Austin Addiction Sciences

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Editorial

Locus Coeruleus and Opioid Dependency

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Received: April 03, 2016; **Accepted:** April 05, 2016; **Published:** April 06, 2016

Editorial

Chronic opiate exposure is a neuronal adaptive condition leading to dependency that is characterized by physical or psychological disturbances, when the drug is withdrawn [1]. These adaptive changes occur in several neuronal networks including Locus Coeruleus (LC) that is a very important region in occurrence of such adaptations [2-5]. The LC, located on the floor of the fourth ventricle in the anterior pons [4,6-9], is the main site of norepinephrine and its neurons show both tonic and phasic discharge activity patterns [4]. The major inputs to the LC are from the medullary Paragigantocellularis (Pgi) nucleus and prepositus hypoglossal nucleus [4], which are the major sources of opioid innervation to the LC [10,11]. The extensive efferent projections from the LC innervate the entire central nervous system including forebrain, cerebellum, brainstem, and spinal cord [4] and modulate sensory processing as well as motor behavior, arousal and cognitive processes [12-16].

The presence of three main classes of opioid receptors namely Mu-Opioid Receptors (MORs), Delta-Opioid Receptors (DORs), and Kappa-Opioid Receptors (KORs) in the rat LC have provided evidence that show this nucleus can be an excellent experimental model in opiate research [17,18]. Opiates as morphine are highly abused substances and exert their effects via the G-protein-coupled MORs [18,19]. The density of MORs in this nucleus is very high [20] and its agonists inhibit the spontaneous activity of the LC neurons [21]. Many studies have demonstrated that the LC could be involved in opiate dependency that some of them studies are reviewed here.

Opiates have long been used to relieve pain due to the strong analgesic properties [18]. But after chronic opiate administration, different adaptations with behavioural consequences are induced in the LC, so dependency and withdrawal symptoms may occur [17].

Opiates can also affect dependency via influencing the LC neuronal activity. They decrease the LC neuronal activity by opening potassium channels [22,23]. A reduction in noradrenergic activity of the LC neurons by clonidine (an alpha-2-adrenergic agonist) as well as nimodipine (an L-type calcium channel antagonist) has been associated with a attenuation in the behavioral signs of withdrawal syndrome [24,25]. Furthermore, there are some reports that show the release of large quantities of noradrenaline [26] result in the hyperactivity of the LC neurons during naloxone-precipitated morphine withdrawal [27,28]. This hyperactivity of the LC neurons may be, in part, due to the up regulation of the cAMP signaling pathway and subsequent changes in the protein phosphorylation and gene expression [29-32]. Also, it has been shown opiates inhibit a resting sodium-dependent inward current by inhibiting adenylate cyclase and activate an outward potassium current in the LC neurons [33].

We have already demonstrated the role of CaMKIIα protein in the LC during dependency. Our results demonstrated an enhancement in expression of CaMKIIα protein in the LC of the morphine dependent rats. In this study, the inhibition of CaMKIIα by administration of KN-93, the specific inhibitor of this enzyme, significantly attenuated some of the withdrawal signs, suggesting a role for CaMKIIα in the modulation of the naloxone-induced withdrawal syndrome in the LC [34].

The possible role of the LC during dependency has also been resulted from observation in which activation of NMDA receptors is contributed to the maintenance of opiate dependence, suggesting NMDA receptor antagonists might be useful in the treatment of the opiate dependence [35]. Furthermore, the opiate withdrawal is associated with an enhancement in glutamate and aspartate release in the LC [36], suggesting an important role of glutamate and NMDA receptors in the opiate withdrawal in the LC.

In conclusion, we pointed the molecular and cellular aspects that mediate the effects of opiate drugs on LC- norepinephrine neurons and influence drug dependence and withdrawal. There has been no comparison between different methods used to reduce withdrawal signs so far. Therefore, to determine which method (s) is more effective, this comparison seems necessary. Also, the study about the combination effect of several methods in reducing withdrawal signs together could be an important step to promote our knowledge about addiction. It seems that these studies would help us to elucidate new therapeutic interventions in addiction.

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Citation: Mehranfard N and Navidhamidi M. Locus Coeruleus and Opioid Dependency. Austin Addict Sci. 2016; 1(1): 1002.

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