Dopamine Excites Nucleus Accumbens Neurons through the Differential Modulation of Glutamate and GABA Release

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Afferent activity into the nucleus accumbens (NAc) occurs in bursts of action potentials. However, it is unclear how synapses in this nucleus respond to such bursts, or how these responses are altered by dopamine (DA). I examined the effects of DA on excitatory and inhibitory responses to trains of stimuli in rat NAc slices. Although DA inhibited both glutamate and GABA release in the NAc, it differentially inhibited release during trains. The inhibition of IPSCs persisted throughout the train of stimuli, whereas the inhibition of EPSCs progressively diminished. This differential modulation may be explained by a calcium-dependent change in the recovery from depression at the GABA synapses, where DA acts by decreasing Ca$^{2+}$ entry. Thus, at later stages of sustained stimulation, DA preferentially inhibits GABA release, producing a net excitatory effect during bursts suggesting a mechanism for enhancing the contrast between competing inputs into the NAc, as well as for affecting long-term plasticity in this structure.

Key words: accumbens; dopamine; depression; burst; presynaptic; calcium

Introduction

The nucleus accumbens (NAc), a part of the ventral striatum, is involved in cue-related reward behaviors, including maladaptive behaviors associated with drugs of abuse. Dopamine (DA) plays a critical role in this, presumably by enhancing cue-driven inputs into the NAc, which helps to facilitate the selection of an appropriate behavioral response. Recent studies support the hypothesis that DA neuron firing encodes an "error signal" (Schultz, 1998): DA neurons fire in response to unexpected rewards and to cues that are predictive of reward. The role of this DA is twofold (McClure et al., 2003). First, DA promotes the selection of an appropriate behavior to acquire the predicted reward. Second, DA release contributes to reinforcement by associating predictive cues with specific outcomes. In support of these ideas, reward-predictive cues excite a subset of NAc neurons (Ghitza et al., 2003; Nicola et al., 2004a), and inactivating DA neurons reduces these excitations in the NAc (Yun et al., 2004). However, the cellular mechanisms underlying how DA excites NAc neurons are unclear.

DA directly modulates a number of postsynaptic conductances in both the NAc and the dorsal striatum (Nicola et al., 2000; Hopf et al., 2003). In addition, in contrast to the dorsal striatum (Nicola and Malenka, 1998), DA robustly inhibits both glutamate and GABA release in the NAc (Pennartz et al., 1992; Nicola and Malenka, 1997). This presynaptic inhibition is particularly important for understanding how DA affects NAc neurons, because the projecting medium spiny neurons (MSNs) have hyperpolarized resting membrane potentials (Uchimura et al., 1989) and do not fire in the absence of excitatory afferent activity. Thus, it is unclear how DA can excite MSNs when one of its primary effects is to inhibit glutamate release, the very transmitter required to produce activity.

The NAc receives excitatory glutamatergic afferents from prefrontal cortex, hippocampus, and amygdala (Pennartz et al., 1994). This afferent activity provides cue-related information to the nucleus. Furthermore, these excitatory afferents recruit a GABAergic feedforward inhibition onto MSNs both through interneurons and through axon collaterals of neighboring MSNs (Chang and Kitai, 1985; Pennartz and Kitai, 1991; Kawaguchi et al., 1995; Taverna et al., 2004). Neurons that project to the NAc burst during relevant behaviors (Cooper, 2002). For example, subpopulations of layer V neurons in the monkey prefrontal cortex respond with a burst during various phases of a goal-directed task (Schultz et al., 2000). In the rat, the instantaneous frequency during these bursts can exceed 50 Hz (Jung et al., 1998). Depending on the brain region, synapses respond to bursts of activity with facilitation, depression, or a combination of these two forms of short-term plasticity (Markram et al., 1998; Dittman et al., 2000; Zucker and Regehr, 2002). However, in the NAc, it is unknown how bursts of activity affect neurotransmitter release. Moreover, it is unclear how neuromodulators such as DA affect this presynaptic short-term plasticity.

Here, I have investigated the effects of DA on trains of synaptic activity at both glutamatergic and GABAergic synapses in the NAc. Although there is frequency-dependent depression of release at both types of synapses, DA differentially affects glutamate...
and GABA responses. DA inhibited the initial EPSC or IPSC of a train. However, the DA inhibition of the IPSC persisted throughout the train, whereas the inhibition of the EPSC progressively diminished. This differential modulation of release results in a net excitatory effect on MSNs under burst-firing conditions and points to a novel mechanism for explaining the functional effect of DA in the NAc.

Materials and Methods
Two- to 4-week-old male Sprague Dawley rats were anesthetized with isoflurane, decapitated and the brain removed, and placed into an ice-cold Ringer’s solution (−3°C) containing (in mM): 119 NaCl, 2.5 KCl, 1.3 MgSO4, 1.0 NaH2PO4, 2.5 CaCl2, 26.2 NaHCO3, and 11 glucose saturated with 95% O2–5% CO2. Coronal slices (350-μm-thick) containing the NAc were cut using a vibratome (Leica, Nussloch, Germany). Slices were submerged in Ringer’s solution and allowed to recover for >1 h at 29°C.

Individual slices were transferred to a poly-d-lysine-coated coverslip and visualized under an Olympus Optical (Melville, NY) upright microscope with differential interference contrast optics and infrared illumination. Slices were perfused with Ringer’s solution at 27°C. Whole-cell patch-clamp recordings were made from MSNs using 2.5–4.0 MΩ pipettes containing (in mM): 123 Cs-glucuronate, 10 HEPES, 0.2 EGTA, 8 NaCl, 2 MgATP, and 0.3 Na3GTP, pH 7.2, osmolarity adjusted to 280. In some experiments, GTP was replaced with 1 mM GDP-β-S. Cells were identified as MSNs by their appearance and by their hyperpolarized resting potential (Uchimura et al., 1989). Neurons were voltage clamped at −80 mV. Trains of EPSCs or IPSCs were evoked (10–50 Hz trains given 15–30 sec apart) with a bipolar stimulating electrode placed in the NAc shell dorsal to the recording site.

Recordings were made using an Axopatch 1-D (Axon Instruments, Foster City, CA) amplifier and were filtered at 2 kHz and collected at 5 kHz using Igor Pro (WaveMetrics, Lake Oswego, OR). Series resistance was monitored on-line by measuring the peak of the capacitance transient in response to a −4 mV voltage step applied before each stimulus. Amplitudes were calculated by comparing a 1 msec period before the peak of the response and a similar period just before the stimulus artifact for the initial response. On subsequent responses in the train, a two-exponential fit of the decay of the previous PSC was made. The amplitude of the response was then calculated as the value of a 1 msec period at the peak compared with the value of the extrapolated curve at that same time. For experiments looking at recovery from depression, test pulses at four different intervals (100, 200, 400, and 800 msec) were interleaved throughout the experiment under control of procedures written in Igor Pro. Similarly, in some experiments, trains at different frequencies were interleaved throughout the experiment.

All drugs were applied by bath perfusion. Stock solutions were made and diluted to a final concentration in Ringer’s immediately before application. d-APV (50 mM) and R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH-23390) were diluted in H2O, sulpiride (10 mM) was diluted in ETOH, and DNQX (10 mM) and picrotoxin (100 mM) were mixed in DMSO. Stock solution of DA (75 mM) was made daily in 50 mM sodium metabsolufite.

Chemicals were obtained from Sigma (St. Louis, MO) or Tocris Cookson (Ballwin, MO). In experiments using GDP-β-S, at least 20 min was allowed before application of DA to ensure that the cell was properly diazolized.

The coefficient of variation (CV) was calculated as the SD/mean amplitude for 20 consecutive sweeps in each condition. Unless otherwise noted, statistical analyses were performed using Student’s t-test, and significance was defined at p < 0.05. Results are presented as means ± SEM.

The integrate-and-fire-simulated neuron was modeled by the following differential equation:

\[
\frac{dV_c}{dt} = \left( g_{EPSC} \times R_i \times (0 - V_m) + g_{IPSC} \times R_i \times (-60 - V_m) \right) / \tau_m + (V_{rest} - V_m),
\]

where \( \tau_m = 10 \text{msec}, R_i = 100 \text{m} \Omega, \) and \( V_{rest} = -80 \text{mV}. \) The example data for control and DA conditions shown in Figure 3 were scaled to conductance values \( g_{EPSC} \) and \( g_{IPSC}. \) The conductance values were set to produce some spikes under control conditions, and \( g_{EPSC} \) was set to twice \( g_{IPSC} \) to reflect the relative abundance of symmetrical synapses on MSNs. This equation was integrated using a Euler function. If the voltage reached a threshold of −45 mV, a spike occurred and \( V_m \) was set to +40 mV for 1.6 msec and then hyperpolarized to −60 mV for 2.4 msec.

Results
Short-term depression at excitatory and inhibitory synapses
Pharmacologically isolated EPSCs (recorded in the presence of 100 μM of the GABA_A receptor antagonist picrotoxin) were recorded from MSNs in acute slices of rat NAc. In response to trains of stimuli (eight stimuli at 25 Hz), EPSCs showed use-dependent short-term depression (Fig. 1A, B). The amplitude of the final EPSC in the train was 28 ± 5% (n = 8) of the first. Stimulation at multiple frequencies showed that the degree of depression is inversely dependent on the frequency of the train (n = 6) (Fig. 1C). To measure the recovery from short-term depression, test pulses were applied at various intervals after the train (Fig. 1D). The average recovery of seven cells was fit well by an exponential curve with a time constant of 406 msec (Fig. 1E).

Stimulation in the presence of glutamate receptor antagonists DNQX (10 μM) and d-APV (50 μM) produces a GABA_A-
mediated IPSC, which is recorded as an inward current when the cell is voltage clamped at −80 mV. IPSCs also showed short-term depression in response to a train of stimuli (Fig. 2 A, B), and this depression was also frequency dependent \((n = 6)\) (Fig. 2C). However, the degree of depression was somewhat less than that observed for EPSCs: the amplitude of the final IPSC was 51 ± 5% of the first \((n = 8)\). Consistent with this, IPSCs showed a more rapid recovery from depression than the EPSCs \((197 \text{ msec})\) (Fig. 2D, E).

**Effects of DA on short-term depression**

At synapses showing use-dependent depression, changing the probability of release alters the amplitude of the initial response but has little effect on later responses in the train (Markram et al., 1998; Selig et al., 1999). Consistent with this principle, the bath application of DA \((75 \mu M)\) inhibited early, but not late, EPSCs in a train (Fig. 3A). At 25 Hz, the initial EPSC was inhibited by 51 ± 10%, whereas the final EPSC was only inhibited by 6 ± 11% \((n = 4)\). The degree of inhibition of the final stimulus exhibited strong frequency dependence \((n = 8)\): in a separate group of neurons stimulated with multiple frequencies, the last EPSC of a 10 Hz train was inhibited by DA, whereas at 50 Hz, the final EPSC actually showed augmentation \((n = 3)\).

Surprisingly, GABAergic synapses responded quite differently to the bath application of DA. Here, DA inhibited each of the IPSCs in a 25 Hz train to a similar extent: the initial IPSC was inhibited 54 ± 6%, and the final IPSC was inhibited 48 ± 8% \((n = 4)\) (Fig. 3C). Moreover, the amount of inhibition of the final IPSC was insensitive to the frequency of the train \((n = 4)\) (Fig. 3D).

The inhibition of both EPSCs and IPSCs by DA was clearly antagonized by the \(D_1\) receptor antagonist SCH-23390 \((10 \mu M)\) (Fig. 4). On the other hand, the \(D_2\) receptor antagonist sulpiride \((10 \mu M)\) had no significant effect on the DA-mediated inhibition of either EPSCs or IPSCs.

**Residual calcium mediates differential effect**

There are several possible explanations for the differential effects of DA on excitatory and inhibitory trains. First, despite previous results pointing to a presynaptic effect (Nicola and Malenka, 1997), perhaps DA acts postsynaptically at GABAergic synapses. Such a mechanisms would produce a scaling effect on trains of IPSCs. However, the CV of the initial IPSC increased after application of DA \((0.15 ± 0.02\) vs \(0.27 ± 0.03\), for control vs DA; \(n = 8; p < 0.01\); paired \(t\) test), which is consistent with a presynaptic effect. Moreover, perfusing the postsynaptic cell with GDP-βS (included in the whole-cell solution) did not alter the inhibition of IPSCs by DA \((n = 4)\) (data not shown).

CV analyses do not distinguish between changes in probabil-
Interestingly, both early and late EPSCs were significantly inhibited with cadmium mimics the effect of DA at excitatory synapses. D1-selective antagonist SCH-23390 (left, 10 μM), which reduces the pᵣ at all terminals, mimicked the effect of DA on IPSCs (60 ± 6 and 51 ± 5%; first and eighth IPSC, respectively; n = 4) (Fig. 5C,D). Thus, a change in n is not necessary to explain the effects of DA on IPSCs.

DA inhibits transmitter release through different mechanisms at glutamatergic and GABAergic synapses (Nicola and Malenka, 1997). That is, DA inhibits glutamate release in a Ca²⁺-independent manner (theoretically acting on release machinery) but inhibits GABA release in a Ca²⁺-dependent manner (presumably by inhibiting Ca²⁺ entry). Perhaps these different mechanisms of inhibiting release have different effects on short-term plasticity. To test this, I asked whether inhibiting Ca²⁺ entry with cadmium mimics the effect of DA at excitatory synapses. Interestingly, both early and late EPSCs were significantly inhibited by cadmium (46 ± 7 and 26 ± 7%; n = 6) (Fig. 5A,B).

One possible explanation for these data is that inhibiting Ca²⁺ entry into the presynaptic terminal not only lowers probability of release, but also slows the recovery from use-dependent depression. This second mechanism would counter the effect of pᵣ on short-term depression and could explain why GABAergic synapses are inhibited throughout the train by DA. To test this, I monitored the recovery from depression of IPSCs after application of either cadmium or DA (Fig. 6). In both cases, the time constant of recovery was delayed by two- to threefold after drug application. Cadmium slowed the recovery from 159 to 376 msec (n = 4), and DA slowed the recovery from 208 to 475 msec (n = 5). Because DA essentially abolishes use-dependent depression of EPSCs (Fig. 3A), the time constant of recovery cannot be measured. However, cadmium did slow the recovery for EPSCs (n = 6) (data not shown).
Effect of DA on signaling in NAc

A simple transformation of the data in Figure 3 demonstrates the net effect of DA signaling in the NAc (Fig. 7A). Inputs onto MSNs consist of both an EPSC and an IPSC attributable to feedforward or cross inhibition. Under normal conditions, this net PSC (defined as EPSC-IPSC) will shift toward inhibition later in a train, because the GABA synapses show less short-term depression than the glutamate synapses. In the presence of DA, however, the GABA synapses will be inhibited throughout the train, whereas the glutamate synapses are not; thus, the train will produce an excitatory PSC. Thus, the net effect of DA (Fig. 7A, hatched area) is to produce excitation.

This effect can be more fully illustrated with a simple integrate-and-fire model neuron that receives two inputs: an excitatory input (reversal potential of 0 mV) and an inhibitory input (reversal potential of −60 mV). The conductance change produced by the two synaptic inputs during repetitive stimulation was based on the example data shown in Figure 3 and were scaled so that, under control conditions, the model cell responded with a few action potentials (Fig. 7B). DA increased the number of action potential in response to the train. Importantly, later stimuli, which were subthreshold under control conditions, now responded with an action potential.

To test the predictions of this model in the slice, I recorded neurons in cell-attached mode (to avoid interfering with the intracellular composition). Both excitatory and inhibitory synaptic transmission were left intact, and the stimulation intensity was set to evoke two to three spikes in response to a train of stimuli. Bath application of DA caused a clear increase in the number of spikes evoked per train (n = 3) (Fig. 8A). Moreover, the distribution of action potentials shifted toward the later stimuli (Fig. 8B).

The net excitation resulting in additional action potentials is caused by the inhibition of GABA release. However, it is not clear whether the GABAergic neurons producing feedforward inhibition follow trains of inputs. If excitatory transmission is intact, stimulation in the slice evokes both monosynaptic IPSCs as well as polysynaptic feedforward inhibition. To determine the polysynaptic response, neurons were held at the reversal potential for AMPA–NMDA receptors (−0–5 mV). Thus, although glutamate transmission is intact, the recorded response is entirely GABAergic (Fig. 8C). Addition of DNQX (10 μM) blocked the polysynaptic IPSC, leaving only the monosynaptic component. Finally, the addition of picrotoxin blocked this monosynaptic IPSC, leaving only the NMDA receptor-mediated EPSC to confirm that the cell was held at the EPSC reversal potential. By subtracting the monosynaptic IPSC from the control IPSC, the polysynaptic component is revealed (Fig. 8D). The relative magnitude of the polysynaptic IPSC (compared with the monosynaptic IPSC) varied; however, the polysynaptic IPSC clearly responded to each of the stimuli in the train (n = 4), indicating that the GABAergic interneurons can clearly follow trains of stimulation.

Discussion

In this study, I have shown that, despite inhibiting glutamate release, DA can have an excitatory effect in the NAc. This is because the inhibition of GABA persists throughout trains of stimuli, whereas the inhibition of glutamate does not. Thus, DA produces a net excitation that grows throughout a train.

Both EPSCs and IPSCs in the NAc show short-term use-dependent synaptic depression in response to trains of stimuli. This is a common phenomenon that has been extensively studied at many different synapses (Zucker and Regehr, 2002). Although the precise mechanisms of this depression are unclear, it is consistent with the depletion of the readily releasable pool of vesicles...
caused by synaptic release. Thus, two factors control the degree of depression: the rate of refilling of the vesicle pool and the probability of release (of available vesicles). Manipulations that lower the probability of release result in a slower exhaustion of the vesicle pool, producing less short-term depression. As a result, the amplitude of responses later in a train is unaffected by manipulating the probability of release. This is a hallmark of use-dependent depression (Tsodyks and Markram, 1997; Selig et al., 1999).

Not every synapse that shows short-term depression behaves in this manner. For example, at the basket cell—granule cell synapse in the dentate gyrus of the hippocampus, reducing the probability of release leaves short-term depression of IPSCs unchanged (Hefti et al., 2002). This can be explained if the short-term depression is independent of transmitter release, but rather is simply dependent on the activity of the presynaptic axon (Kim and Alger, 2001; Hefti et al., 2002). Alternatively, if the manipulation changing the probability of release additionally alters the rate of recovery from depression, a similar result would be obtained.

Dopamine reduces the probability of release of both glutamate and GABA in the NAc. However, this occurs through different mechanisms (Nicola and Malenka, 1997). GABA release is inhibited in a Ca\(^{2+}\)-dependent manner, theoretically as a result of the inhibition of Ca\(^{2+}\) entry into the terminal. The inhibition of glutamate is Ca\(^{2+}\) independent, occurring downstream of Ca\(^{2+}\) entry. Despite these different mechanisms, in response to single stimuli, DA appears to have a comparable effect on release (Nicola and Malenka, 1997). This is confirmed in the present study with the analysis of the initial EPSC or IPSC in a train. However, because of their different mechanisms, DA differentially affects the residual Ca\(^{2+}\) at these two synapses. Thus, any Ca\(^{2+}\)-dependent processes in the terminal will be differentially modulated by DA. Most notably, this could impact Ca\(^{2+}\) dependent recovery from depression, a process that has been studied at a number of synapses, including the climbing fiber synapse onto Purkinje cells in the cerebellum (Dittman and Reghur, 1998), the calyx of Held synapse (Wang and Kaczmarek, 1998), as well as autapses on cultured hippocampal neurons (Stevens and Wesseling, 1998). Specifically, residual Ca\(^{2+}\) speeds up the recovery from short-term depression at synapses, apparently by accelerating the replenishment of the readily releasable pool of vesicles. During a train of stimuli, this action of Ca\(^{2+}\) will result in less short-term depression. Reducing residual Ca\(^{2+}\) slows this recovery toward a baseline rate and increases short-term depression. At inhibitory synapses in the NAc, by inhibiting Ca\(^{2+}\) entry, DA concurrently reduces the probability of release and slows the recovery from depression. These two actions counter each other, resulting in a consistent degree of short-term depression in the presence and absence of DA.

It should be noted that the exact mechanisms of use-dependent depression have not been firmly established, and moreover, may differ at different synapses. For example, the change in recovery may not reflect refilling of the readily releasable pool but could also reflect other processes such as recovery from receptor desensitization.

Unlike the NAC, DA does not appear to inhibit synaptic transmission in the dorsal striatum (Nicola et al., 2000). However, these experiments did not use trains of stimuli. A recent study using the fluorescent dye FM1-43 (N-(3-triethylammonium-propyl)-4-((dibutylamino)styryl) pyridinium dibromide) to monitor synaptic activity did observe a D\(_2\)-dependent inhibition of release (Bamford et al., 2004). Importantly, this inhibition was frequency dependent, being greater at higher frequencies. Interestingly, Bamford et al. (2004) suggest that their results could be attributable to a DA-dependent slowing of the recovery from depression. There are fundamental differences between the presynaptic effects of DA in the dorsal and ventral striatum. In the NAC, low-frequency release is inhibited by DA, whereas in the dorsal striatum, it is not. In the NAC, the inhibition is mediated by D\(_1\) receptors, whereas in the dorsal striatum, it is mediated by D\(_2\).

Finally, in the NAc, DA appears to alter recovery only at GABA terminals, whereas the Bamford et al. (2004) study is consistent with a change in recovery at glutamate terminals. However, despite the differences, these studies illustrate that the presynaptic effects of DA can be more complex than simply reducing the probability of release.

Excitatory afferent activity in the NAc engages feedforward inhibition (Pennartz and Kitai, 1991). However, it is not clear how faithfully the GABA neurons in this circuit follow the excitatory inputs. MSNs, which collateralize within the NAc, do not fire action potentials in response to each stimulus (although this will depend on the convergence of concurrently active inputs). However, the majority of NAc inhibition appears to come from a small population of interneurons (Koos and Tepper, 1999) that fire at higher rates and follow excitatory inputs with higher fidelity. Interestingly, because of the frequency independence of the effects of DA, GABA release will be inhibited independent of the firing rate of the GABAergic interneurons. As long as there is some GABA release (as has been demonstrated here), the net effect of DA will be excitatory.

DA is released in the NAc in response to cues that predict reward (Roitman et al., 2004). This release is thought to promote the selection of the appropriate motor responses necessary to obtain the reward. Theoretically, this occurs by enhancing the contrast between competing inputs, making it easier for the strongest inputs to activate MSNs. Mechanisms to explain this enhancement have been proposed (Schultz, 2002; Nicola et al., 2004), based primarily on postsynaptic effects of DA in the dorsal striatum. However, it is clear that DA has different effects in the dorsal striatum and the NAc (Nicola et al., 2000). The differential inhibition of release at glutamatergic and GABAergic terminals by DA described here provides a simple mechanism for enhancing the contrast of inputs into NAc. Specifically, longer, higher-frequency bursts, presumably encoding more salient information, will be excited to a greater degree than shorter, slower (and less salient) bursts.

The NAc is also a key substrate for the learning of cue–reward relationships (Cador et al., 1989; Parkinson et al., 1999, 2000; Hutcheson et al., 2001). Specifically, both DA and NMDA receptors in the NAc are necessary for this learning (Kelley et al., 1997; Smith-Roe and Kelley, 2000; Di Ciano et al., 2001; Parkinson et al., 2002). For example, either the NMDA receptor antagonist D-APV or the D1 receptor antagonist SCH-23390 blocks the acquisition of lever-pressing for sucrose pellets in rats (Kelley et al., 1997; Smith-Roe and Kelley, 2000). Based on these behavioral results, as well as the anatomical proximity between DA terminals and glutamate synapses (Sesack and Pickel, 1992), it has been proposed that DA acts to gate synaptic plasticity in the NAc. However, \(\text{in vitro}\) plasticity studies have not established a link between DA and NMDAR-dependent plasticity, such as long-term potentiation (LTP) or long-term depression (Pennartz et al., 1993; Thomas et al., 2000), or have observed a loss of LTP (Li and Kauer, 2004). Notably, these studies with DA were conducted in the presence of GABA\(_A\) receptor antagonists. If inhibi-
tion were left intact, high-frequency stimulation would produce a larger NMDA current in the presence of DA caused by the inhibition of GABA release, thereby facilitating synaptic plasticity. Indeed, in agreement with studies in the hippocampus (Wigmstrom and Gustafsson, 1983), inhibiting GABA release in the NAc facilitates LTP (Pennartz et al., 1993).

In vitro electrophysiology studies in the NAc typically look at synaptic responses to single or, at most, paired stimuli. However, it is increasingly clear that relevant information into the NAc are carried by bursts of action potentials (Cooper, 2002). In the present study, I show that the presynaptic effects of DA strongly depend on the temporal history of their inputs. These data provide a possible mechanism that could underlie the role of DA in the nucleus accumbens both on choosing and on learning.

References


