THE ROYAL SOCIETY

Published online 10 March 2003

Synaptic plasticity in the mesolimbic dopamine system

Mark J. Thomas[1] **and Robert C. Malenka**[2*]

[1]*Departments of Neuroscience and Psychology, and Institute of Human Genetics, University of Minnesota, Minneapolis, MN 55455, USA*

[2]*Nancy Friend Pritzker Laboratory, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, CA 94304, USA*

Long-term potentiation (LTP) and long-term depression (LTD) are thought to be critical mechanisms that contribute to the neural circuit modifications that mediate all forms of experience-dependent plasticity. It has, however, been difficult to demonstrate directly that experience causes long-lasting changes in synaptic strength and that these mediate changes in behaviour. To address these potential functional roles of LTP and LTD, we have taken advantage of the powerful *in vivo* effects of drugs of abuse that exert their behavioural effects in large part by acting in the nucleus accumbens (NAc) and ventral tegmental area (VTA); the two major components of the mesolimbic dopamine system. Our studies suggest that *in vivo* drugs of abuse such as cocaine cause long-lasting changes at excitatory synapses in the NAc and VTA owing to activation of the mechanisms that underlie LTP and LTD in these structures. Thus, administration of drugs of abuse provides a distinctive model for further investigating the mechanisms and functions of synaptic plasticity in brain regions that play important roles in the control of motivated behaviour, and one with considerable practical implications.

Keywords: addiction; dopamine; drugs of abuse; nucleus accumbens; ventral tegmental area

1. INTRODUCTION

A fundamental issue in neuroscience is how experience modifies synaptic circuitry in the mammalian brain to mediate long-lasting changes in cognition and behaviour. To address this issue experimentally, two basic questions have been posed. First, what are the molecular mechanisms by which patterns of neural activity can stably modify synaptic efficacy? Progress in answering this question has come chiefly through the study of LTP and LTD using *in vitro* slice preparation of the hippocampus. Indeed, such work has greatly expanded our understanding of the molecular mechanisms underlying synaptic function. The second, no less challenging question is—what are the functional consequences of these modifications on neural circuits and behaviour? A very attractive and, we believe, underused model for the study of these sorts of functional questions is the experience-dependent plasticity elicited by *in vivo* exposure to drugs of abuse.

Repeated exposure to drugs of abuse, most notably psychostimulants such as cocaine, leads to a persistent increase in their rewarding and locomotor effects (Robinson & Berridge 1993; Kalivas 1995; Wolf 1998; Carlezon & Nestler 2002; Everitt & Wolf 2002). This enhanced response is thought to be a model for the intensification of drug craving in human addicts. Pharmacological, biochemical and lesion experiments indicate that these enhanced behavioural responses are mediated, at least in part, by long-lasting drug-induced adaptations in the mesolimbic dopamine system—the chief components of which are the VTA, the NAc and their afferent and efferent connections. In particular, modifications in the VTA appear to mediate the induction of behavioural sensitization, whereas adaptations in the NAc are involved in its long-term maintenance (Robinson & Berridge 1993; Kalivas 1995; Wolf 1998; Carlezon & Nestler 2002; Everitt & Wolf 2002). For example, repeated injection of psychostimulants into the VTA induces behavioural sensitization, whereas in sensitized animals, the injection of psychostimulants into the NAc is sufficient to elicit sensitized responses. Although the detailed modifications in neural circuitry that mediate this drug-induced behavioural plasticity remain unknown, attention is beginning to be focused on the idea that mechanisms of synaptic plasticity in operation in other regions of the brain, such as the hippocampus, may also be at work in the mesolimbic dopamine system where they play critically important roles in both adaptive forms of learning and memory (Hernandez *et al.* 2002) as well as the pathological behaviours that underlie addiction.

2. MECHANISMS OF SYNAPTIC PLASTICITY

(a) *LTP and LTD in the NAc*

Before determining whether drugs of abuse elicit synaptic plasticity in the mesolimbic dopamine system, it was necessary to address the more straightforward question of whether synaptic plasticity can in fact be induced at excitatory synapses in the NAc and VTA? Studies primarily

* Author for correspondence (malenka@stanford.edu).

One contribution of 30 to a Theme Issue 'Long-term potentiation: enhancing neuroscience for 30 years'.

from our laboratory have shown that both LTP and LTD can be elicited at excitatory synapses on medium spiny neurons in the NAc (Kombian & Malenka 1994; Bonci & Malenka 1999; Thomas *et al.* 2000). Experiments thus far have focused primarily on the synapses made by prelimbic cortical afferents and it remains to be determined whether other glutamatergic afferents to the NAc, such as those from the hippocampus, express similar forms of plasticity. There are several similarities between the plasticity at prelimbic afferent-medium spiny neuron synapses and those commonly studied in the CA1 region of the hippocampus. For example, high-frequency tetani of presynaptic fibres induces LTP whereas low-frequency stimulation during modest depolarization of the postsynaptic cell induces LTD. Also as in the hippocampus, activation of NMDA receptors and elevation of postsynaptic calcium levels are required for both LTP and LTD. Alternatively, LTP in the NAc has the unique feature that the enhancement of the AMPA receptor-mediated component of the synaptic response is accompanied by a decrement in the NMDA receptor-mediated component (Kombian & Malenka 1994). Although the significance of this feature is not yet clear, it may be some kind of a negative feedback mechanism to limit further potentiation at synapses having undergone LTP. Although it seems likely that the signalling processes downstream of NMDA receptor activation would be shared between NMDA receptor-dependent forms of plasticity in different brain regions, very little is known about the signalling cascades that regulate either LTP or LTD in the NAc. However, a recent study reports that strong enhancement of ERK2 signalling in the absence of ERK1 can facilitate LTP induction in the NAc while having little influence on LTP in the hippocampus or amygdala (Mazzucchelli *et al.* 2002). This may indicate that different signalling pathways act downstream of NMDA receptor activation to trigger LTP in NAc cells than in other forms of plasticity elsewhere in the brain.

Surprisingly, there are several key differences in the mechanisms of LTD induced in medium spiny neurons by cortical afferent stimulation in the dorsal striatum compared with the NAc (which is also known as the ventral striatum). For example, although activation of mGluRs is reported to be necessary for the induction of LTD in the dorsal striatum (Calabresi *et al.* 2000) it is not required for NAc LTD (Thomas *et al.* 2000). In addition, in contrast to findings in the dorsal striatum, the activation of dopamine receptors is not required for the generation of LTD or for that matter LTP in the NAc. However, in both the dorsal striatum and the NAc a form of LTD dependent on the release of endocannabinoids has been reported (Gerdeman *et al.* 2002; Robbe *et al.* 2002).

(b) *LTP and LTD in midbrain dopamine cells*

Excitatory synapses on dopamine neurons in the midbrain dopamine regions (the VTA and substantia nigra pars compacta) can also undergo both LTP and LTD. LTP at these synapses is NMDA receptor dependent but for reasons that remain unclear, it is difficult to generate in that it requires perforated patch recording and is often small in magnitude (Bonci & Malenka 1999). Nothing is currently known about its underlying mechanisms. LTD, however, is triggered through the activation of postsynaptic voltage-gated calcium channels (Jones *et al.* 2000; Thomas *et al.* 2000). In fact, activation of these channels with depolarizing voltage steps induces LTD even in the absence of synaptic stimulation, indicating that this form of LTD does not necessarily occur specifically at activated synapses. This property would, in theory, enable a subset of activated synapses to effectively decrease excitatory synaptic strength throughout a significant proportion of the dendritic tree.

LTD in the VTA is strongly inhibited by dopamine and amphetamine through the activation of D2-like receptors (Jones *et al.* 2000; Thomas *et al.* 2000)—a modulation with potentially important functional implications. Recent studies have begun to investigate the signalling pathways that mediate LTD in the VTA. Thus, far, the pathways are quite different than those that underlie LTD in other brain regions. For example, although both VTA and hippocampal LTD appear to be mediated by the loss of surface AMPA receptors (Carroll *et al.* 2001), in VTA LTD this appears to involve increases in cAMP and the activation of PKA (Gutlerner *et al.* 2002), whereas at hippocampal synapses PKA activation inhibits AMPA receptor endocytosis. Future studies will be required to determine how the same signalling pathway can subserve seemingly opposite functions in these different brain regions.

3. DRUG-INDUCED SYNAPTIC PLASTICITY

(a) *Midbrain dopamine cells*

In addition to the demonstration of synaptic plasticity at excitatory synapses in mesolimbic dopamine structures, there is abundant correlative evidence that supports the idea that synaptic plasticity may play a role in mediating the behavioural consequences of *in vivo* exposure to drugs of abuse and thus the development of addiction (Robinson & Berridge 1993; Kalivas 1995; Wolf 1998; Hyman & Malenka 2001; Nestler 2001; Carlezon & Nestler 2002; Everitt & Wolf 2002). This includes drug-induced changes in the levels of glutamate-receptor expression and single-unit responses to glutamate as well as the behavioural effects of glutamate-receptor antagonists injected into specific brain loci. A key question that had not been addressed, however, was whether drugs of abuse actually elicit changes in synaptic strength *in vivo*.

To address this issue, Ungless *et al.* (2001) prepared midbrain slices from animals that had received a single injection of cocaine one day earlier, and measured synaptic strength using whole-cell recording techniques. The single *in vivo* exposure to cocaine caused a large and robust potentiation of synaptic strength that appeared to be due, in large part, to an upregulation of the number and/or function of AMPA receptors (figure 1). This potentiation was specific in that it did not occur at excitatory synapses on hippocampal CA1 pyramidal neurons nor on GABA neurons in the VTA. Importantly, this cocaine-induced potentiation occluded LTP induction *in vitro*, indicating that the two processes share some underlying mechanisms. Two additional features of the cocaine-induced potentiation suggest a relationship between this phenomenon and the induction of behavioural sensitization. The first is that cocaine-induced potentiation is detectable 5 but not 10 days after exposure to cocaine. This is analogous to the essential but transient role that the VTA is thought to play in the induction of sensitiz-

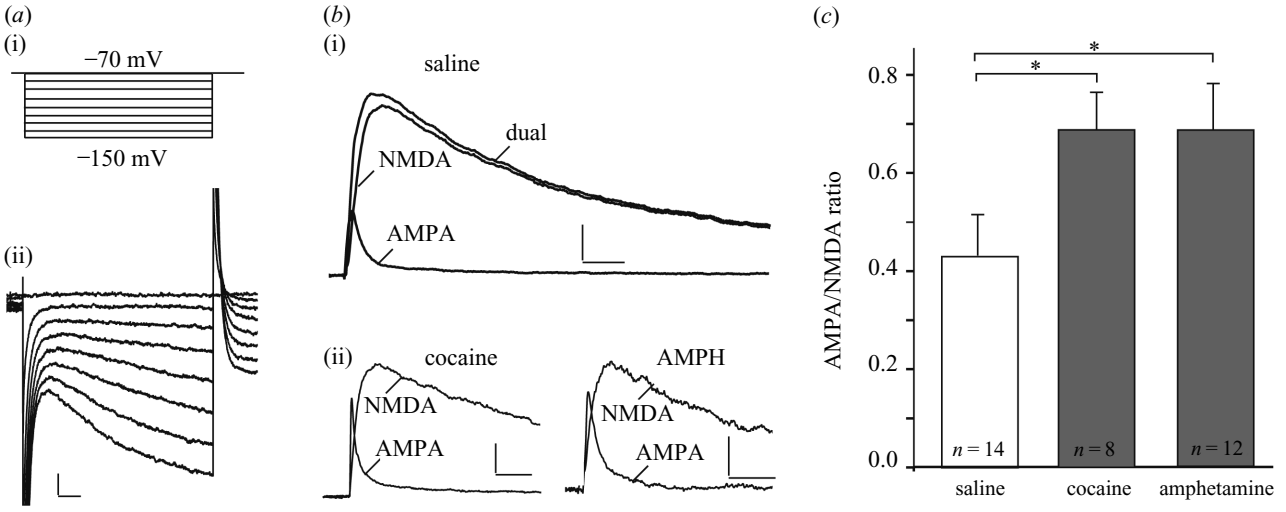

Figure 1. Synaptic strength at excitatory synapses on midbrain DA neurons, as measured by measuring the ratio of AMPA-receptor to NMDA-receptor-mediated synaptic currents, is increased by *in vivo* administration of cocaine or amphetamine. (*a*) An example of I_h currents that are used to identify midbrain DA cells (calibration bars: 20 pA/50 ms). (*b*) (i) An example from a control cell of how AMPA/NMDA ratios were obtained. EPSCs were recorded at +40 mV (dual trace) then D-APV (50 μM) was applied to obtain the AMPA EPSC. The NMDA EPSC was obtained by digital subtraction of the AMPA EPSC from the dual EPSC. (ii) Examples of AMPA and NMDA EPSCs obtained from cocaine- and amphetamine-treated animals (calibration bars: 20 pA/15 ms). (*c*) Summary of AMPA/NMDA ratios obtained from animals that were administered saline, cocaine or amphetamine ($^*p < 0.02$). Numbers within the bars indicate the number of cells examined. (Reprinted with permission from Saal *et al.* (2003).)

ation (Robinson & Berridge 1993; Kalivas 1995; Wolf 1998; Carlezon & Nestler 2002; Everitt & Wolf 2002). The second feature is that like sensitization, cocaine-induced potentiation is blocked *in vivo* by the co-administration of cocaine with an NMDA receptor antagonist. Although the critical site of action of the NMDA receptor antagonist is unknown, a tantalizing observation (A. Bonci *et al.*, personal communication) is that cocaine appears to transiently enhance NMDA receptor-mediated responses in VTA dopamine neurons. This effect appears to be mediated through dopamine receptor activation and may be the first step towards LTP induction by cocaine exposure *in vivo*.

The existence of cocaine-induced potentiation at excitatory synapses on VTA dopamine neurons raises the question of the relationship between this cellular phenomenon and core features of addiction? That this synaptic modification may indeed be functionally important is suggested by recent findings that *in vivo* administration of a wide variety of drugs of abuse with very different molecular mechanisms of action (i.e. amphetamine, morphine, nicotine, ethanol) all cause an enhancement of strength at excitatory synapses on midbrain dopamine cells (Saal *et al.* 2003) (figures 1 and 2). Importantly, non-abused psychoactive drugs such as fluoxetine and carbamazepine did not cause a change. As stress has a profound facilitatory effect on the initiation and reinstatement of drug self-administration (Piazza & Le Moal 1998) the effect of an acute stress was also examined and, like drugs of abuse, was found to cause a robust increase in synaptic strength in midbrain dopamine cells (Saal *et al.* 2003). These results indicate that plasticity at excitatory synapses on dopamine cells may be a key neural adaptation contributing to addiction and its interactions with stress. Specifically, as external stimuli that are associated with the firing of midbrain dopamine cells are granted high appetitive or motivational significance, we suggest that by increasing synaptic drive onto these cells, drugs of abuse or stress enhance the motivational significance of drugs themselves as well as stimuli closely associated with drug seeking and self-administration.

(b) *NAc*

While neural adaptations in the VTA are involved in the induction of behavioural sensitization, long-lasting changes in the NAc are thought to mediate its expression. Thus, Thomas *et al.* (2001) sought to examine synaptic strength at excitatory synapses in NAc slices prepared 10–14 days after repeated (5 day) *in vivo* administration of cocaine—a treatment that caused robust behavioural sensitization. Neurons in the shell, but not the core region of NAc slices prepared from the cocaine-treated animals showed a decrease in strength at excitatory synapses made by prelimbic cortical afferents. LTD was also diminished; an occlusion that suggests that the decrease was due to mechanisms shared with LTD. As is the case for changes in the VTA, the mechanisms responsible for this drug-induced synaptic plasticity in the NAc are unclear. One intriguing hypothesis is suggested by the finding that persistent upregulation of the ΔFosB transcription factor, which is known to occur following repeated cocaine treatment, induces NAc expression of the AMPA receptor subunit GluR2 (Kelz *et al.* 1999). Owing to conductance differences in GluR2-containing versus non-GluR2-containing AMPA receptors, increases in GluR2 expression could potentially reduce AMPA receptor-mediated responses. This hypothesis, however, depends on the existence of a significant population of non-GluR2-containing synaptic AMPA receptors before cocaine exposure. If such a population existed, it should be identifiable because of the strong inward rectification of non-GluR2-containing receptors. Although this hypothesis

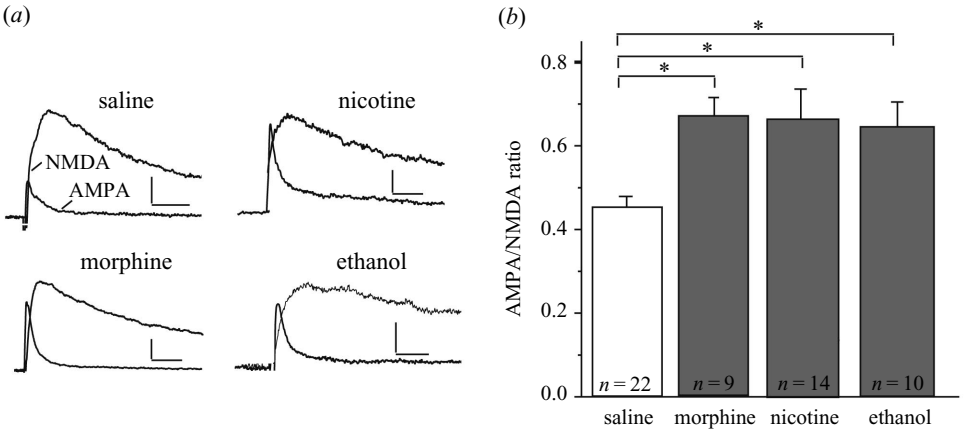

Figure 2. Commonly abused drugs other than psychostimulants also increase the AMPA/NMDA ratio. (*a*) Examples of AMPA and NMDA EPSCs obtained from animals given the indicated substance (calibration bars: 20 pA/15 ms). (*b*) Summary of AMPA/NMDA ratios obtained from animals administered saline, morphine, nicotine or ethanol ($^*p < 0.03$). (Reprinted with permission from Saal *et al.* (2003).)

remains intriguing, preliminary studies have failed to detect inward-rectifying AMPA receptor-mediated responses in NAc medium spiny neurons, suggesting that GluR2 incorporation does not explain the cocaine-induced depression. Another possibility is suggested by the fact that the acute administration of amphetamine to slices blocks LTP in the NAc (Li & Kauer 2000). This effect disappears in slices prepared from animals that have been repeatedly exposed to amphetamine. If this also occurs after *in vivo* cocaine exposure, such an action could initially enhance the likelihood of generating LTD.

4. CONCLUSION

Behavioural studies over the past two decades have provided compelling evidence that drugs of abuse exert powerful control over behaviour in large part because of their actions in the mesolimbic dopamine system. We have found that synaptic plasticity occurs in the NAc and VTA, two main components of this system, and that *in vivo* administration of drugs of abuse causes changes in synaptic strength probably because of the activation of the mechanisms that underlie LTP and LTD in these structures. Although the work reviewed here is still in its infancy, it hopefully illustrates that the powerful *in vivo* effects of drugs of abuse may be a valuable model for studying the role of synaptic plasticity in mediating experience-dependent plasticity. Indeed, it is already apparent that, like other forms of experience-dependent plasticity such as learning and memory (Martin *et al.* 2000), persistent drug-induced behavioural changes probably occur because of their ability to elicit long-lasting changes in synaptic weights in crucial brain circuits. Furthermore, it is important to note that the mesolimbic dopamine system did not evolve to respond to drugs of abuse but rather plays very important roles in adaptive behaviours including various types of learning and memory. Thus, examining the neural adaptations elicited by drugs of abuse will not only inform us about the pathophysiology of addiction but will also provide important information about how neural circuit modifications in the NAc and VTA contribute to normal, motivated behaviour.

REFERENCES

Bonci, A. & Malenka, R. C. 1999 Properties and plasticity of excitatory synapses on dopaminergic and GABAergic cells in the ventral tegmental area. *J. Neurosci.* **19**, 3723–3730.

Calabresi, P., Centonze, D. & Bernardi, G. 2000 Electrophysiology of dopamine in normal and denervated striatal neurons. *Trends Neurosci.* **23**, S57–63.

Carlezon, W. A. & Nestler, E. J. 2002 Elevated levels of GluR1 in the midbrain: a trigger for sensitization to drugs of abuse? *Trends Neurosci.* **25**, 610–615.

Carroll, R. C., Beattie, E. C., Von Zastrow, M. & Malenka, R. C. 2001 Role of AMPA receptor endocytosis in synaptic plasticity. *Nature Rev. Neurosci.* **2**, 315–324.

Everitt, B. J. & Wolf, M. E. 2002 Psychomotor stimulant addiction: a neural systems perspective. *J. Neurosci.* **22**, 3312–3320.

Gerdeman, G. L., Ronesi, J. & Lovinger, D. M. 2002 Postsynaptic endocannabinoid release is critical to long-term depression in the striatum. *Nature Neurosci.* **5**, 446–451.

Gutlerner, J. L., Penick, E. C., Snyder, E. M. & Kauer, J. A. 2002 Novel protein kinase A-dependent long-term depression of excitatory synapses. *Neuron* **36**, 921–931.

Hernandez, P. J., Sadeghian, K. & Kelley, A. E. 2002 Early consolidation of instrumental learning requires protein synthesis in the nucleus accumbens. *Nature Neurosci.* **5**, 1327–1331.

Hyman, S. E. & Malenka, R. C. 2001 Addiction and the brain: the neurobiology of compulsion and its persistence. *Nature Rev. Neurosci.* **2**, 695–703.

Jones, S., Kornblum, J. L. & Kauer, J. A. 2000 Amphetamine blocks long-term synaptic depression in the ventral tegmental area. *J. Neurosci.* **20**, 5575–5580.

Kalivas, P. W. 1995 Interactions between dopamine and excitatory amino acids in behavioral sensitization to psychostimulants. *Drug Alcohol Depend.* **37**, 95–100.

Kelz, M. B. (and 16 others) 1999 Expression of the transcription factor deltaFosB in the brain controls sensitivity to cocaine. *Nature* **401**, 272–276.

Kombian, S. B. & Malenka, R. C. 1994 Simultaneous LTP of non-NMDA- and LTD of NMDA-receptor-mediated responses in the nucleus accumbens. *Nature* **368**, 242–246.

Li, Y. & Kauer, J. A. 2000 Amphetamine interferes with long-term potentiation in the nucleus accumbens. *Soc. Neurosci. Abstr.* **26**, 1398.

Martin, S. J., Grimwood, P. D. & Morris, R. G. M. 2000 Synaptic plasticity and memory: an evaluation of the hypothesis. *A. Rev. Neurosci.* **23**, 649–711.

Mazzucchelli, C. (and 19 others) 2002 Knockout of ERK1 MAP kinase enhances synaptic plasticity in the striatum and facilitates striatal-mediated learning and memory. *Neuron* **34**, 807–820.

Nestler, E. J. 2001 Molecular basis of long-term plasticity underlying addiction. *Nature Rev. Neurosci.* **2**, 119–128.

Piazza, P. V. & Le Moal, M. 1998 The role of stress in drug self-administration. *Trends Pharmacol. Sci.* **19**, 67–74.

Robbe, D., Kopf, M., Remaury, A., Bockaert, J. & Manzoni, O. J. 2002 Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens. *Proc. Natl Acad. Sci. USA* **99**, 8384–8388.

Robinson, T. E. & Berridge, K. C. 1993 The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Brain Res. Rev.* **18**, 247–291.

Saal, D., Dong, Y., Bonci, A. & Malenka, R. C. 2003 Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* **37**(4). (In the press.)

Thomas, M. J., Malenka, R. C. & Bonci, A. 2000 Modulation of long-term depression by dopamine in the mesolimbic system. *J. Neurosci.* **20**, 5581–5586.

Thomas, M. J., Beurrier, C., Bonci, A. & Malenka, R. C. 2001 Long-term depression in the nucleus accumbens: a neural correlate of behavioural sensitization to cocaine. *Nature Neurosci.* **4**, 1217–1223.

Ungless, M. A., Whistler, J. L., Malenka, R. C. & Bonci, A. 2001 Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature* **411**, 583–587.

Wolf, M. E. 1998 The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. *Prog. Neurobiol.* **54**, 679–720.

GLOSSARY

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
EPSC: excitatory postsynaptic current
LTD: long-term depression
LTP: long-term potentiation
mGluR: metabotropic glutamate receptor
NAc: nucleus accumbens
NMDA: *N*-methyl-D-aspartate
VTA: ventral tegmental area