Channels

ISSN: 1933-6950 (Print) 1933-6969 (Online) Journal homepage: https://www.tandfonline.com/loi/kchl20

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To cite this article: Matthew T.C. Brown, Clio Korn & Christian Lüscher (2011) Mimicking synaptic effects of addictive drugs with selective dopamine neuron stimulation, Channels, 5:6, 461-463, DOI: 10.4161/chan.5.6.17120

To link to this article: https://doi.org/10.4161/chan.5.6.17120

Channels 5:6, 461-463; November/December 2011; © 2011 Landes Bioscience

Mimicking synaptic effects of addictive drugs with selective dopamine neuron stimulation

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The synaptic changes induced by initial drug exposure leave a trace on neural systems that can eventually manifest in compulsive drug-seeking behavior. A single injection of cocaine has been shown to induce a change in the AMPA receptor (AMPAR) subunit composition at glutamatergic synapses onto ventral tegmental area (VTA) dopamine (DA) neurons. This change is long-lasting (up to months following self-administration) and represents an important functional change at the synaptic level following cocaine use. We recently published findings that cocaine's action at the DA transporter (DAT) is necessary for the induction of AMPAR redistribution and that this can also be mimicked by selective DA neuron stimulation. The stimulation effect is dependent on D1 receptors within the VTA. Furthermore other addictive drugs, although they act through distinct mechanisms, also induce this synaptic change. Here we discuss literature that expands on these observations in an attempt to further clarify the synaptic changes following early drug use.

Keywords: VTA, dopamine, synaptic plasticity, AMPA receptors, channelrhodopsin, addiction

Submitted: 07/07/11

Accepted: 07/07/11

http://dx.doi.org/10.4161/chan.5.6.17120

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Addendum to: Brown MT, Bellone C, Mameli M, Labouèbe G, Bocklisch C, Balland B, et al. Drug-driven AMPA receptor redistribution mimicked by selective dopamine neuron stimulation. PLoS ONE 2010; 5:15870; PMID:21209835; DOI:10.1371/journal.pone.0015870.

Addictive drugs act in several distinct ways throughout the brain, yet they are associated with a single common disease in humans. One potential explanation for this is that, despite their differences, these distinct mechanisms converge to induce a common change underlying the initiation and progression of drug addiction. The mesolimbic system, and particularly DA neurons of the VTA, has been identified as a key site at which addictive drugs act. Drugs can be separated into three classes according to their mechanism of action.[1] Compounds such as nicotine increase DA neuron firing by acting at ionotropic receptors either directly or on GABA VTA neurons, whereas drugs such as morphine disinhibit DA neurons by decreasing GABA neuron firing via metabotropic receptors. The third class, which includes cocaine, acts at the level of the DA neuron terminals to interfere with DA reuptake. As the common result of these distinct mechanisms of action is an increase in mesolimbic DA, the assumption has been that it is this increase that is responsible for a drug's addiction liability. However, because these drugs have many other actions in the brain—cocaine, for example, also increases serotonin and noradrenaline levels[2] and blocks voltage-gated sodium channels[3]—it has been difficult to test this hypothesis directly.

One effect of drug exposure that persists in the mesolimbic DA system even after the substance has been eliminated from the organism is a modification of glutamatergic transmission onto VTA DA neurons. The first observation of this phenomenon was a reported increase in the AMPA to NMDA receptor (AMPAR/NMDAR) ratio at glutamatergic synapses onto VTA DA neurons 24 h following a single cocaine injection.[4] This change was persistent up to 5 d, but not 10 d, after a single cocaine dose, although subsequent studies have shown that the AMPAR/NMDAR ratio may remain elevated for up to 3 mo in experiments using self-administration paradigms.[5] The exact mechanism by which cocaine induces this

initial change in glutamatergic transmission is still not fully understood, although it is known to depend on NMDARs in DA neurons, as the change is blocked by an NMDAR antagonist[4] and by deletion of the GluN1 subunit from these neurons.[6,7] These findings are made more interesting in the context of addiction by observations that other addictive drugs, including members of the nicotine- and morphine-containing classes, can also induce changes in the AMPAR/NMDAR ratio at glutamatergic synapses onto VTA DA neurons.[8] In addition, it has been shown that stress can increase the AMPAR/NMDAR ratio at these synapses, in agreement with the apparent modulation of drug effects by stressful stimuli.[8,9] These glutamatergic synapses therefore provide a potential point of convergence through which addictive drugs, as well as other stimuli such as stress, could act. However, what the AMPAR/NMDAR ratio may tell us mechanistically regarding drug-induced synaptic plasticity is unclear, as changes in either AMPARs, NMDARs or both could result in an altered ratio.

Many studies have investigated plasticity of the AMPAR at glutamatergic synapses onto VTA DA neurons. It has been shown that, following a single injection of cocaine, the current/voltage relationship of AMPARs becomes rectifying: the receptors flux more current at negative than at positive potentials.[10] This change in the rectification index (RI) is due to the insertion of calcium permeable, GluA2 subunit-lacking AMPARs, which are blocked by polyamines at positive potentials.

Given the inhibition of these AMPARs at positive potentials, the increase in the AMPAR/NMDAR ratio is likely to require a change in NMDAR transmission as well as in AMPAR subunit composition. In early experiments, the lack of change in NMDAR EPSCs following NMDA bath application led to the conclusion that NMDARs did not change and that a change in AMPAR signaling was entirely responsible for the change in ratio.[4] This bath application paradigm was an attempt to directly compare NMDAR pools between groups, which is usually not possible because of the recruitment of an unknown number of axons by electrical stimulation. However, bath application does not isolate synaptic NMDARs and so does not discount a redistribution of NMDARs between synaptic and extrasynaptic compartments. To circumvent this limitation, a recent study used 2-photon laser glutamate uncaging to probe the unitary NMDAR (uNMDAR) EPSCs at individual glutamatergic synapses onto VTA DA neurons. Here it was shown that the uNMDAR EPSC actually decreases in a subpopulation of these synapses.[11] Furthermore, a decrease in uNMDAR amplitude was predictive of an increased RI at these synapses. Thus, while NMDAR surface expression may remain constant, the quality of NMDAR-mediated synaptic transmission seems to change.

Our study focused on AMPAR transmission and aimed to assess the necessity of cocaine-induced DA increases for AMPAR subunit redistribution and to determine whether other drugs that increase DA through distinct mechanisms might also induce this change in AMPARs. Previous experiments have investigated the necessity of DA for cocaine-induced behavioral alterations using mice that lack the DA transporter (DAT); however, a clear consensus has not been reached because of the abnormally high baseline DA levels in these mice and subsequent involvement of other monoamine transporters.[12,13] We therefore used a mouse line in which the DAT contains three point mutations that render it insensitive to cocaine but leave DA reuptake largely untouched.[12] We found that in these mice a single injection of cocaine was incapable of inducing a change in the RI at glutamatergic synapses onto VTA DA neurons. This result indicates that, at least in the case of cocaine, DA increases are crucial to the observed changes in AMPAR transmission at these synapses.

If DA is the critical component of this change, then other addictive drugs that elevate DA should induce the same AMPAR subunit redistribution. Indeed, we found that a single injection of morphine or nicotine, despite their distinct mechanisms of action, induced a change in the RI similar to that caused by cocaine. Nicotine's ability to cause a change in the RI has been confirmed in a separate study.[14] Furthermore, using electron microscopy, we observed a redistribution of the GluA2 subunit away from the synapse, presumably in exchange for GluA2-lacking receptors. These and other data add to a growing body of evidence indicating that many different addictive drugs alter AMPAR subunit distribution at glutamatergic synapses onto VTA DA neurons.[4,8,10,15]

Finally, to probe whether or not DA release alone, without other drug-related effects, is capable of inducing AMPAR subunit redistribution, we designed a system in which we would be able to selectively activate VTA DA neurons. Briefly, we used the Cre-Lox system to infect DAT-expressing neurons of the VTA with a virus containing the sequence for channelrhodopsin 2. By selective light activation of VTA DA neurons in a burst-like manner in vivo, we were able to mimic the AMPAR subunit redistribution previously seen with addictive drugs. Furthermore, this effect was abolished by injection of a D1 antagonist directly into the VTA, providing further evidence that DA alone is sufficient to induce AMPAR plasticity of glutamatergic synapses onto VTA DA neurons and that the changes induced by light-evoked DA release bear similarities to the situation observed with addictive drugs.

Given that VTA neurons can release DA dendritically,[16,17] it is possible that drug- and light-induced plasticity of AMPAR transmission is mediated entirely by intra-VTA DA release, without involvement of the rest of the mesolimbic circuitry. Our data support this possibility, as does a study that found that bath application of cocaine to VTA slices was sufficient to induce rectification of AMPAR transmission.[15]

These results show that selective activation of mesolimbic DA neurons is sufficient to mimic drug-induced synaptic changes. The necessity for a convergence of dopamine and glutamate signaling has previously been suggested and at first appears in conflict with our data showing that increasing DA levels alone is sufficient to alter VTA glutamatergic transmission. However, basal glutamate release in the awake mouse may be sufficient to trigger coincidence detection with

DA neuron activation. Alternatively, it has been shown that DA neurons corelease glutamate,[18,19] providing a source of glutamate that would have been elevated in our preparation.

It should be noted that the drug-induced changes in AMPARs and NMDARs discussed here are certainly not the only effects of addictive drugs. As such, blocking AMPAR subunit redistribution or NMDAR function does not abolish all drug effects. Indeed, although cocaine-induced synaptic potentiation is absent in mice lacking the GluA1 subunit either globally or specifically in midbrain DA neurons, these mice display normal locomotor sensitization to cocaine and, in the case of the conditional knockout, normal conditioned place preference (CPP).[6,20] Mice lacking the NMDAR GluN1 subunit in DA neurons also exhibit normal sensitization and CPP despite deficits in cocaine-induced synaptic strengthening of VTA glutamatergic transmission,[6,21] indicating that such strengthening is not required for locomotor and conditioned drug responses that are considered key elements of the addiction process in rodent models. Nevertheless, conditional knockout of GluA1 from midbrain DA neurons does impair extinction of CPP, while knockout of GluN1 in DA neurons disrupts reinstatement of CPP following extinction.[6] These results clearly indicate a role for plasticity of VTA glutamatergic transmission in certain drug-related behaviors.

An additional important consideration is the heterogeneity of DA neurons within the VTA. A recent study found that AMPAR/NMDAR ratios of DA neurons projecting to different regions of the nucleus accumbens (NAc) or to the medial prefrontal cortex exhibited both differing basal AMPAR/NMDAR ratios and differing modifications induced by either cocaine or aversive stimuli.[22] This stimulus-specific plasticity of VTA glutamatergic transmission may depend on the origin of the excitatory afferents that synapse onto these subpopulations of DA neurons as well as the projection targets of the neurons themselves. Selective excitation of the various glutamatergic inputs to the VTA would allow isolation of different excitatory afferents and could thus shed light on this issue.

While the cocaine-induced changes in VTA glutamatergic transmission discussed here are certainly too brief to act as the substrate of addiction itself, it has recently been shown that changes in VTA transmission induced by one injection of cocaine alter the conditions required for activity-dependent plasticity of VTA glutamatergic synapses.[11] These initial changes could therefore represent an early adaptation of the mesolimbic circuitry that permits the expression of more chronic forms of plasticity underlying addiction.[23,24] Indeed, persistence of cocaine-induced plasticity of glutamatergic transmission in the VTA causes changes at downstream synapses in the NAc.[25] Plasticity in the VTA may thus serve as the initial building block in the development of addiction.

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