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Behavioral Electrophysiology of Psychostimulants

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The motor-activating effects of amphetamine and other psychostimulants such as cocaine depend on an increase in dopamine (DA) transmission in the striatum, a key component of the basal ganglia and the forebrain motive circuit. This review focuses on research aimed at using electrophysiological techniques—including extracellular unit recording and iontophoresis—in alert, fully functioning animals to understand how these drugs alter striatal neuronal processing under behaviorally relevant conditions. The data indicate that DA works in conjunction with glutamate (GLU), an excitatory amino acid, to enhance the signal-to-noise ratio of afferent information. This DA–GLU interaction appears to play a critical role in the amphetamine-induced activation of striatal neurons. The pattern of striatal activation, moreover, changes as the behavioral response changes from unfocused locomotion to highly focused, stereotyped behavior, but interestingly, the striatal response pattern is not reflected in substantia nigra reticulata, a primary target of striatal efferents. Although cocaine also activates striatal neurons during behavior, the underlying mechanisms appear to be complicated by factors unique to this drug and deserve further evaluation. Collectively, these findings provide unique insight into the neuronal processes by which the striatum participates in psychostimulant-induced motor behavior.
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INTRODUCTION

As psychostimulants, cocaine, amphetamine, and a variety of amphetamine derivatives heighten arousal, increase behavioral activation, and harbor the potential for abuse. Identifying the neuronal substrates of these effects is a key goal of psychostimulant research. In pursuit of this goal, many investigators have focused on the mesotelencephalic dopamine (DA) system and its forebrain targets, including dorsal and ventral striatum, prefrontal cortex, and other regions of a broadly defined corticolimbic system (eg, Pierce and Kumaresan, 2006). As part of the so-called motive circuit, these structures and their DA input are critically involved in setting patterns of motor activity, aimed at acquiring food, sex, and other natural reinforcers (Mogenson *et al*, 1993). By acting directly on the DA system, psychostimulants appear to gain control of behavior by usurping motive-circuit operations. The neuronal substrates of this effect, however, remain elusive. It is important, therefore, to understand how motive-circuit neurons respond to cocaine and amphetamine in a behavioral context and to determine how these drugs alter the synaptic action of DA and, in turn, the action of other transmitters under behaviorally relevant conditions. An increasing number of studies have begun to address these and related issues by applying electrophysiological recording techniques to behaving animals. When combined with iontophoresis or intracerebral infusions, this approach can also provide unique insight into how drugs and transmitters interact to process behaviorally relevant information.

This review focuses on what this line of research has revealed about the role of striatal neurons in processing the characteristic patterns of repetitive or stereotyped movement that occur in rats treated with cocaine or amphetamine. In humans, these psychostimulant-induced motor patterns occur simultaneously with perseverative thought processes that closely resemble some forms of psychosis (Segal and Janowsky, 1978). The striatum appears to play a key role because of circuitry that integrates both sensorimotor and motivational information for behavioral output. The neurophysiology of other motive-circuit structures in the rewarding and addictive properties of psychostimulants are reviewed elsewhere (Carelli, 2004; Porrino and Lyons, 2000; Rebec and Sun, 2005; Woodward *et al*, 2000).

STRIATAL ORGANIZATION AND OPERATION

Despite a relatively homogeneous appearance in conventional histological preparations, the striatum is often divided into dorsal and ventral components. Although both share a similar cytoarchitecture, they differ to some extent in the topography of their afferent and efferent connections.

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Dorsal striatum, which is associated with the classic extrapyramidal motor system, forms the neostriatum or main part of the caudate–putamen complex (Parent and Hazrati, 1995). Ventral striatum, in contrast, includes the nucleus accumbens (NAcc), which has been described as a 'gateway' or 'interface' allowing limbic structures access to the motor system (Groenewegen *et al*, 1996). Although these striatal regions may indeed serve different aspects of behavior, they share an anatomy characterized by overlapping connections embedded in an array of compartments and subterritories (Heimer *et al*, 1995).

Major Afferent Connections

Together, dorsal and ventral striatum receive input from the entire cortical mantle. Dorsal striatum receives this input mainly from sensorimotor, auditory, and visual areas of neocortex, whereas input to ventral striatum arises from allocortical and mesocortical areas as well as from the 'cortical-like' basolateral amygdaloid complex (McGeorge and Faull, 1989). Within this overall topography, there is a complex regional organization. Corticostriatal input, for example, terminates in longitudinal bands, and reciprocally interconnected cortical areas terminate in adjacent or interdigitating striatal zones (Selemon and Goldman-Rakic, 1985). Cortical projections may also show varying degrees of convergence and divergence. In the neostriatum, for example, a single cortical area may project to more than one region, and similarly, each region may receive input from more than one cortical area (Flaherty and Graybiel, 1991). Such an arrangement allows for the integration of widespread cortical information.

Electrical stimulation of corticostriatal fibers elicits short-latency activation of striatal target neurons (Wilson, 1993). This effect appears to be mediated by glutamate (GLU), an excitatory amino acid released by corticostriatal terminals (Parent *et al*, 1995). Excitatory GLU afferents also arise from midline thalamus, and like corticostriatal fibers, they terminate on the heads of dendritic spines (Smith and Bolam, 1990). Interestingly, however, cortical and thalamic afferents do not typically converge on the same neurons.

Although GLU fibers, especially those of cortical origin, provide massive input to the striatum, the most thoroughly studied afferent system originates in the midbrain. The mesostriatal DA pathway arises from a continuous collection of cells in the substantia nigra compacta (SNc) and ventral tegmental area (VTA) (Le Moal, 1995). Their axons, which are thin and unmyelinated, project ipsilaterally and undergo extensive collateralization. Branching DA collaterals account for $>20\%$ of all striatal axon terminals. These fibers typically form *en passant* contacts with the same target cells that receive GLU input, but the DA projection is localized to dendritic spine shafts, putting it $<2\,\mu m$ from GLU terminals on spine heads. Moreover, a single DA fiber may make multiple contacts along a single dendrite as well as with dendrites of multiple target cells (Smith and Bolam, 1990). Thus, a single DA neuron can influence many cortical inputs.

Despite their diffuse innervation pattern, DA fibers follow a distinct topography. Dorsal striatum receives DA fibers primarily from ventral and intermediate layers of the SNc, whereas DA input to ventral striatum arises from dorsal and intermediate layers of the VTA as well as from medial SNc (Le Moal, 1995). This topographical organization is reinforced by apparent differences in the regulation of striatal DA transmission. Heterogeneities in the DA transporter, for example, allow for significantly faster removal of extracellular DA in dorsal than in ventral striatum (Garris and Rebec, 2002). This difference may be relevant to evidence that striatal DA participates in a form of 'volume transmission', in which the signaling molecule may travel $>10\,\mu m$ from its release site (Wightman and Zimmerman, 1990).

Information Outflow

The target cells of both GLU and DA afferents are medium spiny neurons, which account for 90–95% of the neuronal population of the striatum (Groves, 1983). Before leaving the striatum, their axons form extensive collateral networks within or near the dendritic arbor of the cell of origin, indicating important local circuit functions. In rats, medium spiny neurons from dorsal striatum project heavily to targets in globus pallidus (GP) and substantia nigra reticulata (SNr) with a smaller projection to entopeduncular nucleus (Heimer *et al*, 1995). Some striatofugal fibers also reach DA neurons either by sending direct projections to SNc and VTA or by contacting DA dendrites in SNr. These dendrites, which arise from DA neurons in ventral SNc, not only allow the striatum to influence DA activity, but because of dendritic DA release (Groves *et al*, 1975), they also allow DA to modulate the striatonigral influence in SNr (Martin and Waszczak, 1996). Interestingly, the efferent system of ventral striatum not only targets ventral pallidum but also SNc, SNr, and VTA, thus providing ventral influence on dorsal striatal circuits (Groenewegen *et al*, 1993). Ventral striatal projections also reach the extended amygdala, lateral hypothalamus, and pontine reticular formation.

The main transmitter in the entire medium spiny projection system is γ-amino-butyric acid (GABA), which is known to exert a strong inhibitory effect (Kita *et al*, 2004; Tepper *et al*, 2004). Activation of striatopallidal or striatonigral neurons, for example, inhibits neuronal activity in GP or SNr, respectively. These projections are themselves subject to additional intrinsic and extrinsic regulation. Further connections along this circuit include 'downstream' links to the pedunculopontine nucleus and 'upstream' projections to motor thalamus. This classic circuitry, especially the connection with motor thalamus, is thought to play a key role in movement (DeLong, 1990). Ventral striatal outflow to ventral pallidum, in contrast, innervates mediodorsal thalamus. This thalamic nucleus is reciprocally related to prefrontal cortex, suggesting that ventral striatal outflow is concerned primarily with the cognitive, emotional, or regulatory aspects of behavior rather than motor inhibition or initiation (Le Moal, 1995).

As the limbic–motor interface, the NAcc is divided into a central core surrounded on its lateral, medial, and ventral aspects by a peripheral shell (Pennartz *et al*, 1994). Both subterritories share some characteristic ventral striatal afferent and efferent connections, but shell is noted for projections to extended amygdala and lateral hypothalamus, whereas core may exert a more direct influence on cortical processing of motor activity via more typical extrapyramidal connections. NAcc core-shell distinctions have also been

made at the neurophysiological (Uzwiak *et al*, 1997; Wood and Rebec, 2004) and neurochemical levels (Rebec *et al*, 1997a) in behaving rats. If, as ample evidence suggests (see Groenewegen *et al*, 1993), NAcc shell processes limbic-related information having little direct access to primary motor pathways, the DA innervation of this region may be uniquely adapted to this processing role.

FUNCTIONAL ACTIVITY OF STRIATAL NEURONS

One of the most striking features of striatal neurons is their relatively low level of spontaneous activity. Discharge rates of <6 spikes/s interrupted by periods of complete silence are typically reported for both *in vitro* and *in vivo* preparations (Calabresi *et al*, 1987; Wilson, 1993). Even awake, unrestrained animals have a low or silent level of unit activity in dorsal and ventral striatum during quiet rest. In fact, a systematic analysis of unit activity in alert but quietly resting rats suggests that $>70\%$ of striatal neurons are silent (Sandstrom and Rebec, 2003). In view of the large number of medium spiny neurons relative to other striatal cell types, it seems reasonable to conclude that slow-firing or silent units correspond to the medium spiny population. Intracellular staining of neurons recorded both intra- and extracellularly supports this conclusion (Wilson and Groves, 1981). Subsequent intracellular-labeling studies have shown that a small group of tonically active striatal neurons, many of which have firing rates >10 spikes/s, correspond to a small population of aspiny interneurons (Chang and Wilson, 1990).

The relatively low level of medium spiny activity reflects the dominance of an inwardly rectifying potassium current that keeps the membrane hyperpolarized (Wilson, 1993). Episodes of firing are the result of maintained plateau depolarizations, which are driven by afferent input (Wilson and Kawaguchi, 1996). Interestingly, however, inward rectification is present on the dendrites, making these cells relatively insensitive to individual excitatory events or uncoordinated input activity. Only when afferent excitation arrives in a coordinated manner, causing depolarization over a relatively large area of the dendritic tree, can sufficient charge reach the cell body to overcome the barrier of inward rectification. At this point, individual inputs, arriving within the context of a coordinated afferent excitation, become more likely to generate spike activity. This model of medium spiny neurons suggests that the temporal pattern of spikes in these units is not a faithful representation of spike activity in a particular afferent fiber, but rather reflects an envelope of afferent activity integrated over periods of 100 ms or longer (Mink, 1996). A further implication is that a change in the level of inhibitory input plays a relatively small role in the transition to a depolarized state. Thus, intrastriatal inhibitory networks, which include GABA collaterals from neighboring medium spiny units, may not be critical for setting the level of spontaneous activity but could be important for coordinating interactions among adjacent neurons during episodes of firing.

Behavior-Related Information Processing

In primates trained to make discrete movements in response to a sensory cue, most striatal neurons increase discharge rate (DeLong, 1990). Detailed analysis of the firing patterns of these neurons has revealed that despite the correlation with movement, the actual role of these units in behavior seems relatively complex. Some striatal neurons, for example, fire preferentially in relation to a limb movement triggered by a cue, whereas others respond only with respect to spontaneous movements (Kimura, 1990). Similarly, saccade-related activity recorded from primates differs when saccades are made under memory-guided *vs* visually guided conditions (Hikosaka *et al*, 1989). A sensory stimulus, moreover, may initiate a change in firing rate only when the stimulus is behaviorally significant, and in ventral striatum, many neurons also have place- and reward-related firing patterns (Apicella *et al*, 1991). Thus, rather than signal simple motor or sensory events, striatal neurons appear to convey context-dependent information representing processes related to selective attention, reinforcement, or other complex functions. Changes in striatal activity, therefore, may represent a mechanism by which such functions gain access to motor output.

Although relatively few studies have assessed the behavioral response properties of striatal neurons in rats, the available data suggest a similar complexity (Aldridge *et al*, 1993). Neuronal responses to discrete movements are common in extreme dorsolateral striatum, which, like primate putamen, receives preferential input from sensorimotor cortex (Carelli and West, 1991; West *et al*, 1990). Rat striatal neurons have also been reported to alter firing rate in association with sensory-triggered movements much like that reported for primates (Gardiner and Kitai, 1992; West *et al*, 1990). Many of these neuronal responses, moreover, depend on the behavioral context in which they occur (eg, a change in firing rate to a sensory-triggered movement may not occur when the movement occurs outside the task). These data confirm a convergence of sensory and motor signals in rat striatum, suggesting that striatal neurons serve an important integrative role.

Behavior-Related Transmitter Interactions

DA appears to act as a gain-enhancing neuromodulator by facilitating the excitatory action of GLU released by striatal afferents (Servan-Schreiber *et al*, 1990). In a direct test of this hypothesis in conscious, unrestrained rats, we recorded striatal unit activity and applied DA and GLU iontophoretically (Pierce and Rebec, 1995). Whereas GLU caused a frank, dose-dependent activation of all recorded units, DA was weakly excitatory or inhibitory. When both substances were applied simultaneously, the excitatory actions of GLU were enhanced, suggesting that DA increases the strength of the GLU signal. We followed up on this conclusion with a detailed assessment of DA–GLU interactions (Kiyatkin and Rebec, 1996). DA (5–80 nA) was applied for prolonged periods (2–3 min) and brief applications of GLU (5–40 nA; 15 s) were made before, during, and after DA iontophoresis. The result was an overall enhancement of the GLU response relative to the DA-induced change. Collectively, these findings indicate that DA has the net effect of amplifying the phasic activation induced by GLU; this effect, moreover, is apparent in relation to the level of background firing. Thus, DA enhances the relative rather than absolute strength of the GLU signal. Further testing revealed that

endogenous DA exerts this effect mainly via D1 receptors (Kiyatkin and Rebec, 1999b). In fact, with D1 receptor blockade, striatal neurons become hyper-responsive to GLU. It appears, therefore, that a primary function of DA release, which is triggered by behaviorally relevant stimuli, is to restrain the absolute magnitude of the GLU response while enhancing its relative strength. By coinciding with the arrival of cerebrocortical information, DA release ensures the controlled flow of this information to relevant neurobehavioral circuits.

The excitatory action of GLU is also regulated by GABA. In alert rats, both spontaneously active and GLU-stimulated striatal neurons are GABA-sensitive. In fact, most units show short-latency inhibitions to leakage of GABA from the iontophoresis pipette (0 nA) and the response progresses to complete silence with a small increase (10–20 nA) in ejection current (Kiyatkin and Rebec, 1999a). Under natural conditions, therefore, the activity of striatal neurons, and thus their integrative functions, depends on a GLU–GABA balance, which is regulated further by DA release.

NEURAL SUBSTRATES OF PSYCHOSTIMULANT-INDUCED CHANGES IN MOTOR ACTIVATION

The motor-activating effects of amphetamine include species–specific forms of investigative behavior, which in the rat are manifest as locomotion and rearing as well as head bobbing and sniffing (Rebec and Bashore, 1984). Expression of these behaviors follows a complex, dose-dependent pattern. At relatively low doses, behavioral activation occurs over a large area. As doses increase, a constricted form of stereotypy emerges in which an early phase of locomotion and rearing gives way to a phase of highly focused head bobbing, sniffing, and occasional oral behavior. Although ample evidence implicates striatal DA release in these dose-dependent effects, this mechanism by itself explains neither the appearance of specific behaviors nor the overall pattern of the response, including the transition from unfocused behavioral activation to episodes of focused stereotypy (Segal and Kuczenski, 1994).

Amphetamine Effects on Striatal Neurons

Procedures designed to monitor amphetamine-induced changes in neuronal activity in ambulant animals are beginning to shed light on the striatal substrates of the motor-activating effects of amphetamine. Early reports, based on the records of striatal multiple-unit activity in behaving rats, indicated a relatively homogeneous, dose-dependent increase to amphetamine (Hansen and McKenzie, 1979). Although this effect correlates with increases in striatal DA transmission, single-unit data indicate a relatively complex striatal response. At a dose that induces unfocused motor activation (1.0 mg/kg *d*-amphetamine), neurons that change activity in close temporal association with movement are excited, but neuronal activity unrelated to movement is inhibited (Haracz *et al*, 1993; West *et al*, 1997). In either case, DA receptor antagonists reverse the neuronal response, supporting a role for DA in both the excitation and inhibition (Rosa-Kenig *et al*, 1993). DA, however, is not the sole mediator of the excitation because this response, and not the inhibition, is also attenuated by cerebrocortical ablations (Tschanz *et al*, 1994). Because these ablations remove most GLU input from striatum, it appears that GLU underlies at least some of the striatal effects of amphetamine. Specifically, DA may facilitate a GLU excitation of motor-related units, whereas the inhibition of non-motor-related activity may reflect an action of DA on neurons that receive weak GLU input (Haracz *et al*, 1998).

Application of amphetamine directly to striatal neurons provides some support for this hypothesis, but also underscores the difficulty of interpreting the neuronal substrates of the behavioral response to systemic drug injections. When amphetamine is applied iontophoretically to striatal neurons in conscious, quietly resting rats, the vast majority of units respond with a dose-dependent (5–40 nA) inhibition (Kiyatkin and Rebec, 1997). DA antagonists block this effect confirming that when cerebrocortical input is relatively weak, which is most likely the case under resting conditions, the amphetamine-induced inhibition involves DA. Interestingly, prolonged amphetamine iontophoresis (5–30 nA; 2–3 min) also inhibited GLU-evoked excitations; in fact, $\geqslant$20 nA amphetamine caused a complete block of the GLU response. In this case, however, iontophoretic amphetamine did not mimic the action of iontophoretic DA, which has the net effect of enhancing the GLU signal (see above). It is possible that amphetamine has a much stronger action than DA when applied directly to neurons because although iontophoretic DA may act postsynaptically, iontophoretic amphetamine is likely to increase DA transmission at all affected synaptic terminals and thus overwhelms any GLU-evoked effect. This view is consistent with the evidence that when applied to NAcc slices, amphetamine attenuates cortically evoked excitations (Nicola *et al*, 1996). In sum, the data suggest that amphetamine-induced striatal inhibitions reflect an increase in DA transmission, whereas excitations, which are likely to occur with systemic amphetamine administration, result from a DA interaction with cerebrocortical GLU release.

A thorough characterization of well-isolated, single units recorded in the striatum indicate that 1.0 mg/kg *d*-amphetamine activates $\sim$80% of the neuronal population (see Rebec, 1998). Interestingly, this pattern breaks down as the dose increases. At 5.0 mg/kg, which induces a phase of focused stereotypy, several different neuronal response patterns emerge (Rebec *et al*, 1997b; Ryan *et al*, 1989). Whereas some striatal neurons continue to show either a simple activation or inhibition throughout the drug response, an increasing number become inhibited during the onset of focused stereotypy. The net result is a more focused neuronal activation pattern that may underlie the transition to a more focused motor response.

Amphetamine Effects in SNr

Perhaps the most important striatal target in rats is SNr, which receives both direct and indirect projections from the striatum and then routes this information to thalamic as well as descending nuclei. The SNr is dominated by GABA-containing projection cells interspersed with clusters of DA neurons and perhaps a small number of GABA- or peptide-containing interneurons (Juraska *et al*, 1977). GABA and, to

some extent, DA and GLU appear to play a critical role in regulating the activity of SNr neurons. These cells are characterized by short biphasic spikes, a tonic level of spontaneous activity, and a sensitivity to depolarizing currents that permits repetitive firing up to 200 spikes/s. SNr units are inhibited by electrical stimulation of the striatum or by GABA iontophoresis (Deniau *et al*, 1978; Waszczak and Walters, 1983), implicating GABA in the main striatal control of SNr projection neurons. Relatively little information is available, however, on SNr function during behavior. A classical view predicts a high level of SNr basal activity that declines during movement. The implication is that tonically active inhibitory SNr outputs normally keep 'downstream' movement generators in check to suppress inappropriate behavior. Movement would be expected to correlate with a reduction in this tonic rate. Although some evidence supports this model, recent data indicate a complex picture in which SNr neuronal activity plays a role in the focal selection of desired motor mechanisms and the inhibition of others (Gulley *et al*, 2002b; Shi *et al*, 2004). In fact, both increases and decreases have been reported to occur in SNr during an operant task. In a detailed study of SNr activity, Hikosaka *et al* (1993) reported task-related changes in neuronal activity to a wide range of stimuli, including the expectation of reward.

If the neuronal patterns established in the striatum are critically involved in shaping the motor response to amphetamine, then one might expect some aspect of these patterns to be manifest in SNr. Yet, we recorded from SNr in ambulant rats and found no simple relationship to firing patterns in the striatum (Gulley *et al*, 2004). During periods of spontaneous movement before drug injection, for example, SNr activity was largely unchanged relative to periods of quiet rest. We also reported a similar result after an analysis of SNr activity in rats performing an operant response for sucrose reward (Gulley *et al*, 2002b); in fact, only discrete motor acts such as head turning elicited a neuronal response and only in a limited number of units. Thus, unlike many striatal neurons, which appear to be sensitive to a general level of motor activation, units in SNr are often tuned to discrete movements. Thus, movement-related changes in the striatum may not have an obvious correlate in SNr. Although this is surprising given that $>80\%$ of striatal neurons project to SNr or GP (Parent and Hazrati, 1995), data from stimulation experiments support this conclusion. For example, fewer than half the units recorded in SNr of behaving primates are altered after electrical stimulation of the striatum (Hikosaka *et al*, 1993). It is also the case that a systemic injection (subcutaneous (s.c.)) of either a low or high dose of amphetamine (1.0 or 5.0 mg/kg *d*-amphetamine) failed to elicit a consistent SNr response (Gulley *et al*, 2004). We recorded neurons that were excited, inhibited, or showed no change despite distinct dose-dependent patterns of motor activity. To assess the striatal contribution to these effects in SNr, some animals received amphetamine directly into the striatum at a behaviorally activating dose. Again, however, no consistent neuronal pattern emerged in SNr. In fact, the most common effect in SNr, recorded in 47% of sampled units, was no change in firing from the preinfusion baseline rate. Thus, widespread changes in striatal activity that occur in conjunction with either spontaneous or amphetamine-related movement are not faithfully represented in SNr.

The complexity of the SNr response to amphetamine is a likely reflection of the complex properties and organization of SNr neurons. Unlike striatal output cells, which are silent in the absence of excitatory input, SNr neurons discharge at roughly the same rate whether excitatory input is present or not. In fact, activity remains relatively stable even during DA receptor blockade in awake animals (Degos *et al*, 2005). Adjustments in the SNr autoactive rate depend instead on fluctuations in the level of inhibitory GABA input, which may arise from several sources including axon collaterals of SNr projection neurons (Fallon and Loughlin, 1995; Gulacsi *et al*, 2003; Rick and Lacey, 1994). It is difficult to determine, therefore, if a particular pattern of striatal activity is faithfully represented in SNr. Functionally, moreover, motor-related inhibitions of SNr activity are relatively brief events that may correspond to movement onset followed by more prolonged excitations even as movement continues. Thus, without precise monitoring of cell firing time-locked to the activity of specific muscle groups, the role of SNr in drug-induced movement is difficult to characterize. Another consideration is that rather than changing the overall level of SNr activity, amphetamine may alter SNr firing in a context-dependent manner. In rats working for sucrose reinforcement, for example, a dose of amphetamine that activated behavior without impairing performance had no effect on the pattern of the SNr response, but significantly altered the relative magnitude of the neuronal change in relation to specific components of the operant task (Gulley *et al*, 2002a). Context also appears critical for SNr involvement in normal, non-drug-related movement (Handel and Glimcher, 2000). Further research is needed to assess how striatal information is integrated into ongoing SNr activity.

Striatal Neuronal Changes Induced by Cocaine

Although cocaine blocks DA transport and amphetamine exerts a more complex action that includes reversed DA transport and vesicular DA diffusion, both drugs elevate the synaptic level of DA (Sulzer *et al*, 2005). Like amphetamine, moreover, cocaine has dose-dependent effects on motor activation patterns. Thus, it should come as no surprise that systemically injected cocaine also has a predominately excitatory effect on striatal neurons in behaving rats and that this effect is blocked by a DA receptor antagonist (White *et al*, 1998). Differences, however, are also apparent. Although amphetamine inhibited some neurons, especially during the expression of focused stereotypy according to the behavioral response properties of individual units (see above), cocaine activated all recorded units throughout the behavioral response. This was the case at either 20 or 40 mg/kg cocaine (s.c.), despite a more focused behavioral response at the higher dose. In an interesting parallel, the pattern of activation of c-Fos, an immediate-early gene, is widespread in the striatum after cocaine but limited to discrete regions after amphetamine (Graybiel *et al*, 1990). It is also interesting that despite similarities in the overall motor pattern induced by these drugs, there are differences in the frequency and expression of individual responses. Thus, although any link between psychostimulant-induced

changes in striatal firing pattern and c-Fos induction is far from clear, both measures are likely indicators of the neuronal mechanisms underlying differences in the behavioral effects of these drugs.

The neuronal action of cocaine is further complicated by evidence that many of the addictive properties of this drug appear to be independent of DA. For example, the euphoria induced by cocaine in experienced users is resistant to DA receptor blockade (Sherer *et al*, 1989), and mice lacking the DA transporter show both self-administration behavior and conditioned place preference to cocaine (Rocha *et al*, 1998; Sora *et al*, 1998). It is interesting, therefore, that iontophoresis of cocaine in alert rats inhibits striatal neurons, but unlike amphetamine iontophoresis, this inhibitory response is not blocked by DA receptor antagonists (Kiyatkin and Rebec, 2000). Because cocaine also disrupts serotonin (5-HT) transport, at least some of the striatal action of this drug may involve an increase in striatal 5-HT. In fact, systemic injection of 3,4-methylenedioxy-methamphetamine (MDMA or ecstasy), an amphetamine derivative with a potent 5-HT-releasing action, increases both behavioral activity and striatal firing rate in rats, and these effects are blocked by 5-HT antagonists (Ball and Rebec, 2005).

Of course, cocaine is a local anesthetic (Catterall and Mackie, 1996), and indeed, iontophoresis of procaine, a local anesthetic with minimal effects on DA transport (Ritz *et al*, 1987), mimics the neuronal effects of cocaine. It is also interesting that after a single intravenous (i.v.) injection of 1.0 mg/kg, cocaine approaches a concentration in brain of 26 μM (Fowler *et al*, 1998), which is above the limit for interfering with Na^+ transport (Reith *et al*, 1986). Although the inhibitory effects of both drugs occurred without a change in spike amplitude or spike duration, both of which are common indicators of local anesthetic effects, a disruption of Na^+ transport cannot be ruled out (Kiyatkin and Rebec, 2000). At low iontophoretic doses (5-40 nA), neuronal activity may decline without a change in spike waveform. In fact, when higher ejection currents were used, spike waveform changes became common. Thus, although a local anesthetic action of systemic cocaine on striatal neurons is possible but still speculative, it is likely that a change in DA transmission alone cannot explain the ability of this drug to interfere with striatal activity. Further support comes from evidence that blockade of striatal DA transport by i.v. cocaine occurs several minutes after maximal behavioral activation in rats (Kiyatkin *et al*, 2000).

CONCLUSIONS

The processing of behaviorally relevant information in striatal neurons is shaped by a complex interaction of state-dependent afferent input and intrinsic membrane properties. Although DA is a key afferent, it seems designed to modulate the excitatory drive of the corticostriatal GLU system, which itself is balanced by an inhibitory GABA network. Downstream processing of these effects is further complicated by multiple mechanisms of control of SNr activity. Thus, within the basal ganglia, the motor-activating effects of psychostimulants must be considered within the context of ongoing neurophysiological and neurochemical responses. A drug-induced change in DA, therefore, is not likely to overwhelm GLU or GABA, but rather to alter the parameters in which these and perhaps other transmitters operate. In the striatum, this alteration is the key mechanism underlying the motor activation induced by psychostimulants.

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