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Molecular substrates of action control in cortico-striatal circuits

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Abstract

The purpose of this review is to describe the molecular mechanisms in the striatum that mediate reward-based learning and action control during instrumental conditioning. Experiments assessing the neural bases of instrumental conditioning have uncovered functional circuits in the striatum, including dorsal and ventral striatal sub-regions, involved in action-outcome learning, stimulus-response learning, and the motivational control of action by reward-associated cues. Integration of dopamine (DA) and glutamate neurotransmission within these striatal sub-regions is hypothesized to enable learning and action control through its role in shaping synaptic plasticity and cellular excitability. The extracellular signal regulated kinase (ERK) appears to be particularly important for reward-based learning and action control due to its sensitivity to combined DA and glutamate receptor activation and its involvement in a range of cellular functions. ERK activation in striatal neurons is proposed to have a dual role in both the learning and performance factors that contribute to instrumental conditioning through its regulation of plasticity-related transcription factors and its modulation of intrinsic cellular excitability. Furthermore, perturbation of ERK activation by drugs of abuse may give rise to behavioral disorders such as addiction.

1. Introduction

The basal ganglia are a network of subcortical nuclei that have long been known to exert a strong coordinating influence on the motor system, particularly on the feed-forward and feedback processes involved in action initiation and execution. More recent research has, however, significantly broadened our understanding of basal ganglia anatomy and the functions with which it is concerned. Although there have been many attempts to paint it as a network serving a single homogeneous function, recent evidence suggests that the basal ganglia are involved in heterogeneous motor functions ranging from simple reflexive, sensorimotor habits to deliberated, goal-directed actions. The latter function is of particular interest given recent advances in our understanding of the nature of the learning and motivational processes involved in the control of actions, in choice between actions and in decision-making more generally.

Much of this recent work has focused on the striatum, which is the largest of the basal ganglia nuclei and serves as the entry point for cortical and thalamic inputs into basal ganglia circuitry. Human and primate research has found evidence of striatal involvement in

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the learning and performance processes engaged by reward-related actions during decision-making tasks and disorders that affect the striatum, such as Parkinson's disease, Huntington's disease and substance abuse, produce impairments in these kinds of action (Balleine *et al*., 2007; Balleine and O'Doherty, 2010; Bechara *et al*., 2002; Cohen and Frank, 2009; Delgado, 2007; Hikosaka, 2007). Parallel research in rodents using paradigms derived from instrumental conditioning has identified sub-regions within the striatum that mediate distinct forms of action control based on an assessment of the learning and performance processes (Balleine *et al*., 2008, 2009; Balleine and Ostlund, 2007; Yin *et al*., 2008). In similar fashion to the primate research, rodent research has identified a network involving the dorsomedial striatum mediating the role of reward-related learning in the cognitive control of action and that has been dissociated anatomically and functionally from a more lateral network engaged during the learning and performance of habits.

How the striatum controls the influence of reward learning on the cognitive control of action selection and initiation at a cellular and molecular level is an area of active research. The primary inputs to striatum are excitatory projections from diverse regions of cortex and thalamus, and synaptic plasticity at corticostriatal synapses is thought to be critical for these aspects of action control (Costa, 2007; Di Filippo *et al*., 2009; Horvitz, 2002; Horvitz, 2009; Wickens *et al*., 2007). The striatum also receives dopaminergic input from the midbrain, and indeed, models of reward learning and action control emphasize the importance of dopamine signals in learning and decision making (Dayan and Balleine, 2002; Redgrave *et al*., 2008; Salamone and Correa, 2002; Schultz, 2007; Schultz and Dickinson, 2000). Dopamine and glutamate signaling interact through multiple cellular mechanisms to shape neural excitability and synaptic plasticity in striatal neurons (Di Filippo *et al*., 2009; Kreitzer, 2009; Lovinger, 2010; Surmeier *et al*., 2007). An important question for current research is to understand the role that these diverse cellular signaling mechanisms play in striatal-based reward learning and action control. In order to address this topic, it is important to have a framework for understanding the cognitive processes mediated by the striatum. Here we use concepts derived from instrumental conditioning in rodents as a model for examining the molecular mechanisms that underlie striatal function. We suggest that signaling molecules that are sensitive to combined dopamine and glutamate receptor signaling have a key role in learning and action control in the striatum and that alteration in the activity of these signaling molecules may underlie many of the abnormalities in these behavioral processes induced by genetic conditions, neurodegeneration and addiction.

2. Actions, habits and the striatum

As the main input nucleus of the basal ganglia, the striatum receives excitatory glutamatergic afferents from cortical, limbic and thalamic regions, as well as heavy dopaminergic input from the midbrain (Sesack *et al*., 2003; Smith *et al*., 1998). Traditionally, the striatum has been divided into dorsal and ventral subdivisions. The ventral subdivision contains the nucleus accumbens (NAc), which itself consists of core and shell sub-regions (Zahm, 2000; Zahm and Brog, 1992). The glutamatergic inputs to striatum are topographically organized, with limbic and ventral prefrontal regions projecting to the ventral striatum, sensorimotor cortical regions projecting to the dorsolateral striatum (DLS) and association areas of the prefrontal cortex projecting to the dorsomedial striatum (DMS) (Alexander et al., 1986; Groenewegen et al., 1990) – see Figure 1A. This pattern of connectivity has lead to the idea that cortico-basal-ganglia loops are organized into functional circuits that mediate distinct components of behavior (Alexander *et al*., 1990; Joel and Weiner, 1994; Pennartz *et al*., 2009; Voorn *et al*., 2004). Indeed, early studies of maze task performance in animals concluded that the dorsal striatum was necessary for implementing a "response" strategy, defined in terms of a reliance on egocentric information (e.g., turn left) or simple stimulus-response associations to encode goal locations (see

(Packard and Knowlton, 2002; White, 2009; Yin and Knowlton, 2006) for review). In contrast, the ventral striatum, specifically the nucleus accumbens, was described as having a role in the expression of conditioned emotional responses to cues and contexts associated with appetitive (or aversive) events, such as access to mates, drugs of abuse, and food or liquid rewards (see Belin *et al*., 2009; Berridge, 2009; Cardinal *et al*., 2002; Day and Carelli, 2007 for review). Furthermore, behavior mediated by the striatum in these tasks were found to depend on glutamate and dopamine signaling (Burns *et al*., 1994; Cory-Slechta *et al*., 1999; Di Ciano *et al*., 2001; Packard, 1999; Packard and Teather, 1997; Packard and White, 1991; Smith-Roe and Kelley, 2000) suggesting that combined activation of these neurotransmitter systems in the striatum is necessary for normal striatal function.

More recently, the application of instrumental procedures has more precisely elucidated the various action-related functions mediated by the striatum – see Figure 1B. One of the most important aspects of this research has been the repeated demonstration that, contrary to appearance, instrumental actions, such as lever pressing, can be controlled at different times by fundamentally distinct learning and motivational processes. In particular, various instrumental procedures and tests have been used to establish whether and when an animal's actions are deliberated or goal-directed and when they are elicited, automatic or habitual. Generally, actions are considered goal directed if it can be demonstrated both that an animal has encoded the outcome resulting from its actions and uses that information to select among potential actions. More specifically, Balleine & Dickinson (1998) argued, based on human action theory, that for any action to be labeled goal-directed it must be shown to satisfy two criteria; referred to as the goal and the contingency criteria. To satisfy the goal-criterion, performance of an action must be shown to be sensitive to changes in the encoded value of the outcome, whereas to satisfy the contingency criterion an action must be shown to depend on the contingent or causal relationship between the action its specific consequences. If the performance of an action persists in a situation where either its causal relationship to the outcome or the value of the outcome declines then it is difficult to claim it is truly goal-directed.

Using these criteria, considerable evidence has accumulated suggesting that, in rodents, actions acquired in instrumental conditioning can be goal-directed (Dickinson and Balleine, 1994, 2002). In these experiments, rats learn to perform different actions (e.g., responses on a left or right lever) for different types of outcomes (e.g., grain pellet or sucrose solution). To assess the goal criterion, one of the two outcomes is then devalued, either by feeding the outcome to satiety or pairing its consumption with illness. In a subsequent choice test, conducted in extinction (i.e. in the absence of any feedback), rats have consistently been found to show a preference for the lever that previously delivered the still valued outcome over the lever that delivered the now devalued outcome (Adams and Dickinson, 1981; Colwill and Rescorla, 1985). In addition to changes in outcome value, a goal-directed action should be sensitive to changes in the causal relationship between an action and its consequences or outcome and, again, considerable evidence suggests that rodents are highly sensitive to changes in this relationship. Thus, when a previously action-dependent outcome is delivered in a manner that is independent of that action, rodents reduce their performance of that action, an effect referred to as contingency degradation (Balleine and Dickinson, 1998; Hammond, 1980). Generally, therefore, the changes in behavior induced by contingency degradation and outcome devaluation show that rats encode information about the relationship between their actions and specific outcomes, and use these action-outcome associations, along with information about the desirability of a particular outcome - provided by the animal's motivational system - to guide decisions about actions (Dickinson and Balleine, 2002).

Although instrumental actions can, from observation, appear to be goal-directed, they are often not; indeed, although action execution can be controlled or deliberated, often it is automatic or reflexive, under the control of internal or external states and stimuli. This sensorimotor process has been argued to form the core of a distinct functional capacity involving the formation of habitual actions. Habits are, therefore, revealed particularly in their persistence, even in the face of sometimes quite extreme negative consequences, and in their sensitivity to the motivational functions of reward-related cues (Dickinson, 1994). Recent papers have associated habit learning with various addictive behaviors (Cardinal and Everitt, 2004; Dickinson *et al*., 2002; Miles *et al*., 2003; Robbins and Everitt, 2002), suggestions that have their source in the classic theories of stimulus-response learning (Hull, 1943). From this perspective, rewarding events reinforce or strengthen associations between contiguous sensory and motor processes allowing the sensory process to elicit the motor response in a manner that is no longer regulated by its consequences. The determining features of habit learning are, therefore, quite distinct of those regulating goal-directed action, notably: (1) habitual actions have been found to be insensitive to post-training outcome devaluation; and (2) the suggestion that S-R learning is strengthened or reinforced whenever a response is rewarded under a particular stimulus - irrespective of the specific outcome delivered or other stimuli present – suggests that this learning is not regulated by the contingent relationship between action and outcome but by their contiguity.

In line with these proposed features of habits, there is considerable evidence that whenever changes in the rate of reward are constrained – e.g., at asymptote when actions are overtrained (Adams and Dickinson, 1981) or by time when trained on interval schedules of reinforcement (Holman, 1975) – instrumental performance becomes insensitive to changes in outcome value. Likewise, habitual actions have been found to be relatively insensitive to changes in the action-outcome contingency; Dickinson et al (1998) found that, when overtrained, the instrumental actions of rats are insensitive to the imposition of an omission contingency, an effect that has been replicated in mice (Frankland et al, 2004).

Importantly, a growing number of studies have found evidence that goal-directed and habitual actions rely on different regions of the striatum for their acquisition and performance, suggesting that these two distinct forms of action control depend on distinct cortical-basal ganglia networks. Beginning with work in our lab, we have found evidence that a posterior portion of the dorsomedial striatum (pDMS) in rodents together with inputs from the association, most notably prelimbic (PL), area of prefrontal cortex, is critical for the acquisition and performance of goal-directed actions (Balleine & Dickinson, 1998; Yin *et al*., 2005b); pretraining lesions of the PL or the pDMS render instrumental performance insensitive to outcome devaluation and contingency degradation. Unlike the prefrontal cortex, however, both pre- and post-training lesions of the pDMS have been found to render rats' instrumental responding insensitive to these tests, indicating that this region is required not only for learning, but is also necessary for using these associations to direct performance.

In contrast to the pDMS, the dorsolateral striatum (DLS), which receives inputs from sensorimotor regions of frontal and pre-frontal cortex, is critical for both the learning and performance that mediates habitual responding. Although habits are normally insensitive to tests of goal-directed action control, the instrumental actions of rats with lesions of DLS remain sensitive to outcome devaluation and contingency degradation despite being extensively overtrained (Yin *et al*., 2004) indicating that DLS lesions prevented the establishment of habitual responding and preserved the goal-directed control of instrumental performance (cf. Graybiel, 2008 for review).

3. Pavlovian-instrumental interactions and the ventral striatum

In addition to goal-directed and habitual actions, animals learn through Pavlovian conditioning to associate stimuli with outcomes or other events and, as a result, develop conditioned reflexive responses to these stimulus presentations. Although they are considered separate forms of learning, Pavlovian and instrumental conditioning interact in multiple ways. For example, conditioned stimuli (CS's) that have been associated with a particular outcome can themselves bias instrumental actions. Procedures have been developed for measuring the effect of CS's on the choice and vigor of instrumental actions, a paradigm known as Pavlovian-instrumental transfer (PIT). When associated with an appetitive event, such as a specific food, Pavlovian CS's can become predictors of both the sensory specific features of that food (e.g., specific taste, texture etc) and the general affective state induced by the food (Konorski, 1967). Importantly, evidence suggests that these two predictive relations can induce quite distinct kinds of effects on instrumental performance (cf. Corbit and Balleine, 2005). For example, in a choice situation, where two actions are associated with distinct instrumental outcomes, a CS associated with the same outcome as one of the two actions tends to bias choice towards that action. In paradigms of this kind, often referred to as outcome-selective PIT, rats are generally allowed to choose between actions that result in the same or a different outcome to that predicted by the CS and, in these tasks, typically perform more of the action trained with the outcome predicted by the CS than the other action.

In situations in which CS's are presented that predict appetitive outcomes that are not made available by either available choice, performance tends to be controlled by the general appetitive significance of the outcome and, as a result, performance is generally elevated on all actions. This latter effect has been found to reflect the arousal-inducing properties of the CS gated by primary motivational state; e.g., CS's associated with nutritive outcomes elevate responding when rats are hungry but not when they are thirsty - and when associated with fluid outcome when the rats are thirsty rather than hungry (Dickinson and Balleine, 2002). Outcome-specific PIT therefore requires that the rats use a representation of the outcome associated with the CS to direct instrumental action, whereas the general form of PIT requires that the cue elicit a state of arousal.

The ability of cues to modulate instrumental actions depends on the nucleus accumbens (NAc – refer Figure 1A and 1B), a region within the ventral striatum. Like the dorsal striatum, the NAc receives input from prefrontal cortex, as well as limbic association cortices such as the amygdala and hippocampus (Berendse et al., 1992; Brog et al., 1993; Groenewegen et al., 1999). The NAc itself consists of core and shell sub-regions. The core's pattern of output projections is similar to the dorsal striatum, with inputs from cortex and thalamus and projections to the ventral pallidum and substantia nigra pars reticulata (SNr). The shell, in addition to the typical basal ganglia circuitry, contains projections to hypothalamic and brainstem motor regions, and has thus been considered part of the extended amygdala (Heimer et al., 1997). The NAc core and shell regions are critical for the ability of Pavlovian CS's to influence action selection. In particular, lesions of the NAc shell render animal's choice performance insensitive to CS presentation during outcome-specific PIT (Corbit et al., 2001 - refer Figure 1B). Animals still show a general arousing effect of cues on instrumental performance. In contrast, lesions of the NAc core make animals insensitive to the general arousing effect of CS presentations during PIT, without affecting outcome specific transfer (Corbit et al., 2001; Hall et al., 2001).

4. The emerging functional architecture of the basal ganglia

Although striatal sub-regions mediate specific functions, striatal function has to be considered within the context of cortico-basal ganglia circuitry. The vast majority of striatal neurons are medium spiny neurons (MSN's), which are GABAergic projection neurons. MSN's form the striatal output, which consists of striatonigral and striatopallidal pathways (see Figure 1A for review). Striatonigral neurons project to basal ganglia output structures, namely the substantia nigra pars reticulata (SNr) and the internal segment of the globus pallidus (GPi), and constitute the direct pathway by which information flows from striatum to basal ganglia output. Striatopallidal neurons project to the external segment of the globus pallidus (GPe), which itself projects to the SNr and GPi via the subthalamic nucleus. This relay constitutes the indirect pathway of information flow through the basal ganglia. Although the direct and indirect pathways form the main intrinsic connections between basal ganglia nuclei, they are not the only pathways; recent research has described several important connections including direct path collateral projections to the external globus pallidus (GPe) (Nadjar et al, 2006) which, in turn, not only projects to the STN but also the GPi and SNr and to the substantia nigra pas compacta (SNc) (Smith et al, 1998) (Figure 1A). Furthermore, although the basal ganglia form a predominantly feed forward network, there are substantial feedback pathways throughout the network including bidirectional connections between GPe and STN and between the GPe and dorsal striatum (Smith et al, 1998; Kita, 2007).

The topographical organization of basal ganglia connectivity has given rise to a functional anatomy based not only on its feed-forward connections but on a series of functionally segregated loops that feedback to the striatum via the thalamus directly and indirectly via the cortex (Alexander *et al*., 1986; Leblois *et al*., 2006; McHaffie *et al*., 2005; Smith *et al*., 2004). Although unique functions of direct and indirect thalamic feedback to the striatum have not yet been described, as elaborated above it is clear that, topographically speaking, distinct cortico-striatal thalamic loops mediate quite specific aspects of action control based on distinct learning and plasticity processes. These distinct functions in many ways reflect differences in regional inputs from cortical and thalamic structures. Thus, whereas regions associated with cognitive function (e.g., medial parafasicular nucleus and prefrontal cortical areas; (Smith *et al*., 2004)) tend to converge on the dorsomedial striatum, motor regions of the thalamus and cortex (i.e., ventrolateral and ventral anterior nuclei and sensorimotor cortices; (McFarland and Haber, 2000)) tend to converge on the dorsolateral striatum and more motivational/emotional structures on the ventral striatum (including mediodorsal thalamus, amygdala, and insular cortex). Although these inputs are not exclusively segregated in this way, and the functions of the loops within which these structures are positioned have not yet been fully characterized, it seems likely that their functional significance is predominantly derived from the nature of these extrinsic inputs to the basal ganglia.

Summary

Based on the evidence described above, it is clear that the striatum contains functional sub-regions that are necessary for specific forms of learning and action control – refer Figure 1B. Within the dorsal striatum, the pDMS and DLS mediate the acquisition and performance of goal-directed and habitual behavior, respectively. Evidence is also emerging to suggest that medial agranular cortex and projections from that region to the dorsocentral region of dorsal striatum may be necessary for the acquisition of heterogeneous chains of actions (Ostlund et al, 2009; Wu et al, 2009). In the NAc, although the core is not necessary for instrumental learning, evidence suggests it mediates the effects of changes in the experienced reward value of the outcome on instrumental performance (Corbit et al, 2001). Furthermore, core and shell are necessary for the general excitatory and outcome-specific effects of CS's on

instrumental performance, respectively. Although the striatum has functionally defined sub-regions, this functional specialization may be determined, in part, by extrinsic inputs to striatum. In addition, the basal ganglia contain intrinsic feed-forward and feedback circuits that may be crucial for striatal function. In particular, striato-midbrain-striatal connections have been found that connect neighboring striatal regions through the VTA and SNc. This spiraling architecture links ventral striatum to the DMS, and the DMS to the DLS (Haber et al., 2000). Such an arrangement may enable striatal sub-regions to work cooperatively to support the transition from goal-directed to habitual behavior, as well as enable Pavlovian incentive information (from NAc) to influence action control guided by outcome information mediated by dorsal striatum (Corbit, Janak & Balleine, 2007; Corbit and Janak, 2007; Yin et al., 2008).

5. The molecular basis of instrumental reward-based learning and action control in the striatum

The striatum receives dopaminergic and glutamatergic inputs that form synapses in close proximity on striatal neurons (Sesack et al., 2003). This convergence of inputs in the striatum enables DA and glutamate signals to interact, and the integration of these signals is crucial for normal striatal function. At the intracellular level, signaling molecules that are sensitive to the combined activity of DA and glutamate receptors have been shown to regulate cellular excitability, corticostriatal synaptic plasticity, and behavior.

5.1 Molecular mechanisms of excitability and synaptic plasticity in striatum

One of the most important striatal inputs is that from the midbrain dopamine neurons in the ventral tegmental area (VTA) and SNc. These projections are essentially topographical with the more medial VTA projecting to NAc shell and the more lateral to NAc core. Likewise, more medial SNc projects to DMS whereas a more lateral region projects to the DLS. These projections terminate on MSN's and on tonically active, cholinergeric interneurons. The projection neurons that receive this dopaminergic input comprise the striatopallidal and striatonigral pathways, and differ in their expression of dopamine receptor subtypes. Striatonigral MSN's primarily express the D1 receptor; whereas striatopallidal neurons primarily express the D2 receptor sub-types (Gerfen et al., 1990). The dopamine D1 and D2 receptors have opposing effects on cellular physiology, which is due, in part, to their opposing effects on the enzyme adenylyl cyclase (AC). Activation of the D1 receptor increases AC activity, which increases cAMP formation and stimulates cAMP-dependent protein kinase (PKA) (see Greengard, 2001; Greengard *et al*., 1999 for review). PKA phosphorylates multiple cellular targets, including ion channels, neurotransmitter receptors, transcription factors, and other phosphoproteins. D1 receptor activation generally serves to increase MSN excitability and increase the potential for corticostriatal synaptic plasticity (Surmeier et al., 2007). Unlike D1 receptor activation, D2 receptor activation inhibits AC activity and reduces cAMP formation. This and other indirect effects of D2 receptor activation have a net effect of reducing striatal cell excitability (Surmeier et al., 2007).

It should be no surprise, therefore, that theories of basal ganglia function based on the distribution of DA receptor subtypes in the striatum and the effects of the direct and indirect pathways on basal ganglia output activity, have generally hypothesized that the striatonigral and striatopallidal circuits provide a functional architecture for the promotion or inhibition of action initiation (Albin *et al*., 1989; Eyny and Horvitz, 2003; Gerfen, 2000; Smith *et al*., 1998; Surmeier *et al*., 2007). However, this view may not fully capture basal ganglia function. First, as described above and elsewhere (e.g., (Redgrave *et al*., 2010)), the direct and indirect pathway architecture offers an incomplete description of the complex intrinsic basal ganglia circuitry. Second, although there are clear opposing effects of direct and

indirect pathway stimulation on motor output (e.g., (Kravitz *et al*., 2010), there is less clear evidence dissociating these pathways on cognitive and motivational processes (e.g., (Di Ciano *et al*., 2001; Floresco, 2007; Salamone *et al*., 2002)). We suggest that the functional role of DA receptor subtypes may be characterized more accurately within the context of basal ganglia functional loops described above. A further description of the role dopamine signaling in the striatum plays in learning and action control can be found in the sections below.

In addition to DA receptors, striatal MSNs contain glutamate receptors, including AMPA, NMDA and group I metabotropic glutamate receptors (mgluR's). Activation of ionotropic glutamate receptors in MSN's directly or indirectly causes an influx of ca^{++} and activation of ca^{++} dependent intracellular signaling molecules, such as calcium-and-calmodulin-dependent protein kinase II (CamKII) and the protein phosphatase PP-2B (calcineurin) – refer to Figure 2. Activation of mgluR's in striatum activates phospholipase C (PLC), which increases formation of inositol trisphosphate (IP3), and the release of intracellular calcium, which initiates a number of cellular processes, including an increase in the activity of the multi-functional kinase cyclin dependent kinase 5 (cdk5) (Liu et al., 2001). These signaling pathways influence a variety of cellular operations, and, as described below, provide a regulatory effect on dopamine signaling.

5.2 Dopamine-glutamate interactions and plasticity

DA and glutamate signaling interact in the striatum to influence neural excitability and synaptic plasticity. How DA and glutamate interact depends on the activity state of the MSN. At rest, striatal MSNs display a hyperpolarized membrane potential known as the down state (−80 mV) (Kreitzer, 2009; Nisenbaum and Wilson, 1995). During the down state, dopamine signaling acts to suppress MSN activity in response to glutamatergic inputs; however, during coordinated glutamatergic input, MSN's shift to a less hyperpolarized up state (−60 mV), during which spiking is more likely to occur (Carr *et al*., 2003; Surmeier *et al*., 1992). During the up state, dopamine signaling facilitates changes in membrane potential caused by glutamate receptor activation, thereby increasing cell excitability (Carter and Sabatini, 2004; Flores-Hernandez *et al*., 2002; Hallett *et al*., 2006; Surmeier *et al*., 1995). Based on these properties, DA signaling has been hypothesized to act as a filter to reduce the effects of uncoordinated glutamatergic inputs on MSN activity and amplify the effects on MSN activity of coordinated glutamatergic inputs.

In addition to modulating the efficacy of glutamatergic inputs, DA is critical for synaptic plasticity at glutamatergic corticostriatal synapses. Long-term potentiation (LTP) and long-term depression (LTD) can be induced at corticostriatal synapses, and both forms of plasticity depend on dopamine (Di Filippo et al., 2009). LTP induction depends on coordinated activation of D1 and NMDA receptors (Calabresi et al., 1992; Kerr and Wickens, 2001); whereas LTD induction depends on D2 and mGluR1 receptor activation at indirect pathway neurons (Kreitzer and Malenka, 2005; Shen et al., 2008). LTD induction in striatum depends on the generation of a retrograde endocannabinoid signal that activates pre-synaptic CB1 receptors located on glutamatergic terminals, and causes a reduction in glutamate release (Adermark and Lovinger, 2007; Gerdeman *et al*., 2002; Kreitzer and Malenka, 2005). Thus, although the cellular mechanisms differ, coordinated DA and glutamate signaling enable corticostriatal LTP and LTD induction.

The ability of DA to influence glutamate-dependent signaling in MSN's relies on a complex interaction of intracellular signaling pathways (Nakano et al., 2010). Much of this interaction centers on Dopamine- and cAMP-regulated phosphoprotein, 32 Kda (DARPP-32). DARPP-32 contains multiple phosphorylation sites, which enables it to serve as a dual-function protein (see Greengard *et al*., 1999; Svenningsson *et al*., 2004 and Figure

2 for review). During D1 receptor stimulation, PKA phosphorylates DARPP-32 at its Thr-34 residue. When phosphorylated at Thr-34, DARPP-32 becomes a potent inhibitor of the protein phosphatase PP-1. PP-1 dephosphorylates a number of cellular proteins, including ion channels, transcription factors and signaling kinases. Thr-34 DARPP-32 phosphorylation therefore affects a number of cellular processes through its inhibition of PP-1. In contrast, during glutamate receptor stimulation, calcium-mediated signaling activates cdk5, which phosphorylates DARPP-32 at its Thr-75 residue. When phosphorylated at Thr-75, DARPP-32 becomes an inhibitor of PKA. In addition, glutamate-mediated calcium influx activates PP-2B, which dephosphorylates DARPP-32 at Thr-34. Thus, DARPP-32 phosphorylation serves to integrate DA and glutamate signaling, and through its inhibition of PP-1 or PKA regulates a variety of cellular responses to extracellular signals.

One of the signaling pathways regulated by DARPP-32 in the striatum is extracellular signal regulated kinase (ERK), a member of the mitogen activated protein kinase (MAPK) signaling family. D1 receptor activation increases ERK phosphorylation in a manner that depends on DARPP-32's inhibition of PP-1 (Valjent et al., 2005). PP-1 ordinarily dephosphorylates another phosphatase, the striatal-enriched phosphatase (STEP). PP-1's dephosphorylation of STEP allows STEP to dephosphorylate ERK (Paul et al., 2003). PP-1 inhibition by Thr-34 DARPP-32 increases phosphorylated STEP and, as a consequence, reduces ERK dephosphorylation by STEP (Valjent et al., 2005) (Figure 2). DARPP-32's inhibition of PP-1 also prevents PP-1 from dephosphorylating a kinase upstream of ERK. Thus, D1 receptor activation increases ERK phosphorylation by preventing its dephosphorylation by STEP and by preventing the dephosphorylation of kinases upstream of ERK. In addition, PKA activates ERK by phosphorylating rap1, a kinase upstream of ERK (Grewal et al., 2000).

ERK activation is also sensitive to glutamate receptor signaling. NMDA and AMPA receptor activation increases ERK phosphorylation through activation of calcium-dependent signaling pathways (Fasano *et al*., 2009; Mao *et al*., 2004; Perkinton *et al*., 1999; Wang *et al*., 2007) (Figure 2). However, glutamate negatively regulates ERK signaling through calcium-mediated phosphorylation of DARPP-32 at Thr-75 and dephosphorylation of DARPP-32 at Thr-34. This prevents DARPP-32 from inhibiting PP-1, which allows STEP to dephosphorylate ERK (Paul et al., 2003). Activation of mgluR's in striatum appears to activate ERK through a calcium-dependent process and a calcium-independent process that depends on the scaffolding protein homer 1b/c (Mao et al., 2005).

Based on its complex regulation by phosphatases and kinases, ERK appears to be maximally activated during combined D1 and glutamate receptor signaling. This has lead to the suggestion that ERK acts to detect coincident activity of glutamate and DA signals (Girault et al., 2007). This may make ERK particularly important for mediating neural and behavioral processes that depend on coincident activation of these signaling pathways. In striatum, ERK has been shown to have an important role in regulating MSN excitability and corticostriatal plasticity. One target for ERK phosphorylation is the inwardly rectifying *A*-type K+ channel $K_V4.2$. $K_V4.2$ channels are fast-inactivating K^+ channels located in distal dendrites that reduce spike initiation and limit action potential back propagation (Song et al., 1998; Tkatch et al., 2000). ERK phosphorylation of the $K_V4.2$ channel increases its open probability and therefore increases MSN excitability (Birnbaum et al., 2004). In this way, ERK activation may have a role in regulating striatal activity and ongoing behavior. In addition to targets in the cellular membrane, ERK regulates immediate-early gene expression through its phosphorylation of regulators of transcription, such as mitogen- and stress-activated protein kinase 1 (MSK1), ribosomal s6 kinase (rsk) and elk-1 (Sgambato et al., 1998). Rsk, in turn, phosphorylates the transcription factor cAMP response element binding protein (CREB) (Xing et al., 1996). CREB has a critical role in learning and

synaptic plasticity (Bailey and Kandel, 1993). In MSN's, DARPP-32, ERK and CREB are required for long-lasting forms of LTP and LTD (Calabresi et al., 2000; Mazzucchelli et al., 2002; Pittenger et al., 2006). This signaling pathway, activated by coordinated DA and glutamate receptor signaling, and resulting in DARPP-32, ERK and CREB phosphorylation, may have a critical role in corticostriatal plasticity and learning.

5.3 Molecular processes involved in goal-directed and habitual behavior

The learning processes that mediate the acquisition of goal-directed and habitual actions are likely the result of synaptic plasticity in the striatum, specifically corticostriatal synaptic plasticity. Numerous pieces of evidence support this hypothesis. First, lesions of cortical regions that project to the striatum have the same effect as striatal lesions on instrumental learning (Ostlund and Balleine, 2005). Second, treatments that disrupt corticostriatal plasticity prevent learning. Infusions into the pDMS of the NMDA antagonist AP-5, which is known to block LTP at corticostriatal synapses, prevents the acquisition of action-outcome associations during instrumental learning (Yin et al., 2005a). Likewise, disruption of cannabinoid signaling, which is critical for corticostriatal LTD, interferes with both instrumental learning and habit formation (Crombag *et al.*,; Hilario *et al*., 2007). Similarly, disruption of AC5, an isoform of AC enriched in striatum, disrupts corticostriatal LTD and prevents stimulus-response learning (Kheirbek et al., 2009). Third, the degree of potentiation at corticostriatal synapses is correlated with acquisition of an instrumental response for intracranial self-stimulation (Reynolds et al., 2001), suggesting that corticostriatal plasticity is directly related to acquisition of an instrumental response.

Further indirect evidence supports the notion that glutamate-dependent signaling is necessary for goal-directed learning. Disruption of AMPA signaling impairs instrumental performance following outcome devaluation. Mice lacking the gluR1 subunit of the AMPA receptor show no preference for the valued compared to the devalued action following specific satiety (Johnson et al., 2005). Because this mouse lacks gluR1 subunits throughout the brain, it may be that other regions that project to striatum and are important for outcome encoding (e.g., basolateral amygdala) may mediate this effect. Furthermore, it is not known whether this deficit reflects impaired learning or performance. In subsequent studies, however, GluR1 deficient mice showed no effect of sensory-specific satiety on instrumental responding in a heterogeneous instrumental chain. Normally, devaluation of the instrumental outcome reduces responding on the distal action in an instrumental chain (Corbit and Balleine, 2003). GluR1 deficient mice showed no effect of devaluation on distal responses, but showed an effect of general satiety on proximal responses. Thus, these mice appear to have a specific deficit in using sensory-specific outcome representations to guide instrumental behavior (Johnson et al., 2007).

DA also has an important role in goal-directed and habitual behavior. DA release in the striatum during reward learning tasks is well documented, and is thought to reflect a reward prediction error as defined in reinforcement learning (Schultz et al., 1997; Schultz and Dickinson, 2000). However, the effects of DA antagonists during goal-directed learning have been difficult to interpret. One difficulty with assessing the effects of DA antagonists in the striatum is that they also impair motor performance; hence a supposed learning deficit may in fact be due to the animal's inability to carry out the motor actions necessary for learning, yet learning, if it were possible, may be intact (e.g., (Darvas and Palmiter, 2010; Robinson *et al*., 2007; Robinson *et al*., 2006). Despite these challenges, it has been shown that 6-hydroxydopamine (OHDA) infusions that deplete DA in the pDMS prior to instrumental learning result in impaired performance on a contingency degradation paradigm, but leave outcome devaluation intact (Lex and Hauber, 2010). In the dorsolateral striatum, 6-OHDA infusions in the DLS prevent the development of habitual, i.e. outcome insensitive, instrumental responding (Faure et al., 2005). In subsequent studies, it was shown

that DA agonists infused into this area did not restore habitual responding in DA-depleted animals, suggesting that, although acquisition of habitual behavior is DA dependent, performance of habitual actions is not (Faure et al., 2010). Data from studies of conditioned approach behavior, which is stimulus bound and ostensibly mediated by a similar mechanism, also shows a transition from DA dependent to DA-independent responding as a result of training experience (Choi et al., 2005). Although focused on different learning and performance processes, these data are consistent in suggesting an initial dependence on DA in the striatum during learning of habitual and goal-directed actions, whereas performance of at least habitual actions appears to become DA independent after acquisition.

Intracellular signaling activity sensitive to DA has also been implicated in the performance of goal-directed and habitual actions. Regulators of cAMP formation have been shown to alter instrumental performance. One such regulator of cAMP in the striatum is the lipid sphingosine-1-phosphate, which regulates cAMP formation through a G protein-coupled receptor (GPR6). GPR6 is found specifically in striatopallidal neurons, and mice with a Gpr6 mutation showed reduced cAMP formation (Lobo et al., 2007). Behaviorally, Gpr6 null mice showed increased response rates in a progressive ratio task and reduced sensitivity to contingency degradation (Lobo et al., 2007). Additional tests demonstrated that these mice had normal outcome valuation, suggesting that the enhanced responding in the progressive ratio was likely the result of an altered ability to initiate actions. A similar finding was observed in mice with a mutation of cdk5. Mice with a cdk5 mutation show increased striatal cell excitability and increased responses on a progressive ratio schedule (Benavides et al., 2007). Since cdk5 negatively regulates PKA, the behavioral effects of cdk5 mutation presumably are the result of increased PKA activity. Thus, inhibition of DA-dependent signaling through Gpr6 mutation in the indirect pathway, or disinhibition of DA-dependent signaling through cdk5 mutation in the direct pathway increases action initiation as measured by progressive ratio responding.

ERK signaling has an important role in both the acquisition and performance of goal-directed actions (Shiflett and Balleine, 2011; Shiflett *et al*., 2010). Instrumental training increases ERK phosphorylation in the pDMS. Furthermore, inhibition of ERK activation by infusion of the MEK/ERK inhibitor U0126 into the pDMS prior to an instrumental training episode prevents accurate performance in a subsequent devaluation task. These results demonstrate that the opportunity to acquire action-outcome associations activates ERK in the pDMS, and blocking ERK activation in this region prevents encoding of this relationship. In addition to a role in learning, ERK is necessary for the performance of goal-directed actions. Inhibition of ERK activity in the pDMS after training but prior to a devaluation choice extinction test was found to impair choice performance; during the test, rats showed no preference for the valued action compared to the devalued action (Shiflett et al, 2010). ERK inhibition did not affect the amount of food consumed during the specific-satiety procedure, suggesting that ERK inhibition does not interfere with the devaluation process itself, nor did ERK inhibition impair rats' ability to make instrumental responses generally. Rather, it appears that ERK is specifically required in order to use outcome information, including the desirability of an outcome, to direct instrumental action. Interestingly, ERK inhibition in the DLS did not affect action-outcome learning; however, DLS ERK inhibition prior to the devaluation test impaired task performance, suggesting that the DLS has some role to play in the performance of goal-directed actions, and that this function requires ERK signaling. Given the role of the DLS in S-R learning, it is possible the DLS contributes to the ability of environmental stimuli to promote the selection (and, therefore, the performance) of actions related to salient cues. To the extent that ERK activity is engaged by a form of action-selection process, it should be expected that blocking ERK phosphorylation will tend to reduce action selection and performance, particularly of actions associated with a non-devalued outcome.

Regulation of gene expression in the striatum likely underlies the long-lasting memory associated with goal-directed and habitual behavior. Evidence in support of this comes from the finding that instrumental acquisition is associated with immediate-early gene induction in the striatum, and with more extensive training, expression becomes more prominent in lateral striatum (Hernandez et al., 2006). Additionally, interference with transcriptional regulation in the striatum during learning prevents development of habitual behavior. In particular, the transcription factor CREB is likely involved in the development of habitual behavior. Rats trained in a plus maze task that used a response strategy to encode the goal location show elevated phosphorylated CREB levels in the DLS after learning compared to rats that used a place strategy, which showed elevated CREB phosphorylation in the hippocampus (Colombo et al., 2003). Furthermore, when infused in DLS, a mutant form of CREB that impairs CREB-dependent gene expression also impairs acquisition of a response strategy (Brightwell et al., 2008). CREB may enable learning by mediating corticostriatal plasticity. A dominant-negative CREB mutation that is specific to the dorsal striatum impairs acquisition of a stimulus-response task, and impairs LTP and LTD induction at corticostriatal synapses (Pittenger et al., 2006). Although it is not known whether these tasks are governed in a goal-directed, habitual, or Pavlovian manner, the results suggest a critical involvement of CREB in the striatum for learning.

Although the striatum is clearly engaged during learning and performance of goal-directed and habitual actions, this does not necessarily entail that the striatum is the long-term store of associations that underlie these behaviors. Given that coordinated engagement of various components of cortico-basal ganglia circuitry is necessary for learning and task performance, it may not be plausible or even accurate to identify the location of the "engram" that encodes a particular action-outcome or stimulus-response association as lying within any one structure in this circuit. However, what differentiates various regions within the circuit is their recruitment during distinct task components (acquisition, retrieval, action selection and initiation) and, based on this interpretation, striatal sub-regions are clearly necessary, if not themselves sufficient, for both learning and performance of goal-directed and habitual actions.

5.4 Molecular processes involved in Pavlovian-instrumental interactions

The ability of conditioned stimuli to influence instrumental action depends critically on DA signaling in the NAc. DA release in the NAc has been shown to gradually shift from presentation of appetitive outcomes to the cues that predict those outcomes during Pavlovian conditioning (Day et al., 2007). During tests of Pavlovian-instrumental transfer (PIT), which measures the effect of cue presentation on instrumental responding, DA antagonist infusion into the NAc abolishes PIT (Lex and Hauber, 2008), as do lesions of the ventral tegmental area (VTA), which provides DA input to the NAc (Corbit *et al*., 2007; Murschall and Hauber, 2006). Intra-NAc infusion of the psychostimulant amphetamine, which enhances DA signaling, increases the general form of PIT (Wyvell and Berridge, 2000). DA-dependent signaling has also been shown to have a role in PIT. Mice with a knockout of AC5 signaling show impairments in PIT (Kheirbek et al., 2008). AC5 KO mice show normal sensitivity of instrumental performance to outcome devaluation, suggesting that AC5-dependent signaling has a specific role in expression of Pavlovian responses. AC5 KO's show reduced ERK phosphorylation in the NAc following D1 receptor stimulation, suggesting that the impairment in behavior observed in these animals may be due to impaired ERK signaling (Kheirbek et al., 2008).

The role of glutamate during PIT is less well understood, in part because of the use of different PIT paradigms and whether the NAc core or shell was targeted. For example, infusions into the NAc of the AMPA antagonist CNQX or the NMDA antagonist dizocilpine have no effect on the general form of PIT (Murschall and Hauber, 2005). However, mice

lacking the gluR1 subunit of the AMPA receptor show deficits in outcome-specific PIT (Johnson et al., 2007). It may be that outcome-specific PIT has more of a requirement for glutamate signaling than the general form of PIT (Crombag *et al*., 2008; Mead and Stephens, 2003). However, because the GluR1 knockout was not restricted to the striatum, it is not entirely clear whether the deficit in PIT in GluR1-deficient mice can be ascribed to impaired AMPA signaling in the striatum. More direct evidence implicating glutamate signaling in outcome-specific PIT comes from transgenic mice that express a constitutively active form of CamKII that is restricted to the striatum (Wiltgen et al., 2007). Changes in CaMKII phosphorylation regulate cellular excitability through a variety of mechanisms, most notably through the phosphorylation of the $K_V4.2$ channel (Varga et al., 2004) and of AMPA receptor channels (Carvalho et al, 2000). The transgene that mimics the constituitively active state is expressed only in the striatum and is under the control of a tetracycline promoter. As such, its expression can be regionally and temporally localized. Whether the transgene was turned off or on, both Pavlovian conditioning and instrumental conditioning were normal in these mice; performance during Pavlovian conditioning, during instrumental acquisition and in the outcome devaluation and contingency degradation tests did not differ from wildtype controls. However, with the transgene turned on, mice show impaired performance on an outcome-specific PIT task, and performance on the PIT task was immediately restored when the transgene was turned off (see Wiltgen et al, 2007). This implicates CamKII and striatal excitability in the ability of Pavlovian cues to bias choice performance in instrumental conditioning.

ERK signaling in the NAc plays an important role in PIT. ERK phosphorylation in the NAc increases during presentation of a reward-associated CS (Shiflett et al., 2008). Furthermore, infusion of the ERK inhibitor U0126 into the NAc prior to testing prevents PIT. Intra-NAc U0126 infusion has no effect on instrumental responding generally, which indicates that ERK inhibition causes a specific impairment in the ability of CS's to motivate instrumental behavior. Like CamKII, ERK may enable PIT through its effects on cell excitability. ERK is known to modulate excitability through $K_V4.2$ channel phosphorylation, which gives rise to increased MSN excitability. ERK could also influence behavioral responses to cues through its effects on CREB. CREB phosphorylation in the NAc occurs during presentation of emotionally salient stimuli (Barrot *et al*., 2002; Barrot *et al*., 2005; Shaw-Lutchman *et al*., 2002). In addition, CS's associated with rewards increase CREB phosphorylation in the NAc (Shiflett et al., 2009). Treatments that block CREB phosphorylation in the NAc, such as viral-mediated expression of an inactive form of CREB, or over-expression of an inhibitor of CREB function, such as inducible cAMP early repressor (ICER) increases behavioral responses to emotionally salient stimuli, whereas increasing CREB activation reduces behavioral responses (Barrot *et al*., 2002; Barrot *et al*., 2005; Green *et al*., 2006a; Green *et al*., 2006b). This process seems to depend on an alteration in MSN excitability. Constitutive expression of active CREB increases MSN excitability and NMDA-mediated up-state transitions, suggesting that increased MSN excitability reduces behavioral responses to stimuli including behavioral responsese to cocaine (Dong et al., 2006; Huang et al., 2008). Furthermore, artificial reduction in NAc activity by overexpressing K^+ channels reduces behavioral responses to cocaine (Dong et al., 2006.) It may be that "phasic" increases in CREB in the NAc caused by presentation of an emotionally-salient stimulus mediate learning, whereas long-term alterations in CREB caused by repeated drug exposure results in constitutive changes in MSN excitability that may alter responsiveness to salient environmental stimuli.

6. Conclusions

Although our understanding of the molecular mechanisms responsible for striatal function is far from complete, some general conclusions can be drawn. It is clear that learning, whether

in the form of action-outcome or stimulus-response associations, depends upon the integration of glutamate and dopamine signals (Horvitz, 2009). Although this review focused on intracellular mechanisms that integrate DA and glutamate signals, interactions between these signaling systems occurs through multiple cellular mechanisms. The general theme is that under conditions of coordinated glutamatergic input to the striatum, DA facilitates the ability of glutamate signals to drive MSN activity and initiate corticostriatal plasticity. Not coincidentally, the conditions that give rise to coordinated glutamate and DA release in the striatum are situations in which learning and decision-making take place. Furthermore, it is likely that goal-directed learning is based on corticostriatal LTP in the pDMS, and that acquisition of habits is based on LTD in the DLS. This is based, in part, on the observation that LTP is more easily induced in the DMS, whereas LTD is more easily induced in the DLS (Partridge et al., 2000).

DA and glutamate signals interact in a complex fashion at the level of intracellular signaling molecules. Highlighted in this review is the special importance of the ERK signaling cascade, which, because of its sensitivity to combined glutamate and DA receptor activation, may serve to detect coincident activity in these signaling pathways (Girault et al., 2007). The complex regulation of ERK activity by DARPP-32 and other signaling pathways seems to favor conditions of combined D1 and NMDA receptor activation for maximal ERK activation. ERK activation may enable synaptic plasticity in the striatum through transcriptional regulation. In particular, ERK phosphorylates the transcription factor CREB, which is known to be necessary for lasting forms of corticostriatal LTP and LTD. It is not entirely clear how ERK and CREB are involved in corticostriatal LTD if the translational modifications necessary for corticostriatal LTD are pre-synaptic (Yin et al., 2006). Nor is it known whether ERK is necessary for the acquisition of habitual behavior. It may be that a post-synaptic translational component of LTD exists in corticostriatal LTD, and much like LTD in other regions, requires ERK activation (Thiels et al., 2002). A question for future research is whether the plasticity induced in these learning situations primarily affects the striatopallidal indirect or striatonigral direct pathway neurons. Such information will be useful in understanding how learning alters striatal activity to enable performance of goal-directed or habitual actions (Stalnaker *et al*., 2010; Thorn *et al*., 2010; Yin *et al*., 2009).

In addition to its role in learning, ERK activation in the pDMS has been shown to be necessary for flexible responding following outcome devaluation. ERK may enable this behavioral flexibility by conferring MSN's with plasticity of cellular excitability. During the outcome devaluation task, outcome value information (perhaps provided by DA release in striatum) is combined with action-outcome information (perhaps provided by glutamate release in striatum). Selection and initiation of actions may depend on the ability of these inputs to generate MSN activity, a function that may be mediated by ERK. Similar to its role in the dorsal striatum, ERK activation in the NAc is required for environmental stimuli to modulate instrumental performance. Like outcome devaluation, outcome-selective PIT requires the integration of outcome information, in this case stimulus-outcome information with action-outcome information to direct responding. ERK alters excitability through its phosphorylation of $K_V4.2$ channels, which results in enhanced activity in response to glutamatergic input. It may be that the loss of ERK signaling prevents accurate performance following outcome devaluation or during the PIT task because DA and glutamate signals are unable to be integrated properly to modulate MSN activity and thereby allow for initiation of the appropriate action. If this is the case, then ERK should have its behavioral effects by phosphorylating cytosolic targets. Treatments that block the nuclear transport of ERK but preserve its cytosolic signaling may be instructive in this regard (Paul et al., 2007). Further tests of this hypothesis would include an examination of $K_V4.2$ phosphorylation during choice performance following outcome devaluation and whether disruption of $K_V4.2$ phosphorylation prevents flexible responding.

Many of the signaling molecules described in this review have been implicated in drug addiction (Berke and Hyman, 2000). This may be expected when one considers drug-seeking behavior and the response to drug-associated cues are governed by the same neural processes that underlie natural rewards. What makes drugs of abuse unique from natural rewards, and may give rise to features of addictive behavior, is the overactivity of these signaling mechanisms that results from drug exposure. Indeed, exposure to abused substances may involve abnormal corticostriatal plasticity and changes in MSN excitability (Bamford et al., 2008). Many of the signaling molecules discussed here have been implicated in various aspects of addiction-related behavior (Ortiz *et al*., 1995; Tropea *et al*., 2008; Valjent *et al*., 2000; Walters and Blendy, 2001); e.g., in similar fashion to its role in processing natural rewards, inhibition of ERK activation in the NAc prevents expression of a drug conditioned place preference (Miller and Marshall, 2004). Placing the molecular alterations as a result of repeated drug exposure in the context of striatal function may help to understand to what extent addictive behavior is a disorder of mechanisms regulating goal-directed action, habit, or control of behavior by Pavlovian cues.

Understanding the relationship between molecular processes and adaptive behavior is an important but daunting goal of neuroscience research. The role of a particular signaling molecule, such as ERK, in behavior has not only to be understood within its functional context; e.g., how ERK regulates gene expression and cellular activity but also, in turn, has to be understood within a wider context; i.e. how changes in gene expression and cellular activity regulate basal ganglia network activity and ultimately specific aspects of adaptive behavior. At the same time, an effective framework for understanding specific psychological functions is necessary for interpreting the effects of neural manipulations on behavior. This is particularly relevant for translational research, whose goal is to enable research findings to inform therapeutic strategy. The research described in this review attempts to make these links between molecular changes in striatum, adaptive behavior and, more broadly, adaptive psychological capacities that control those behavioral effects. It is our belief that the sort of research described in this review will facilitate the development of effective treatments for disorders of the striatum, such as neurodegenerative conditions and addiction.

Abbreviation list

AC	adenylyl cyclase
Cdk5	cyclin dependent kinase 5
CREB	cAMP response element binding protein
CS	conditioned stimulus
DA	dopamine
D1	dopamine D1 receptor
D2	dopamine D2 receptor
DARPP-32	Dopamine- and cAMP-regulated phosphoprotein
DMS	dorsomedial striatum
DLS	dorsolateral striatum
ERK	extracellular signal regulated kinase
GPe	globus pallidus external
GPi	globus pallidus internal
IMD	intermediodoral nucleus of the thalamus

LTD	long term depression
LTP	long term potentiation
MD	mediodorsal thalamus
mGLUr	metabotropic glutamate receptors
MSK1	mitogen- and stress-activated protein kinase 1
MSN	medium spiny neuron
NAc	nucleus accumbens
pDMS	posterior dorsomedial striatum
PIT	Pavlovian-instrumental transfer
PKA	protein kinase A
PL	prelimbic region of the medial prefrontal cortex
PO	posterior nucleus of the thalamus
PP	protein phosphatase
R-O	response-outcome
Rsk	ribosomal s6 kinase
S-R	stimulus-response
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
STEP	striatal-enriched phosphatase
STN	subthalamic nucleus
VA/VL	ventroanterior/ventrolateral nucleus of the thalamus
VP	ventral pallidum
VS	ventral striatum
VTA	ventral tegmental area

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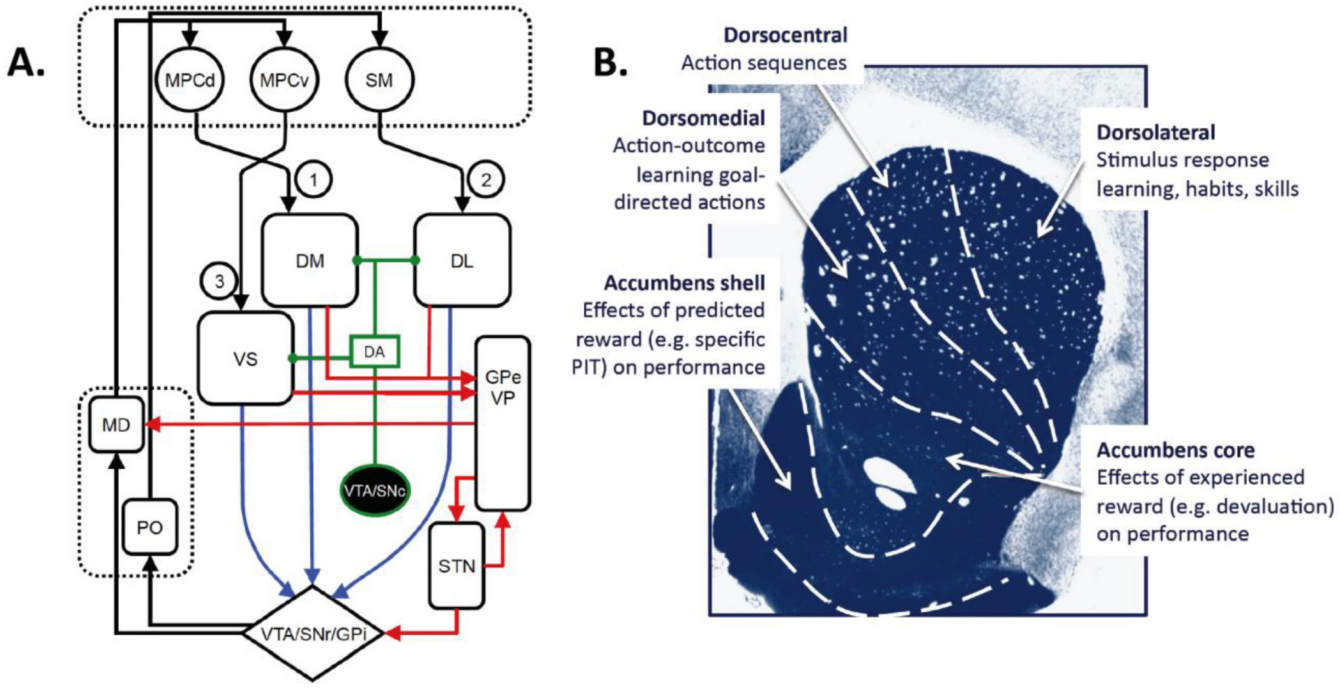

Figure 1.

A. Corticostriatal circuits involved in decision making. The learning processes controlling the acquisition of reward-related actions are mediated by converging projections from regions of dorsomedial prefrontal cortex (dMPC) to the rodent dorsomedial striatum (DM), whereas (2) the processes mediating the acquisition of stimulus-bound actions, or habits, are thought to be mediated by projections from sensorimotor cortex (SM) to the rodent dorsolateral striatum (DL). Reward and predictors of reward are the major motivational influences on the performance of goal-directed and habitual actions and are thought to be mediated by corticostriatal circuits involving, particularly, ventral MPC and amygdala inputs (not shown) to ventral striatum (VS). These corticostriatal connections are parts of distinct feedback loops that project back to their cortical origins via ventral tegementum/ substantial nigra/globus pallidus (SNr/Gpi) (blue arrows) and the mediodorsal (MD)/ posterior (PO) nuclei of the thalamus and project out to premotor and motor cortices through the globus pallidus and ventral pallidum (red arrows). Dopamine (green arrows) is an important modulator of plasticity in the dorsal striatum whereas its tonic release has long been associated with the motivational processes mediated by the ventral circuit. **B**. The major functional divisions of the striatum. The regions shown are anatomically continuous but, recent findings suggest, functionally heterogeneous. With regard to instrumental conditioning the dorsal and ventral striatum are broadly distinguished by their involvement in learning and performance respectively; the dorsal region in the acquisition of goal-directed actions (dorsomedial region), heterogeneous chains of actions (dorsocentral region) and habits (dorsolateral region); the ventral striatum in the motivation of these actions by experienced reward (the nucleus accumbens core) and predicted reward (the nucleus accumbens shell).

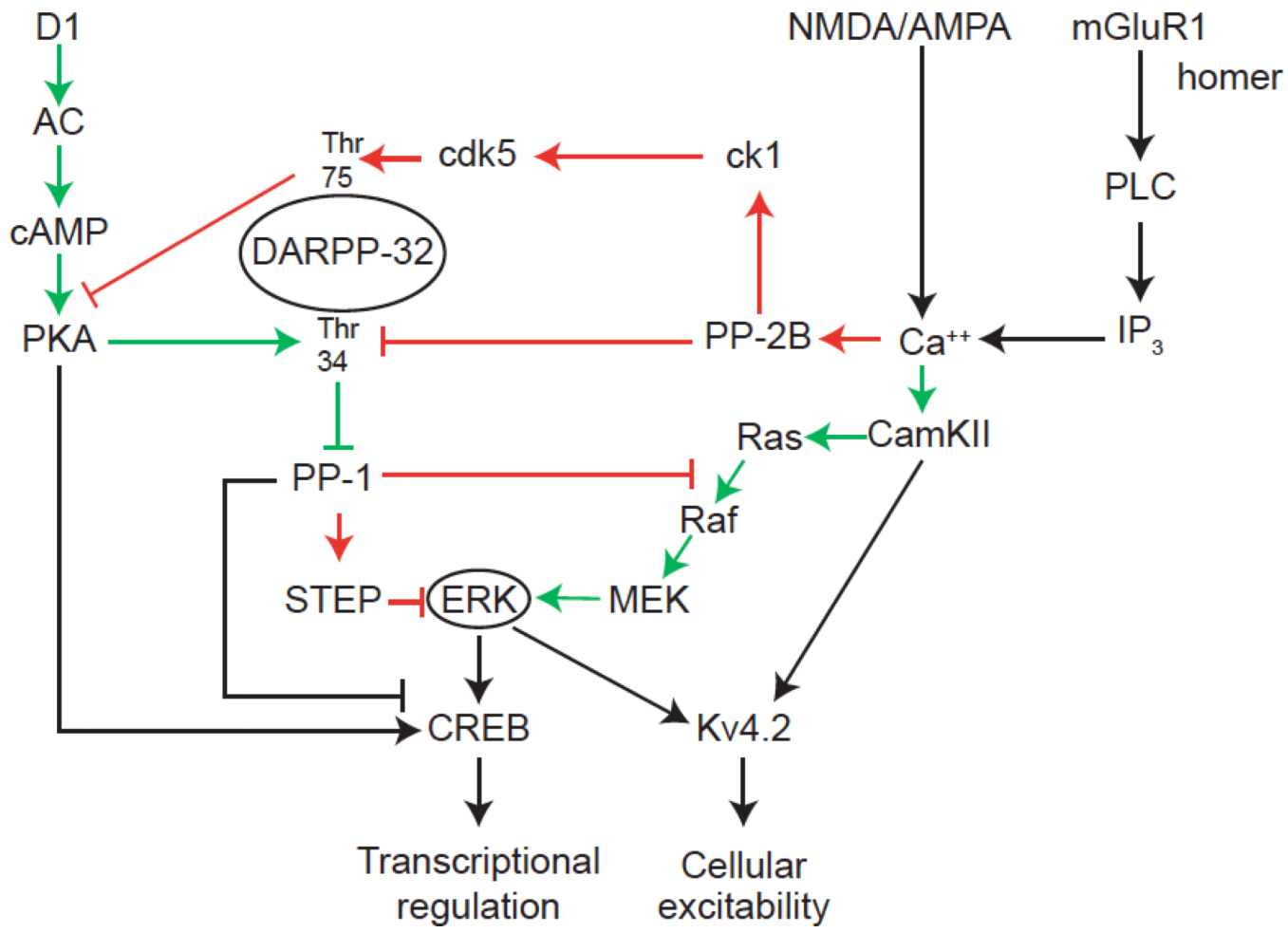

Figure 2.

Intracellular signaling pathways integrate dopamine and glutamate signals. D1 receptor activation increases adenylyl cyclase (AC) activation, cAMP formation, and PKA activation. PKA phosphorylates DARPP-32 at Thr-34 residue, making it a potent inhibitor of protein phosphatase-1 (PP-1). Inhibition of PP-1 indirectly increases extracellular signal regulated kinase (ERK) activation, by preventing PP-1 from dephosphorylating striatal-enriched phosphatase (STEP), which, when dephosphorylated, inhibits ERK. NMDA and AMPA receptor activation increases ca++ influx, whereas mGluR1 activation causes release of intracellular calcium through the phospholipase C (PLC), inositol trisphosphate (IP3) pathway. Ca++ activates a number of signaling pathways, including calcium and calmodulin-dependent kinase II (CamKII), and protein phosphatase 2B (PP-2B). PP-2B activation results in Thr-75 DARPP-32 phosphorylation, through casein kinase (ck) and cyclin-dependent kinase 5 (cdk5). When phospohrylated at Thr-75, DARPP-32 becomes an inhibitor of PKA. PP-2B also dephosphoryltes DARPP-32 at Thr-34. These effects negatively regulate ERK activation. CamKII activates ERK via the ras-raf-mek cascade. Thus ERK activation depends on the phosphorylation state of DARPP-32, which itself is sensitive to the relative activation of glutamate and DA receptors. ERK regulates gene expression through its phosphorylation of transcription factors, such as cAMP response element binding protein (CREB), and regulates neural excitability through its phosphorylation of the Kv4.2 channel. Red arrows indicate negative regulation of ERK, green arrows indicate positive regulation of ERK.