Muscarinic Modulation of Striatal Function and Circuitry

Joshua A. Goldberg, Jun B. Ding, and D. James Surmeier

Abstract Striatal cholinergic interneurons are pivotal modulators of the striatal circuitry involved in action selection and decision making. Although nicotinic receptors are important transducers of acetylcholine release in the striatum, muscarinic receptors are more pervasive and have been more thoroughly studied. In this review, the effects of muscarinic receptor signaling on the principal cell types in the striatum and its canonical circuits will be discussed, highlighting new insights into their role in synaptic integration and plasticity. These studies, and those that have identified new circuit elements driven by activation of nicotinic receptors, make it clear that temporally patterned activity in cholinergic interneurons must play an important role in determining the effects on striatal circuitry. These effects could be critical to the response to salient environmental stimuli that serve to direct behavior.

Keywords Striatum • Medium spiny projection neuron • Acetylcholine • Cholinergic interneuron • Muscarinic receptor • Synaptic integration • Thalamus • Synaptic plasticity • Neuromodulation • Autoreceptor • Parkinson's disease

1 Introduction

The basal ganglia are a richly interconnected set of subcortical nuclei intimately involved in the regulation of action selection and decision making (Albin et al. 1989; DeLong and Wichmann 2009; Frank and Claus 2006; Gerfen 1992; Houk et al. 2007; Kimura et al. 2003; Mink 1996; Morris et al. 2004; Wichmann and DeLong 1996). The striatum is the largest nucleus of this group and serves as the initial integrator of cortical and thalamic information relevant to this process.

D.J. Surmeier (✉)
Department of Physiology, Northwestern University Feinberg School of Medicine, 303 E Chicago Ave, Chicago, IL 60611, USA
e-mail: j-surmeier@northwestern.edu

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Essentially all cortical areas – sensory, motor, and associational – project to the striatum (Bolam et al. 2000; Gerfen 1992; Wilson 2004). Wide regions of the thalamus also project to the striatum, with a particularly prominent contribution from the intralaminar thalamic nuclei that are responsive to salient or novel sensory events (Doig et al. 2010; Matsumoto et al. 2001; McHaffie et al. 2005; Smith et al. 2004). Both cortical and thalamic projections are glutamatergic, forming excitatory synaptic connections with principal GABAergic, spiny projection neurons (SPNs) and interneurons. SPNs constitute the vast majority of striatal neurons (~90–95%) with each of the four interneuron populations constituting a few percent of the total.

Of the interneuron populations, all but one is GABAergic. The only non-GABAergic interneuron in the striatum is the cholinergic interneuron (Bolam et al. 1984; Kemp and Powell 1971; Phelps et al. 1985). Despite constituting only a few percent of all striatal neurons, these giant, aspiny interneurons are responsible for striatal levels of acetylcholine (ACh), choline acetyltransferase, and choline esterase that are among the highest in the brain (Contant et al. 1996; Mesulam et al. 1992). Because cholinergic interneurons are autonomous pacemakers, whose basal spiking at 3–10 Hz is only transiently modulated up or down by synaptic input, ACh release from the dense interneuronal terminal plexus is virtually continuous, covering all regions of the striatum (Bennett and Wilson 1999; Goldberg and Wilson 2010; Kawaguchi 1993; Wilson et al. 1990).

Both nicotinic and muscarinic receptors transduce ACh signals in the striatum. However, the cellular distribution of nicotinic receptors (nAChRs) is more restricted than that of muscarinic receptors (mAChRs), being limited to interneurons and afferent terminals (Wilson 2004). In contrast, muscarinic receptors are robustly expressed by the axon terminals of major projections systems to the striatum and by all striatal neurons that have been examined, including principal SPNs. The focus of this chapter will be on the part played by muscarinic receptors in the regulation of striatal circuitry in health and disease.

2 Striatal Muscarinic Receptors

Five mAChRs have been cloned (Caulfield and Birdsall 1998; Eglen 2005; Wess 1996). These receptors can be divided into two classes on the basis of their coupling to G-proteins: M1-class (M1, M3, M5) and M2-class (M2, M4). M1-class receptors couple to Gq/11 Gα proteins that activate phospholipase C (PLC) isoforms resulting in phosphatidylinositol 4,5-bisphosphate (PIP2) hydrolysis to inositol 1,4,5-triphosphate (IP3) and diacyl glycerol (DAG). M2-class receptors couple to Gi/o G proteins that inhibit adenylyl cyclase (AC) through Giα subunits and close Cav2 Ca^{2+} channels and open Kir3 channels through associated Gβγ subunits (Wess 1996; Wess et al. 2007). All five of the cloned mAChRs are expressed in the striatum, with the M1 and M4 subtypes being the most abundant at the tissue level (Alcantara et al. 2001; Bernard et al. 1992; Hersch et al. 1994; Yan et al. 2001; Zhang et al. 2002).

3 Muscarinic Modulation of Canonical Striatal Circuits

In an attempt to organize the relevant literature, the effects of mAChRs on three canonical striatal circuits will be discussed. These are (1) the corticostriatal circuit engaging SPNs, (2) the corticostriatal feed-forward circuit through GABAergic interneurons, and (3) the thalamostriatal feed-forward circuit through cholinergic interneurons.

3.1 The Corticostriatal Circuit

The most basic striatal microcircuit is the one formed by glutamatergic cortical pyramidal neurons and SPNs (Bolam et al. 2000; Wilson 2004). The synapses formed by cortical pyramidal neurons are exclusively on dendritic spines of SPNs. These spines are absent from soma and the most proximal dendrites, rising to a peak density (1–2 μm^{-1}) 50–60 μm from the soma and then falling off very gradually in density to the tips of the sparsely branching dendrites (250–400 μm) (Wilson 1994). Individual cortical axons are sparsely connected to any one SPN, typically making one or two en passant synapses (Parent and Parent 2006). There is no obvious organization to the cortical synapses on the dendritic tree of SPNs, but this could simply be that this organization is difficult to see, as the striatum lacks the lamination characteristic of other regions where this is apparent (e.g., cerebral cortex).

Glutamatergic synapses onto SPNs are richly invested with M2-class mAChRs. These presynaptic mAChRs diminish glutamate release, reducing the excitatory effect of a cortical volley on SPNs (Akaike et al. 1988; Briggs et al. 1981; Malenka and Kocsis 1988). Using an elegant paired recording approach, Pakhotin and Bracci (2007) were able to show that a single cholinergic interneuron spike was able to significantly reduce electrically evoked glutamatergic evoked postsynaptic currents (EPSCs) in nearby SPNs. As expected from the signaling linkages of mAChRs, the presynaptic inhibition was mediated by reducing the opening of Cav2 Ca^{2+} channels controlling terminal exocytosis. This modulation appears to be exclusively of Ca^{2+} channels with a Cav2.1 pore-forming subunit (Barral et al. 1999). A recent study using a novel optical quantal analysis has beautifully characterized the mAChR modulation of release probability at this synapse, confirming previous inferences from less direct measurements (Higley et al. 2009). Because the release of ACh is sustained by the autonomous activity of cholinergic interneurons, the presynaptic mAChR signaling results in the tonic inhibition of glutamatergic synapses on SPNs (Pakhotin and Bracci 2007). Thus, either antagonizing M2-class mAChRs or suppressing the activity of interneurons results in an increased frequency of glutamatergic miniature mEPSCs in SPNs.

What has not been fully appreciated by these studies is the heterogeneity of glutamatergic afferent fibers reaching the striatum. As mentioned earlier, both

cortical and thalamic glutamatergic neurons project to the striatum and form synapses on SPNs (Dube et al. 1988; Wilson 2004). Contrary to widely held prejudice, thalamic synapses are nearly as numerous as cortical synapses. Moreover, while some thalamic axons form synapses on dendritic shafts, other thalamic axons synapse on spine heads, just as cortical axons do (Doig et al. 2010; Dube et al. 1988). There seems to be no qualitative difference between SPNs of the direct and indirect pathway (see below) in their innervation by cortex or thalamus (Ding et al. 2008; Doig et al. 2010), in spite of earlier reports that only direct pathway SPNs (dSPNs) were innervated by thalamic axons (Sidibe and Smith 1996; Smith et al. 2004).

Although sharing anatomical features, the physiological properties of these two synapses are quite different. Using a parahorizontal slice that preserves a significant component of the connectivity between cortex, thalamus, and the striatum (Arbuthnott et al. 1985; Kawaguchi et al. 1989; Smeal et al. 2007) Ding et al. (2008) found that corticostriatal synapses exhibited paired-pulse facilitation regardless of which type of SPN they targeted (see below), indicating that glutamate release probability at this synapse was relatively low. In contrast, thalamostriatal synapses exhibited paired-pulse depression, indicating that glutamate release probability was high. Thus, the corticostriatal synapse was "tuned" to repetitive activity, whereas the thalamostriatal synapse was tuned to transient, episodic activity. Thalamostriatal synapses also had a significantly higher complement of NMDA receptors relative to those of the AMPA type. Interestingly, thalamostriatal synapses on cholinergic interneurons were facilitating (not depressing), suggesting a different origin. Activation of M2-class mAChRs decreased release probability at both types of synapse (Ding et al. 2008).

The postsynaptic effects of SPN mAChR activation are more complex and less well characterized. Early studies clearly suggested that M1 mAChR signaling increased the responsiveness of SPNs to both intrasomatic current injection and to synaptic stimulation (Akaike et al. 1988; Dodt and Misgeld 1986; Galarraga et al. 1999; Hsu et al. 1996). Subsequent studies have largely confirmed this view, putting it on a firmer mechanistic footing (Figueroa et al. 2002; Gabel and Nisenbaum 1999; Howe and Surmeier 1995; Lin et al. 2004; Olson et al. 2005; Perez-Burgos et al. 2008; Perez-Rosello et al. 2005; Shen et al. 2005).

One of the complications in sorting out the effects of mAChR signaling that was not fully appreciated until recently is the heterogeneity of SPNs. SPNs can be divided into two broad classes on the basis of their axonal projections (Fujiyama et al. 2011; Gerfen et al. 1990; Robertson et al. 1992). So-called dSPNs have axonal projections to the GABAergic output nuclei of the basal ganglia: the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr). These dSPNs also extend an axon collateral to the GABAergic neurons of the external segment of the globus pallidus (GPe). Indirect pathway SPNs (iSPNs) extend axonal projections only to the GPe. GPe neurons project to the glutamatergic neurons of the subthalamic nucleus (STN) and to the output nuclei (GPi/SNr). Thus, the indirect pathway forms a multisynaptic (or indirect) circuit between the striatum and the basal ganglia output nuclei. These differences in axonal trajectory are

paralleled by differences in dendritic anatomy that result in iSPNs being more responsive to intrasomatic current injection than dSPNs (Fujiyama et al. 2011; Gertler et al. 2008). In addition, although both types of SPN co-express M1 and M4 mAChRs, the latter is less abundant in iSPNs than in dSPNs (Bernard et al. 1992; Yan et al. 2001).

Understanding the actions of mAChRs requires some context about SPNs physiology. Both types of SPN have a similar core physiological phenotype. At rest, SPNs are dominated by dendritically positioned, inwardly rectifying, Kir2 K^+ channels that hold the membrane potential near the K^+ equilibrium potential (~−90 mV), far from spike threshold (Mermelstein et al. 1998; Shen et al. 2007; Wilson 1993). This is the so-called down-state (Stern et al. 1998; Wilson and Groves 1981). Synaptic release of glutamate on spine heads can produce a localized depolarization of sufficient magnitude to open voltage-dependent Ca^{2+} channels (Carter and Sabatini 2004). However, if this input lacks spatial or temporal convergence, the constitutively open Kir2 K^+ channels shunt this synaptic current, minimizing the somatodendritic depolarization it produces. Kv4 and Ca^{2+} activated, small conductance K^+ (SK) channels might contribute to this shunting (Day et al. 2008; Higley et al. 2009). On the other hand, if synaptic activity is convergent, the inward currents generated can overwhelm those of the Kir2 K^+ channels, causing them to block as Mg^{2+} and polyamines are swept from the cytoplasm into their pore (Lopatin and Nichols 1996; Wilson and Kawaguchi 1996). Although the battle between synaptically generated currents and Kir2 K^+ channels has been thought to be largely independent of postsynaptic boosting by voltage-dependent channels (Wilson and Kawaguchi 1996), more recent studies have found that in distal dendrites, spatially convergent synaptic input can recruit low threshold Cav3 Ca^{2+} channels and NMDA receptors to produce a regenerative event (Plotkin et al. 2011).

Closure of dendritic Kir2 K^+ channels leads to an elevation of the input impedance of SPN dendrites and a reduction in their electrotonic length (Day et al. 2008; Wilson 1993). With this transition, the SPN *somatic* membrane can reach a potential near spike threshold. Membrane potential transitions to near spike threshold seen in recordings from SPNs in vivo are called an up-state (Stern et al. 1998; Wilson and Groves 1981). Up-states can last hundreds of milliseconds, during which SPNs spike. The voltage trajectory to spike threshold is influenced by slowly inactivating Kv1 and Kv7 (KCNQ) K^+ channels that appear to be localized largely in the somata and axon initial segment (AIS) (Nisenbaum et al. 1994; Shen et al. 2004, 2005). Voltage-dependent Nav1 Na^+ channels and Kv4 K^+ channels also help shape this trajectory (Akins et al. 1990; Carrillo-Reid et al. 2009; Tkatch et al. 2000). During the spike, high-voltage-activated Cav2 Ca^{2+} channels open, leading to activation of SK K^+ channels, which regulate – in concert with Kv1 and Kv7 channels – the relatively slow, modestly adapting discharge of SPNs (Galarraga et al. 2007).

Activation of postsynaptic M1 mAChRs leads to a beautifully coordinated modulation of these channels, resulting in a sustained elevation in the responsiveness to synaptic release of glutamate without modulating the function

of glutamate receptors themselves. In dendrites, M1 receptor activation diminishes the open probability of both Kv4 and Kir2 K^+ channels, increasing input resistance and producing a modest depolarization (Akins et al. 1990; Figueroa et al. 2002; Hsu et al. 1996; Shen et al. 2007). The Kv4 channel modulation is attributable to signaling mechanisms that have been characterized in pyramidal neurons (Hoffman and Johnston 1998). The Kir2 modulation is mediated by depletion of membrane phosphatidylinositol 4,5-bisphosphate (PIP2) by activation of PLC. This modulation is stronger in iSPNs than dSPNs, possibly as a consequence of expression of Kir2 subunits that are more sensitive to fluctuations in membrane PIP2 concentration (Shen et al. 2007). Complementing this dendritic modulation, M1 signaling reduces opening of Kv7 K^+ channels (also likely to be through a PIP2-dependent mechanism) and reduces Cav2 Ca^{2+} channel opening (through a PKC-dependent mechanism), leading to reduced SK K^+ channel opening (Howe and Surmeier 1995; Shen et al. 2005; Vilchis et al. 2000). In addition, M1 receptor signaling enhances the persistent component of the Nav1 Na^+ channel opening (Carrillo-Reid et al. 2009). Thus, by modulating ion channels in both dendritic and somatic compartments, SPNs become transiently more likely to spike repetitively in response to a synaptic barrage from cortical pyramidal neurons.

If one considers then how the release of ACh modulates the corticostriatal microcircuit as a unit, there appears to be a paradox. ACh inhibits presynaptic glutamate release, but potentiates the postsynaptic response to glutamate without changing glutamate receptors themselves (Higley et al. 2009). This paradox is more apparent than real. First, presynaptic "inhibition" preferentially reduces glutamate release to a single action potential; when a burst of action potentials reach the terminal, the effect on glutamate release is much less affected and is enhanced in some circumstances; that is, the reduction in release probability is largely overcome with repetitive spiking. As a consequence, presynaptic inhibition can be viewed as a means of tuning synapses to repetitive stimulation (rather than simply being inhibited). At the same time, the postsynaptic membrane has been modulated to be more responsive to repetitive synaptic input. Thus, cholinergic interneurons serve to bias the corticostriatal circuitry toward a preferential responsiveness to bursts of cortical activity.

It is also important to consider the other mode of cholinergic interneuron spiking. In response to salient stimuli, interneurons will interrupt their tonic, low frequency spiking with a burst of spikes followed by a pause in activity that can last for a second (Aosaki et al. 1994; Apicella et al. 1997; Kimura et al. 1984; Raz et al. 1996). This burst–pause pattern can be evoked by stimulation of thalamic axons in a pattern like that evoked by salient stimuli (Ding et al. 2010). The burst of ACh release produced by this pattern results in a strong, rapid presynaptic modulation that is over in less than a hundred milliseconds, as it relies upon M2-class receptor, membrane delimited G-protein signaling. In contrast, the postsynaptic effects of M1 receptor signaling are slow, because they rely upon membrane enzymes and soluble second messengers; this modulation appears to last about a second – the duration of the thalamically evoked pause. In this situation, the pre- and postsynaptic modulations are largely separated in time. In this way, the thalamically

generated burst–pause pattern of interneuron activity might serve to reset the corticostriatal circuit (allowing a reassessment of ongoing action selection) and then preferentially enhance the responsiveness in iSPNs that are responsible for action suppression.

Within the context of this response, the recently described disynaptic linkage between cholinergic interneurons and SPNs through an undefined GABAergic interneuron makes some sense (Witten et al. 2010). This nicotinic receptor-mediated activation of GABAergic interneurons also links cholinergic interneurons (Sullivan et al. 2008). The identity of the GABAergic interneurons participating in this network remains to be determined, but a likely candidate is the parvalbumin, fast-spiking interneuron (Koos and Tepper 2002). Acting through this network, transient elevation in the spiking of cholinergic interneurons will shut down SPNs at the same time that M2-class receptors are inhibiting their excitatory glutamatergic input.

Although ACh has an important role in modulating the moment-to-moment activity of the corticostriatal network, it also has important part to play in regulating long-term changes in synaptic strength. The best studied form of plasticity in the striatum is long-term depression (LTD) at corticostriatal synapses onto SPNs. Unlike the situation at many other synapses, striatal LTD induction requires pairing of postsynaptic depolarization with moderate- to high-frequency afferent stimulation at physiological temperatures (Kreitzer and Malenka 2005; Lovinger et al. 1993). Typically for the induction to be successful, postsynaptic L-type calcium channels and mGluR5 receptors need to be co-activated. Both L-type calcium channels and mGluR5 receptors are found near glutamatergic synapses on SPN spines, making them capable of responding to local synaptic events (Carter and Sabatini 2004; Carter et al. 2007; Day et al. 2006; Olson et al. 2005; Testa et al. 1994). The induction of LTD requires the postsynaptic generation of endocannabinoids (ECs) (Gerdeman et al. 2002). ECs diffuse retrogradely to activate presynaptic CB1 receptors and decrease glutamate release probability. Ongoing work suggests that both of the abundant striatal ECs, anandamide and 2-arachidonylglycerol (2-AG), are involved in SPN signaling (Gao et al. 2010; Giuffrida et al. 1999; Lerner et al. 2010; Tanimura et al. 2010). A key question about the induction of striatal LTD is whether activation of D_2 receptors is necessary. Activation of D_2 receptors is a potent stimulus for anandamide production (Giuffrida et al. 1999). Studies have consistently found that in iSPNs, D_2 receptor activation is necessary (Kreitzer and Malenka 2007; Shen et al. 2008; Wang et al. 2006). This could be due to the need to suppress A2a adenosine receptor signaling impeding efficient EC synthesis and LTD induction (Fuxe et al. 2007; Shen et al. 2008). Indeed, Lerner et al. (2010) demonstrate quite convincingly that antagonism of A2a receptors promotes EC-dependent LTD induction in iSPNs.

The question then is can EC-dependent LTD be induced in dSPNs that do not express D_2 receptors? When a minimal local stimulation paradigm is used, LTD does not appear to be induced in these SPNs (Kreitzer and Malenka 2007; Shen et al. 2008). However, using macroelectrode stimulation, EC-dependent LTD is readily inducible in identified dSPNs (Wang et al. 2006), consistent with the high

probability of SPN induction seen in previous work (Calabresi et al. 2007). How could induction of LTD in dSPNs be dependent upon D_2 receptors? There are a couple of possibilities. One is that D_2 receptor stimulation reduces DA release through a presynaptic mechanism, preferentially reducing stimulation of D_1 receptors that oppose the induction of LTD in dSPNs (Shen et al. 2008). The other possibility is that for LTD to be induced in dSPNs, ACh release and postsynaptic M1 muscarinic receptor signaling must fall (Calabresi et al. 2007; Wang et al. 2006). D_2 receptor stimulation slows the autonomous spiking of cholinergic interneurons and also inhibits ACh release (Aosaki et al. 1998; Deng et al. 2007; Maurice et al. 2004). Tozzi et al. (2011) have put this latter possibility on firm experimental ground showing that decreasing ACh release and M1 receptor signaling is critical to the reduction of corticostriatal glutamatergic transmission in *both* dSPNs and iSPNs. They also show that the interaction between D_2 and A2a receptors is critical to the regulation of interneuron activity, particularly in parkinsonian states.

Long-term potentiation (LTP) at glutamatergic synapses is less well characterized because it is more difficult to induce in the in vitro preparations typically used to study plasticity. Most of the work describing LTP at glutamatergic synapses has been done with sharp electrodes (either in vivo or in vitro), not with patch clamp electrodes in brain slices that afford greater experimental control and definition of the cellular and molecular determinants of induction. Previous studies have argued that LTP induced in SPNs by pairing HFS of glutamatergic inputs and postsynaptic depolarization depends upon co-activation of M1, D_1, NMDA, and TrkB receptors (Calabresi et al. 2007; Jia et al. 2010; Kerr and Wickens 2001). The involvement of NMDA receptors in LTP induction is clear. The involvement of TrkB receptors and its ligand, brain-derived neurotrophic factor (BDNF), is less well characterized but plausible given the expression of TrkB receptors in both classes of SPN (Lobo et al. 2010). However, the necessity of D_1 receptors is another matter. Although D_1 receptors appear to play an obligatory role in dSPNs, in iSPNs A2a receptor activation, not D_1 receptor activation, is necessary (Shen et al. 2008). The role of M2 and M1 receptors in LTP induction needs more study. Antagonism of M2 receptors appears to promote LTP induction, either by enhancing glutamate or ACh release (Calabresi et al. 1998a, 1999). On the other hand, Calabresi et al. (1999) have suggested that M1 receptors are necessary for LTP induction in SPNs. Although plausible, more mechanistic studies in identified neurons need to be conducted, particularly in light of the apparent lack of M1 receptor effect on postsynaptic glutamate receptors (Higley et al. 2009). If M1 receptors are critical to LTP induction, it would suggest that cholinergic interneurons are full partners with dopaminergic neurons in the regulation of synaptic plasticity with the corticostriatal circuit. In this scenario, bidirectionality of plasticity is dependent not only upon differential expression of dopamine and adenosine receptors in SPNs (Shen et al. 2008), but also by the co-expression of adenosine and dopamine receptors in cholinergic interneurons.

For the sake of completeness, another component of the corticostriatal circuitry needs to be considered. SPNs have a richly branching recurrent axon collateral that

arborizes in the neighborhood of its parent cell body (Fujiyama et al. 2011; Kawaguchi et al. 1989). This feedback could provide the substrate for lateral inhibition (Groves 1983) and has figured prominently in several models of striatal processing (Beiser et al. 1997). However, the functional significance of this feedback circuit has been controversial. In large measure, this is because the synapses formed by recurrent collaterals are onto distal dendrites (Bolam et al. 1983; Wilson and Groves 1980), making their physiological effects difficult to see with a somatic electrode (Jaeger et al. 1994). Using paired patch clamp recordings from neighboring SPNs, it has been possible to more reliably see the effects of collateral activation (Czubayko and Plenz 2002; Guzman et al. 2003; Koos et al. 2004; Taverna et al. 2008; Tunstall et al. 2002), but the percentage of synaptically connected neighbors has been small (~10–15%) in randomly selected SPNs in brain slices. Using D_1 and D_2 BAC transgenic mice to direct sampling, it was found that although iSPNs project to both themselves and dSPNs, dSPNs connect essentially only with other dSPNs (Taverna et al. 2008). The percentage of SPNs showing demonstrable connectivity doubled when sampling was not random. More recent work using optogenetic approaches to activate SPNs has inferred an even higher degree of connectivity (Chuhma et al. 2011). Whether these approaches will yield a pattern of connectivity consistent with that inferred from paired recordings remains to be determined. It is very likely that these connections are modulated by ACh and mAChR signaling, but this has yet to be definitively determined.

3.2 The Feed-Forward Thalamostriatal Circuit

The other major glutamatergic projection to the striatum originates in the thalamus (Smith et al. 2004). This input targets both direct and iSPNs (Ding et al. 2008; Doig et al. 2010). The synapses formed by this projection are found both on dendritic shafts and spine heads, in the same regions as those formed by the corticostriatal projection. In contrast to the corticostriatal synapses, those formed by thalamic axons have a high release probability, making them well suited to signaling transient events (Ding et al. 2008). Another major target of this projection is the cholinergic interneuron. Like the corticostriatal feed-forward circuit involving FS interneurons, the thalamostriatal projection makes a feed-forward connection to SPNs through cholinergic interneurons (Ding et al. 2010). There appear to be two phases to this feed-forward system. The first phase is a rapid and transient inhibition of cortically driven activity in SPNs. This is mediated by a presynaptic, M2/M4 receptor-dependent inhibition of glutamate release (Ding et al. 2010) and a postsynaptic, GABAergic inhibition (Witten et al. 2010). Whether this GABAergic inhibition relies upon nicotinic receptor activation of PV GABAergic interneurons remains to be determined (Koos and Tepper 2002; Sullivan et al. 2008). The second phase is mediated by postsynaptic M1 receptors that enhance the somatic excitability of both SPNs (Perez-Rosello et al. 2005; Pisani et al. 2007), but preferentially enhances the dendritic excitability of iSPNs by decreasing Kir2 K^+

channel opening (Shen et al. 2007). With a burst of thalamic activity like that seen after presentation of a salient stimulus, cholinergic interneurons exhibit a burst–pause pattern of activity that engage both phases of the response, but because the inhibitory effects are fast (milliseconds in duration) and the postsynaptic effects are slow (hundreds of milliseconds), the two modulations do not conflict and lead to a patterned change in SPN activity that could underlie the alerting response.

There also is a feedback component of this microcircuit that is mediated by mAChRs on cholinergic interneurons themselves. Cholinergic interneurons express M1, M2, and M4 receptors (Alcantara et al. 2001; Hersch et al. 1994; Yan and Surmeier 1996). Application of muscarinic agonists can silence cholinergic interneurons, and focal stimulation of the slice can induce what has been described as muscarinic inhibitory postsynaptic potential (IPSP) in these neurons. Both these effects are mediated by postsynaptic M2-class receptors (Bonsi et al. 2008; Calabresi et al. 1998b). Activation of the M2-class receptors downregulates Cav2.1 and Cav2.2 channels in cholinergic interneurons (Yan and Surmeier 1996). Because $Ca_V2.2$ channels activate the SK channels that determine the size of the AHP in these neurons (Goldberg and Wilson 2005), activation of mAChRs reduces AHPs and induces irregular discharge (Ding et al. 2006). This mechanism complements the collateral inhibition mediated by GABAergic interneurons (Sullivan et al. 2008), suggesting that the temporal pattern of activity of cholinergic interneurons is a meaningful network parameter.

3.3 The Feed-Forward Corticostriatal Circuit

Fast-spiking (FS), PV GABAergic interneurons receive a prominent glutamatergic input from cortical pyramidal neurons and, in turn, convey this activity through perisomatic synapses to both dSPNs and iSPNs (Bennett and Bolam 1994; Gittis et al. 2010; Kita 1993; Koos and Tepper 1999; Planert et al. 2010). This feed-forward inhibition is thought to contribute to action selection by suppressing SPN activity in circuits associated with unwanted actions (Gage et al. 2010; Kita et al. 1990; Parthasarathy and Graybiel 1997). Activation of M1 or M4 mAChRs inhibits this synapse – a fact which is puzzling given the potent excitatory impact of nAChRs on the FS interneurons (Barral et al. 1999; Koos and Tepper 2002). Conceptually, this can be resolved by noting that the presynaptic inhibition of GABA release is dependent upon postsynaptic M1 mAChRs that trigger the release of ECs (Narushima et al. 2007). Hence, this mechanism complements the M1-mAChR-mediated modulation of postsynaptic ion channels described earlier that serve to increase SPN excitability. Although both types of SPN are targeted in this circuit, paired recordings in BAC mice have found some preferential connectivity of FS interneurons with dSPNs (Gittis et al. 2010). Whether the M1 mAChR-mediated modulation of FS interneuron synapses is stronger in dSPNs is unclear.

Somatostatin (SOM)/neuropeptide Y (NPY) expressing GABAergic interneurons also form another, less well studied, part of the feed-forward corticostriatal

circuit (Tepper et al. 2010). If these interneurons are like the SOM expressing, Martinotti interneurons of cortex (Wang et al. 2004), their innervation of distal dendrites could make it difficult to accurately judge their importance (Gittis et al. 2010), as with SPN recurrent collaterals. Whether this component of feed-forward circuit differentially controls dSPNs and iSPNs remains to be determined. These interneurons express M3 (M1 class) receptors with their strongest expression being on axon terminals innervating SPNs (Hersch et al. 1994).

4 Muscarinic Signaling in Parkinson's Disease and Dystonia

In Parkinson's disease, striatal DA levels fall as the dopaminergic neurons in the substantia nigra pars compacta (SNc) die. A concomitant of this fall is a rise in striatal cholinergic signaling (Barbeau 1962; DeBoer et al. 1996; Lehmann and Langer 1983; McGeer et al. 1961). This rise is thought to be in large measure responsible for the symptoms of the disease and has motivated the use of mAChR antagonists in the treatment of PD (Lang and Blair 1989; Pisani et al. 2007; Wooten 1990). The elevation in cholinergic signaling is attributable to the loss of negative modulation of interneuron spiking and transmitter release by D_2 dopamine receptors (Aosaki et al. 1998; DeBoer et al. 1996; Maurice et al. 2004; Pisani et al. 2007). In addition, DA depletion triggers an up-regulation in the expression of RGS4 in cholinergic interneurons, resulting in an attenuation of M2-class autoreceptor signaling and enhanced ACh release (Ding et al. 2006; Dolezal and Wecker 1990).

DA depletion and the elevation in cholinergic signaling in PD models have a variety of effects on the striatal circuitry. One dramatic effect is the pruning of iSPN spines and glutamatergic synapses (Day et al. 2006; McNeill et al. 1988). This remodeling requires calcium influx through L-type Ca^{2+} channels that are located near synapses, as it is dramatically reduced in Cav 1.3 KO mice or in wild-type mice treated with L-type channel antagonists (Day et al. 2006; Olson et al. 2005). It is easy to imagine that this structural adaptation is homeostatic (Turrigiano et al. 1998). The loss of inhibitory D_2 receptor signaling and the elevation of excitatory M_1 receptors signaling should drive spiking above the neuronal set point, leading to pruning. Indeed, genetic deletion of M_1 receptors significantly attenuates loss of glutamatergic synapses following DA depletion (Shen et al. 2007). In agreement with a homeostatic model, iSPN pruning can be blunted in vitro by inhibiting calcineurin activity or knocking down the transcriptional regulator MEF2 (Tian et al. 2010). Underscoring the importance of M1 mAChRs in PD, Tozzi et al. (2011) have recently shown that following DA depletion, cholinergic interneurons become more sensitive to inhibition by D_2 receptor signaling and that this shift is likely to be responsible for the enhanced ability of D_2 receptor agonists to inhibit corticostriatal synapses on SPNs.

Another major motor disorder with cholinergic determinants is dystonia. Dystonia, characterized by muscle contraction, involuntary twisting, and abnormal

posture (Fahn 1988), is the third most common movement disorder after PD and essential tremor. DYT1 dystonia, the most common form of early onset generalized dystonia, is a hereditary disorder caused by a deletion in the *dyt1* gene, causing a mutation in the torsinA protein (Ozelius et al. 1997). In a recent series of studies, using a transgenic mouse model of DYT1 expressing mutant torsinA protein, Pisani et al. (2006) found that contrary to the situation in wild-type mice activation of dopamine D2 receptors in mutant mice increased the release of ACh (Pisani et al. 2006; Sciamanna et al. 2009). Additionally, in agreement with the role of M1 receptors in regulating the induction of synaptic plasticity (see above), LTD was lost and LTP enhanced at corticostriatal synapses in mutant mice. Plasticity could be normalized by antagonizing M1 mAChRs (Martella et al. 2009). These studies suggest that mAChR antagonists should be an effective therapy for dystonia and support the notion that dystonia is a muscarinic "disinhibition" disorder (Defazio et al. 2007).

5 Summary

Striatal cholinergic interneurons are pivotal modulators of the striatal circuitry in action selection and decision making. In this chapter, we have described the presynaptic actions of M_2 receptor and postsynaptic actions of M_1 receptor on SPNs and cholinergic interneurons. Recent studies have highlighted the roles of these receptors in synaptic integration and plasticity, and how they differ between the two populations of SPNs. These studies make it clear that temporally patterned activity in cholinergic interneurons is a major determinant of the response to salient environmental stimuli that serve to direct behavior. Moreover, they underscore the need to revisit the clinical potential of anticholinergic therapies for treating movement disorders such as dystonia and Parkinson's disease.

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