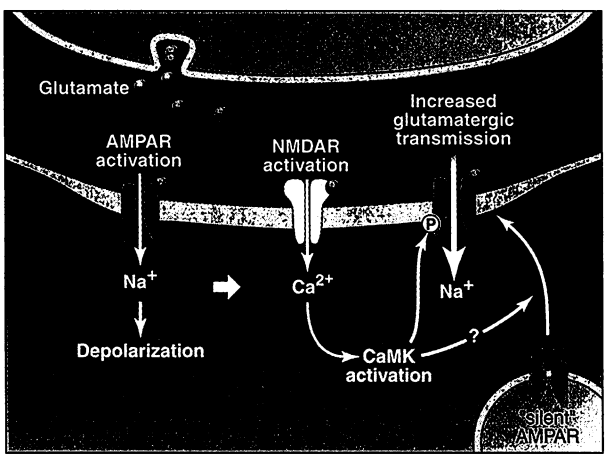
Ungless *et al.* (*11*) now report that a single in vivo dose of cocaine increases transmission at synapses between glutamatergic nerve terminals and dopamine neurons in the ventral tegmental area (VTA) of the rat brain. These dopamine neurons mediate the rewarding effects of cocaine and other drugs of abuse. Glutamatergic neurons release the excitatory neurotransmitter glutamate in the VTA in response to various stimuli that may include drugs of abuse. Cocaine increases glutamatergic transmission apparently by enhancing the effects of glutamate on postsynaptic VTA dopamine neurons rather than by increasing glutamate release into synapses. The enhanced postsynaptic effects of glutamate in the VTA are similar to those associated with LTP in the hippocampus and other brain regions. Ungless *et al.* therefore propose that similar molecular events underlie both LTP and some of the long-lasting neural changes induced by cocaine.

The molecular events accompanying LTP have been elucidated by studying glutamatergic synapses in the CA1 region of the hippocampus (*2*–*4*). Activation of one class (AMPA) of glutamate receptors, and the subsequent depolarization of postsynaptic neurons, leads to activation of another class (*N*-methyl-D-aspartate, NMDA) of glutamate receptors. NMDA receptors, but not the majority of AMPA receptors, are permeable to calcium ions. As a result, calcium ions flow into postsynaptic neurons through NMDA receptor channels, and Ca^{2+}/calmodulin-dependent kinases and their signaling pathways are activated (see the figure). These signaling pathways increase glutamatergic transmission in two ways: through phosphorylation (and increased opening) of AMPA receptor channels and by triggering the recruitment of so-called "silent" AMPA receptors (which are not normally active) to postsynaptic membranes, where they boost the response of postsynaptic neurons to glutamate. Changes in gene expression, perhaps modulated by the transcription factor CREB, could yield even longer lasting increases in synaptic efficacy.

Are the cocaine-induced molecular events that enhance glutamatergic transmission in the VTA similar to the molecular events accompanying LTP in the hippocampus? One way in which cocaine, an inhibitor of dopamine transport, could enhance glutamatergic transmission is by increasing extracellular concentrations of dopamine within the VTA. Dopamine could then act on glutamatergic nerve terminals, or on the dopamine neurons themselves, to initiate the changes that eventually lead to increased sensitivity of these neurons to glutamate. Alternatively, by modifying dopaminergic transmission in target regions of the VTA (such as the prefrontal cortex and amygdala), cocaine could alter the activity of glutamatergic neurons in regions that innervate the VTA. It will be interesting to see whether other drugs of abuse, such as opiates, alcohol, and nicotine, also enhance glutamatergic transmission in the VTA or in other brain regions implicated in addiction (such as the nucleus accumbens, a major limbic target of VTA dopamine neurons).



Memories of addiction. Cocaine-induced increases in glutamatergic transmission in the VTA. Enhanced glutamatergic transmission in the VTA may be similar to that associated with LTP in the hippocampus. Analogous to the molecular events associated with hippocampal LTP, cocaine may indirectly lead to activation of AMPA glutamate receptors (AMPAR), resulting in depolarization of postsynaptic dopamine neurons in the VTA. NMDA glutamate receptors (NMDAR) would then be activated, leading to an influx of Ca^{2+} ions into dopamine neurons and the activation of Ca^{2+}/calmodulin-dependent kinases (CaMK). These kinases could phosphorylate and increase the activity of AMPA receptors and could also stimulate the trafficking of preexisting AMPA receptors to the postsynaptic membranes of dopamine neurons, leading to enhanced glutamatergic transmission. [Adapted from (*2*)]

Ungless and colleagues note that enhanced glutamatergic transmission induced by a single dose of cocaine lasted for 5 days, but returned to baseline levels within 10 days (*11*). Repeated dosing with cocaine (or other drugs of abuse) would be expected to boost VTA glutamatergic transmission still further, particularly as cocaine is known to sensitize dopamine neurons by increasing AMPA receptor activity (*6*, *7*, *12*) (although the opposite effect, tolerance, may also occur). Experiments with repeated doses of cocaine will be crucial for understanding the dramatic findings of Ungless *et al.* within the context of addiction.

The fields of learning and memory and of addiction have tended to direct their efforts toward nonoverlapping brain regions. The hippocampus, which is unquestionably crucial for declarative and spatial learning, is central to memory research. More recently, the amygdala and the part it plays in conditioning to aversive (negative emotional) stimuli has come under the spotlight. In contrast, the addiction field has centered its efforts on the mesolimbic dopamine system, composed of the VTA and its forebrain targets, such as the nucleus accumbens (also known as the ventral striatum).

These anatomical distinctions, however, are becoming increasingly arbitrary. The amygdala is clearly important in addictive behavior, and animals will strive to electrically stimulate the hippocampus (among other brain areas), indicating that this region is also important in the reward response. Conversely, the nucleus accumbens modulates emotional valence (value) and, hence, the strength of memories encoded in the hippocampus. Moreover, striatal neurons direct formation of habit memories and regulate compulsive behavior. Thus, there is substantial convergence of both the molecular pathways and the neural circuits associated with learning and memory and with drug addiction.

The long-lived neural changes that underpin addictive behavior—exemplified by the relapses seen in many human addicts even after years of abstinence—are becoming clearer thanks to knowledge gleaned from the learning and memory field. Electrophysiological analyses of synaptic plasticity of the caliber of the Ungless *et al.* work will be crucial for understanding the precise nature of the lifelong "memories" that sustain addiction.

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