Cocaine-evoked synaptic plasticity: a key to addiction?

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Drugs of abuse are known to induce changes in synaptic strength in the reward neurons of the brain. Two recent studies shed some light on how drug-induced plasticity might mediate addictive behavior long after drug use.

A wave of recent studies indicates that addictive drugs, such as cocaine, morphine, nicotine, ethanol and amphetamines, induce long-term synaptic plasticity in neurons of the brain's reward system. Such drug-evoked plasticity has been reported in the ventral tegmental area (VTA), the nucleus accumbens and the prefrontal cortex[1,2]. However, for this synaptic plasticity to serve as a viable explanation for the mechanism underlying drug addiction, two additional criteria must be met. First, the cocaine-evoked synaptic plasticity must persist well beyond the early events of drug exposure and withdrawal. Second, manipulations that selectively reverse the drug-induced synaptic plasticity must also reverse the behavioral addiction.

In a recent paper in *Nature*, Conrad *et al.*[3] provide new evidence to address these issues, offering more conclusive evidence that synaptic plasticity is the cellular mechanism that directly underlies addictive behaviors long after drug exposure.

One leading hypothesis to explain drug addiction is that the learning mechanisms that are normally used to reinforce natural rewards are 'hijacked'[4]. Drugs generate a pathological reinforcement of associated behaviors until they become exclusive and compulsive[5]. All addictive drugs increase dopamine in the mesolimbic reward system[6], and a memory trace formed when dopamine levels are high may underlie the cravings that ultimately lead to relapse. The cellular substrate for many forms of learning and memory is thought to involve long-term changes in synaptic efficacy, so a simple model to link learning and addiction predicts that addictive drugs might induce long-term synaptic plasticity in the reward system.

A core component of addiction is a susceptibility to relapse, a risk that increases in the first months of withdrawal and may persist for years. Conrad *et al.*[3] examined synaptic transmission in the nucleus accumbens of rats after 45 d of withdrawal from 10 d of cocaine self-administration. They found that even a month and a half after drug withdrawal, synaptic transmission in the nucleus accumbens did not return to normal. The authors used a special protein, BS^3, to cross-link receptors at the cell surface, forming large aggregates that were then analyzed with SDS-PAGE and western blotting. These biochemical assays indicated that there was a substantial increase of the AMPA glutamate receptor subunit GluR1. To demonstrate that these receptors were actually integrated into functional synapses, the authors carried out patch-clamp recordings in slices of the accumbens *ex vivo* and found evidence for GluR2-lacking channels. Such receptors can be recognized because they conduct synaptic currents more easily at negative than at positive potentials. The authors concluded that the persistent changes in synaptic transmission are the result of alterations in the subunit composition of glutamate receptors at excitatory synapses, so that the AMPA receptors at these synapses switch from those that contain the GluR2 subunit to GluR1 homomeric channels (**Fig. 1**).

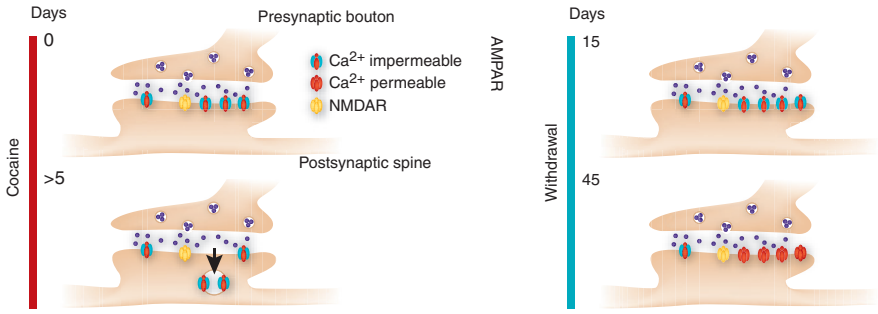

Figure 1 Timeline of cocaine-evoked synaptic plasticity in the nucleus accumbens. At baseline, excitatory synapses express NMDA (yellow) and AMPA receptors; the latter contain the subunits GluR1 (red) and GluR2 (green), and are thus calcium impermeable. After 5 d of cocaine exposure, the number of AMPA receptors in the nucleus accumbens shell decreases, whereas NMDA receptors remain unchanged[10]. During early withdrawal, in 2 weeks, AMPA receptors increase as a result of a synaptic scaling, eventually exceeding baseline[10]. Conrad *et al.*[3] now suggest that calcium impermeable-receptors are gradually exchanged during late withdrawal for calcium-permeable ones, which are probably GluR1 homomeric channels (red).

The GluR2 subunit is important in AMPA receptor function, as it prevents calcium from passing through the channel and reduces the flux of sodium and potassium as well. Without this subunit, sodium and potassium pass more readily and the channels allow calcium influx. As a consequence, neurons of the nucleus accumbens become more excitable, and as calcium can now enter the cell at negative potentials, new signaling cascades may be recruited as well.

The specific composition of the AMPA receptors also makes them accessible to selective pharmacological intervention. AMPA receptors that lack GluR2 are blocked by polyamines, whereas AMPA receptors that contain GluR2 are not. By injecting polyamines directly into the nucleus accumbens, the authors were able to suppress cue-induced cocaine seeking.

These results raise the hope that targeting calcium-permeable AMPAR receptor may be a promising strategy for addiction treatment. However, several questions remain to be addressed. Is the nucleus accumbens the only site at which this plasticity is involved in the persistent maintenance of addictive behaviors? What happens in other parts of the reward pathway where drug administration induces synaptic plasticity, such as the VTA?

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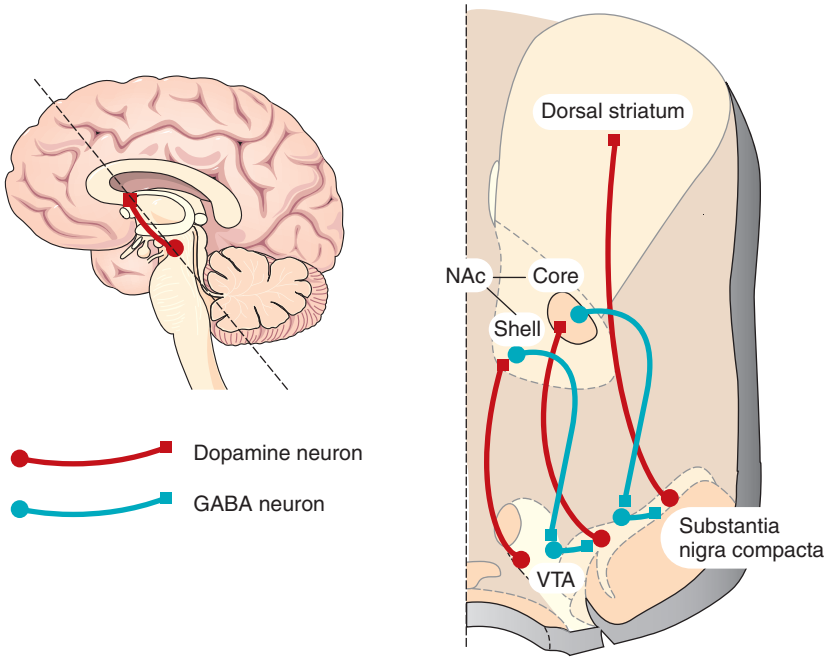

Figure 2 The spiral to addiction. Schematics represent a sagittal section of the brain (left) and a slice obtained along the dotted line (right). Dopamine neurons of the medial VTA project to the most medial part of the nucleus accumbens, the shell. These GABAergic neurons then back-project onto an interneuron in the VTA, which in turn connects to a dopamine neurons of the lateral VTA. These cells then send their axons to the nucleus accumbens core, from which cells project to the substantia nigra, pars compacta. The nigra cells finally innervate the dorsal striatum. It has been suggested that cocaine, and perhaps other addictive drugs, gradually activate this spiraling connection. Animals develop a cocaine seeking habit once the dorsal striatum is recruited[9].

Some answers to these questions may come from recent advances in the description of the anatomical layout of the midbrain dopamine system[7,8]. These data show that the nucleus accumbens and the VTA are part of a 'spiraling' network (**Fig. 2**). Dopamine neurons from the medial VTA project to the shell, the most medial part of the nucleus accumbens. From there, GABAergic cells back-project, via an interneuron, to dopamine neurons in the lateral VTA, which then project to the more lateral core of the nucleus accumbens. The neurons in the core of the nucleus accumbens project to neurons in the substantia nigra pars compacta, and these neurons finally send their axons to the dorsal striatum.

A recent paper[9] now implicates the recruitment of these dorsal parts of the dopamine system in cocaine-seeking habits that are important for addiction. In an elegant pharmacological *in vivo* study, the intrastriatal disconnection of the spiral interrupted the development of cocaine seeking in rats. The accumbens core was surgically lesioned on one side and the dopamine receptors in the contralateral dorsal striatum were blocked. With increasing doses of the dopamine receptor antagonist, cocaine seeking was gradually controlled, just as when dopamine receptor antagonists were injected in the striatum on both sides.

Thus, it seems that the spiral is engaged sequentially during the development of addiction, but the question of how this happens remains unanswered. An appealing idea is that synaptic plasticity induced early in the spiral amplifies signals as they pass through the system and makes it easier to induce plasticity later in the spiral. If this were the case, one would predict that the changes in the nucleus accumbens, such as the ones described by Conrad *et al.*[3], would take place late in the development of addiction and would be contingent on plasticity in the VTA. Direct experimental evidence for such a hierarchical organization of drug-evoked plasticity is not available, but it is perhaps noteworthy in this context that plasticity in the VTA appears as early as 4 h after a single exposure to cocaine[1], whereas synaptic changes in the nucleus accumbens typically take 5 d of consecutive injections[10].

Another element of the spiral that remains poorly understood is whether plasticity of GABAergic transmission in the returning limb of the spiral also contributes to the development or maintenance of drug addiction. One of the few studies looking at plasticity of GABAergic transmission in the VTA suggested that *in vivo* exposure to morphine can block the capacity of GABAergic transmission to undergo potentiation[11]. This already happens after a single exposure, but may contribute to the excitability of dopamine neurons in the long run. Repetitive injections of cocaine are required to downregulate GABAergic transmission[12].

These findings have an obvious appeal as a candidate for translating basic research into a therapeutic intervention; pharmacological manipulations on the basis of GluR2 might be a useful approach to control reinforcement, craving and relapse. Of course, there are many reasons why such an approach might prove to be unfeasible, not the least of which is that subunit-selective AMPA receptor pharmacology is still in its infancy. For instance, polyamines such as the drugs used by Conrad *et al.*[3] also affect Ca^{2+}-permeable AMPA receptors expressed on many interneurons. One promising sign, however, is that synaptic incorporation of calcium-permeable AMPA receptors occurs with drug exposure not only in the accumbens, but also in the VTA[13,14]. Pharmacological targeting may therefore interfere with addiction at multiple levels and at various time-points of the disease. If pharmacological substances that specifically inhibit calcium-permeable AMPA receptors become available for human use one day, it would certainly be interesting to test their effects on reinforcement, craving and relapse. However, only large-scale clinical studies will tell whether such drugs can work in the harsh clinical reality of treating addicts who typically have a history of years of drug abuse with uncontrollable and frequent relapse.

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