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DISCLOSURE

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# Normalizing drug-induced neuronal plasticity in nucleus accumbens weakens enduring drug-seeking behavior

Persistent drug-seeking behavior following long-term abstinence is a major challenge for treating cocaine or heroin addiction. Glutamatergic projections have been suggested to be a final common pathway for the initiation of drug seeking (Kalivas *et al*, 2005). In a clinical setting, neuroimaging studies have shown that cue/drug exposure increased the activity of PFC and nucleus accumbens (NAc), as well as self-reported drug craving in cocaine addicts (Goldstein and Volkow, 2002). In animal studies, a challenge of cocaine or heroin increases the synaptic release of glutamate in cocaine- or heroin-withdrawn rats as a result of the activation of corticostriatal pathways; inactivation of the corticostriatal pathway has been shown to be effective in inhibiting cocaine- or heroin-induced drug seeking (Kalivas *et al*, 2005).

Dendritic spines are the primary anatomical sites of excitatory synapses in NAc. It has been hypothesized that long-term structural plasticity in NAc contributes to certain long-lasting behaviors, including sensitization (Robinson and Kolb, 2004). Although there has been a paucity of experimental evidence that directly relates central structural plasticity to changes in specific behaviors, the density of spines on medium-sized spiny neurons in NAc is reportedly increased after repeated cocaine exposure (Robinson and Kolb, 2004; Pulipparacharuvil *et al*, 2008). By using 3D confocal image analysis of medium spiny neurons in the NAc labeled with lipophilic fluorescence dye, the spine density was found to be higher than that of spines quantified by Golgi staining (Shen *et al*, 2009). Withdrawal from cocaine injection was also reported to be associated with an increased density of larger diameter spines and reduced density of thinner spines. Moreover, a cocaine challenge after 3-week abstinence from daily cocaine treatment significantly increased the density of spines and the effect was found to be more pronounced in larger spines (Shen *et al*, 2009). These results indicate that long-lasting increases in synaptic connectivity in the NAc may provide a common ground for persistent drug seeking associated with drug addiction.

*N*-acetylcysteine can drive the cystine-glutamate antiporter and increase the glutamate levels after cocaine or heroin exposure. The acute or chronic administration of *N*-acetylcysteine has been shown to inhibit cocaine or heroin seeking in rats (Kalivas *et al*, 2005; Zhou and Kalivas, 2008). As well, the increase in spine head diameter induced by cocaine was also abolished in the animals pretreated with *N*-acetylcysteine. These results indicate that repeated treatment of *N*-acetylcysteine cannot only inhibit the reinstatement of drug seeking induced by cue or cocaine, but also reverse cocaine-induced neuroplasticity in dendritic spines. Importantly, the inhibition of drug seeking and normalization of spine head diameter were still present at 2 weeks after the last injection of *N*-acetylcysteine. Thus, pretreatment with *N*-acetylcysteine produces an enduring inhibition in cocaine or heroin relapse in the animal reinstatement model and normalizes changes in accumbens dendritic spines. It is hypothesized that *N*-acetylcysteine may reverse cocaine-induced neuroplasticity associated with relapse (Zhou and Kalivas, 2008). A better understanding of the normalization of the plasticity could provide guidance to develop novel therapeutic targets for treating drug addiction.

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# Orexin/hypocretin in psychiatric disorders: present state of knowledge and future potential

The orexins (or hypocretins) are hypothalamic neuropeptides involved in the regulation of a variety of complex behaviors, ranging from feeding to sleep and arousal (Adamantidis and de Lecea, 2009). Recent evidence has shown that these peptides can modulate the mesocorticolimbic dopamine circuit, and thus they have also been implicated in the pathology of numerous psychiatric disorders, including schizophrenia, depression, and addiction. Orexin-containing neurons constitute a small population of lateral and perifornical hypothalamic neurons, but project widely throughout the brain, including a substantial projection to the ventral tegmental area (VTA), a region involved in motivation and reinforcement processes. Hence, orexin can modulate dopaminergic firing, enhance synaptic transmission, and increase dopamine release in target areas of VTA neurons, such as the nucleus accumbens and the prefrontal cortex.

The potential links between orexin and schizophrenia or depression have only recently been explored. Preclinical data suggest that certain neuroleptic drugs associated with weight gain can activate orexin neurons (Deutch and Busber, 2007), suggesting a secondary target for the drugs' actions. Furthermore, in patients suffering from schizophrenia, cerebrospinal fluid levels of orexin A are lower in those treated with neuroleptic drugs. Thus, the orexin system may be a potential target for the side effects of neuroleptic drugs and a promising candidate for pharmacological treatment in schizophrenia. Depression is associated with sleep disturbances and circadian abnormalities. Dampened diurnal variations in orexin have been observed in depressed subjects (Salomon *et al*, 2003). Although diminished orexin signaling does not recapitulate the full spectrum of symptoms observed in depression, orexin signaling appears to be involved in the antidepressant-like effect of calorie restriction (Lutter *et al*, 2008). This raises the interesting possibility that orexin receptor agonists, which are currently in development for narcolepsy treatment, may also have antidepressant-like activity.

Evidence supporting the central role of orexin in drug reward and addiction is abundant (reviewed in Bonci and Borgland, 2009). In preclinical studies, blockade of orexin signaling has been shown to sufficiently inhibit two main behaviors defining addiction: motivated drug seeking and relapse. Orexin neurons are activated by preference to a context associated with drug intake. Furthermore, orexin receptor 1 antagonists block stress- or cue-induced reinstatement of extinguished cocaine or ethanol seeking, as well as high-fat food, ethanol, and nicotine self-administration. However, the antagonists do not block self-administration of cocaine, water, or food, suggesting that the effects of orexin signaling on self-administration of natural or drug rewards may be specific to the qualities of the reinforcer (Bonci and Borgland, 2009). Some of the behavioral actions of orexins may be due to their neuroplastic effects at glutamatergic synapses in the VTA. Interestingly, the involvement of the VTA in the neuronal and behavioral changes caused by cocaine requires input from orexin neurons (Borgland *et al*, 2006). It will be interesting to determine whether orexin-mediated neuroplasticity in the VTA underlies the effects of other drugs of abuse, such as morphine. Orexin receptor antagonists, in particular those to the orexin 1 receptor, may be clinically useful in the treatment of craving or the prevention of relapse.

In summary, orexin activation of the mesolimbic dopamine system may underlie some of its actions in schizophrenia, depression, or addiction. New therapeutic strategies to either activate (in depression) or inactivate (in schizophrenia or addiction) the orexin system may prove to be effective approaches in the treatment of such disorders.

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