tempel and Zukin, 1987). Previous studies have shown that LC neurons display significant tolerance to the inhibitory effect of acute opiate administration, as during chronic opiate exposure the neuronal firing rate returns to the baseline levels (Aghajanian, 1978). In addition, coerulear neurons undergo remarkable dependence to opiate effects following long-term use of these drugs. This is revealed by enhancement of LC firing rate following injection of opioid-receptor antagonists in opiate dependent animals (Aghajanian, 1978; Rasmussen and Aghajanian, 1989; Valentino and Wehby, 1989). In this regard, it is noteworthy