Published in final edited form as:
*Biol Psychiatry*. 2011 June 1; 69(11): 1013–1014. doi:10.1016/j.biopsych.2011.04.001.

# Cocaine and synaptic alterations in the nucleus accumbens

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## Abstract

In laboratory animals, repeated cocaine exposure produces long-lasting behavioral alterations such as psychomotor sensitization and conditioned place preference (CPP) that are thought to model various aspects of addictive behavior. A great deal of effort has gone into examining the relationship of electrophysiological, and particularly synaptic alterations, to psychomotor sensitization and CPP. Many of these studies have focused on alterations within the nucleus accumbens because it is one of the main targets of the mesolimbic dopamine system that originates with dopamine neurons in the ventral tegmental area (VTA) and is critical for many cocaine-induced behaviors. Medium spiny neurons (MSNs), which are the majority of nucleus accumbens neurons, also receive significant glutamatergic inputs from the prefrontal cortex, basolateral amygdala, and hippocampus that convey information about drug-associated environmental stimuli. Thus electrophysiological and synaptic alterations within nucleus accumbens MSNs are likely to affect sensitization and CPP behavior.

In the 1990's, the laboratory of Frank White found decreased excitability of accumbens medium spiny neurons following short withdrawal (3d) from repeated cocaine injections [1] and long-lasting (<30d) reductions in D1 dopamine receptor (D1R)-mediated inhibition of accumbens neuronal activity [2]. Reports of cocaine-induced synaptic alterations *per se* within nucleus accumbens emerged in 2001 when the labs of Antonello Bonci and Robert Malenka used the ratio of currents mediated through the glutamate receptor ion channels AMPAR and NMDAR as an *in vivo* marker of alterations of synaptic strength [3]. Assays of AMPAR/NMDAR ratios as well as biochemical studies of AMPA receptor surface expression indicate a rapid decline of this ratio from baseline shortly after repeated cocaine exposure, suggesting a mechanism similar to long-term depression (LTD), followed by a slow increase of this ratio over 1–2 weeks to levels exceeding baseline ratios, suggesting a mechanism similar to long-term potentiation (LTP). Meanwhile repeated cocaine-induced alterations of dendritic spine morphology of nucleus accumbens medium spiny neurons were first identified in 1999 [4]. While it is easy to hypothesize how these alterations relate to the electrophysiological alterations and cocaine-related behavior, the actual relationships have been difficult to determine.

## Cell-type specific synaptic plasticity in the accumbens

Accumbens MSNs are comprised of two general cell types: one expresses primarily D1 dopamine receptors (D1R) and projects equally to the ventral pallidum and ventral tegmental area while the other cell type expresses primarily D2 dopamine receptors (D2R) and projects primarily to the ventral pallidum [5]. Although much has been revealed regarding the structural and physiological alterations to accumbens neurons in general, very

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There are no conflicts of interest for any authors of this manuscript.

little is known about whether these two cell-types undergo differential synaptic alterations. The advent of D1R-eGFP and D2R-eGFP BAC transgenic mice that express enhanced green fluorescent protein (eGFP) in D1R and D2R MSNs have given us a better picture of cell-type specific cocaine-induced changes in the accumbens. Recently it was shown that following long-term withdrawal from repeated cocaine injections, spine density was increased in a persistent manner on only D1R MSNs suggesting that these two populations have differential structural adaptations to cocaine and highlights the importance of examining the different accumbens cell-types after repeated cocaine exposure [6].

In this issue, Kim et al. investigated using D1R-eGFP and D2R-eGFP transgenic mice, whether the D1R and D2R expressing MSN's differed in their synaptic profile and neuronal morphology 1 day after 5d of once daily repeated cocaine injections in their home cages. Repeated cocaine decreased excitability of D1R neurons, similar to what was previously found when a random population of accumbens neurons were recorded [7, 8], suggesting that these latter observations likely occurred within D1R neurons. Repeated cocaine also increased the frequency, but not amplitude, of mEPSCs (miniature excitatory post-synaptic currents) within D1R neurons. In contrast, repeated cocaine did not affect excitability of D2R neurons, but did reduce mEPSCs frequency, but not amplitude. These results indicate selective alterations in basal glutamatergic transmission on D1R neurons. Repeated cocaine also reduced the frequency and amplitude of mIPSCs (miniature inhibitory post-synaptic currents) within D1R neurons, but not D2R neurons, indicating that basal GABAergic transmission was altered. Finally, at the morphological level they examined the density of spines, the key sites where excitatory inputs arrive on MSNs. Again repeated cocaine increased spine density on D1R, but not D2R, neurons. Collectively, these results indicate that repeated cocaine injections in the home cage induce early neural adaptations in a cell-type specific manner, and the ability of cocaine to induce behavioral changes might be related to early differences of neural adaptations in the two distinct anatomical pathways.

Future experiments can extend this study to assess these alterations under different environmental conditions as well as whether these alterations persist for longer withdrawal times that correspond with persistent sensitized behavior. The current Kim et al. data suggest homeostatic responses in only D1R neurons following repeated injections to mice in their home cages. However while cocaine injections to rats in their home cage also induce the neural activity marker Fos primarily within D1R neurons, repeated cocaine injections to rats outside their home cage, as in most behavioral experiments, induce the neural activity marker Fos in both D1R and D2R neurons [9, 10].

## Synaptic Plasticity of accumbens neurons associated with relapse provoking stimuli

Relapse of drug craving for drugs of abuse is often provoked by re-exposure to the drugs or to stressful situations [11]. Currently, little is known whether these relapse-related factors, including cocaine-priming and stress, alter synaptic strength in cocaine-experienced animals. In this issue Rothwell et al. first confirmed that longer-term withdrawal from repeated cocaine injections increased AMPA/NMDA ratios in nucleus accumbens. The interesting finding was that forced swim stress exposure following repeated cocaine injections acutely decreased AMPA/NMDA ratios similar to that previously observed following acute cocaine test injections after repeated drug exposure. They also found cocaine-priming injections that reinstate cocaine CPP after extinction acutely decreased accumbens AMPA/NMDA ratios. Thus two different stimuli previously associated with relapse to drug-seeking produce similar synaptic alterations.

Acute stress and cocaine-priming injections may decrease AMPAR/NMDAR ratios in nucleus accumbens by internalizing AMPA receptors as part of a short-lasting homeostatic synaptic scaling mechanism that compensates for overly strong excitatory drive during stress or cocaine injections [12]; both stress and cocaine increase excitatory glutamate transmission to the nucleus accumbens during cocaine-seeking [13]. Thus it is possible that the observed acute reductions of AMPAR/NMDAR ratios are a response to excessive excitatory drive that merely coincide with behavior rather than being the cause of the behavior. In future studies, it will be important to first correlate synaptic alterations in accumbens neurons with reinstatement behavior at different times before and after acute induction of the behavior, and then manipulate these ratios to determine a causal role in mediating the behavior. The critical question in the current study is whether the repeated cocaine-induced increase of AMPAR/NMDAR ratios present prior to acute stress or cocaine-priming is the cause of stress- or cocaine-induced reinstatement behavior, or if the acutely induced decrease of AMPA/NMDA ratios is rapid enough to mediate the behavior. While stress and cocaine-priming stimuli can provoke reinstatement behavior within seconds to minutes, the current study assessed AMPA/NMDA ratios 2 hours or 24 hours after the stimuli. Either way these studies are part of an interesting line of studies examining potential neural mechanisms capable of having profound effects on drug-induced behavior.

## Acknowledgments

This research was supported by the Intramural Research Program of the National Institute on Drug Abuse.

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