ADDICTION

Appetite for drugs

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NRN0406_JQ1_HL
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Orexins, also known as hypocretins, are neuropeptides that are important for arousal, motivation, feeding and adaptive behaviours. In the mammalian brain, orexin-containing neurons in the lateral hypothalamus project to the ventral tegmental area (VTA) — a crucial site of synaptic plasticity induced by addictive drugs. Writing in *Neuron*, Borgland and colleagues show that, in rats, orexin A can potentiate glutamatergic neurotransmission of VTA dopamine neurons, and contribute to cocaine-induced behavioural changes.

From recordings of VTA neurons in rat midbrain slices, the researchers found that bath application of orexin A potentiated NMDA (*N*-methyl-D-aspartate) receptor-mediated excitatory postsynaptic currents. This effect was blocked by inhibitors of phospholipase C (PLC) or protein kinase C (PKC), suggesting the involvement of PLC/PKC-dependent intracellular pathways. Further pharmacological studies showed that orexin A potentiates mainly NR2A subunit-containing NMDA receptors, and the process requires translocation of intracellular NMDA receptors to the synapse.

Potentiation of NMDA receptors is crucial for the development of behavioural sensitization — a form of experience-dependent plasticity characterized by a long-lasting increase in drug-induced activation of locomotion, increased motivation for drug intake and enhanced drug reward. So, does orexin A also contribute to cocaine-induced effects? Systemic administration of SB334867, an antagonist of orexin receptor type 1 (OXR1, which has high affinity for orexin A), blocked cocaine-induced long-term plasticity at excitatory synapses on VTA dopamine neurons.

Systemic administration of SB334867 before cocaine injection attenuated the development of cocaine-induced behavioural sensitization, as measured by increased locomotor activity. Similar effects were observed when the inhibitor was directly microinjected into the VTA, suggesting that OXR1 activation at VTA dopamine neurons is responsible for cocaine-sensitization. However, application of the inhibitor at the end of cocaine treatment did not have any effect on the increase in locomotor activity, which indicates that orexin A is not required for the expression of behavioural sensitization.

In a previous study, the researchers showed similar findings with corticotropin-releasing factor (CRF). Therefore, orexin and CRF might mediate learned arousal and stress responses to the environment by regulating synaptic plasticity, and this neuroadaptive process could be 'hijacked' by drug abuse. Because arousal and stress can trigger drug-seeking behaviours, and as it is during periods of abstinence, rather than periods of intoxication, that addicts seek treatment, the peptide signalling pathways for orexin and CRF might be potential targets for the development of addiction medications.

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ORIGINAL RESEARCH PAPER Borgland, S. L. *et al.* Orexin A in the VTA is critical for the induction of synpatic plasticity and behavioral sensitisation of cocaine. *Neuron* **49**, 589–601 (2006)

FURTHER READING Volkow, N. D. & Li, T. K. Drug addiction: the neurobiology of behaviour gone awry. *Nature Rev. Neurosci.* **5**, 963–970 (2004) | Ungless, M. A. *et al.* Corticotropin-releasing factor requires CRF binding protein to potentiate NMDA receptors via CRF receptor 2 in dopamine neurons. *Neuron* **39**, 401–407 (2003)

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