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Addictive Drugs and Stress Trigger a Common Change at VTA Synapses

In this issue of *Neuron*, Saal et al. find that exposure to any of five addictive drugs or exposure to a brief stressor produces a shared cellular modification of excitatory synapses in the ventral tegmental area (VTA). This common response may represent a starting point for dissecting early changes that underlie addiction.

Different drugs of abuse are chemically distinct, bind to separate molecular targets, and have markedly different effects on behavior. For example, morphine binds to opioid receptors often found on GABAergic neurons in the CNS and produces hypnotic, euphoric, and analgesic effects, while cocaine binds to dopamine and norepinephrine transporters present on a small number of CNS neurons and nerve terminals and is a psychomotor stimulant. Despite such mechanistic differences, drugs of abuse also exert certain actions in common, all localized to the midbrain dopaminergic system. These common actions are most likely those required for the development of addiction.

The ventral tegmental area (VTA) is a dopaminergic nucleus in the brain that is required for processing normal reward-driven behavior. In addition, nearly all addictive drugs produce an acute increase in the release of dopamine from VTA neurons at their terminals in the nucleus accumbens. Interest in glutamatergic function in the VTA crystallized in recent years as considerable evidence suggested that long-lasting changes in glutamate transmission are necessary and sufficient for behavioral sensitization to drugs of abuse (Wolf, 1998; Everitt and Wolf, 2002). In this phenomenon, various behaviors (e.g., locomotor activity) are enhanced following daily administration of an addictive drug—it has also been called "reverse tolerance." Two features of sensitization have linked it to the gradual enhancement of drug craving, a central symptom of addiction and a major cause of drug relapse (Robinson and Berridge, 1993). First, nearly all drugs of abuse elicit behavioral sensitization, indicating an important common target in the brain. Second, sensitization is extremely long-lasting, for example, lasting for up to a year in rats (half of the rat's lifespan). The persistence of sensitization has been likened to the persistence of drug craving in humans, a devastating feature of addiction that makes full recovery very difficult, as most ex-smokers can attest.

The VTA is essential for behavioral sensitization. Addictive drugs delivered directly into the VTA trigger sensitization (Vezina, 1993), and certain receptor antagonists delivered into the VTA block sensitization to peripherally administered drugs. Furthermore, glutamatergic synaptic transmission in the VTA is crucial to initiate sensitization (reviewed in Wolf, 1998). An NMDA receptor antagonist delivered to the VTA prevents sensitization to peripherally administered morphine or psychostimulant. Moreover, glutamate receptor subunit expression is altered after a sensitizing drug regimen, and a heightened sensitivity to glutamate is observed in dopamine neurons from sensitized animals. Even local overexpression in VTA of GluR1, an AMPA receptor subunit, produces behaviors mimicking sensitization. Together, these data suggest similarities to long-term synaptic changes, like long-term potentiation (LTP) described in other systems. This raises the intriguing idea that exposure to an addictive drug may elicit pathological LTP at excitatory synapses in the mesolimbic dopamine system (Nestler, 2001; Hyman and Malenka, 2001).

In brain slices, patterned electrical stimulation can elicit both LTP and LTD at glutamate synapses on VTA neurons, and exposure to the psychomotor stimulants amphetamine and cocaine results in both acute and long-lasting alterations in synaptic plasticity (Jones et al., 2000; Ungless et al., 2001). How can exposure to an addictive drug in vivo be linked to changes in excitatory synaptic function that can only be detected in vitro? Recently, Ungless et al. (2001) examined excitatory synaptic properties of VTA brain slices taken from mice 24 hr after a single exposure to cocaine, in search of signs that LTP had taken place. They found that they could not elicit further LTP at synapses on dopamine cells, as expected if LTP were already maximally induced. Furthermore, they observed a change in the ratio between the portion of the EPSC mediated by synaptic current through AMPA receptors and the portion mediated by NMDA receptors (the AMPA/NMDA ratio). This ratio is increased after LTP induction in the hippocampus and the increase is thought to result from the insertion of new AMPA receptors (but not new NMDA receptors) at potentiated synapses (Malinow and Malenka, 2002). Ungless et al. found that excitatory synapses on dopamine neurons from cocaine-treated animals had 2-fold higher AMPA/NMDA ratios when compared with those from saline-treated animals. Importantly, AMPA/NMDA ratios in slices from mice treated with both cocaine and MK-801 (an NMDA receptor antagonist that blocks LTP) were unchanged. Synapses in hippocampus showed no differences between saline- or cocaine-treated mice. Animals also exhibited behavioral sensitization after the same drug treatment, for the first time correlating sensitization with LTP in the VTA. Together these findings demonstrate that cocaine triggers widespread LTP at excitatory synapses on dopamine neurons. These results also indicate that the AMPA/NMDA ratio can be used as a molecular signature for the induction of LTP at potentiated synapses.

In this issue of *Neuron*, Saal et al. (2003) have taken this work one important step farther. If LTP at excitatory VTA synapses has any bearing on the development of addiction, it must occur not only in response to cocaine, a psychomotor stimulant with a known molecular target in the VTA, but also in response to multiple addictive substances. Here the authors show that representatives

of four classes of addictive drugs all increase AMPA/NMDA ratios in VTA slices 24 hr after drug treatment in vivo. Morphine, nicotine, ethanol, and either cocaine or amphetamine, drugs with little in common beyond their abuse potential, all have the same effect. Two other psychoactive drugs with low abuse potential were tested in similar experiments. Neither fluoxetine, the serotonin transporter blocker and antidepressant better known as Prozac, nor carbamazepine, a widely prescribed antiepileptic agent that slows recovery from inactivation of voltage-dependent Na^+ channels, has any effect on AMPA/NMDA ratios at VTA synapses. Thus, the authors have revealed a single action of a diverse group of compounds with distinct molecular targets but sharing the potential for producing addiction; drugs that lack this potential, despite similar molecular targets, do not alter VTA synapses.

The paper provides one last intriguing result: acute stress, here in the form of a brief forced swim in cold water, potently increases the AMPA/NMDA ratio at VTA synapses measured 24 hr later. Like the cocaine-induced ratio increases reported previously, blockade of NMDA receptors prior to the stressor entirely prevents the change in AMPA/NMDA ratios. A glucocorticoid receptor antagonist, RU486, blocks stress-induced changes as well, implicating glucocorticosteroids as an intermediary in the response to stress. In an interesting follow-up to this experiment, the investigators tested whether glucocorticoid receptor activation was required for cocaine-induced changes in the VTA. However, RU486 does not affect cocaine's ability to elicit increased AMPA/NMDA ratios at VTA synapses. Thus, stress and drugs of abuse (at least cocaine) interact with the VTA via distinct pathways, although both stress and cocaine require NMDA receptor activation to trigger this change. The work raises questions about the detailed mechanisms of drug action. How does activation of opiate receptors, dopamine transporters, $GABA_A$ channels, nicotinic acetylcholine receptors, and glucocorticoid receptors increase AMPA/NMDA ratios in the VTA? How rapidly do the drugs or stress alter VTA synapses? Do all of these drugs, like cocaine and stress, require NMDA receptor activation to induce the ratio change? Are the NMDA receptors necessary for the ratio change those NMDA receptors at VTA synapses required for LTP?

Many larger questions are raised by this work. Clearly, addiction to nicotine does not produce concomitant addiction to cocaine or alcohol. Experiencing stress is not sufficient on its own to initiate addiction to drugs. And a single or even multiple exposures to alcohol, nicotine, cocaine, or morphine are generally not enough to produce addiction. How exactly does the brain interpret a global potentiation of synapses in the VTA after any of these stimuli? Perhaps the threshold for moving from drug exposure to addiction is reduced by recent exposure to any addictive drug or to stress. The duration of these effects seems extremely important. If all glutamatergic synapses on VTA dopamine neurons are potentiated 24 hr after drug exposure or stress, for how long does the potentiation last? Does the potentiation period represent a window of vulnerability to stress or drug exposure?

Stress and glucocorticoids have been of particular interest to researchers in the addiction field because of their clear interaction with drug taking in animals and perhaps in humans as well (Shaham et al., 2000; Marinelli and Piazza, 2002). Both the acquisition of drug taking and relapse in an already addicted animal are promoted by either a single drug exposure or stress (Piazza and Le Moal, 1998; Pacchioni et al., 2002). It is possible that the work by Saal et al. (2003) identifies a neural substrate responsible for this common effect of abused drugs and stress. Beyond the importance to our understanding of the basic mechanisms underlying drug addiction, this study could point the way toward potential therapeutic approaches to relapse in human addicts.

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Filling the Interstices: Ghrelin Neurons Plug Several Holes in Regulation of Energy Balance

Of several circulating hormones that act on hypothalamus to affect body energy balance, only ghrelin is also expressed in hypothalamic neurons. From the studies of Horvath and colleagues appearing in this issue of *Neuron*, it appears that neuronal ghrelin acts presynaptically to stimulate release of the orexigenic peptide, neuropeptide Y, and other neurotransmitters, thus defining a new and subtle modulatory circuit.

Food intake and energy expenditure are very closely