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Striatal cholinergic interneurons and Parkinson's disease

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Abstract

Giant, aspiny cholinergic interneurons (ChIs) have long been known to be key nodes in the striatal circuitry controlling goal directed actions and habits. In recent years, new experimental approaches, like optogenetics and monosynaptic rabies virus mapping, have expanded our understanding of how ChIs contribute to the striatal activity underlying action selection and the interplay of dopaminergic and cholinergic signaling. These approaches also have begun to reveal how ChI function is distorted in disease states affecting the basal ganglia, like Parkinson's disease (PD). This review gives a brief overview of our current understanding of the functional role played by ChIs in striatal physiology and how this changes in PD. The translational implications of these discoveries, as well as the gaps that remain to be bridged, are discussed as well.

Graphical abstract

Cholinergic interneurons (ChIs) play an important role in regulating the striatal circuit. In addition to integrating cortical and thalamic glutamatergic input, ChIs integrate intrastriatal GABAergic signals and neuromodulatory signals, including those from dopaminergic neurons. The output of ChIs modulates nearly all striatal cell types through a mixture of muscarinic and nicotinic receptors.

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Introduction

The striatum has long been known to be a hotbed of cholinergic signaling as its expression of acetylcholine (ACh) and proteins necessary for its synthesis and degradation are among the highest in the brain; moreover, it was recognized early on that this signaling was largely attributable to giant, aspiny interneurons (Lehmann & Langer, 1983). Although the exclusivity of cholinergic interneurons (ChIs) in this regard has been challenged (Dautan *et al.*, 2014), there is no denying of the importance of ChIs to striatal function.

One of the enduring themes in the ChIs story is the interplay between cholinergic and dopaminergic signaling. Early clinical observation led to the hypothesis that these two signaling systems had to be in ‘balance’ for the striatum to function normally in movement control (McGeer *et al.*, 1961; Barbeau, 1962). In PD, which is characterized by loss of dopaminergic signaling, this ‘balance’ was partially restored with anti-cholinergic drugs, alleviating symptoms (McGeer *et al.*, 1961; Barbeau, 1962). With the advent of levodopa therapy, the use of anti-cholinergic drugs has waned because of their side-effect profile, but Barbeau’s ‘seesaw’ remains a conceptual cornerstone of our thinking about striatal function (even if it is not acknowledged) (Surmeier & Graybiel, 2012). Although there is a great deal of experimental support for the idea that dopamine (DA) and ACh exert opposing effects on striatal circuitry, there also is evidence that they work in concert with one another to create temporal patterns of activity in the striatum that are important for proper movement (and thought) control. The basis for the interaction between DA and ACh and how that interaction controls the pattern of striatal activity, particularly in ChIs and principal spiny projection neurons (SPNs) is the main subject of this review. There are a number of excellent reviews that complement or elaborate the topics broached here (Zhou *et al.*, 2002; Pisani *et al.*, 2007; Bonsi *et al.*, 2011; Schulz & Reynolds, 2013; Lim *et al.*, 2014).

Intrinsic determinants of ChIs activity

The spiking of ChIs – and their influence on striatal circuitry – is governed by both cell autonomous and synaptic (non-cell autonomous) factors. In the presence of antagonists of ionotropic glutamate and GABA, muscarinic or dopaminergic receptors, ChIs spike regularly at a rate between 2 and 10 Hz at near physiological temperatures (Bennett & Wilson, 1999; Bennett *et al.*, 2000). Acutely isolated ChIs, where all synaptic input has been disrupted, also spike in a regular fashion (Maurice *et al.*, 2004), much like that seen in ex vivo brain slices. Hence, ChIs are autonomous pacemakers.

The mechanisms underlying autonomous pacemaking are reasonably well understood. The depolarizing phase of the pacemaking cycle is controlled by a mixture of hyperpolarization and cyclic nucleotide activated cation (HCN) channels, voltage dependent Nav1 Na⁺ channels and Kir2, Kv1 and Kv4 K⁺ channels (Song *et al.*, 1998; Bennett *et al.*, 2000; Hattori *et al.*, 2003; Maurice *et al.*, 2004; Wilson, 2005; Tubert *et al.*, 2016). Ca²⁺ entry through Cav2 Ca²⁺ channels during the spike activates large (BK) and small conductance (SK) K⁺ channels that shape spike width and spike patterning (Bennett *et al.*, 2000; Goldberg & Wilson, 2005). Another slower Ca²⁺-dependent K⁺ channel mediates the slow-after-hyperpolarization (sAHP) that is seen after a burst of spikes (Wilson & Goldberg, 2006). The molecular composition of the channel has not been discovered yet, but it has been shown that Cav1 Ca²⁺ channels are likely to be responsible, at least in part, for the Ca²⁺ currents that activate these channels (Sanchez *et al.*, 2011). Unexpectedly, Kv1 K⁺ channels also contribute to the sAHP in ChIs (Tubert *et al.*, 2016).

This combination of intrinsic conductances interacts to generate regular, irregular or bursting spike patterns (Sanchez *et al.*, 2011). The regular and bursting patterns are mutually exclusive, and depend upon whether SK or sAHP conductances are dominant (Goldberg & Wilson, 2005). The relative engagement of these two groups may depend upon dendritic Ca²⁺ dynamics (Markram *et al.*, 1998), but it remains to be resolved experimentally.

The same channels that govern the autonomous spiking of ChIs also control spiking during somatic current injection, which is intended to mimic dendritic currents arising from excitatory synaptic input. Blocking SK channels accelerates spike rate (Sanchez *et al.*, 2011), whereas blocking HCN channels slows spiking (Zhao *et al.*, 2016). Spike frequency accommodation during more sustained or stronger current injection has been studied less, but the available data suggests that it depends upon the same channels that mediate the sAHP, as blocking Kv1 channels attenuates accommodation (Peng *et al.*, 2011; Sanchez *et al.*, 2011; Tubert *et al.*, 2016).

Extrinsic determinants of ChIs activity

There are two major extrinsic determinants of ChIs activity. One is neuromodulatory, arising from the release of neurotransmitters that activate G-protein coupled receptors (GPCRs). GPCRs and their intracellular signaling cascades covalently or allosterically modify channels and their gating, altering pacemaking and conventional synaptic transmission in a variety of ways. The list of neuromodulators shaping ChIs activity is a long one (Lim *et al.*,

2014). But from the standpoint of PD, the modulatory effects of DA are ostensibly the most important; they also are the best studied. The axons of substantia nigra pars compacta (SNc) dopaminergic neurons broadly arborize within the striatum, providing a rich source of DA signaling to ChIs (Moss & Bolam, 2008; Matsuda *et al.*, 2009). ChIs co-express D2 and D5 DA receptors (Dawson *et al.*, 1988; Bergson *et al.*, 1995; Yan *et al.*, 1997; Centonze *et al.*, 2003). D2 receptors (D2Rs) signal through Gi proteins to inhibit adenylyl cyclase (AC) and voltage-dependent Cav2 Ca²⁺ channels in many cell types. In ChIs, D2Rs inhibit Cav2 channel currents through a membrane delimited pathway that is controlled by regulator of G protein signaling 9 (RGS9) (Yan *et al.*, 1997; Cabrera-Vera *et al.*, 2004). This signaling pathway is most clearly manifested in the ability of D2Rs to suppress ACh release (Yan *et al.*, 1997). D2Rs also stimulate phospholipase C and protein kinase C through a non-canonical pathway to promote phosphorylation and inactivation of voltage-dependent Nav1 Na⁺ channels, slowing or stopping on-going pacemaking (Carr *et al.*, 2003; Maurice *et al.*, 2004). D2Rs also reduce the amplitude of HCN currents driving pacemaking, presumably by reducing cyclic adenosine monophosphate (cAMP), which allosterically enhances HCN gating (Deng *et al.*, 2007).

The effects of D5 receptors (D5Rs) signaling are less clear-cut. In acutely isolated ChIs, D5Rs signaling through AC and protein kinase A increases zinc-sensitive GABA_A receptors currents (Yan & Surmeier, 1997); these GABA_A receptors are nominally extra-synaptic, but this inference has not been tested. D5Rs signaling enhances a sAHP in ChIs, slowing pacemaking (Bennett & Wilson, 1998). However, D5Rs also have been implicated in long-term potentiation (LTP) of glutamatergic synapses (Suzuki *et al.*, 2001; Oswald *et al.*, 2015).

Taken together, it appears that D2/D5Rs activation slows pacemaking and blunts ACh release. This inference is consistent with studies examining the effects of activity evoked DA release on ChIs (Ding *et al.*, 2010; Chuhma *et al.*, 2014). The discrepancy between these studies and those using bath application of D1 receptors (D1Rs) agonists (Aosaki *et al.*, 1998; Centonze *et al.*, 2003; Ding *et al.*, 2011) remains to be resolved, but could stem from bath application enhancing the release of tachykinins by direct pathway SPNs (dSPNs); tachykinins excite ChIs by activating neurokinin 1 (NK1) receptors (Aosaki & Kawaguchi, 1996; Bell *et al.*, 1998; Richardson *et al.*, 2000; Govindaiah *et al.*, 2010).

There are a wide variety of other GPCRs that modulate ChI activity but a summary of their effects is beyond the scope of this review. The reader is referred to an excellent recent review on this topic (Lim *et al.*, 2014).

The other extrinsic determinant of ChIs activity is classical, fast synaptic transmission mediated by ionotropic glutamate and GABA receptors. ChI glutamatergic synapses have long been thought to be primarily of thalamic origin, contrasting ChIs from SPNs (Berendse & Groenewegen, 1990; Lapper & Bolam, 1992; Thomas *et al.*, 2000). Neurons in the intralaminar parafascicular nucleus (PF) of the thalamus richly innervate the proximal dendrites of ChIs, providing a potent synaptic control of spiking (Lapper & Bolam, 1992; Bernard *et al.*, 1997; Ding *et al.*, 2010; Doig *et al.*, 2014). However, the relative importance of the thalamus in controlling ChIs is being challenged by recent work using a novel monosynaptic rabies virus (msRV) approach (Wall *et al.*, 2010; Guo *et al.*, 2015). Although

there are caveats to the quantitation and the functional interpretation of these studies, the work by Guo et al. suggests that the cortical glutamatergic innervation of ChIs is considerably stronger and more diverse than previously thought, outnumbering that of the thalamus by nearly a factor of three. For example, the cingulate cortex appears to provide a rich innervation of ChIs (Guo *et al.*, 2015). This makes excellent functional sense given the role of this cortical region (and ChIs) in set-shifting or re-evaluation of internally directed actions (Walton *et al.*, 2007; Aoki *et al.*, 2015). Moreover, recent optogenetic studies have shown that cortical neurons can clearly regulate ChIs activity and induce patterns of activity resembling those seen *in vivo* (Doig *et al.*, 2014; Kosillo *et al.*, 2016; Tanimura *et al.*, 2016). Nevertheless, much remains to be done. The number, strength, subcellular distribution and receptor complement of this diverse array of ChIs connections remains to be explored. The unusual kainate (Wisden & Seeburg, 1993) and NMDA receptors (Landwehrmeyer *et al.*, 1995; Standaert *et al.*, 1999) expressed by ChIs are also ripe for study.

Another interesting implication of the msRV work by Guo et al. is the suggestion that the majority (> half) of ChI synapses are of striatal origin, arising from GABAergic principal SPNs and interneurons. While both anatomical and physiological studies support the proposition that SPNs and interneurons synapse on ChIs (Sullivan *et al.*, 2008; Chuhma *et al.*, 2011; English *et al.*, 2011; Gonzales *et al.*, 2013), the magnitude of this connection has been under appreciated. As with the glutamate receptors, there have not been any systematic attempts to correlate the type and function of ChI GABA_A synapses with their molecular architecture (Yan & Surmeier, 1997)

Another hot topic in the field is the mechanisms responsible for the burst-pause or pause pattern of spiking seen in presumptive ChIs (tonically active neurons or TANs) *in vivo* following presentation of a reward or a reward associated cue (Schulz & Reynolds, 2013). The issue is whether the pause is generated by dopaminergic suppression of intrinsic mechanisms underlying ChIs spiking or whether it is generated by GABAergic inhibition. As concluded by Schulz et al., it is highly likely that there are both synaptic and intrinsic mechanisms involved; perhaps these mechanisms shift with learning (Schulz & Reynolds, 2013). In the initial stages of learning, DA is released at the time of the ChIs pause, making it potentially responsible. But with time this DA signal wanes; yet, the ChI response is retained, perhaps because DA has altered the ability of striatal GABAergic interneurons to suppress spiking. Of course, it is possible that this learned signal has nothing to do with the striatum per se but is pallidal in origin (Gittis *et al.*, 2014).

ChIs regulation of striatal circuitry and SPNs

ChIs have a massive axonal arborization with as many as half a million vesicular release sites (Bolam *et al.*, 1984; Contant *et al.*, 1996), rivaling SNc DA axons. Functionally, the release of ACh controls the striatal circuitry through both presynaptic and postsynaptic mechanisms involving the activation of nicotinic ACh receptors (nAChRs) and muscarinic ACh receptors (mAChRs) (Schoffelman *et al.*, 1986; Yan & Surmeier, 1996; Bernard *et al.*, 1998; Alcantara *et al.*, 2001; Ding *et al.*, 2006).

Modulation of extrinsic and intrinsic presynaptic terminals by ACh

For almost two decades it has been known that ACh modulates the release of glutamate from presynaptic terminals in striatum. As there are no glutamatergic neurons within the striatum, this innervation arises from extrinsic sites (see above). mAChRs localized on presynaptic terminals reduce the probability of glutamate release (Malenka & Kocsis, 1988; Barral *et al.*, 1999; Higley *et al.*, 2009). Accordingly, increasing ChIs firing rate reduces excitatory transmission onto SPNs (Pakhotin & Bracci, 2007; Ding *et al.*, 2010; Pancani *et al.*, 2014). This same modulatory mechanism reduces glutamate release onto ChIs (Pakhotin & Bracci, 2007).

Although M2 and M4 mAChRs, both of which are $G_{i/o}$ -coupled and could mediate presynaptic inhibition, are found in the striatum, it remains uncertain which of them control glutamate release (Hersch *et al.*, 1994; Levey *et al.*, 1994; Hersch & Levey, 1995). Early reports attributed the presynaptic inhibition of corticostriatal glutamate release to M2 mAChRs (Smolders *et al.*, 1997; Calabresi *et al.*, 1998). However, there also was some suggestion that M3 mAChRs were involved (Sugita *et al.*, 1991; Hsu *et al.*, 1995). More recently, work with subtype specific mAChR knockout mice and selective allosteric modulators has implicated M4 mAChRs in regulating corticostriatal glutamate release (Pancani *et al.*, 2014).

There are several caveats of these studies that should be recognized. First, the glutamatergic synapses formed on ChIs are heterogeneous in origin, raising the possibility that both M2 and M4 (and possibly M3) mAChRs are important, but on different types of terminal (Guo *et al.*, 2015). Another important concern is development. Many of the studies done to date have been with juvenile rodents; mAChR expression is developmentally regulated (Bairam *et al.*, 2006; Pancani *et al.*, 2015). This is pertinent to the M4 mAChR regulation of glutamate release, which is prominent in young mice (Pancani *et al.*, 2014), but apparently not in mature mice (Shen *et al.*, 2015). Use of optogenetic tools in bacterial artificial chromosome (BAC)-Cre transgenic mice should allow these issues to be addressed.

There are several reports suggesting that ACh also can enhance glutamate release in the striatum by activating nAChRs. Both biochemical and microdialysis work suggest that presynaptic $\alpha 7$ nAChR enhance glutamate release (Kaiser & Wonnacott, 2000; Campos *et al.*, 2010). Following chronic nicotine treatment, $\alpha 4\beta 2$ nAChRs indirectly modulate glutamate release by enhancing DA release and D2R signaling (Xiao *et al.*, 2009) (see below). But much remains to be done, particularly given the robust expression of non- $\alpha 7$ nAChRs by cortical and thalamic glutamatergic neurons projecting to the striatum (Allen Brain Atlas; www.brain-map.org). If glutamatergic terminals are regulated by both nAChRs and mAChRs, then how can their opposing actions be reconciled? The obvious answer to this question is timing. As noted above, *in vivo* the temporal structure of ChIs spiking appears to be information bearing. Fast nAChRs and slow mAChRs would allow this information to be conveyed to terminals. Of course, it is also possible that nAChRs and mAChRs are on anatomically and functionally distinct glutamatergic terminals.

The other major extrinsic innervation of the striatum known to be controlled by ACh arises from dopaminergic neurons in the mesencephalon. Both mAChRs and nAChRs mediated

modulation of striatal DA release has been examined. Mesencephalic dopaminergic neurons express M5 mAChRs (Liao *et al.*, 1989; Weiner *et al.*, 1990). The discovery of selective allosteric modulators of the M5 mAChRs has moved their study forward. Using fast scan cyclic voltammetry in coronal slices, it was found that activation of M5 mAChRs reduced DA overflow in striatum (Foster *et al.*, 2014). Because M5 mAChRs have been detected on DA neurons and not on other striatal neurons, these effects are presumably mediated by presynaptically localized M5 mAChRs.

But the greatest interest in the last few years has come from the ‘rediscovery’ of presynaptic modulation of DA release by nAChRs. Early pharmacological work had shown that nAChRs promoted striatal DA release (Rapier *et al.*, 1990; Grady *et al.*, 1992; el-Bizri & Clarke, 1994; Soliakov *et al.*, 1995). Indeed, dopaminergic neurons express $\alpha 4$ and $\beta 2$ subunits at high levels, and lower levels of $\alpha 5$ –7, and $\beta 3$ subunits (Clarke & Pert, 1985; Le Novère *et al.*, 1996; Sharples *et al.*, 2000; Jones *et al.*, 2001; Quik *et al.*, 2003; Grady *et al.*, 2007). In contrast with the earlier release studies, work examining phasic DA release using cyclic voltammetry suggested that tonic nAChRs signaling increased the initial release probability of DA following an action potential but limited subsequent DA release during a burst of action potentials; conversely, desensitizing (by applying nicotine at concentrations achieved by smoke) or antagonizing nAChRs increased DA release during burst spiking (Zhou *et al.*, 2001; Rice & Cragg, 2004; Zhang & Sulzer, 2004; Exley & Cragg, 2008). Given that dopaminergic and cholinergic signaling have traditionally been viewed as having opposite effects on striatal function, this made perfectly good sense. While this was easy to link to the tonic activity of ChIs, it was more difficult to relate to the phasic alterations in ChIs activity associated with movement and learning. It was then shown that phasic thalamic stimulation induced a burst-pause response in ChIs and that the pause was dependent upon nAChR-dependent DA release and ChI D2Rs activation (Ding *et al.*, 2010). This suggested that phasic activation of ChIs could induce DA release without action potentials. Using optogenetic methods to synchronously activate ChIs, this inference was confirmed by two groups and shown to depend upon $\alpha 4\beta 2$ nAChRs (Cachope *et al.*, 2012; Threlfell *et al.*, 2012). These observations helped explain older data implicating glutamatergic signaling in nAChR-mediated enhancement of DA release (Cheramy *et al.*, 1996; Garcia-Munoz *et al.*, 1996; Wonnacott *et al.*, 2000); rather than being dependent upon glutamate receptors on dopaminergic terminals (Wang, 1991; Desce *et al.*, 1992), the glutamate dependence arose from the interposition of ChIs.

Nevertheless, these new findings suggest that phasic activity in ChIs could ‘hijack’ dopaminergic terminals to produce phasic alterations in striatal DA release that are completely independent of the activity of parent dopaminergic cell bodies (Surmeier & Graybiel, 2012). As interesting as this possibility is, there are a number of open questions that need to be answered before the physiological significance of the work is clear. One question is the extent to which synchronous activity of ChIs is necessary for release of DA. In the dorsal striatum, it appears that a high degree of synchrony – like that achievable with optogenetic approaches but not necessarily that achievable *in vivo* – is necessary (Threlfell *et al.*, 2012). Ironically, synchrony among ChIs increases in models of PD where dopaminergic axons are lost (Raz *et al.*, 1996); could the synchrony of ChIs in this state be a network attempt to boost flagging DA release? Another obvious question is why synchrony

is necessary at all. Is this an artifact of the uncertain relationship between the assay site (the voltammetry electrode) and the axon of a stimulated ChI? What is needed to answer this question is an optical DA sensor that could be widely distributed in space, perhaps like the false fluorescent transmitters (Sames *et al.*, 2013). Answering these questions should move us closer to an understanding of the interaction between DA and ACh in the striatum.

In spite of the prominence of intrinsic GABAergic synaptic connections in the striatum, relatively little is known about how ACh modulates them. Decades ago it was shown that M2-class mAChRs diminished GABA release from striatal synaptosomes (Marchi *et al.*, 1990). Subsequently, this inference was confirmed by electrophysiological studies (Sugita *et al.*, 1991; Szabo *et al.*, 1998; Koos & Tepper, 2002). What is less clear is whether this presynaptic effect is targeting SPNs or interneurons. Koos *et al.* have shown that the synaptic connection between GABAergic fast-spiking interneurons (FSIs) and SPNs is modulated by presynaptic mAChRs (Koos & Tepper, 2002). Indeed, ChIs form synapses on the synaptic terminals of parvalbumin-positive FSIs (Chang & Kita, 1992). As expected, the receptor mediating this inhibition is of the M2-class (M2, M4) mAChRs (Grilli *et al.*, 2009).

Another GABAergic interneuron in the striatum, the persistent low-threshold spiking (PLTS) interneuron (PLTSI), expresses M2 mAChRs (Bernard *et al.*, 1998), but it remains to be determined how these receptors regulate PLTSI activity or GABA release. The seeming restriction of synaptic terminal M2 mAChRs to those of ChIs (Hersch *et al.*, 1994; Hersch & Levey, 1995), suggest that they do not regulate PLTSI GABA release. However, recent work suggests that PLTSIs and ChIs form a mutually excitatory loop mediated by cholinergic actions on PLTSIs and nitric oxide actions on ChIs (Elghaba *et al.*, 2016).

Yet another class of GABAergic interneuron in the striatum expresses tyrosine hydroxylase (TH) immunoreactivity (THINs) (Tepper *et al.*, 2010). THINs don't release dopamine (Xenias *et al.*, 2015), but are modulated by D1-class GPCRs (Ibanez-Sandoval *et al.*, 2015). More importantly for PD, the synaptic inputs to THINs are up-regulated following lesioning in the DA innervation of the striatum (Unal *et al.*, 2015), suggesting that they make an important contribution to the alteration in striatal circuitry in PD. How ChIs regulate THINs remains to be determined.

Local, recurrent collaterals of GABAergic SPNs are another potential target of ChIs. Both dSPNs and indirect pathway SPNs (iSPNs) express M1 mAChRs and dSPNs express M4 mAChRs (Bernard *et al.*, 1992), which are members of the M2-class of mAChRs known to control GABA and glutamate release (Yan & Surmeier, 1996; Yan *et al.*, 2001). Surprisingly, the data on whether this happens or not is very incomplete. The one piece of data on this point suggests that recurrent collateral synapses are negatively modulated by M1 mAChRs (Perez-Rosello *et al.*, 2005); however, it is far from clear whether this is a direct effect or indirectly mediated by endocannabinoids (eCb) (Oldenburg & Ding, 2011).

Postsynaptic modulation of striatal neurons by ACh

SPNs, unlike striatal interneurons, exclusively respond to ACh through postsynaptic mAChRs, not nAChRs. However, the response of dSPNs and iSPNs is complicated by the fact that the two differentially express M1 and M4 mAChRs (Hersch *et al.*, 1994; Yan *et al.*,

2001). Both express the G_q-linked M1 mAChRs, activation of which leads to modulation of several ion channels, including Kir2, Kv7 (KCNQ), Kv4 K⁺ channels, Cav2 Ca²⁺ channels and Nav1 Na⁺ channels (Howe & Surmeier, 1995; Shen *et al.*, 2005; Shen *et al.*, 2007; Carrillo-Reid *et al.*, 2009; Perez-Ramirez *et al.*, 2015). The functional consequences of these effects remain to be fully explored, in part because the sub-cellular distribution of these channels is not uniform. In iSPNs, where the suppression of Kir2, Kv7 and Kv4 K⁺ channels is strongest, M1 mAChRs signaling increases dendritic excitability, the ability of excitatory synaptic input to summate and to generate a spike (Shen *et al.*, 2007; Day *et al.*, 2008). The M1 mAChRs suppression of Cav2 channels controlling Ca²⁺ activated small conductance K⁺ (SK) channels works in concert (Perez-Burgos *et al.*, 2010; Wang *et al.*, 2014). What is less obvious is how M1 mAChRs mediated reductions in Cav1 channel opening or augmented slow inactivation of Nav1 channels fits into this scenario. It is possible that the modulation of Cav1 channels has less of an effect on electrogenesis, than the generation of signaling molecules linked to synaptic plasticity, like eCb (Wang *et al.*, 2006); in this scenario, M1 mAChRs would blunt eCb-dependent long-term depression (LTD), which would fit with their global enhancement of iSPNs excitability. The modulatory actions of M1 mAChRs in dSPNs are murkier. M1 mAChRs (and their suppression of Cav1 channels) have been implicated in eCb-LTD induction, but their effects of dendritic M1 mAChRs on excitability and integration have yet to be defined.

Signaling by Gi-linked M4 mAChRs, which are present just in dSPNs, also appears to be complicated. M4 mAChRs have been reported to enhance Cav1 Ca²⁺ channel opening and the response to depolarizing somatic current injection (Hernandez-Flores *et al.*, 2015). However, in dendrites near axospinous synapses, M4 mAChRs block D1R activation of AC, promoting LTD and blunting LTP of excitatory, glutamatergic synapses (Shen *et al.*, 2015).

In contrast to SPNs, striatal GABAergic interneurons are robustly activated by nAChRs. Whole cell patch-clamp recordings from SPNs showed that nicotine enhanced GABAergic transmission onto SPNs (de Rover *et al.*, 2002). It was thought that nAChRs -expressing GABA interneurons were activated by ACh, which then enhancing release of GABA onto SPNs. Indeed, optogenetic studies in transgenic mice that allowed identification of different neuronal classes has shown nAChR -mediated activation of FSIs and neurogliaform GABAergic interneurons (English *et al.*, 2011; Faust *et al.*, 2016).

Before concluding this section, it is important to mention that there are non-canonical means by which ChIs have been reported to alter striatal circuitry. In particular, using optogenetic approaches it was shown that ChIs are capable of releasing glutamate (Higley *et al.*, 2011; Nelson *et al.*, 2014). The extent to which glutamate release from ChIs depends upon optogenetic manipulation and the functional consequences of this co-transmission have yet to be determined. It would be extremely valuable to determine if paired neuron recordings between ChIs and SPNs could reproduce co-transmission. It's of some note that the ability of ChIs to activate GABAergic interneurons was completely dependent upon nAChRs and did not have a glutamatergic component (Faust *et al.*, 2016).

ChIs modulation of striatal synaptic plasticity

How cholinergic signaling modulates SPN synaptic plasticity has yet to be definitively worked out. Early work argued that M1 mAChR activation was necessary for the induction of striatal LTP (Calabresi *et al.*, 1999). Several lines of evidence suggest that M1 AChRs also blunt striatal LTD induction (Wang *et al.*, 2006; Bonsi *et al.*, 2008; Tozzi *et al.*, 2011). Precisely how M1 mAChRs might accomplish this endpoint is not clear. One possibility is that M1 mAChRs inhibit Ca^{2+} entry through Cav1 Ca^{2+} channels which are necessary for LTD induction (Wang *et al.*, 2006). Regardless, the dependence of LTD induction in dSPNs (and iSPNs) upon D2R stimulation has been attributed to the need to suppress ACh release and M1R mAChR stimulation (Wang *et al.*, 2006; Tozzi *et al.*, 2011).

One complication in these experiments is they all have relied upon macroelectrode stimulation. However, in experiments using minimal local stimulation (MLS) a different picture has emerged. With this stimulation paradigm, eCb dependent LTD is nominally limited to D2R-expressing iSPNs (Kreitzer & Malenka, 2007; Shen *et al.*, 2008; Nazzaro *et al.*, 2012). LTD induction in iSPNs depends upon postsynaptic D2R activation, which diminishes regulator of G-protein signaling 4 (RGS4)-mediated inhibition of mGluR5-dependent eCb production (Lerner & Kreitzer, 2012). But is eCb-dependent LTD inducible in the other major population of SPNs that do not express D2Rs – the D1R dominated dSPNs? A number of studies using MLS have failed to find LTD in dSPNs (Kreitzer & Malenka, 2007; Shen *et al.*, 2008; Nazzaro *et al.*, 2012). But this failure is attributable to the inadvertent stimulation of dopaminergic fibers by MLS (Threlfell *et al.*, 2012), as antagonism of D1Rs enables a robust eCb-LTD induction in dSPNs with MLS (Shen *et al.*, 2008). More recently, postsynaptic M4R signaling in dSPNs was found to promote LTD induction through suppression of RGS4 – establishing a clear mechanistic parallel to the situation in iSPNs (Lerner & Kreitzer, 2012; Shen *et al.*, 2015).

What remains to be resolved is why there is a difference in the D2R dependence of eCb-LTD induction in dSPNs with macroelectrode stimulation and MLS. It could be that macroelectrode stimulation more effectively activates ChIs. It could also be that this type of stimulation recruits a different population of glutamatergic inputs to SPNs. Optogenetic and chemogenetic approaches that allow much better control over what is stimulated should provide more definitive answers to this question.

ChIs regulation of behavior

What role do ChIs play in behavior? The ability of an organism to shift between different behaviors is critical to “normal” functioning and survival (Balleine & Ostlund, 2007; Hart *et al.*, 2014; Aoki *et al.*, 2015). The two behavioral modes that the striatum is tasked with policing are habit-mediated and goal-directed behaviors; the former is thought to be under control of the dorsolateral striatum (DLS) and the latter, the dorsomedial striatum (DMS) (Aoki *et al.*, 2015). ChIs in both the DLS and DMS are implicated in regulation of this process (Balleine *et al.*, 2007; Hart *et al.*, 2014; Stalnaker *et al.*, 2016). ChIs appear to be important elements in the neural machinery that changes behavior as environmental contingencies change, but not in initial learning of goal-directed behavior. Unilateral

activation of ChIs decreases ongoing locomotion (consistent with the circuitry mechanisms discussed above) as one would expect for initiation of set-shifting (Kondabolu *et al.*, 2016). In the nucleus accumbens (NAc), reinforcement learning can take place in the absence of ChIs, but extinction learning is compromised (Lee *et al.*, 2016). Similarly, in the DMS, lesioning ChIs produces so-called “perseverative” errors, causing difficulty in task-shifting without altering the ability to learn new paradigms (Aoki *et al.*, 2015). Thalamostriatal projections to ChIs help to regulate behavioral switching and attentional set-shifting (Aosaki *et al.*, 1994; Kimura *et al.*, 2004; Brown *et al.*, 2010; Ding *et al.*, 2010; Smith *et al.*, 2011; Bradfield *et al.*, 2013). What is less well understood is how cingulate cortex, which is involved in evaluating the outcomes of actions, complements the PF in shaping ChIs activity to achieve this behavioral endpoint. What also is largely unexplored is how ChIs activity, particularly pauses and bursts, shape the striatal circuitry responsible for action and habit selection. Given the strong presynaptic inhibition, preferential enhancement of iSPNs activity and biasing of dSPNs toward LTD, it is tempting to speculate that ChIs activity promotes the association of sensory and motor stimuli with iSPNs activity and weakens its association with dSPNs.

The contribution of ChIs to striatal pathophysiology in PD

As mentioned above, in PD, the loss of dopaminergic neurons innervating the striatum leads to an elevation in cholinergic signaling. The ability of cholinergic signaling to increase the excitability of iSPNs and promote LTD in dSPNs discussed above, should re-inforce the imbalance in the excitability of these SPNs by falling DA levels and promote the hypokinetic symptoms of the disease. The cholinergic modulation of SPNs is not a trivial concomitant of DA depletion, but an important driver of striatal adaptations (Shen *et al.*, 2007; Shen *et al.*, 2015). Moreover, chemogenetic silencing of ChIs in PD models leads to significant alleviation of symptoms (Maurice *et al.*, 2015). But precisely how cholinergic signaling rises in PD is still a matter of debate. The basal, autonomous discharge rate of ChIs does not increase (Ding *et al.*, 2006). What does change is the ability of M2/M4 autoreceptors to inhibit ACh release; this falls in response to upregulation of RGS4 protein which attenuates M2/M4 mAChRs signaling (Ding *et al.*, 2006).

But in PD models there are other alterations in ChI spiking. For example, in a primate model of PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), ChIs activity becomes highly synchronized and rhythmic (Raz *et al.*, 1996). The excitability of ChIs also is enhanced in PD rodent models, in part because of down-regulation in Kv1.3 K⁺ channels (Fino *et al.*, 2007; Tubert *et al.*, 2016). The most straightforward interpretation of these results is that the ability of extrinsic, excitatory synaptic input to drive ChIs spiking rises in PD.

As noted above, the intralaminar thalamus (IL) sends a robust glutamatergic projection to ChIs (Sadikot *et al.*, 1992; Sidibe & Smith, 1999). IL convey sensory information to the striatum and contribute to attention shifting, behavior switching and reinforcement processes (Matsumoto *et al.*, 2001; Minamimoto & Kimura, 2002; Kimura *et al.*, 2004; Minamimoto *et al.*, 2005; Smith *et al.*, 2011; Bradfield *et al.*, 2013). In rodents, activation of IL evokes a burst-pause firing pattern in ChIs (Ding *et al.*, 2010) and elevates ACh release (Consolo *et*

al., 1996a; Consolo *et al.*, 1996b). In primates, the situation appears to be more complicated. *In vivo*, stimulation of centromedian (CM)/PF suppresses ChIs firing, most likely through GABAergic signaling (Zackheim & Abercrombie, 2005; Nanda *et al.*, 2009). But most likely this is a reflection of an unnatural pattern or strength of stimulation that engages the intrastriatal GABAergic circuitry discussed above and doesn't mean that PF fails to activate at least a subset of ChIs in primates. That said, could the PF projection to ChIs drive an elevation in ChIs discharge rate? In fact, electrophysiological recording in rodent PD models has found that the spiking and oscillatory activity of PF neurons are increased (Yan *et al.*, 2008; Parr-Brownlie *et al.*, 2009). But, in the primate PD models where the evidence for altered spike patterning in ChIs is strongest and in humans, PF neurons are substantially depleted (Xuereb *et al.*, 1991; Heinsen *et al.*, 1996; Henderson *et al.*, 2005; Brooks & Halliday, 2009; Halliday, 2009; Villalba *et al.*, 2014). Clearly, more work is needed but it is possible that the increased synchrony of ChIs spiking seen in the primate models stems from both increased synchrony among the remaining PF neurons (as seen in the rodent models) and a reduction in the number of PF neurons (increasing the coherence of synaptic input to ChIs). It should be noted that in rodent PD models, the bulk of the evidence argues against any loss of PF neurons (Freyaldenhoven *et al.*, 1997; Henderson *et al.*, 2005; Aymerich *et al.*, 2006; Sedaghat *et al.*, 2009; Kusnoor *et al.*, 2012), possibly reflecting the much shorter duration of these experiments or the toxins used to generate the models. It is also possible that the aberrant activity patterns in ChIs in PD models has nothing to do with the thalamus and stems from aberrant cortical activity (Magill *et al.*, 2001; Goldberg *et al.*, 2004; Sharott *et al.*, 2005; Hammond *et al.*, 2007; Guo *et al.*, 2015). It remains to be determined whether alterations in evoked ChIs activity in PD models is solely dependent upon alterations in the temporal structure of their synaptic input or whether there are alterations in the strength or distribution of these synaptic connections with ChIs. It is also unclear whether there are structural changes in the projections of ChIs in PD models. Indeed, retrograde tracing experiments suggest that ChI innervation of iSPNs is up-regulated in PD models (Salin *et al.*, 2009).

ChIs and levodopa-induced dyskinesia

Although DA replacement therapy is remarkably effective at reducing the motor symptoms of PD, prolonged L-3,4-dihydroxyphenylalanine (L-DOPA) exposure can result in the development of debilitating involuntary movements, or dyskinesias. Over time, the therapeutic window of L-DOPA shortens, and the severity of the dyskinesia increases. These L-DOPA-induced dyskinesias (LIDs) therefore limit the effectiveness of L-DOPA based therapies for treating the symptoms of PD.

The severity of LIDs in humans is quantified by a subjective measure called the modified abnormal involuntary movement scale (mAIMS). A related behavioral test can also be used to assess the appearance of LIDs in rodents (Lundblad *et al.*, 2002), and these measures demonstrate reliable predictive validity. Although amantadine is currently used clinically for alleviating LIDs, the drug has negative side-effects, including hallucinations, confusion, falling, and nausea (Pahwa *et al.*, 2015), motivating the search for a more effective anti-dyskinetic therapy.

Such a therapy should come from a better understanding of the mechanisms governing LIDs. Several lines of evidence suggest that aberrant D1R-dependent potentiation of dSPNs glutamatergic synapses is a central feature of the LIDs pathophysiology (Picconi *et al.*, 2003; Jenner, 2008; Feyder *et al.*, 2011). This aberrant plasticity is attributable in part to slow oscillations in striatal DA levels after taking levodopa that result in sustained stimulation of G_oL-coupled D1Rs necessary for the induction of dSPN LTP. Sustained D1Rs signaling also suppresses G_i-coupled M4 mAChR signaling in dSPNs that normally helps balance D1Rs signaling (Sanchez *et al.*, 2009; Jeon *et al.*, 2010). Indeed, endogenous cholinergic signaling through M4 mAChRs promotes the induction of LTD at dSPN glutamatergic synapses through G_i-protein mediated inhibition of AC. In a rodent model, boosting M4 mAChRs signaling with positive allosteric modulators (PAMs) diminished dSPN LTP induction and alleviated dyskinetic behaviors (Shen *et al.*, 2015).

Interestingly, longer term treatment with high doses of levodopa in PD animal models appears to results in enhanced, rather than depressed, ChIs activity. Using the Pitx3^{ak} mouse line, in which dopaminergic neurons are progressively lost, it was found that treatment with high doses of levodopa (25 mg/kg/bid as opposed to 3–6 mg/kg/day) leads to a form of dyskinesia that is alleviated by suppressing ChIs activity or ablating ChIs (Ding *et al.*, 2011; Lim *et al.*, 2014; Won *et al.*, 2014). It is unclear whether the model itself is responsible for the discrepancy with studies using chemical lesioning of dopaminergic neurons in wild-type mice. For example, ChIs autoreceptor function appears to be dramatically down-regulated in the Pitx3 model, as is the density of D2/D3 DA receptors (Cremer *et al.*, 2015). The autoreceptor down-regulation is common to the Pitx3 and 6-OHDA lesion models (Ding *et al.*, 2006), but the DA receptor down-regulation is not. There could be other adaptations as well. For example, histamine H2 receptors have a stronger excitatory effect on ChIs in LID mice (Lim *et al.*, 2015). These changes undoubtedly will have profound effects on the striatal circuitry and how it responds to levodopa treatment. For example, deletion of M1 mAChRs significantly attenuates spine loss in iSPNs following DA depletion (Shen *et al.*, 2007). In mice with a normal complement of ChIs, re-establishing iSPN axospinous connectivity following L-DOPA administration appears to be as important to LIDs as the aberrant synaptic changes found in dSPNs (Fieblinger *et al.*, 2014; Shen *et al.*, 2015).

Recent work by the Quik lab has used a conventional, 6-OHDA lesion PD mouse models and lower (2–3 mg/kg/day) levodopa dosing for a prolonged period of time (~3 wks). Using optogenetic tools, it was found that in this model stimulation of ChIs with brief light pulses worsened LIDs through a mAChR-dependent mechanism, but that stimulation with longer light pulses lessened LIDs severity through nAChR-dependent mechanism (Bordia *et al.*, 2016). As intriguing as these results are, they are difficult to interpret because there was no attempt to correlate the optical stimulation protocol with ChIs spiking or output. Moreover, the effects of ChIs stimulation on the response to subsequent levodopa administration were not examined. Nevertheless, the apparent ability of nAChRs to alleviate LIDs is consistent with earlier studies (Quik *et al.*, 2013a; Quik *et al.*, 2013b; Bordia *et al.*, 2015) and needs to be rigorously pursued. It also is worth considering the possibility that prolonged levodopa treatment triggers adaptations in ChI signaling mechanisms that alter their response to levodopa therapy.

Concluding remarks

There have been major advances in our understanding of the role played by ChIs in the striatal circuitry and behavior in the last decade. This has largely been a consequence of advances in tool development. However, a host of major questions remain unanswered, particularly about the role of ChIs in controlling interneuronal circuits and in disease states, like PD. Answering these questions in the coming years should not only give us insight into what the striatal circuit is doing to control behavior, but also provide new therapeutics for psychomotor disorders involving the basal ganglia.

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