

Editorial

Orexin in Addiction, Current State and Potential Clinical Applications

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EDITORIAL

Addiction has been one of the least understood disorders of the central nervous system. The complexities of deregulations in neurotransmitters and also variety of involved nuclei of the brain make finding the main culprit a dilemma. However, it is understood that one of the main changes in addiction is a biased attention to the stimuli related to the drugs that in healthy subjects can be ignored. This biased attention seems to be triggered by a malfunction of circuitry of reward-punishment, which is conditioned by the euphoria induced by the drug (reward), and in later stages by the physiological discomfort of inaccessibility of the drug (punishment). Several clinical studies have shown promising results by controlling the bias of the attention in drug users [1,2], which has suggested it as a potential main target for therapeutic efforts.

On the other hand, orexin a neuropeptide discovered less than two decades ago, has been shown to be a critical neurotransmitter in arousal, sleep, reward circuitry and attention. In an interesting study, it was shown that oral administration of a blocking agent for orexin receptors (both OX_1 and OX_2) in humans can induce objective and subjective signs of sleep [3]. In addition, animal models have shown that blockade of OX_1 receptor before chronic use of morphine can prevent somatic signs of withdrawal [4,5]. Furthermore, orexin cells in lateral hypothalamus have been shown to project to Basal Forebrain Cholinergic System (BFCS) which plays a major role in attention [6,7]. Growing evidence suggests the BFCS is responsible for allocation of attention in selective attention tasks [8]. Moreover, anatomical connection from brainstem to lateral hypothalamus and furthermore to BFCS suggests that orexin is critical in the attention to both internal psychological state and environmental cues [7]. Orexin antagonists, both systematically and locally, have been shown to impair the tasks that require attention, learning and memory [4,9].

Nicotine [10,11], amphetamine [12,13], and modafinil [14,15], have been shown to increase the activity of orexin neurons in lateral hypothalamus and consequently the activity of BFCS cholinergic and non-cholinergic neurons. Interestingly, cataleptic patients with lower orexin neurons have shown more

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tolerance toward addiction [16].

From what we know so far, it is very plausible that the behavioral attentional modulation mentioned earlier affects the orexin neurons and BCFS. Then the main question is how we can combine the two methods, one behavioral and one chemical to have synergistic effect on modulation of attention in drug users? Similar to desensitization theories of addiction, two contradictory hypotheses can be drawn from what we know so far. First, we may need to train the drug users to be resistant in the situation of high activity of orexin neurons. Therefore, it would be beneficial for them to be trained to modulate their biased attention while we pharmacologically induce biased attention by using agonists of orexin receptors in a controlled environment. Second hypothesis is that we need to help the behavioral training by disrupting the function of orexin neurons using antagonists of orexin. Both hypotheses can be tested in animal models to evaluate which one may lead to new therapeutic effects. Orexin seems to play a crucial role in the future clinical treatment of drug addicts.

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