HHS Public Access

Author manuscript

Prog Neurobiol. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Prog Neurobiol. 2015 April ; 0: 91–107. doi:10.1016/j.pneurobio.2015.02.002.

Striatal cholinergic dysfunction as a unifying theme in the pathophysiology of dystonia

K.L. Eskow Jaunarajs[1], **P. Bonsi**[2], **M.F. Chesselet**[3], **D.G. Standaert**[1,*], and **A. Pisani**[2,4,*]

[1]Department of Neurology, Center for Neurodegeneration and Experimental Therapeutics, University of Alabama at Birmingham, Birmingham, USA

[2]IRCCS Fondazione Santa Lucia, Laboratory of Neurophysiology and Plasticity, Rome, Italy

[3]Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, USA

[4]Department of Systems Medicine, University of Rome “Tor Vergata”, Italy

Abstract

Dystonia is a movement disorder of both genetic and non-genetic causes, which typically results in twisted posturing due to abnormal muscle contraction. Evidence from dystonia patients and animal models of dystonia indicate a crucial role for the striatal cholinergic system in the pathophysiology of dystonia. In this review, we focus on striatal circuitry and the centrality of the acetylcholine system in the function of the basal ganglia in the control of voluntary movement and ultimately clinical manifestion of movement disorders. We consider the impact of cholinergic interneurons (ChIs) on dopamine-acetylcholine interactions and examine new evidence for impairment of ChIs in dysfunction of the motor systems producing dystonic movements, particularly in animal models. We have observed paradoxical excitation of ChIs in the presence of dopamine D2 receptor agonists and impairment of striatal synaptic plasticity in a mouse model of DYT1 dystonia, which are improved by administration of recently developed M1 receptor antagonists. These findings have been confirmed across multiple animal models of DYT1 dystonia and may represent a common endophenotype by which to investigate dystonia induced by other types of genetic and non-genetic causes and to investigate the potential effectiveness of pharmacotherapeutics and other strategies to improve dystonia.

1. Introduction

In 1911, the German neurologist Hermann Oppenheim described a group of cases of a type of childhood torsion disorder (translated in (Klein and Fahn, 2013)). Though he was not the

*Corresponding authors: Antonio Pisani, MD, PhD, Department of System Medicine, University of Rome “Tor Vergata”, Italy, V. Oxford 1, 00133 Rome, Italy, Tel.: +39-06501703153, Fax: +39-06501703316, pisani@uniroma2.it; David G. Standaert, M.D., Ph.D. Department of Neurology, Center for Neurodegeneration and Experimental Therapeutics, University of Alabama at Birmingham, Birmingham, Alabama, USA, dstandaert@uab.edu.

first to observe these types of conditions, he was the first to name them: “dystonia musculorum deformans.” Since that time, dystonias have undergone an evolution of classification from disorders to syndromes to diseases. The modern concept of dystonia has its roots in the work of Marsden in the 1970's, who recognized the commonalities among diverse forms of dystonia, ranging from the generalized childhood disorder described by Oppenheim to the more focal abnormalities such as torticollis, blepharospasm and writers' cramp which are commonly seen in adults. An updated consensus on the description and classification of dystonia has recently been published (Albanese et al., 2013):

> “Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.”

Clinical manifestation and treatment of dystonia

The clinical features of dystonia are represented by an amalgamation of dystonic movements and postures to create sustained postural twisting (torsion dystonia). The speed of muscle contractions may be slow or rapid, but are sustained at the peak of movement. The muscle contractions tend to have a consistent directional character. Voluntary movements can exacerbate underlying dystonic symptoms. Conversely, specific voluntary movements or sensory contacts may temporarily ameliorate dystonic movements; this phenomenon is known as a sensory trick or gestes antagonistes. Overflow of movement to other body parts during activation of the affected region is also a feature of dystonia.

Some types of dystonias, particularly DOPA-responsive dystonia (DRD) may respond very well to low doses of dopamine replacement therapy with L-DOPA. The classic form of DRD arises from a deficit in dopamine synthesis induced by a mutation in the GTP cyclohydrolase I gene that regulates production of tetrahydrobiopterin, a necessary co-factor for tyrosine hydroxylase (Segawa et al., 1976). However, most other forms of dystonia are treated pharmacologically with high doses of anticholinergics, such as trihexyphenidyl (Artane®; (Fahn, 1983; Burke et al., 1986; Jankovic, 2013). Anticholinergics are generally well-tolerated by children but in adults can have significant side effects, including drowsiness, confusion, and memory difficulties. Other drugs may also be of benefit, including some dopaminergic agents and some GABAergics (Jankovic, 2013). Botulinum toxin injections within affected musculature are often helpful in focal and segmental dystonias (Tsui et al., 1986; Jankovic, 2013). The most effective surgical intervention is deep brain stimulation within the globus pallidus internus (GPi) or the subthalamic nucleus (STN), though pallidotomy has also been used with some success in intractable cases (Lozano et al., 1997; Ondo et al., 1998; Yoshor et al., 2001; Eltahawy et al., 2004).

Neuroanatomical basis for dystonia

At present there is no adequate neural model that fully accounts for the symptoms of all forms of dystonia. The neuropathology in isolated forms of dystonia is often normal (Standaert, 2011). However, in those cases where it has been possible to identify

pathological abnormalities, two main brain areas have been implicated: the cerebellum and the basal ganglia.

Several lines of evidence have supported a role for the cerebellum in the neurophysiology of dystonia. For example, lesions and tumors of the cerebellum and its associated brainstem afferents are found in some forms of acquired dystonia, particularly cervical dystonia (LeDoux and Brady, 2003; Prudente et al., 2013). There is also evidence for selective degeneration of the cerebellum in familial forms of ataxia which include dystonic movements (Manto, 2005). Recent evidence suggests that abnormalities in cerebellothalamocortical connectivity predict the penetrance of DYT1 dystonia, a form of inherited isolated dystonia (Argyelan et al., 2009).

Some animal studies have also indicated cerebellar involvement (Raike et al., 2012; Song et al., 2014) or alterations in cerebellothalamocortical connectivity (Ulug et al., 2011). For example, the primary anomalies found in genetically dystonic rats (dt) are cerebellar (LeDoux, 2011); dt rats display higher levels of glutamate decarboxylase messenger RNA in cerebellar Purkinje cells and decreased levels in deep cerebellar nuclei (Naudon et al., 1998). Pharmacological manipulation of the cerebellum can also induce dystonia in animal models (Raike et al., 2005).

Striatal dysfunction appears to be a feature of most if not all forms of dystonia. For example, focal lesions of the basal ganglia often result in dystonia, particularly when the putamen is involved (Pettigrew and Jankovic, 1985; Lera et al., 1994). In idiopathic dystonia patients, the putamen has been reported to be about 10% larger (Black et al., 1998; Bradley et al., 2009) and fMRI studies have indicated increased activation in the basal ganglia (Blood et al., 2004; Peller et al., 2006). Furthermore, the most effective surgical intervention for dystonia is deep brain stimulation within either the GPi or the STN, main output nuclei of the basal ganglia (Ostrem and Starr, 2008). Animal models of dystonia have also supported an important role for striatal involvement (Sato et al., 2008; Yokoi et al., 2011; Yokoi et al., 2012; Zhang et al., 2012; Song et al., 2013).

Considering forms of dystonia to be the consequence of exclusively cerebellar or striatal origin may be a false dichotomy. The cerebellum and striatum are highly inter-connected on a functional level, and abnormalities in one may well lead to dysfunction of the other (Bostan et al., 2010).

Role of acetylcholine in the pathophysiology of dystonia

While the basal ganglia are a participant in most, if not all, forms of dystonia, the precise mechanisms responsible are unclear. A significant contribution of the striatal dopamine and acetylcholine systems is likely; anticholinergic and dopaminergic drugs are the most effective pharmacological treatments for most types of dystonia (Jankovic, 2013) and acetylcholine agonists and dopaminergic drugs can induce dystonia in humans and primates (Cools et al., 1975; Muenter et al., 1977; Casey et al., 1980; Shafrir et al., 1986; Mitchell et al., 1990; Uca et al., 2014). Furthermore, dystonia is a key feature extant in Parkinson's disease and primate models of Parkinson's disease that primarily affect dopamine and acetylcholine systems (Poewe et al., 1988; Perlmutter et al., 1997; Tabbal et al., 2006).

While the concept of reciprocal interactions between dopamine and acetylcholine in the striatum was developed in the sixties and seventies, emerging work from many laboratories using novel tools, including optogenetics and designer receptors is emphasizing the centrality of striatal cholinergic transmission in the control of voluntary movement and the clinical manifestations of movement disorders (Bonsi et al., 2011). These studies have demonstrated that acetylcholine exerts a powerful influence on striatal dopamine neurotransmission and has a critical role in the plasticity underlying motor learning.

Of particular interest for dystonia, recent evidence suggests that impairment of the reciprocal modulation between striatal dopamine and acetylcholine is a nodal pathophysiological event in DYT1 dystonia, a genetic form of dystonia caused by mutation of the gene encoding for the protein torsinA. Data collected in the past few years show that in rodent models of DYT1, the D2 receptor agonist quinpirole causes a paradoxical excitation of cholinergic interneurons (ChIs), rather than the physiological inhibition. This phenotype is broadly expressed, and is found across many different mouse and rat models based on mutant forms of torsinA (Pisani et al., 2006; Grundmann et al., 2012; Sciamanna et al., 2012). The ensuing imbalance in cholinergic tone appears to be responsible for the impairment of bidirectional corticostriatal synaptic plasticity observed in all of these models, and may be the basis for the abnormal motor learning and patterns of motor activity observed in human dystonia (Martella et al., 2009; Quartarone and Hallett, 2013; Martella et al., 2014).

Collectively, these findings confirm the existence of a specific phenotype linked to DYT1 mutation across a range of species analyzed. This core electrophysiological abnormality provides a unifying theme for understanding the pathophysiology of dystonia.

The current review will attempt to provide a context for the role of striatal acetylcholine interneuron function in the pathogenesis of dystonia by examining striatal anatomy and function, ChI activity, and the changes that occur in this system to alter dopamine-acetylcholine balance and induce the subsequent development of movement abnormality.

2. Striatal Circuitry

As is the case with most movement disorders, the phenotypic movement disorder characterized by dystonia can at present best be explained within a framework of striatal circuitry. Traditionally, this circuitry consists of excitatory connections from cortex and thalamus synapsing onto projection neurons termed medium-size spiny neurons (MSNs). There are two main types of MSNs, which project either directly to the output nuclei of the basal ganglia (direct pathway), the GPi and the substantia nigra pars reticulate (SNpr), or indirectly via the STN (indirect pathway). Both pathways ultimately influence thalamic circuits. ChIs play a central role in both pathways, modulating their output by influencing striatal dopaminergic and glutamatergic projections or by directly modulating striatal output via cholinergic receptors located on MSNs. While the “direct” versus “indirect” segregation hypothesis is oversimplified (for extensive discussion of this issue, see (Calabresi et al., 2014)), it serves as a useful tool to investigate movement control. In dystonia, traditional thought suggests that the direct pathway is overactive, leading to reduced output of the globus pallidus internal segment and enhanced thalamic input to the cortex (Berardelli et al.,

1998). We suggest that ChI dysfunction is a major driver of this abnormal activity through direct and indirect actions on MSN output.

2.1 Striatal inputs

The activity of direct and indirect pathway neurons largely hinges on their modulation by a wide range of neurotransmitter systems. The main inputs onto MSNs consist of glutamatergic corticostriatal and thalamostriatal neurons and dopaminergic nigrostriatal neurons, discussed in the current review. Minor projections to the striatum include raphe-striatal serotonergic input, locus coeruleus noradrenergic projections, and excitatory glutamatergic transmission arising from the amygdala and are discussed elsewhere (Pan et al., 2010). Recent evidence has also suggested a cholinergic projection from the pedunculopontine nucleus may innervate the striatum (Dautan et al., 2014), though its functional role is, as yet, unclear.

2.1.1. Cortex—Corticostriatal glutamatergic projections are centrally involved in motivated behavior, and originate from layer III and V pyramidal neurons in functionally diverse cortical areas in monkeys, dogs, cats, and rodents (Mathai and Smith, 2011). In rodents, corticostriatal glutamatergic projections consist of two distinct classes of cortical neurons, intratelencephalic and pyramidal tract neurons (Shepherd, 2013). In the rat, the intratelencephalic neurons are mainly located in layer III and upper layer V of the cortex, and send axonal projections to the ipsilateral and contralateral cortex and striatum. Conversely, layer V pyramidal tract neurons send axonal projections to the brainstem and spinal cord, from which axon collaterals innervating the striatum originate (Reiner et al., 2003). In non-human primates, distinct populations of corticostriatal projection neurons have been identified by single-axon tracing studies, though electrophysiological studies did not support these observations (Mathai and Smith, 2011). Even in rodents, anatomical evidence that intratelencephalic neurons preferentially innervate direct pathway neurons, whereas pyramidal tract neurons mainly target indirect pathway neurons (Lei et al., 2004) was not supported by electrophysiology, which showed a contrasting main excitatory drive of intratelencephalic neurons to both direct and indirect neurons (Ballion et al., 2008).

The corticostriatal system represents a massive, and highly convergent, source of synaptic inputs to striatal MSNs (Fig. 1A; (Ingham et al., 1989; Raju et al., 2008). Multiple cortical areas innervate the striatum in a highly topographic manner according to the functional segregation of striatal territories (Alexander et al., 1986) with the dorsolateral putamen primarily receiving sensorimotor cortical afferents (Parent and Hazrati, 1995). Somatosensory and motor cortical information representing the same body parts converge onto overlapping regions in the putamen (Flaherty and Graybiel, 1991, 1993). Cortical inputs to the striatum preferentially target spine heads of MSNs forming asymmetric synapses (Mathai and Smith, 2011). Structurally, ChIs are well-located to modulate corticostriatal signaling, with ChIs synapsing on glutamatergic neuron dendrites and spines. Acetylcholine modulates corticostriatal signaling by acting via presynaptic muscarinic receptors. While traditionally muscarinic M2 and perhaps, M3 receptors were suggested to be involved in this process (Hsu et al., 1995; Calabresi et al., 1998), more specific

pharmacologic tools and knock-out mice have now indicated that M4 receptors are the key regulator of corticostriatal synapses (Pancani et al., 2014).

The plasma membrane of MSN dendritic spines and shafts expresses a variety of both ionotropic AMPA and NMDA receptor subunits and metabotropic glutamate receptors (mGluRs) subtypes. However, significant numbers of these receptors are localized extrasynaptically (Paquet and Smith, 2003; Fujiyama et al., 2004; Galvan et al., 2006). The role of postsynaptic glutamate receptors abundance and subsynaptic localization in determining the strength of corticostriatal inputs and, hence, in contributing to long term plasticity has been demonstrated (Dunah and Standaert, 2003; Gubellini et al., 2004; Calabresi et al., 2007b; Wickens, 2009; Gardoni et al., 2010).

2.1.2. Thalamus—Thalamostriatal innervation may originate from most thalamic nuclei (Fig. 1A; (Smith et al., 2014). Recently, thalamic nuclei innervated by the dentate nucleus (the ventral motor and other intralaminar thalamic nuclei) have been proposed to mediate the communication between the cerebellum and the basal ganglia (Bostan et al., 2010; Bostan and Strick, 2010; Bostan et al., 2013). Hence, dysfunction of this pathway has been suggested to play a role in the pathophysiology of dystonia and other movement disorders (Jinnah and Hess, 2006; Neychev et al., 2008; Calderon et al., 2011).

The centromedian/parafascicular (CM/Pf) complex represents the main source of thalamostriatal projections in primates and non-human primates (Smith et al., 2014). CM/Pf neurons send massive and topographically organized projections to specific regions of the dorsal striatum (Sadikot et al., 1992a; Parent and Parent, 2005; Galvan and Smith, 2011). In rodents, the lateral part of Pf is considered to be the homologue of the primate CM and projects mainly to the sensorimotor region (i.e., the dorsolateral part) of the caudate-putamen complex, whereas the medial rodent Pf displays strong similarities with the primate Pf, projecting to associative and limbic striatal regions of the striatum. Through these projections, the CM/Pf gains access to the entire striatal complex, thereby making the CM/Pf-striatal system a functionally organized network that may broadly affect basal ganglia functions.

The differential expression of the vesicular glutamate transporter 1 (vGluT1) in corticostriatal terminals and vGluT2 in thalamostriatal fibers (Fremeau et al., 2001; Fremeau et al., 2004) allowed the characterization of the synaptic connectivity of corticostriatal and thalamostriatal terminals. Thalamostriatal projections give rise to asymmetric synapses and, similar to corticostriatal afferents, the principal synaptic targets of most non-CM/Pf thalamostriatal projections are dendritic spines of striatal projection neurons (Kemp and Powell, 1971b; Dube et al., 1988; Raju et al., 2006; Lacey et al., 2007; Raju et al., 2008). In contrast, most CM/Pf striatal afferents establish asymmetric synapses with dendritic shafts of MSNs (Dube et al., 1988; Sadikot et al., 1992b; Smith et al., 1994; Sidibe and Smith, 1996; Raju et al., 2006; Lacey et al., 2007; Raju et al., 2008) and several types of striatal interneurons including ChIs (Meredith and Wouterlood, 1990; Lapper and Bolam, 1992; Sidibe and Smith, 1999) and parvalbumin-positive GABA interneurons (Rudkin and Sadikot, 1999; Sidibe and Smith, 1999). Whereas the massive vGluT2-positive thalamostriatal projection from Pf terminates exclusively in the striatal matrix (Herkenham

and Pert, 1981; Sadikot et al., 1992b; Raju et al., 2006), the pattern of synaptic innervation of corticostriatal vGluT1-positive terminals does not differ between patch/striosome and matrix compartments (Raju et al., 2006). The convergence of thalamic and cortical inputs upon single MSNs is consistent with in vivo and in vitro electrophysiological analyses showing that single direct or indirect pathway neurons respond to both cortical and thalamic stimulation in rodents (Kocsis and Kitai, 1977; Vandermaelen and Kitai, 1980; Ding et al., 2008; Ellender et al., 2011; Ellender et al., 2013; Huerta-Ocampo et al., 2013).

Thalamic modulation of striatal ChI activity, by gating corticostriatal transmission, regulates behavioral switching and attentional set-shifting (Kimura et al., 2004; Ding et al., 2010; Smith et al., 2011; Sciamanna et al., 2012; Bradfield et al., 2013b; Bradfield et al., 2013a). Indeed, ChIs receive synaptic inputs from CM/Pf (Fig. 1B) (Lapper and Bolam, 1992; Sidibe and Smith, 1999), whose alterations affect striatal acetylcholine release (Consolo et al., 1996a; Consolo et al., 1996b; Zackheim and Abercrombie, 2005; Nanda et al., 2009). The removal of Pf inputs to ChIs reduces the firing rate of these neurons and produces an enduring deficit in goal-directed learning (Bradfield et al., 2013b). CM stimulation strongly affects the in vivo activity patterns of striatal tonically active neurons (TANs) that are believed to correspond to ChIs (Wilson et al., 1990; Nanda et al., 2009). The reward-associated pause responses in striatal TANs (Goldberg and Reynolds, 2011) are almost completely abolished by inactivation of the CM/Pf complex in monkeys (Matsumoto et al., 2001).

ChIs are also structurally well-located to act upon excitatory thalamostriatal circuits (Fig. 1B). Like corticostriatal terminals, thalamic inputs to the striatum also express nicotinic receptors, which serve to enhance glutamate release, particularly via alpha7 containing receptors that are highly calcium permeable. It is unknown whether there are differences in nicotinic receptor subunit composition between corticostriatal and thalamostriatal synapses that may distinctively alter glutamatergic influence from these inputs. On the other hand, muscarinic receptors act to decrease glutamatergic inputs, likely in a similar manner to corticostriatal synapses (M4, M2 and/or M3; (Ding et al., 2010)).

2.1.3. Substantia Nigra pars compacta—The striatum is modulated by dopaminergic signals from mesolimbic nuclei. Dopaminergic neurons in the substantia nigra pars compacta mostly project to the dorsal striatum, while neurons from ventral tegmental area reach the nucleus accumbens (McGeorge and Faull, 1989; Berendse and Groenewegen, 1990; O'Donnell and Grace, 1995). In the classical models of the basal ganglia, dopamine regulates the balance between the activation of the direct and indirect striatofugal pathways (Albin et al., 1989; Wichmann and DeLong, 1996). Dopamine D1 receptor signaling enhances dendritic excitability and glutamatergic transmission in striatonigral MSNs, whereas D2 receptor signaling exerts the opposite effect in striatopallidal MSNs (Surmeier et al., 2007). This segregation of D1 and D2 receptor-expressing MSNs, with an overlap limited to less than 5–15% of neurons is essential for fine control of striatal circuitry (Gertler et al., 2008; Matamales et al., 2009; Valjent et al., 2009). While D5 receptor isoform (D1-class) is largely expressed in striatal interneurons, conversely in MSNs D5 receptors appear to have a low expression level (Rivera et al., 2002). The use of D5 knockout mice suggests that the involvement of D5 receptors in LTD induction is related to the recruitment of PLTS

interneurons (Centonze et al., 2003). In addition, the lack of specific compounds targeting D5 receptors hampers the definition of their precise functional role. D3-D4 (D2-class) receptors are scarcely expressed in the dorsal striatum (Le Moine and Bloch, 1996).

Striatal dopamine plays a key role in long term plasticity of glutamatergic corticostriatal synapses (Cragg, 2003; Picconi et al., 2003; Calabresi et al., 2007a; Kreitzer and Malenka, 2008; Pawlak and Kerr, 2008). Dopaminergic and cortical afferents partially converge on individual spines of MSNs (Freund et al., 1984; Bolam and Smith, 1990; Smith et al., 1994; Smith et al., 2014). The postsynaptic responses induced by cortical stimulation are modulated by dopamine acting through pre-and post-synaptic mechanisms dependent on the type and localization of dopamine receptors and the physiological state of striatal MSNs (Gonon, 1997; Reynolds et al., 2001; Cragg and Rice, 2004; Surmeier et al., 2007; Rice and Cragg, 2008). Indeed loss of the dopaminergic input in Parkinson's disease models causes profound alterations in corticostriatal synaptic plasticity (Calabresi et al., 2007b), which are associated with pruning of dendritic spines on MSNs (Ingham et al., 1989; Stephens et al., 2005; Zaja-Milatovic et al., 2005; Smith and Villalba, 2008; Villalba et al., 2009; Villalba and Smith, 2010). Likewise, reduced dopamine release and changes in corticostriatal synaptic plasticity have been indicated in multiple genetic mouse models of DYT1 dystonia (Pisani et al., 2006; Balcioglu et al., 2007; Hewett et al., 2010; Page et al., 2010; Sciamanna et al., 2012; Song et al., 2012). While decreased D1 receptor activation has been linked to changes in *GNAL* (Corvol et al., 2007), the primary gene involved in DYT25, these mouse models have not yet been investigated for alterations in striatal synaptic plasticity.

The similarity between the overall pattern of synaptic connectivity of non-CM/Pf thalamic and cortical terminals with MSNs (Moss and Bolam, 2008) suggests that these two pathways may be regulated in the same manner by nigrostriatal dopamine afferents. Indeed, these glutamatergic terminals are located close to dopaminergic synapses, suggesting that dopamine may modulate most glutamatergic terminals in the rodent striatum (Smith et al., 2014). Conversely, axo-dendritic thalamic inputs from CM and dopaminergic terminals do not display significant structural relationships (Smith et al., 1994), thus it is likely that the interactions between dopaminergic afferents and CM/Pf or non-CM/Pf thalamostriatal synapses differ.

Likewise, cholinergic interneurons are closely localized with dopamine terminals, as discussed in detail below. In brief, dopamine terminals express a number of acetylcholine receptors, particularly nicotinic receptors, that influence dopamine release in the striatum. In support, nicotinic agonists and nicotine itself enhance striatal dopamine release (Damsma et al., 1988; Toth et al., 1992; Puttfarcken et al., 2000; Campos et al., 2010). In vitro, synchronous optogenetic activation of ChIs increases dopamine release through beta2-subunit containing nicotinic acetylcholine receptors on nigrostriatal dopamine terminals (Cachope et al., 2012; Threlfell et al., 2012), suggesting a system by which ChIs may act in concert to enhance striatal dopaminergic tone, likely driven by thalamostriatal inputs onto cholinergic neurons (Ding et al., 2010). Recent studies also suggest that nicotinic receptor modulation of dopamine release impacts the co-release of GABA from nigrostriatal terminals (Nelson et al., 2014), though it is unclear what effect this may have on striatal function.

Multiple lines of evidence suggest that dysfunctions in dopamine signaling can induce dystonic symptoms (Wichmann, 2008; Tanabe et al., 2009; Bragg et al., 2011). Early imaging studies detected various DA-related abnormalities in patients with different forms of dystonia, such as altered receptor binding in basal ganglia (Perlmutter et al., 1997; Naumann et al., 1998; Brashear et al., 1999). Furthermore clinical reports showed that dystonia may be associated with either mutations in genes encoding proteins critical for dopamine biosynthesis (GTP-cyclohydrolase and tyrosine hydroxylase), as well as polymorphisms in the D5R dopamine receptor subtype; with other disease processes affecting dopamine (e.g. Parkinson's disease); or with complications resulting from anti-dopamine therapies (Goodchild et al., 2013).

2.1.4 Cortical, Striatal, Cerebellar and Thalamic Connectivity—In a recent study, Vo and colleagues (2014) used magnetic resonance diffusion tensor imaging (DTI) to identify brain microstructural changes associated with the severity of clinical manifestations in individuals with limb dystonia. The authors found that clinical manifestations were greatest in subjects with relatively intact microstructure in somatotopically relevant white matter regions. Significant phenotype-related differences were observed in thalamocortical tracts, but not in corticostriatal or corticospinal pathways, suggesting that the thalamocortical motor system is a major determinant of dystonia phenotype. Conversely, cerebellothalamic microstructural abnormalities were associated with genotype, rather than with phenotype, in the dystonia subjects. Reductions in structural connectivity involving cerebellothalamic projections have been described in dystonia mutation carriers, whether or not they exhibited symptoms of the disorder, whereas abnormalities involving thalamocortical projections were identified only in non-manifesting gene carriers (Argyelan et al., 2009; Niethammer et al., 2011). These observations suggest that the thalamocortical tract regulates penetrance by controlling the transmission of aberrant cerebellothalamic signals to the cerebral cortex (Niethammer et al., 2011). In accordance with this model, recent observations showed that thalamocortical projections somatotopically linked to symptomatic body areas were intact in manifesting gene carriers, and that more severely affected individuals were distinguished by relative preservation of these pathways. In contrast, the same individuals exhibited reductions in the integrity of somatotopic projections related to asymptomatic body areas and fully nonpenetrant mutation carriers exhibited similar changes (Vo et al., 2014).

2.2. Intrinsic Striatal Circuitry

Six types of neurons in the striatum have been identified according to morphology, size of soma and dendrites as well as neurochemical properties (Kemp and Powell, 1971b). More than 95% of striatal neurons is represented by GABAergic MSNs, whereas the remaining 5% is constituted by five classes of interneurons: large cholinergic cells, three subtypes of GABAergic interneurons, and tyrosine hydroxylase-immunoreactive neurons (Kawaguchi, 1993; Tepper et al., 2010).

2.2.1. Medium spiny neurons—MSNs have a medium sized soma (10-20 μm), and an extensive dendritic tree densely studded with spines (Jiang and North, 1991). Their axons also extensively arborize within a 250-450 μm area around the cell bodies, and these axonal

plexus provide symmetrical synapses with other striatal neurons (Kemp and Powell, 1971a; Preston et al., 1980; Somogyi et al., 1981). During intracellular electrophysiology recordings from striatal slices, MSNs show very negative resting potentials (-90 mV) and a low input resistance at the resting membrane potential (40 MΩ; (Jiang and North, 1991).

MSNs contain enzymes involved in the synthesis of GABA (Ribak et al., 1979; Fisher et al., 1986), and are the source of the GABAergic output of the neostriatum, innervating the basal ganglia output structures, globus pallidus and substantia nigra (Kawaguchi et al., 1995). MSNs of the matrix include two functionally distinct subpopulations that express different proportions of dopaminergic, cholinergic, and other receptors (Benarroch, 2012). A MSN population projects to the inhibitory output neurons of the globus pallidus internus and substantia nigra pars reticulata and constitutes the direct pathway. Another MSN subpopulation projects to the globus pallidus externus, disinhibits the subthalamic nucleus, promoting the tonic inhibitory output of the globus pallidus internus/substantia nigra reticulata, and constitutes the indirect pathway. A third subpopulation of MSNs, restricted to the striosomes, receive inputs from the limbic cortex and project to the dopaminergic neurons of substantia nigra pars compacta, thereby mediating limbic modulation of basal ganglia function.

MSNs express a number of muscarinic acetylcholine receptors, but likely do not contain nicotinic acetylcholine receptors. In particular, ChIs can exert direct control of both direct and indirect pathway MSNs through muscarinic M1 receptors, found on MSN dendrites and spines, by reducing KCNQ and Kir2 currents (Galarraga et al., 1999; Shen et al., 2005; Shen et al., 2007). MSNs also differentially express inhibitory muscarinic M4 receptors; M4 receptors are preferentially expressed on direct pathway neurons (Bernard et al., 1992; Yan et al., 2001). In a recent study, activation of M4 receptors was found to enhance calcium currents by acting on Ca_v1 channels, increasing excitability of direct pathway neurons but not indirect pathway neurons (Hernandez-Flores et al., 2015). Thus, targeting direct pathway abnormalities in dystonia may be possible by influencing M4 receptors, while targeting the M1 receptor could inflict more global alterations in MSN function.

2.2.2. GABAergic interneurons—Neostriatal medium-sized aspiny GABAergic interneurons can be classified into three subtypes by physiological, chemical, and morphological criteria. These three classes of interneurons can be differentiated by the selective expression of either the calcium-binding proteins parvalbumin or calretinin, or a number of neuropeptides and enzymes, including neuropeptide Y, somatostatin, and nitric oxide synthase (Kawaguchi et al., 1995; Tepper et al., 2010).

Parvalbumin-immunoreactive fast-spiking (FS) interneurons express the KV3.1 potassium channel (Lenz et al., 1994) and, in vitro, exhibit a fast-spiking (>200 Hz) phenotype characterized by very short-duration action potentials with large and rapid afterhyperpolarizations at constant spike frequency interrupted by periods of silence in response to depolarizing current pulses. FS cells have more negative resting potentials and lower input resistances than the other two classes of GABAergic interneurons.

Cells immunoreactive for NADPH diaphorase, somatostatin, and nitric oxide synthase were identified as persistent and low-threshold spike (PLTS) interneurons. These interneurons are 12-25 μm in diameter. In comparison with cholinergic and parvalbumin-positive cells, PLTS have fewer dendritic branches. Their axonal arborizations are less dense within the region of the dendritic field, are more extensive, and are relatively unbranched for longer distances within the striatum. With respect to FS cells, PLTS neurons have longer-duration action potentials, less negative resting potentials, longer lasting afterhyperpolarizations and very high input resistances. The physiological properties of PLTS interneurones are unique among striatal cells, because of their ability to generate Ca2+-dependent low threshold spikes, as well as large and persistent Na+ current-dependent plateau potentials in response to depolarization or excitatory synaptic stimulation (Beatty et al., 2012).

Calretinin-immunoreactive interneurons were initially described in rats as medium sized aspiny neurons, 12–20 μm in diameter, that issued a small number of smooth, aspiny dendrites (Bennett and Bolam, 1993). While in rodents these cells account for nearly 0.5% of striatal neurons, in primates including humans the proportion of calretinin-positive neurons is 3 to 4-fold parvalbumin-or somatostatin-immunoreactive cells (Wu and Parent, 2000). Three or four morphologically distinct types of striatal calretinin-positive neurons have been described. Thus far, no electrophysiological recordings from identified calretinin-positive interneurons have been obtained.

Cholinergic regulation of GABAergic interneurons has been shown in a number of recent studies and cholinergic terminals have been found to innervate GABAergic interneurons, particularly FS interneurons (Chang and Kita, 1992). Collectively, acetylcholine acts to reduce evoked striatal GABAergic release via muscarinic receptors (Marchi et al., 1990; Raiteri et al., 1990). However, interaction with FS interneurons occurs via both nicotinic and muscarinic receptors in a complex manner. Activation of non-desensitizing somatodendritic nicotinic receptors depolarizes FS interneurons, while presynaptic muscarinic receptor activation inhibits GABAergic transmission onto MSNs (Koos and Tepper, 2002). Nicotinic activation of FS interneurons is believed to exert influence during fast changes in acetylcholine tone, such as the pause-rebound effect observed in ChIs following behaviorally relevant stimuli (Aosaki et al., 1995); muscarinic receptors may be activated by more persistant changes in acetylcholine levels. Muscarinic M2 receptors have also been reported on PLTS neurons (Bernard et al., 1998) and may further explain the global inhibitory effects of acetylcholine on striatal GABA release.

2.2.3. Tyrosine-hydroxylase-immunoreactive interneurons—Since Dubach et al. (1987) first described medium sized striatal interneurons immunoreactive for tyrosine hydroxylase in the caudate nucleus of normal monkeys, many reports confirmed the existence of such neurons in rodents and humans (Tepper et al., 2010). Thereafter, an electrophysiological analysis revealed four distinct types of striatal tyrosine hydroxylase-immunoreactive neurons (Ibanez-Sandoval et al., 2010). Of note, the number of these neurons increased by a factor of 2–4 times following dopaminergic denervation in rats (Tashiro et al., 1989). Connectivity of ChIs with tyrosine-hydroxylase-immunoreactive neurons has not been elucidated to date and their functional relevance is, as yet, unknown.

2.2.4. Cholinergic interneurons—ChIs are large (20–50 μm) aspiny cells expressing choline acetyltransferase (ChAT), the biosynthetic enzyme for acetylcholine, which are preferentially distributed in the matrix area flanking the patches border (van Vulpen and van der Kooy, 1998). This localization may result in greater influence of cholinergic signaling on pathways originating or terminating in the matrix, such as nigrostriatal and preferentially, striatopallidal pathways. Their widespread dendritic and axonal fields suggest a role of synaptic integration over relatively large regions (Bolam et al., 1984; Smith and Bolam, 1990; Wilson et al., 1990; Kawaguchi et al., 1995; Miura et al., 2007). Accordingly, ChIs are the synaptic targets of striatal afferents originating from the cerebral cortex, the intralaminar thalamic nuclei, the substantia nigra, the locus coeruleus, the dorsal raphe nucleus, as well as of MSN collaterals and FS interneurons (Olson et al., 1972; Pazos et al., 1985; Bolam et al., 1986; Lavoie et al., 1989; Lapper and Bolam, 1992; Martone et al., 1992; Dimova et al., 1993; Sidibe and Smith, 1999; Thomas et al., 2000; Pisani et al., 2003; Bonsi et al., 2007; Smith and Villalba, 2008; Aosaki et al., 2010; Bonsi et al., 2011).

ChIs are characterized by peculiar electrophysiological properties among striatal neurons: less negative resting potential (-60 mV), higher input resistance, long lasting action potential, prominent I_h current in response to hyperpolarization, and autonomous firing activity, even in the absence of synaptic inputs (Bolam et al., 1984; Wilson et al., 1990; Kawaguchi, 1993; Aosaki et al., 1995; Bennett and Wilson, 1998; Bennett et al., 2000; Zhou et al., 2002). The single spike-firing pattern relies on medium-duration afterhyperpolarization (AHP) current, generated by rapid small conductance calcium-activated potassium channels (SK) associated with $Ca_V2.2$ calcium channels. Periodic bursting is driven by a delayed and slowly decaying AHP current, associated with Ca_V1 calcium channels (Bennett et al., 2000; Goldberg and Wilson, 2005; Wilson and Goldberg, 2006; Goldberg et al., 2009).

2.3. Striatal outputs

In the widely held view of basal ganglia organization, the striatum controls the basal ganglia outflow through direct and indirect pathways. The direct striatonigral pathway promotes movement initiation through MSNs that contain dopamine D1-class receptors and project to the GPi and SNpr, thereby disinhibiting thalamocortical and brainstem circuitry and promoting movement. The indirect striatopallidal pathway exerts a tonic inhibitory tone on motor activity through MSNs that express dopamine D2-class receptors and inhibit globus pallidus externus (GPe) neurons, thus relieving the inhibition on STN and increasing GPi/SNr neuron firing.

A direct demonstration of the largely non-overlapping contributions of the two pathways to several different forms of motor behaviors came from experiments where the striatal signaling protein dopamine- and cAMP-regulated phosphoprotein Mr 32kDa (DARPP-32) was selectively deleted in striatonigral or striatopallidal neurons. Indeed, cell type–specific deletion of DARPP-32 in striatonigral neurons decreased basal and cocaine-induced locomotion and abolished dyskinetic behaviors in response to L-DOPA in animal models of Parkinson's disease. Conversely, the loss of DARPP-32 in striatopallidal neurons produced a

robust increase in locomotor activity and a strongly reduced cataleptic response to the antipsychotic drug haloperidol (Bateup et al., 2010).

However, recent studies using novel techniques allowing for in vivo selective analysis of direct/indirect pathway MSN activity have also provided evidence that is likely to change the traditional view of basal ganglia function. Notably, both direct- and indirect-pathway neurons increase their activity before movement initiation, and therefore are necessary to initiate motor activity (Cui et al., 2013). In contrast, they behave differently during sequence performance; disparate subsets of direct and indirect pathway neurons are engaged during sequence initiation, execution and termination (Jin et al., 2014). These findings have been supported with evidence in dystonia patients. For instance, according to the traditional “rate model”, hyperkinetic movement disorders such as dystonia were believed to stem from decreased discharge rates of the direct pathway (GPi) and increased discharge rates of the indirect pathway (GPe). Conversely, rather than worsening dystonic movements, lesions of the GPi are beneficial for many patients. Recent in vivo neurophysiology from dystonia patients undergoing DBS implantation suggest that discharge rates in both the GPi and GPe are reduced (Hendrix and Vitek, 2012), supporting the idea of a collective dysfunction between the direct and indirect pathways.

Altogether these observations challenge the classic model of basal ganglia function, which postulates that direct pathway neurons would be active during movement to facilitate it, whereas indirect pathway neurons would be inhibited during movement and active during lack of movement. Rather, coactivation of direct and indirect pathways seems critical for action selection during movement initiation, since direct pathway neurons may select the desired motor program, whereas indirect pathway neurons may inhibit competing motor programs (Mink, 2003). Normal motor functions are achieved when the activities of these two pathways are in balance. Hypokinetic (e.g., Parkinson's disease) and hyperkinetic (e.g., Huntington's disease) movement disorders of basal ganglia origin are thought to result from imbalanced activities between the two pathways (Albin et al., 1989).

3. Striatal Acetylcholine Signaling

The striatal acetylcholine-dopamine balance has long been considered a key factor in normal basal ganglia function (Calabresi et al., 1989; Cragg, 2006; Ding et al., 2006; Pisani et al., 2007; Aosaki et al., 2010). Accordingly, dysfunction of acetylcholine release in the striatum is believed to underlie different movement disorders, such as Parkinson's disease, Huntington's disease, dystonia and Tourette syndrome (Pisani et al., 2007). Furthermore, many of these disorders can be treated with pharmacotherapies that target acetylcholine receptor systems (Corner, 1952; Lang et al., 1983; Sanberg et al., 1998; Brocks, 1999; Silver et al., 2000).

Both subtypes of acetylcholine receptors—nicotinic and muscarinic—are expressed throughout the striatum on distinct populations of neurons (Fig. 2). The functional implications of acetylcholine on movement depend largely on the collective receptor expression and function, consisting of diverse cellular and subcellular localizations. Besides the local striatal innervation, a number of cholinergic projections arise from nuclei of the

basal forebrain, including the medial septal nucleus, the nucleus basalis of Meynert, the vertical nucleus of the diagonal band and the horizontal limb of the diagonal band nucleus, as well as from the pedunculopontine-lateral dorsal tegmental nuclei (Fig. 2) (Everitt and Robbins, 1997).

3.1. Muscarinic receptors

Muscarinic receptors are a family of five G protein-coupled receptors consisting of two major groups: M1-like (M1, M3, and M5) and M2-like receptors (M2 and M4). All 5 muscarinic receptors are expressed in the striatum, with the highest levels being the M4 and M1 receptor subtypes, respectively.

M1-like receptors are coupled to Gq proteins that activate phospholipase C, resulting in activation of inositol trisphosphatase (IP3) and diacyl-glycerol (DAG), ultimately increasing intracellular calcium. M1 receptors are found primarily on striatal MSNs of both the direct and indirect pathways, where they are localized extrasynaptically or on dendritic spine necks (Hersch et al., 1994; Yan et al., 2001). Here, activation of M1 receptors results in enhanced responsivity to glutamatergic stimulation by diminishing the activity of potassium channels. There is also evidence that M1 receptor-induced activation of protein kinase C (PKC) enhances phosphorylation of NMDA receptors on MSNs, further enhancing the glutamatergic influence on these neurons (Ben-Ari et al., 1992). Striatopallidal neurons express M1 receptors that interact with adenosine A2A receptors and activate DARPP-32 signaling. On corticostriatal glutamatergic neurons, M1 receptors act as heteroreceptors and modulate glutamate release (Alcantara et al., 2001). M1 receptors are also localized on striatal GABAergic interneurons, though their functional role is unclear (Bernard et al., 1992; Alcantara et al., 2001).

Striatal M3 receptors are sparse, accounting for only 8% of the total striatal muscarinic receptor population (Hersch et al., 1994). M3 receptors are found on dendrites of medium spiny neurons, though limited to striatopallidal neurons (Yan et al., 2001). M3 receptors have been linked to decreased striatal dopamine release based on knock-out mouse studies (Zhang et al., 2002); this may occur by the stimulation of GABA release onto dopaminergic neurons. There is some evidence that presynaptic M3 receptors can also inhibit corticostriatal glutamate release (Niittykoski et al., 1999); however, the pharmacological tools used in these studies are insuffient to fully determine the subtype mediating these effects.

M5 receptor expression is quite low in the striatum (<5% of total muscarinic receptor binding (Hersch et al., 1994)) and may be limited to nigrostriatal dopaminergic terminals, where they may serve to inhibit striatal dopamine release (Foster et al., 2014).

M2-like receptors are coupled to Gi proteins that serve to inhibit adenylyl cyclase activity and close Ca_V2 calcium channels while opening Kir3 channels. Striatal M2 receptors act as inhibitory heteroreceptors on NPY-somatostatin-positive GABAergic interneurons and corticostriatal glutamatergic terminals (Hersch et al., 1994; Bernard et al., 1998). They also act as the primary autoreceptors for ChIs (Bernard et al., 1998). M2 receptors are mostly

extrasynaptic (Bernard et al., 1998), suggesting they are involved in “spillover” neurotransmission.

M4 receptors are the primary inhibitory muscarinic receptor on striatal medium spiny neurons, particularly those of the direct pathway where they are co-expressed with D1 receptors. Labeling is particularly dense in striosomes (Bernard et al., 1999). While labeling is also present in cholinergic neurons, these receptors are largely intracellular (Bernard et al., 1999). M4 knock-out mice and specific M4 receptor positive allosteric modulators have shown that these receptors are also localized on corticostriatal glutamatergic neurons, where, similarly to M2 receptors they diminish glutamate release via presynaptic inhibition (Pancani et al., 2014). M4 mRNA is also reported in striatal GABAergic interneurons (Bernard et al., 1998).

No investigations to date have examined alterations in muscarinic receptor levels in human dystonia patients and investigations in animal models are limited. However, in a genetic hamster model of primary paroxysmal dystonia there were no changes in muscarinic ligand binding in any brain region (Hamann et al., 2006).

3.2. Nicotinic receptors

Nicotinic receptors are ligand-gated ionotropic cholinergic receptors consisting of five subunits forming a central pore (for review see (Hurst et al., 2013)) Two subfamilies of subunits have been cloned: an alpha family (α2-α10) and a beta family (β2-β4). Receptors may be either homomeric for certain types of alpha subunits or heteromeric combinations of alpha and beta subunits. Receptor subunit consistency alters the permeability of the non-selective cation channel and its receptivity to acetylcholine and agonist binding. However, the alpha subunit is required for acetylcholine binding. Beta subunits may regulate the activity and sensitivity of nicotinic agonists and antagonists by altering binding and dissociation rates. α7 subunit-expressing receptors have high relative permeability to calcium while β2 subunit-expressing receptors have a high affinity for nicotine. The α5 and β3 subunits are complementary subunits, in that they cannot form functional channels but alter the properties of the receptor. For example, expression of α5 subunits increases the calcium permeability and alters the desensitization rate of the receptor (Wang et al., 1996).

The most common type of nicotinic receptor in the striatum is of the α4(non-α6)β2* type (∼70% of nicotinic receptors), though the α5, α6, and β3 subunits are also expressed at lower levels (∼20% of nicotinic receptors). α4β2* receptors are thought to be localized on both dopaminergic and non-dopaminergic neurons, including serotonergic raphestriatal efferents, and striatal GABAergic and ChIs. Striatal dopaminergic terminals also express several other types of nicotinic receptors, including α6β2β3, α6α4β2β3 and α4α5β2 (Zoli et al., 2002; Champtiaux et al., 2003). Only striatal non-dopaminergic terminals express α2α4β2 nicotinic receptors (Zoli et al., 2002). Conversely, corticostriatal afferents typically present with α7* containing subunits on nerve terminals (Marchi et al., 2002), which serve to stimulate release of glutamate. Though the subunit composition remains unknown, nicotinic receptors are also localized on fast-spiking GABAergic interneurons (Koos and Tepper, 2002) and on medium spiny projection neurons (Liu et al., 2007). Some evidence suggests these receptors may be of the α4β2* and α4α5β2* subtypes.

The main role for nicotinic receptors in the striatum appears to be modulation of dopamine release on nigrostriatal terminals (Giorguieff et al., 1976; Chesselet, 1984; Threlfell et al., 2012). Recent evidence suggests that dopamine transmission in the dorsal striatum is dependent upon α5 subunits, while α4α6β2β3 nicotinic receptors are required for dopamine neurotransmission in the nucleus accumbens core (Exley et al., 2012). Burst phase dopaminergic activity is concomitantly associated with ChI “pauses” in activity. As such, stimulation of nicotinic receptors on dopaminergic terminals is thought to act as a “filter” to enhance contrast between the tonic and burst phases of dopamine neuron activity (Exley et al., 2012).

The nicotinic receptor system has not been investigated in human dystonia patients and only superficially in one animal model of dystonia. Bao and colleagues (2010) found that transgenic DYT1 mice were more sensitive to phasic stimulation of dopamine release, an effect which was blocked by antagonism of nicotinic receptors with mecamylamine. Furthermore, mice expressing mutation of the β2 nicotinic receptor subunit do show increased sensitivity to nicotine-induced dystonic arousal complex (O'Neill et al., 2013). Collectively, acetylcholine receptor expression and signaling is clearly an area that is not well-understood and warrants further investigation.

4. Striatal Acetylcholine-Dopamine Interaction

Both dopamine terminals and ChIs densely innervate the striatum. Both also express the corresponding plethora of receptors necessary to interact with the other neurotransmitter system; dopamine terminals express nicotinic receptors (and perhaps M5 receptors), while ChIs likewise express D2 and D5 receptors. As such, striatal signaling is likely to involve an interaction between these two modulatory systems. Recent studies emphasize the importance of dopamine-mediated regulation of ChIs in modulating striatal outflow, and influencing the integration, processing and transmission of information along the dual striatofugal systems. Accordingly, an abnormal increase of striatal acetylcholine represents a key neurochemical sign of Parkinson's disease, supporting the importance of the acetylcholine-dopamine balance in proper striatal functioning (Pisani et al., 2007). In particular, D2 receptors located on ChIs have been identified as key mediators of the dopamine-dependent balance in the expression of striatal bidirectional synaptic plasticity (Wang et al., 2006).

The striatal acetylcholine and dopamine systems are traditionally viewed as antagonistic. Electrophysiologically, it is clear that dopamine suppresses acetylcholine release through dopamine receptors on ChIs. The modulatory effect of dopamine on striatal acetylcholine release is achieved through activation of D2 and D5 dopamine receptors located on ChIs. Activation of D2 receptors inhibits acetylcholine release, while D5 stimulation enhances GABA currents via protein kinase A (PKA) (Bertorelli and Consolo, 1990; DeBoer et al., 1996; Yan et al., 1997). As such, stimulation of both receptors likely serves to dampen acetylcholine release, though this has not been directly tested.

Although early studies may have suggested that acetylcholine likewise suppressed dopamine release, multiple lines of evidence indicated that stimulation of nicotinic receptors led to an increase in dopamine release (Giorguieff et al., 1976; Chesselet, 1984; Rapier et al., 1988;

el-Bizri and Clarke, 1994). However, demonstrating the role played by ChIs was limited by technical difficulties, such as the inability to regulate nicotinic function without rapid desensitization and the difficulty of coordinating ChI activation. More recent techniques such as optogenetics and designer receptor systems have provided new insights and confirmed a stimulatory effect of acetylcholine on dopamine release by way of nicotinic receptors. Recently, viral transfection of cholinergic cells with Cre-dependent channelrhodopsin2 revealed that synchronous activation of ChIs elevates striatal dopamine release and that this is dependent on nicotinic receptor activation (Threlfell et al., 2012). Similar results were obtained in the nucleus accumbens (Cachope et al., 2012). Furthermore, stimulation of thalamic projections to ChIs completely recapitulated these effects, suggesting that thalamic neurons can modulate dopamine release indirectly via ChIs.

The effects of muscarinic receptor activation add further complexity to the dopamine-acetylcholine interaction. Some studies have reported that stimulation of striatal muscarinic receptors leads to reductions in striatal dopamine release (Kemel et al., 1989; Xu et al., 1989; De Klippel et al., 1993). However, other findings have suggested that muscarinic receptor activation acts to enhance dopamine release, particularly by acting on M5 receptors (Lehmann and Langer, 1982; Zhang et al., 2002; Threlfell et al., 2010). In contrast, Foster and colleagues (2014) found that somatodendritic activation of M5 receptors using the novel M5 receptor positive allosteric modulator, VU0238429 acts to enhance nigral neuronal firing, while striatal M5 receptor activation inhibits dopamine release. Obviously, more work is critical in determining the precise role of muscarinic receptors on dopamine signaling and would be aided by more selective pharmacological compounds.

Collectively, these findings suggest that the interaction between the dopamine and acetylcholine systems in the striatum is more complex than the traditional “see-saw” model would suggest. Dopamine likely dampens acetylcholine release, while the effects of acetylcholine on dopamine release appear to be complementary rather than antagonistic, likely acting through nicotinic receptor activation. Further research using novel techniques to selectively modulate particular neurons and particular receptor subtypes will likely shed further light on their functional interplay.

5. Acetylcholine and Movement Control

ChIs are believed to correspond to the TANs recorded in vivo from the primate striatum, which respond to conditioned stimuli with a pause response in their ongoing firing activity and play significant roles in the selection of appropriate behavioral responses to environmental events (Kimura et al., 2003; Cragg, 2006; Apicella, 2007; Aosaki et al., 2010). The pause response begins with an initial depolarizing phase followed by a pause in spike firing and ensuing rebound excitation. The onset of the pause phase coincides with a surge in firing activity of dopaminergic neurons in the substantia nigra pars compacta. ChIs scattered in widespread portions of the striatum acquire the pause response during learning and their activity becomes synchronized. The mechanisms underlying the pause response of ChIs are complex and still not completely understood. An intact innervation from both the dopaminergic nigrostriatal system and thalamic nuclei involved in sensorimotor integration are required for the expression of the pause response (Aosaki et al., 1994; Matsumoto et al.,

2001), though a short-latency corticostriatal excitatory response to reward-related cues remains after inactivation of the thalamostriatal inputs. Moreover, the potentiation of GABAergic transmission may also play a role (Suzuki et al., 2001; Bonsi et al., 2003; Bonsi et al., 2004; Reynolds et al., 2004). In vitro experiments suggest that an initial excitation of ChIs in response to thalamic stimulation induces acetylcholine release and activation of presynaptic nicotinic receptors located on dopaminergic terminals, causing in turn the release of dopamine and postsynaptic D2 receptor activation, which prolongs the AHP by inhibiting H-current and sodium channels (Aosaki et al., 2010; Ding et al., 2010).

In vivo and in vitro studies have shown that the efficacy of both excitatory and inhibitory synapses of striatal ChIs undergoes long-term plastic changes (Suzuki et al., 2001; Bonsi et al., 2004; Reynolds et al., 2004), which are likely involved in the generation of the firing activity pattern in striatal ChIs. In acute slice preparations, the high frequency stimulation of glutamatergic afferent fibers induces a long-term potentiation (LTP) of both the AMPA-mediated excitatory and GABAergic inhibitory postsynaptic potentials, which is dependent on D5 receptor activation, and on a critical level of intracellular Ca^{2+} rise through Ca_V1 channels (Suzuki et al., 2001; Bonsi et al., 2004). Furthermore, spike-timing-dependent plasticity (STDP) protocols induced both depression and potentiation of synaptic efficacy (Fino et al., 2008). STDP–LTP was mainly presynaptic and involved NMDA-receptor activation, while long-term depression (STDP–LTD) had a postsynaptic origin and involved metabotropic glutamate receptors.

The pattern of spiking and pauses of ChIs is able to filter the striatal output by directly and indirectly influencing MSN activity (Bonsi et al., 2011). The pauses in ChIs activity can powerfully enhance the salience of dopamine signaling (Threlfell et al., 2010) and transform the reward signal arising from dopaminergic neurons into a gating signal for LTD induction at MSNs (Wang et al., 2006). When the burst-pause response of ChIs was reproduced in a striatal slice preparation by high-frequency thalamic stimulation, it triggered a transient presynaptic muscarinic M2-class receptor-mediated suppression of cortical inputs to both direct and indirect pathway MSNs, followed by a prolonged muscarinic M1 receptor-dependent enhancement of postsynaptic responsiveness in striatopallidal neurons which extends during the pause response, when the cortical drive resumes, thus creating a late temporal window when the corticostriatal input can selectively drive activity in the striatopallidal network thought to control action suppression (Ding et al., 2010). Therefore the pause-response of ChIs provides a neural substrate for attentional shift and cessation of ongoing motor activity in response to salient environmental stimuli.

6. Cholinergic Function in Animal Models of Dystonia

In the last decade, a number of dystonia animal models have been generated, ranging from invertebrates, such as Caenorhabditis elegans and Drosophila melanogaster, to rodents and non-human primates (Tassone et al., 2011; Oleas et al., 2013). The phenotypic correlation, in most dystonia models, has revealed some inconsistencies especially when evaluating the behavioural, motor phenotypic features, neurochemical and neuroanatomical changes. In spite of these apparent discrepancies, that may be attributed to different experimental factors, but also to the intrinsic nature of a very heterogeneous disorder (Breakefield et al.,

2008; Tanabe et al., 2009), the electrophysiological phenotype appears to be constantly reproducible across different mouse lines as well as in rat. Indeed, they produced convergent evidence suggesting common pathogenic features in dystonia (Ledoux et al., 2013), such as the involvement of basal ganglia and the prominent role of dopamine signaling (Augood et al., 2004; Perlmutter and Mink, 2004; Pisani et al., 2006; Wichmann, 2008; Zhao et al., 2008; Bragg et al., 2011; Albanese and Lalli, 2012; Goodchild et al., 2013).

By far the most extensively studied type of dystonia is DYT1, or early-onset torsion dystonia, in which multiple genotypic models have been generated. Various transgenic rodent models that overexpressed wild-type torsinA or mutant ΔE-torsinA have been produced using different promoters (Oleas et al., 2013). The mouse lines overexpressing human ΔE-torsinA were generated using as promoter either neuron-specific enolase (Shashidharan et al., 2005), the human cytomegalovirus (hMT mice; (Sharma et al., 2005)) or a murine prion protein promoter (Grundmann et al., 2007). Another transgenic mouse line overexpresses human ΔE-torsinA specifically in dopaminergic neurons of the midbrain (Page et al., 2010). In addition to overexpression models, DYT1 heterozygous knock-in mouse lines have been generated which recapitulate the trinucleotide deletion in DYT1/Tor1a gene observed most often in patients with DYT1 dystonia, and the loss of one of a pair of glutamic acid residues in the protein torsinA (Dang et al., 2005; Goodchild et al., 2005). Brain region-specific DYT1 conditional KO mice have been used to understand how specific brain region or cell types contribute to the pathophysiology of the disease: the cerebral cortex-specific (DYT1 cKO; (Yokoi et al., 2008)), the striatum-specific (DYT1 sKO; (Yokoi et al., 2011)), and the cholinergic neuron-specific (DYT1 ChKO; (Sciamanna et al., 2012)) DYT1 conditional KO mice. In addition to mouse models, a transgenic rat has been recently generated by overexpressing human ΔE-torsinA from the human torsinA promoter (Grundmann et al., 2012).

Most of the DYT1 rodent models show only subtle neurochemical and behavioral alterations (Raike et al., 2005). Furthermore, these abnormalities are not consistently observed in the different models. Indeed, transgene overexpression may result in non-physiological and ectopic protein expression, as well as in differences in the transgene insertion site, copy number, expression level, and pattern of expression. However, alterations in striatal physiology were consistently observed in different rodent models of DYT1 dystonia (Pisani et al., 2006; Martella et al., 2009; Grundmann et al., 2012; Sciamanna et al., 2012; Martella et al., 2014). Electrophysiological experiments identified a remarkable anomaly consisting in the reversal of the normal inhibitory response of striatal ChIs to dopamine D2 receptor activation, termed paradoxical excitation. D2 receptor activation is coupled to inhibition of $Ca_V2.2$/N-type channels in ChIs. In ChIs recorded from mice overexpressing mutant torsinA, the sensitivity to quinpirole-mediated inhibition of the total calcium evoked currents (HVA) was increased. The functional increase of the $Ca_V2.2$ - mediated current fraction should enhance the inhibitory effect of quinpirole. Conversely, the paradoxical excitation observed could result from the complex regulation of the pacemaking activity of these interneurons. Calcium currents are selectively coupled to calcium-dependent potassium conductances mediating the after-hyperpolarization (AHP). In transgenic mice, the membrane depolarization coupled to the increase in firing discharge induced by quinpirole was coupled to a reduction in the mAHP amplitude, thereby reducing the

threshold for action potential discharge. Accordingly, chelation of intracellular calcium completely abolished the effect of quinpirole, suggesting that activation of calcium-dependent potassium conductances plays a role in the altered D2 receptor-mediated response (Sciamanna et al., 2011).

This alteration was observed in all rodent models tested to date (transgenic, knock-in and ChKO mice, Fig. 3), suggesting that it may be considered as an endophenotypic trait of DYT1 dystonia. It is also associated with imbalanced expression of corticostriatal synaptic plasticity: LTD and synaptic depotentiation were lost, while the amplitude of LTP was enhanced both in transgenic and knock-in mice (Fig. 4; Martella et al., 2009, 2014).

In addition to the evidence of impaired bidirectional plasticity, cholinergic dysfunction has been also implicated in the altered synaptic integration between corticostriatal and thalamostriatal inputs (Sciamanna et al., 2012b). In mice with the DYT1 dystonia mutation, activation of thalamostriatal inputs evoked a shortened pause and elicited an abnormal rebound firing activity in ChIs. This pattern of firing activity caused a profound disruption of the temporal sequence of synaptic activity mediated by M1 and M2 muscarinic receptors in MSNs, consisting of an increase in postsynaptic M1-dependent currents and a decrease of M2-mediated presynaptic inhibition, and resulting in an altered synaptic integration between thalamostriatal and corticostriatal inputs. Functionally, such a “delayed”, aberrant integration might impact the action selection process, ultimately favouring DYT1 gene mutation carriers to develop clinically manifesting dystonic movements.

In agreement with a central role of acetylcholine, by lowering endogenous acetylcholine tone or by blocking postsynaptic M1 muscarinic receptors, the normal synaptic sequence was restored. These observations provide robust evidence that striatal ChI activity is profoundly affected in DYT1 dystonia models, resulting in distortion of striatal network activity.

Recent developments have facilitated the investigation of several other types of isolated dystonias, including DYT6 (THAP1), DYT11 (myoclonus-dytonia, SGCE), and DYT25 (GNAL). While mouse models of DYT11 and DYT25 have shown alterations in striatal dopamine function (Corvol et al., 2007; Herve, 2011; Alcacer et al., 2012; Zhang et al., 2012), nothing is presently known of the effects of altering these genes on cholinergic function due to their novelty.

A role of ChIs in DYT1 dystonia was first indirectly suggested by the pattern of expression of the gene product, torsinA during normal striatal development. A striking increase in levels was noted specifically in striatal ChIs during the third week of postnatal development, suggesting that this protein plays a role in the maturation of circuits involving these interneurons (Oberlin et al., 2004). Interestingly, a recent mouse model of DYT1 dystonia stresses the importance of torsinA during phases of synaptogenesis which require high levels of protein synthesis (Liang et al., 2014). The specific function of torsinA in relation to striatal development and how its mutation causes the changes in responsiveness of ChIs to D2 receptor stimulation remains to be explored.

Symptomatic rodent models have also indicated a role for acetylcholine in dystonia. For example, dystonia musculorum (Dst(dt-J) mutants show spastic ataxia and dystonic movements and have been shown to have several neurochemical alterations, including enhanced acetylcholinesterase activity in the basal ganglia (Clement et al., 2012). Interestingly, mice which carry a missense mutation in the gene encoding beta-2 neuronal nicotinic receptor subunit (CHRNB2) exhibit paroxysmal dystonic movements induced by low doses of nicotine (Teper et al., 2007; O'Neill et al., 2013).

Surprisingly, few studies have analyzed the mechanism of action of anticholinergic drugs, despite the evidence that it still represents one of the few medical options for the treatment of dystonia (Jankovic, 2013). Presumably, their symptomatic effect is centrally mediated and, at least in part, they act by counteracting the imbalance between striatal dopamine and acetylcholine. The alterations in striatal physiology observed in both genetic and symptomatic rodent models of dystonia support the idea that the disruption of the balance between dopamine and acetylcholine transmission within the striatum causes the impairment of the striatal output. Indeed, restoring a normal level of cholinergic transmission with anticholinergic drugs is able to rescue the deficits in corticostriatal synaptic plasticity in DYT1 transgenic and in knock-in mice (Martella et al., 2009; Martella et al., 2014). The restorative effects of anticholinergic drugs on synaptic plasticity have been linked to reversal of motor learning abnormalities in DYT1 knock-in mice (Dang et al., 2012). In line with the concept that an excessive cholinergic transmission overactivates muscarinic M1 receptors on MSNs thus preventing LTD induction in favor of LTP (Bonsi et al., 2008), pharmacological agents reducing cholinergic transmission (hemicholinium) as well as cholinergic receptor antagonists (pirenzepine, trihexyphenidyl) were able to restore a normal expression of LTD and synaptic depotentiation (SD). A recent detailed electrophysiological study demonstrated that M1 muscarinic antagonism is specifically required to offset plasticity deficits in knock-in mice. In striatal slice preparations, trihexyphenydil, pirenzepine, and the novel selective M1 antagonist VU0255035 were able to restore a normal LTD, as well as SD (Maltese et al., 2014). These observations are in line with the evidence that, in a model of haloperidol-induced catalepsy, anticholinergic drugs displaying a higher affinity for M1 receptors, were more potent in counteracting catalepsy (Erosa-Rivero et al., 2014). These observations are of particular interest as dystonic reactions can appear as a consequence of pharmacological treatment with neuroleptics, and suggest that highly selective antagonists of M1 receptors might be useful in the treatment of dystonia, although subtype selectivity will be of key relevance in order to obtain clinical efficacy without adverse effects.

7. Conclusions

One of the most daunting challenges for dystonia research is the inability to adequately investigate potential therapeutics in animal models, due to the lack of a consistent behavioral endpoint. The establishment of a stable endophenotype for dystonia would allow comparison of outcomes across genetic and non-genetic animal models. As such, it is important to determine non-behavioral endpoints that could serve as a marker of efficacy for the development of treatments for dystonia. While animal models have been developed for some genetic forms of dystonia, the majority do not display recognizable dystonia, with some notable recent exceptions (Liang et al., 2014). Animal models that do have overt

dystonic limbs or postures typically involve methods of induction that present useful experimental tools but may not reproduce mechanisms occurring in the clinical population (Wilson and Hess, 2013).

In multiple dystonia rodent models we have established that a consistent alteration in striatal physiology occurs characterized by paradoxical excitation of ChIs in the presence of a D2 receptor agonist, and accompanied by abnormal expression of bidirectional synaptic plasticity at corticostriatal synapses. This abnormality is thought to stem from a hypercholinergic state, whereby overactivation of M1 receptors on MSNs hampers production of LTD. As such, perseveration of unwanted sensorimotor learning may occur, one of the hallmark pathophysiological findings in dystonia patients and in some carriers for genetic dystonia (Ghilardi et al., 2003; Quartarone et al., 2008; Carbon et al., 2010; Peterson et al., 2010). Abnormal electrophysiological activation of ChIs and subsequent changes in synaptic plasticity could be a useful endophenotype for the investigation of pharmacotherapeutics and perhaps other therapies. Indeed, in the rodent models these changes are rectified following administration of the most common treatment administered to dystonia patients, trihexyphenidyl.

While this electrophysiological abnormality is consistent among multiple DYT1 rodent models, it is unknown whether alterations in striatal plasticity and hypercholinergic activity are also key players in other types of dystonia, both genetic and non-genetic. Addressing this question was not possible until the recent development of mouse models for other genetic forms of dystonia. Recent advances in experimental tools may also be able to aid us in answering such questions. Techniques using optogenetics, DREADDs and CRISPR will offer unparalleled abilities to alter specific targets in order to determine their significance in motor learning and control. In addition, the development of protocols for directed differentiation of human pluripotent stem cells into striatal interneurons would be an ideal tool to obtain human neurons for confirming findings from animal models or gaining new insights into mechanisms of dystonia (Capetian et al., 2014). Surely, the most exciting advances are yet to come, as they are only now becoming widely used and applied to examine movement disorders, particularly dystonia.

Acknowledgments

We wish to thank Dr. K. Grundmann for sharing data on transgenic rats and Dr. M. Maltese for helping preparing illustrations. This work was supported by: Ministero Salute (Progetto Finalizzato RF-2010-2311657 to AP), Dystonia Medical Research Foundation (DMRF) and Foundation for Dystonia Research (FDR) to AP, Johnson Family Dystonia Research Accelleration Fund (DGS), the UAB Bachmann-Strauss Center of Excellence in Dystonia (DGS), and NIH grants P50NS037409 and P01NS087997 (DGS).

References

Albanese A, Lalli S. Update on dystonia. Curr Opin Neurol. 2012; 25:483–490. [PubMed: 22610459]

Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013; 28:863–873. [PubMed: 23649720]

Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci. 1989; 12:366–375. [PubMed: 2479133]

Alcacer C, Santini E, Valjent E, Gaven F, Girault JA, Herve D. Galpha(olf) mutation allows parsing the role of cAMP-dependent and extracellular signal-regulated kinase-dependent signaling in L-3,4-dihydroxyphenylalanine-induced dyskinesia. J Neurosci. 2012; 32:5900–5910. [PubMed: 22539851]

Alcantara AA, Mrzljak L, Jakab RL, Levey AI, Hersch SM, Goldman-Rakic PS. Muscarinic m1 and m2 receptor proteins in local circuit and projection neurons of the primate striatum: anatomical evidence for cholinergic modulation of glutamatergic prefronto-striatal pathways. J Comp Neurol. 2001; 434:445–460. [PubMed: 11343292]

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986; 9:357–381. [PubMed: 3085570]

Aosaki T, Kimura M, Graybiel AM. Temporal and spatial characteristics of tonically active neurons of the primate's striatum. J Neurophysiol. 1995; 73:1234–1252. [PubMed: 7608768]

Aosaki T, Miura M, Suzuki T, Nishimura K, Masuda M. Acetylcholine-dopamine balance hypothesis in the striatum: an update. Geriatr Gerontol Int. 2010; 10(Suppl 1):S148–157. [PubMed: 20590830]

Aosaki T, Tsubokawa H, Ishida A, Watanabe K, Graybiel AM, Kimura M. Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. J Neurosci. 1994; 14:3969–3984. [PubMed: 8207500]

Apicella P. Leading tonically active neurons of the striatum from reward detection to context recognition. Trends Neurosci. 2007; 30:299–306. [PubMed: 17420057]

Argyelan M, Carbon M, Niethammer M, Ulug AM, Voss HU, Bressman SB, Dhawan V, Eidelberg D. Cerebellothalamocortical connectivity regulates penetrance in dystonia. J Neurosci. 2009; 29:9740–9747. [PubMed: 19657027]

Augood SJ, Hollingsworth Z, Albers DS, Yang L, Leung J, Breakefield XO, Standaert DG. Dopamine transmission in DYT1 dystonia. Adv Neurol. 2004; 94:53–60. [PubMed: 14509654]

Balcioglu A, Kim MO, Sharma N, Cha JH, Breakefield XO, Standaert DG. Dopamine release is impaired in a mouse model of DYT1 dystonia. J Neurochem. 2007; 102:783–788. [PubMed: 17550429]

Ballion B, Mallet N, Bezard E, Lanciego JL, Gonon F. Intratelencephalic corticostriatal neurons equally excite striatonigral and striatopallidal neurons and their discharge activity is selectively reduced in experimental parkinsonism. Eur J Neurosci. 2008; 27:2313–2321. [PubMed: 18445222]

Bateup HS, Santini E, Shen W, Birnbaum S, Valjent E, Surmeier DJ, Fisone G, Nestler EJ, Greengard P. Distinct subclasses of medium spiny neurons differentially regulate striatal motor behaviors. Proc Natl Acad Sci U S A. 2010; 107:14845–14850. [PubMed: 20682746]

Beatty JA, Sullivan MA, Morikawa H, Wilson CJ. Complex autonomous firing patterns of striatal low-threshold spike interneurons. J Neurophysiol. 2012; 108:771–781. [PubMed: 22572945]

Ben-Ari Y, Aniksztejn L, Bregestovski P. Protein kinase C modulation of NMDA currents: an important link for LTP induction. Trends Neurosci. 1992; 15:333–339. [PubMed: 1382331]

Benarroch EE. Effects of acetylcholine in the striatum. Recent insights and therapeutic implications. Neurology. 2012; 79:274–281. [PubMed: 22802594]

Bennett BD, Bolam JP. Characterization of calretinin-immunoreactive structures in the striatum of the rat. Brain Res. 1993; 609:137–148. [PubMed: 8508297]

Bennett BD, Wilson CJ. Synaptic regulation of action potential timing in neostriatal cholinergic interneurons. J Neurosci. 1998; 18:8539–8549. [PubMed: 9763496]

Bennett BD, Callaway JC, Wilson CJ. Intrinsic membrane properties underlying spontaneous tonic firing in neostriatal cholinergic interneurons. J Neurosci. 2000; 20:8493–8503. [PubMed: 11069957]

Berardelli A, Rothwell JC, Hallett M, Thompson PD, Manfredi M, Marsden CD. The pathophysiology of primary dystonia. Brain. 1998; 121(Pt 7):1195–1212. [PubMed: 9679773]

Berendse HW, Groenewegen HJ. Organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum. J Comp Neurol. 1990; 299:187–228. [PubMed: 2172326]

Bernard V, Normand E, Bloch B. Phenotypical characterization of the rat striatal neurons expressing muscarinic receptor genes. J Neurosci. 1992; 12:3591–3600. [PubMed: 1527598]

Bernard V, Levey AI, Bloch B. Regulation of the subcellular distribution of m4 muscarinic acetylcholine receptors in striatal neurons in vivo by the cholinergic environment: evidence for

regulation of cell surface receptors by endogenous and exogenous stimulation. J Neurosci. 1999; 19:10237–10249. [PubMed: 10575021]

Bernard V, Laribi O, Levey AI, Bloch B. Subcellular redistribution of m2 muscarinic acetylcholine receptors in striatal interneurons in vivo after acute cholinergic stimulation. J Neurosci. 1998; 18:10207–10218. [PubMed: 9822774]

Bertorelli R, Consolo S. D1 and D2 dopaminergic regulation of acetylcholine release from striata of freely moving rats. J Neurochem. 1990; 54:2145–2148. [PubMed: 1971013]

Black KJ, Ongur D, Perlmutter JS. Putamen volume in idiopathic focal dystonia. Neurology. 1998; 51:819–824. [PubMed: 9748033]

Blood AJ, Flaherty AW, Choi JK, Hochberg FH, Greve DN, Bonmassar G, Rosen BR, Jenkins BG. Basal ganglia activity remains elevated after movement in focal hand dystonia. Ann Neurol. 2004; 55:744–748. [PubMed: 15122718]

Bolam JP, Smith Y. The GABA and substance P input to dopaminergic neurones in the substantia nigra of the rat. Brain Res. 1990; 529:57–78. [PubMed: 1704287]

Bolam JP, Wainer BH, Smith AD. Characterization of cholinergic neurons in the rat neostriatum. A combination of choline acetyltransferase immunocytochemistry, Golgi-impregnation and electron microscopy. Neuroscience. 1984; 12:711–718. [PubMed: 6382048]

Bolam JP, Ingham CA, Izzo PN, Levey AI, Rye DB, Smith AD, Wainer BH. Substance P-containing terminals in synaptic contact with cholinergic neurons in the neostriatum and basal forebrain: a double immunocytochemical study in the rat. Brain Res. 1986; 397:279–289. [PubMed: 2432992]

Bonsi P, De Persis C, Calabresi P, Bernardi G, Pisani A. Coordinate high-frequency pattern of stimulation and calcium levels control the induction of LTP in striatal cholinergic interneurons. Learn Mem. 2004; 11:755–760. [PubMed: 15537735]

Bonsi P, Florio T, Capozzo A, Pisani A, Calabresi P, Siracusano A, Scarnati E. Behavioural learning-induced increase in spontaneous GABAA-dependent synaptic activity in rat striatal cholinergic interneurons. Eur J Neurosci. 2003; 17:174–178. [PubMed: 12534982]

Bonsi P, Sciamanna G, Mitrano DA, Cuomo D, Bernardi G, Platania P, Smith Y, Pisani A. Functional and ultrastructural analysis of group I mGluR in striatal fast-spiking interneurons. Eur J Neurosci. 2007; 25:1319–1331. [PubMed: 17425558]

Bonsi P, Martella G, Cuomo D, Platania P, Sciamanna G, Bernardi G, Wess J, Pisani A. Loss of muscarinic autoreceptor function impairs long-term depression but not long-term potentiation in the striatum. J Neurosci. 2008; 28:6258–6263. [PubMed: 18550768]

Bonsi P, Cuomo D, Martella G, Madeo G, Schirinzi T, Puglisi F, Ponterio G, Pisani A. Centrality of striatal cholinergic transmission in Basal Ganglia function. Front Neuroanat. 2011; 5:6. [PubMed: 21344017]

Bostan AC, Strick PL. The cerebellum and basal ganglia are interconnected. Neuropsychol Rev. 2010; 20:261–270. [PubMed: 20811947]

Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. Proc Natl Acad Sci U S A. 2010; 107:8452–8456. [PubMed: 20404184]

Bostan AC, Dum RP, Strick PL. Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn Sci. 2013; 17:241–254. [PubMed: 23579055]

Bradfield LA, Hart G, Balleine BW. The role of the anterior, mediodorsal, and parafascicular thalamus in instrumental conditioning. Front Syst Neurosci. 2013a; 7:51. [PubMed: 24130522]

Bradfield LA, Bertran-Gonzalez J, Chieng B, Balleine BW. The thalamostriatal pathway and cholinergic control of goal-directed action: interlacing new with existing learning in the striatum. Neuron. 2013b; 79:153–166. [PubMed: 23770257]

Bradley D, Whelan R, Walsh R, Reilly RB, Hutchinson S, Molloy F, Hutchinson M. Temporal discrimination threshold: VBM evidence for an endophenotype in adult onset primary torsion dystonia. Brain. 2009; 132:2327–2335. [PubMed: 19525326]

Bragg DC, Armata IA, Nery FC, Breakefield XO, Sharma N. Molecular pathways in dystonia. Neurobiol Dis. 2011; 42:136–147. [PubMed: 21134457]

Brashear A, Mulholland GK, Zheng QH, Farlow MR, Siemers ER, Hutchins GD. PET imaging of the pre-synaptic dopamine uptake sites in rapid-onset dystonia-parkinsonism (RDP). Mov Disord. 1999; 14:132–137. [PubMed: 9918356]

Breakefield XO, Blood AJ, Li Y, Hallett M, Hanson PI, Standaert DG. The pathophysiological basis of dystonias. Nat Rev Neurosci. 2008; 9:222–234. [PubMed: 18285800]

Brocks DR. Anticholinergic drugs used in Parkinson's disease: An overlooked class of drugs from a pharmacokinetic perspective. J Pharm Pharm Sci. 1999; 2:39–46. [PubMed: 10952768]

Burke RE, Fahn S, Marsden CD. Torsion dystonia: a double-blind, prospective trial of high-dosage trihexyphenidyl. Neurology. 1986; 36:160–164. [PubMed: 3511401]

Cachope R, Mateo Y, Mathur BN, Irving J, Wang HL, Morales M, Lovinger DM, Cheer JF. Selective activation of cholinergic interneurons enhances accumbal phasic dopamine release: setting the tone for reward processing. Cell Rep. 2012; 2:33–41. [PubMed: 22840394]

Calabresi P, Stefani A, Mercuri NB, Bernardi G. Acetylcholine-dopamine balance in striatum: is it still a target for antiparkinsonian therapy? EXS. 1989; 57:315–321. [PubMed: 2533102]

Calabresi P, Picconi B, Tozzi A, Di Filippo M. Dopamine-mediated regulation of corticostriatal synaptic plasticity. Trends Neurosci. 2007a; 30:211–219. [PubMed: 17367873]

Calabresi P, Centonze D, Gubellini P, Pisani A, Bernardi G. Blockade of M2-like muscarinic receptors enhances long-term potentiation at corticostriatal synapses. Eur J Neurosci. 1998; 10:3020–3023. [PubMed: 9758172]

Calabresi P, Galletti F, Saggese E, Ghiglieri V, Picconi B. Neuronal networks and synaptic plasticity in Parkinson's disease: beyond motor deficits. Parkinsonism Relat Disord. 2007b; 13(Suppl 3):S259–262. [PubMed: 18267247]

Calabresi P, Picconi B, Tozzi A, Ghiglieri V, Di Filippo M. Direct and indirect pathways of basal ganglia: a critical reappraisal. Nat Neurosci. 2014; 17:1022–1030. [PubMed: 25065439]

Calderon DP, Fremont R, Kraenzlin F, Khodakhah K. The neural substrates of rapid-onset Dystonia-Parkinsonism. Nat Neurosci. 2011; 14:357–365. [PubMed: 21297628]

Campos F, Alfonso M, Duran R. In vivo modulation of alpha7 nicotinic receptors on striatal glutamate release induced by anatoxin-A. Neurochem Int. 2010; 56:850–855. [PubMed: 20347906]

Capetian P, Pauly MG, Azmitia LM, Klein C. Striatal cholinergic interneurons in isolated generalized dystonia-rationale and perspectives for stem cell-derived cellular models. Front Cell Neurosci. 2014; 8:205. [PubMed: 25120431]

Carbon M, Argyelan M, Habeck C, Ghilardi MF, Fitzpatrick T, Dhawan V, Pourfar M, Bressman SB, Eidelberg D. Increased sensorimotor network activity in DYT1 dystonia: a functional imaging study. Brain. 2010; 133:690–700. [PubMed: 20207699]

Casey DE, Gerlach J, Christensson E. Dopamine, acetylcholine, and GABA effects in acute dystonia in primates. Psychopharmacology (Berl). 1980; 70:83–87. [PubMed: 6775341]

Centonze D, Grande C, Usiello A, Gubellini P, Erbs E, Martin AB, Pisani A, Tognazzi N, Bernardi G, Moratalla R, Borrelli E, Calabresi P. Receptor subtypes involved in the presynaptic and postsynaptic actions of dopamine on striatal interneurons. J Neurosci. 2003; 23:6245–6254. [PubMed: 12867509]

Champtiaux N, Gotti C, Cordero-Erausquin M, David DJ, Przybylski C, Lena C, Clementi F, Moretti M, Rossi FM, Le Novere N, McIntosh JM, Gardier AM, Changeux JP. Subunit composition of functional nicotinic receptors in dopaminergic neurons investigated with knock-out mice. J Neurosci. 2003; 23:7820–7829. [PubMed: 12944511]

Chang HT, Kita H. Interneurons in the rat striatum: relationships between parvalbumin neurons and cholinergic neurons. Brain Res. 1992; 574:307–311. [PubMed: 1638402]

Chesselet MF. Presynaptic regulation of neurotransmitter release in the brain: facts and hypothesis. Neuroscience. 1984; 12:347–375. [PubMed: 6146946]

Clement C, Lalonde R, Strazielle C. Acetylcholinesterase activity in the brain of dystonia musculorum (Dst(dt-J)) mutant mice. Neurosci Res. 2012; 72:79–86. [PubMed: 21978551]

Consolo S, Baldi G, Giorgi S, Nannini L. The cerebral cortex and parafascicular thalamic nucleus facilitate in vivo acetylcholine release in the rat striatum through distinct glutamate receptor subtypes. Eur J Neurosci. 1996a; 8:2702–2710. [PubMed: 8996820]

Consolo S, Baronio P, Guidi G, Di Chiara G. Role of the parafascicular thalamic nucleus and N-methyl-D-aspartate transmission in the D1-dependent control of in vivo acetylcholine release in rat striatum. Neuroscience. 1996b; 71:157–165. [PubMed: 8834399]

Cools AR, Hendriks G, Korten J. The acetylcholine-dopamine balance in the basal ganglia of rhesus monkeys and its role in dynamic, dystonic, dyskinetic, and epileptoid motor activities. J Neural Transm. 1975; 36:91–105. [PubMed: 1151371]

Corner BD. Dystonia musculorum deformans in siblings; treated with artane (trihexyphenidyl). Proc R Soc Med. 1952; 45:451–452. [PubMed: 14957878]

Corvol JC, Valjent E, Pascoli V, Robin A, Stipanovich A, Luedtke RR, Belluscio L, Girault JA, Herve D. Quantitative changes in Galphaolf protein levels, but not D1 receptor, alter specifically acute responses to psychostimulants. Neuropsychopharmacology. 2007; 32:1109–1121. [PubMed: 17063155]

Cragg SJ. Variable dopamine release probability and short-term plasticity between functional domains of the primate striatum. J Neurosci. 2003; 23:4378–4385. [PubMed: 12764127]

Cragg SJ. Meaningful silences: how dopamine listens to the ACh pause. Trends Neurosci. 2006; 29:125–131. [PubMed: 16443285]

Cragg SJ, Rice ME. DAncing past the DAT at a DA synapse. Trends Neurosci. 2004; 27:270–277. [PubMed: 15111009]

Cui G, Jun SB, Jin X, Pham MD, Vogel SS, Lovinger DM, Costa RM. Concurrent activation of striatal direct and indirect pathways during action initiation. Nature. 2013; 494:238–242. [PubMed: 23354054]

Damsma G, Westerink BH, de Vries JB, Horn AS. The effect of systemically applied cholinergic drugs on the striatal release of dopamine and its metabolites, as determined by automated brain dialysis in conscious rats. Neurosci Lett. 1988; 89:349–354. [PubMed: 2458554]

Dang MT, Yokoi F, McNaught KS, Jengelley TA, Jackson T, Li J, Li Y. Generation and characterization of Dyt1 DeltaGAG knock-in mouse as a model for early-onset dystonia. Exp Neurol. 2005; 196:452–463. [PubMed: 16242683]

Dang MT, Yokoi F, Cheetham CC, Lu J, Vo V, Lovinger DM, Li Y. An anticholinergic reverses motor control and corticostriatal LTD deficits in Dyt1 DeltaGAG knock-in mice. Behav Brain Res. 2012; 226:465–472. [PubMed: 21995941]

Dautan D, Huerta-Ocampo I, Witten IB, Deisseroth K, Bolam JP, Gerdjikov T, Mena-Segovia J. A major external source of cholinergic innervation of the striatum and nucleus accumbens originates in the brainstem. J Neurosci. 2014; 34:4509–4518. [PubMed: 24671996]

De Klippel N, Sarre S, Ebinger G, Michotte Y. Effect of M1-and M2-muscarinic drugs on striatal dopamine release and metabolism: an in vivo microdialysis study comparing normal and 6-hydroxydopamine-lesioned rats. Brain Res. 1993; 630:57–64. [PubMed: 8118706]

DeBoer P, Heeringa MJ, Abercrombie ED. Spontaneous release of acetylcholine in striatum is preferentially regulated by inhibitory dopamine D2 receptors. Eur J Pharmacol. 1996; 317:257–262. [PubMed: 8997608]

Dimova R, Vuillet J, Nieoullon A, Kerkerian-Le Goff L. Ultrastructural features of the choline acetyltransferase-containing neurons and relationships with nigral dopaminergic and cortical afferent pathways in the rat striatum. Neuroscience. 1993; 53:1059–1071. [PubMed: 7685068]

Ding J, Peterson JD, Surmeier DJ. Corticostriatal and thalamostriatal synapses have distinctive properties. J Neurosci. 2008; 28:6483–6492. [PubMed: 18562619]

Ding J, Guzman JN, Tkatch T, Chen S, Goldberg JA, Ebert PJ, Levitt P, Wilson CJ, Hamm HE, Surmeier DJ. RGS4-dependent attenuation of M4 autoreceptor function in striatal cholinergic interneurons following dopamine depletion. Nat Neurosci. 2006; 9:832–842. [PubMed: 16699510]

Ding JB, Guzman JN, Peterson JD, Goldberg JA, Surmeier DJ. Thalamic gating of corticostriatal signaling by cholinergic interneurons. Neuron. 2010; 67:294–307. [PubMed: 20670836]

Dube L, Smith AD, Bolam JP. Identification of synaptic terminals of thalamic or cortical origin in contact with distinct medium-size spiny neurons in the rat neostriatum. J Comp Neurol. 1988; 267:455–471. [PubMed: 3346370]

Dunah AW, Standaert DG. Subcellular segregation of distinct heteromeric NMDA glutamate receptors in the striatum. J Neurochem. 2003; 85:935–943. [PubMed: 12716425]

el-Bizri H, Clarke PB. Regulation of nicotinic receptors in rat brain following quasi-irreversible nicotinic blockade by chlorisondamine and chronic treatment with nicotine. Br J Pharmacol. 1994; 113:917–925. [PubMed: 7858886]

Ellender TJ, Huerta-Ocampo I, Deisseroth K, Capogna M, Bolam JP. Differential modulation of excitatory and inhibitory striatal synaptic transmission by histamine. J Neurosci. 2011; 31:15340–15351. [PubMed: 22031880]

Ellender TJ, Harwood J, Kosillo P, Capogna M, Bolam JP. Heterogeneous properties of central lateral and parafascicular thalamic synapses in the striatum. J Physiol. 2013; 591:257–272. [PubMed: 23109111]

Eltahawy HA, Saint-Cyr J, Giladi N, Lang AE, Lozano AM. Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation. Neurosurgery. 2004; 54:613–619. discussion 619-621. [PubMed: 15028135]

Erosa-Rivero HB, Bata-Garcia JL, Alvarez-Cervera FJ, Heredia-Lopez FJ, Gongora-Alfaro JL. The potency and efficacy of anticholinergics to inhibit haloperidol-induced catalepsy in rats correlates with their rank order of affinities for the muscarinic receptor subtypes. Neuropharmacology. 2014; 81:176–187. [PubMed: 24534110]

Everitt BJ, Robbins TW. Central cholinergic systems and cognition. Annu Rev Psychol. 1997; 48:649–684. [PubMed: 9046571]

Exley R, McIntosh JM, Marks MJ, Maskos U, Cragg SJ. Striatal alpha5 nicotinic receptor subunit regulates dopamine transmission in dorsal striatum. J Neurosci. 2012; 32:2352–2356. [PubMed: 22396410]

Fahn S. High dosage anticholinergic therapy in dystonia. Neurology. 1983; 33:1255–1261. [PubMed: 6136938]

Fino E, Deniau JM, Venance L. Cell-specific spike-timing-dependent plasticity in GABAergic and cholinergic interneurons in corticostriatal rat brain slices. J Physiol. 2008; 586:265–282. [PubMed: 17974593]

Fisher RS, Buchwald NA, Hull CD, Levine MS. The GABAergic striatonigral neurons of the cat: demonstration by double peroxidase labeling. Brain Res. 1986; 398:148–156. [PubMed: 3542121]

Flaherty AW, Graybiel AM. Corticostriatal transformations in the primate somatosensory system. Projections from physiologically mapped body-part representations. J Neurophysiol. 1991; 66:1249–1263. [PubMed: 1722244]

Flaherty AW, Graybiel AM. Two input systems for body representations in the primate striatal matrix: experimental evidence in the squirrel monkey. J Neurosci. 1993; 13:1120–1137. [PubMed: 7680067]

Foster DJ, Gentry PR, Lizardi-Ortiz JE, Bridges TM, Wood MR, Niswender CM, Sulzer D, Lindsley CW, Xiang Z, Conn PJ. M5 receptor activation produces opposing physiological outcomes in dopamine neurons depending on the receptor's location. J Neurosci. 2014; 34:3253–3262. [PubMed: 24573284]

Fremeau RT Jr, Voglmaier S, Seal RP, Edwards RH. VGLUTs define subsets of excitatory neurons and suggest novel roles for glutamate. Trends Neurosci. 2004; 27:98–103. [PubMed: 15102489]

Fremeau RT Jr, Troyer MD, Pahner I, Nygaard GO, Tran CH, Reimer RJ, Bellocchio EE, Fortin D, Storm-Mathisen J, Edwards RH. The expression of vesicular glutamate transporters defines two classes of excitatory synapse. Neuron. 2001; 31:247–260. [PubMed: 11502256]

Freund TF, Powell JF, Smith AD. Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. Neuroscience. 1984; 13:1189–1215. [PubMed: 6152036]

Fujiyama F, Kuramoto E, Okamoto K, Hioki H, Furuta T, Zhou L, Nomura S, Kaneko T. Presynaptic localization of an AMPA-type glutamate receptor in corticostriatal and thalamostriatal axon terminals. Eur J Neurosci. 2004; 20:3322–3330. [PubMed: 15610164]

Galarraga E, Hernandez-Lopez S, Reyes A, Miranda I, Bermudez-Rattoni F, Vilchis C, Bargas J. Cholinergic modulation of neostriatal output: a functional antagonism between different types of muscarinic receptors. J Neurosci. 1999; 19:3629–3638. [PubMed: 10212321]

Galvan A, Smith Y. The primate thalamostriatal systems: Anatomical organization, functional roles and possible involvement in Parkinson's disease. Basal Ganglia. 2011; 1:179–189. [PubMed: 22773963]

Galvan A, Kuwajima M, Smith Y. Glutamate and GABA receptors and transporters in the basal ganglia: what does their subsynaptic localization reveal about their function? Neuroscience. 2006; 143:351–375. [PubMed: 17059868]

Gardoni F, Ghiglieri V, Luca M, Calabresi P. Assemblies of glutamate receptor subunits with post-synaptic density proteins and their alterations in Parkinson's disease. Prog Brain Res. 2010; 183:169–182. [PubMed: 20696320]

Gertler TS, Chan CS, Surmeier DJ. Dichotomous anatomical properties of adult striatal medium spiny neurons. J Neurosci. 2008; 28:10814–10824. [PubMed: 18945889]

Ghilardi MF, Carbon M, Silvestri G, Dhawan V, Tagliati M, Bressman S, Ghez C, Eidelberg D. Impaired sequence learning in carriers of the DYT1 dystonia mutation. Ann Neurol. 2003; 54:102–109. [PubMed: 12838525]

Giorguieff MF, Le Floc'h ML, Westfall TC, Glowinski J, Besson MJ. Nicotinic effect of acetylcholine on the release of newly synthesized (3H)dopamine in rat striatal slices and cat caudate nucleus. Brain Res. 1976; 106:117–131. [PubMed: 1268701]

Goldberg JA, Wilson CJ. Control of spontaneous firing patterns by the selective coupling of calcium currents to calcium-activated potassium currents in striatal cholinergic interneurons. J Neurosci. 2005; 25:10230–10238. [PubMed: 16267230]

Goldberg JA, Reynolds JN. Spontaneous firing and evoked pauses in the tonically active cholinergic interneurons of the striatum. Neuroscience. 2011; 198:27–43. [PubMed: 21925242]

Goldberg JA, Teagarden MA, Foehring RC, Wilson CJ. Nonequilibrium calcium dynamics regulate the autonomous firing pattern of rat striatal cholinergic interneurons. J Neurosci. 2009; 29:8396–8407. [PubMed: 19571130]

Gonon F. Prolonged and extrasynaptic excitatory action of dopamine mediated by D1 receptors in the rat striatum in vivo. J Neurosci. 1997; 17:5972–5978. [PubMed: 9221793]

Goodchild RE, Kim CE, Dauer WT. Loss of the dystonia-associated protein torsinA selectively disrupts the neuronal nuclear envelope. Neuron. 2005; 48:923–932. [PubMed: 16364897]

Goodchild RE, Grundmann K, Pisani A. New genetic insights highlight ‘old’ ideas on motor dysfunction in dystonia. Trends Neurosci. 2013; 36:717–725. [PubMed: 24144882]

Grundmann K, Reischmann B, Vanhoutte G, Hubener J, Teismann P, Hauser TK, Bonin M, Wilbertz J, Horn S, Nguyen HP, Kuhn M, Chanarat S, Wolburg H, Van der Linden A, Riess O. Overexpression of human wildtype torsinA and human DeltaGAG torsinA in a transgenic mouse model causes phenotypic abnormalities. Neurobiol Dis. 2007; 27:190–206. [PubMed: 17601741]

Grundmann K, Glockle N, Martella G, Sciamanna G, Hauser TK, Yu L, Castaneda S, Pichler B, Fehrenbacher B, Schaller M, Nuscher B, Haass C, Hettich J, Yue Z, Nguyen HP, Pisani A, Riess O, Ott T. Generation of a novel rodent model for DYT1 dystonia. Neurobiol Dis. 2012; 47:61–74. [PubMed: 22472189]

Gubellini P, Pisani A, Centonze D, Bernardi G, Calabresi P. Metabotropic glutamate receptors and striatal synaptic plasticity: implications for neurological diseases. Prog Neurobiol. 2004; 74:271–300. [PubMed: 15582223]

Hamann M, Raymond R, Varughesi S, Nobrega JN, Richter A. Acetylcholine receptor binding and cholinergic interneuron density are unaltered in a genetic animal model of primary paroxysmal dystonia. Brain Res. 2006; 1099:176–182. [PubMed: 16764832]

Hendrix CM, Vitek JL. Toward a network model of dystonia. Ann N Y Acad Sci. 2012; 1265:46–55. [PubMed: 22823747]

Herkenham M, Pert CB. Mosaic distribution of opiate receptors, parafascicular projections and acetylcholinesterase in rat striatum. Nature. 1981; 291:415–418. [PubMed: 6165892]

Hernandez-Flores T, Hernandez-Gonzalez O, Perez-Ramirez MB, Lara-Gonzalez E, Arias-Garcia MA, Duhne M, Perez-Burgos A, Prieto GA, Figueroa A, Galarraga E, Bargas J. Modulation of direct pathway striatal projection neurons by muscarinic M(4)-type receptors. Neuropharmacology. 2015; 89:232–244. [PubMed: 25290553]

Hersch SM, Gutekunst CA, Rees HD, Heilman CJ, Levey AI. Distribution of m1-m4 muscarinic receptor proteins in the rat striatum: light and electron microscopic immunocytochemistry using subtype-specific antibodies. J Neurosci. 1994; 14:3351–3363. [PubMed: 8182478]

Herve D. Identification of a specific assembly of the g protein golf as a critical and regulated module of dopamine and adenosine-activated cAMP pathways in the striatum. Front Neuroanat. 2011; 5:48. [PubMed: 21886607]

Hewett J, Johanson P, Sharma N, Standaert D, Balcioglu A. Function of dopamine transporter is compromised in DYT1 transgenic animal model in vivo. J Neurochem. 2010; 113:228–235. [PubMed: 20132487]

Hsu KS, Huang CC, Gean PW. Muscarinic depression of excitatory synaptic transmission mediated by the presynaptic M3 receptors in the rat neostriatum. Neurosci Lett. 1995; 197:141–144. [PubMed: 8552280]

Huerta-Ocampo I, Mena-Segovia J, Bolam JP. Convergence of cortical and thalamic input to direct and indirect pathway medium spiny neurons in the striatum. Brain Struct Funct. 2013

Hurst R, Rollema H, Bertrand D. Nicotinic acetylcholine receptors: from basic science to therapeutics. Pharmacol Ther. 2013; 137:22–54. [PubMed: 22925690]

Ibanez-Sandoval O, Tecuapetla F, Unal B, Shah F, Koos T, Tepper JM. Electrophysiological and morphological characteristics and synaptic connectivity of tyrosine hydroxylase-expressing neurons in adult mouse striatum. J Neurosci. 2010; 30:6999–7016. [PubMed: 20484642]

Ingham CA, Hood SH, Arbuthnott GW. Spine density on neostriatal neurones changes with 6-hydroxydopamine lesions and with age. Brain Res. 1989; 503:334–338. [PubMed: 2514009]

Jankovic J. Medical treatment of dystonia. Mov Disord. 2013; 28:1001–1012. [PubMed: 23893456]

Jiang ZG, North RA. Membrane properties and synaptic responses of rat striatal neurones in vitro. J Physiol. 1991; 443:533–553. [PubMed: 1822537]

Jin X, Tecuapetla F, Costa RM. Basal ganglia subcircuits distinctively encode the parsing and concatenation of action sequences. Nat Neurosci. 2014; 17:423–430. [PubMed: 24464039]

Jinnah HA, Hess EJ. A new twist on the anatomy of dystonia: the basal ganglia and the cerebellum? Neurology. 2006; 67:1740–1741. [PubMed: 17130402]

Kawaguchi Y. Physiological, morphological, and histochemical characterization of three classes of interneurons in rat neostriatum. J Neurosci. 1993; 13:4908–4923. [PubMed: 7693897]

Kawaguchi Y, Wilson CJ, Augood SJ, Emson PC. Striatal interneurones: chemical, physiological and morphological characterization. Trends Neurosci. 1995; 18:527–535. [PubMed: 8638293]

Kemel ML, Desban M, Glowinski J, Gauchy C. Distinct presynaptic control of dopamine release in striosomal and matrix areas of the cat caudate nucleus. Proc Natl Acad Sci U S A. 1989; 86:9006–9010. [PubMed: 2813435]

Kemp JM, Powell TP. The synaptic organization of the caudate nucleus. Philos Trans R Soc Lond B Biol Sci. 1971a; 262:403–412. [PubMed: 4399121]

Kemp JM, Powell TP. The termination of fibres from the cerebral cortex and thalamus upon dendritic spines in the caudate nucleus: a study with the Golgi method. Philos Trans R Soc Lond B Biol Sci. 1971b; 262:429–439. [PubMed: 4107496]

Kimura M, Yamada H, Matsumoto N. Tonically active neurons in the striatum encode motivational contexts of action. Brain Dev. 2003; 25(Suppl 1):S20–23. [PubMed: 14980367]

Kimura M, Minamimoto T, Matsumoto N, Hori Y. Monitoring and switching of cortico-basal ganglia loop functions by the thalamo-striatal system. Neurosci Res. 2004; 48:355–360. [PubMed: 15041188]

Klein C, Fahn S. Translation of Oppenheim's 1911 paper on dystonia. Mov Disord. 2013; 28:851–862. [PubMed: 23893442]

Kocsis JD, Kitai ST. Dual excitatory inputs to caudate spiny neurons from substantia nigra stimulation. Brain Res. 1977; 138:271–283. [PubMed: 589476]

Koos T, Tepper JM. Dual cholinergic control of fast-spiking interneurons in the neostriatum. J Neurosci. 2002; 22:529–535. [PubMed: 11784799]

Kreitzer AC, Malenka RC. Striatal plasticity and basal ganglia circuit function. Neuron. 2008; 60:543–554. [PubMed: 19038213]

Lacey CJ, Bolam JP, Magill PJ. Novel and distinct operational principles of intralaminar thalamic neurons and their striatal projections. J Neurosci. 2007; 27:4374–4384. [PubMed: 17442822]

Lang AE, Sheehy MP, Marsden CD. Acute anticholinergic action in focal dystonia. Adv Neurol. 1983; 37:193–200. [PubMed: 6134443]

Lapper SR, Bolam JP. Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurons in the dorsal striatum of the rat. Neuroscience. 1992; 51:533–545. [PubMed: 1488113]

Lavoie B, Smith Y, Parent A. Dopaminergic innervation of the basal ganglia in the squirrel monkey as revealed by tyrosine hydroxylase immunohistochemistry. J Comp Neurol. 1989; 289:36–52. [PubMed: 2572613]

Le Moine C, Bloch B. Expression of the D3 dopamine receptor in peptidergic neurons of the nucleus accumbens: comparison with the D1 and D2 dopamine receptors. Neuroscience. 1996; 73:131–143. [PubMed: 8783237]

LeDoux MS. Animal models of dystonia: Lessons from a mutant rat. Neurobiol Dis. 2011; 42:152–161. [PubMed: 21081162]

LeDoux MS, Brady KA. Secondary cervical dystonia associated with structural lesions of the central nervous system. Mov Disord. 2003; 18:60–69. [PubMed: 12518301]

Ledoux MS, Dauer WT, Warner TT. Emerging common molecular pathways for primary dystonia. Mov Disord. 2013; 28:968–981. [PubMed: 23893453]

Lehmann J, Langer SZ. Muscarinic receptors on dopamine terminals in the cat caudate nucleus: neuromodulation of [3H]dopamine release in vitro by endogenous acetylcholine. Brain Res. 1982; 248:61–69. [PubMed: 6289994]

Lei W, Jiao Y, Del Mar N, Reiner A. Evidence for differential cortical input to direct pathway versus indirect pathway striatal projection neurons in rats. J Neurosci. 2004; 24:8289–8299. [PubMed: 15385612]

Lenz S, Perney TM, Qin Y, Robbins E, Chesselet MF. GABA-ergic interneurons of the striatum express the Shaw-like potassium channel Kv3.1. Synapse. 1994; 18:55–66. [PubMed: 7825124]

Lera G, Bhatia K, Marsden CD. Dystonia as the major manifestation of Leigh's syndrome. Mov Disord. 1994; 9:642–649. [PubMed: 7845405]

Liang CC, Tanabe LM, Jou S, Chi F, Dauer WT. TorsinA hypofunction causes abnormal twisting movements and sensorimotor circuit neurodegeneration. J Clin Invest. 2014; 124:3080–3092. [PubMed: 24937429]

Liu Z, Otsu Y, Vasuta C, Nawa H, Murphy TH. Action-potential-independent GABAergic tone mediated by nicotinic stimulation of immature striatal miniature synaptic transmission. J Neurophysiol. 2007; 98:581–593. [PubMed: 17553945]

Lozano AM, Kumar R, Gross RE, Giladi N, Hutchison WD, Dostrovsky JO, Lang AE. Globus pallidus internus pallidotomy for generalized dystonia. Mov Disord. 1997; 12:865–870. [PubMed: 9399208]

Maltese M, Martella G, Madeo G, Fagiolo I, Tassone A, Ponterio G, Sciamanna G, Burbaud P, Conn PJ, Bonsi P, Pisani A. Anticholinergic drugs rescue synaptic plasticity in DYT1 dystonia: role of M1 muscarinic receptors. Mov Disord. 2014; 29:1655–1665. [PubMed: 25195914]

Manto MU. The wide spectrum of spinocerebellar ataxias (SCAs). Cerebellum. 2005; 4:2–6. [PubMed: 15895552]

Marchi M, Sanguineti P, Raiteri M. Muscarinic receptors mediate direct inhibition of GABA release from rat striatal nerve terminals. Neurosci Lett. 1990; 116:347–351. [PubMed: 2243614]

Marchi M, Risso F, Viola C, Cavazzani P, Raiteri M. Direct evidence that release-stimulating alpha7* nicotinic cholinergic receptors are localized on human and rat brain glutamatergic axon terminals. J Neurochem. 2002; 80:1071–1078. [PubMed: 11953457]

Martella G, Maltese M, Nistico R, Schirinzi T, Madeo G, Sciamanna G, Ponterio G, Tassone A, Mandolesi G, Vanni V, Pignatelli M, Bonsi P, Pisani A. Regional specificity of synaptic plasticity deficits in a knock-in mouse model of DYT1 dystonia. Neurobiol Dis. 2014; 65:124–132. [PubMed: 24503369]

Martella G, Tassone A, Sciamanna G, Platania P, Cuomo D, Viscomi MT, Bonsi P, Cacci E, Biagioni S, Usiello A, Bernardi G, Sharma N, Standaert DG, Pisani A. Impairment of bidirectional synaptic plasticity in the striatum of a mouse model of DYT1 dystonia: role of endogenous acetylcholine. Brain. 2009; 132:2336–2349. [PubMed: 19641103]

Martone ME, Armstrong DM, Young SJ, Groves PM. Ultrastructural examination of enkephalin and substance P input to cholinergic neurons within the rat neostriatum. Brain Res. 1992; 594:253–262. [PubMed: 1280527]

Matamales M, Bertran-Gonzalez J, Salomon L, Degos B, Deniau JM, Valjent E, Herve D, Girault JA. Striatal medium-sized spiny neurons: identification by nuclear staining and study of neuronal subpopulations in BAC transgenic mice. PLoS One. 2009; 4:e4770. [PubMed: 19274089]

Mathai A, Smith Y. The corticostriatal and corticosubthalamic pathways: two entries, one target. So what? Front Syst Neurosci. 2011; 5:64. [PubMed: 21866224]

Matsumoto N, Minamimoto T, Graybiel AM, Kimura M. Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviorally significant sensory events. J Neurophysiol. 2001; 85:960–976. [PubMed: 11160526]

McGeorge AJ, Faull RL. The organization of the projection from the cerebral cortex to the striatum in the rat. Neuroscience. 1989; 29:503–537. [PubMed: 2472578]

Meredith GE, Wouterlood FG. Hippocampal and midline thalamic fibers and terminals in relation to the choline acetyltransferase-immunoreactive neurons in nucleus accumbens of the rat: a light and electron microscopic study. J Comp Neurol. 1990; 296:204–221. [PubMed: 2358532]

Mink JW. The Basal Ganglia and involuntary movements: impaired inhibition of competing motor patterns. Arch Neurol. 2003; 60:1365–1368. [PubMed: 14568805]

Mitchell IJ, Luquin R, Boyce S, Clarke CE, Robertson RG, Sambrook MA, Crossman AR. Neural mechanisms of dystonia: evidence from a 2-deoxyglucose uptake study in a primate model of dopamine agonist-induced dystonia. Mov Disord. 1990; 5:49–54. [PubMed: 2296259]

Miura M, Saino-Saito S, Masuda M, Kobayashi K, Aosaki T. Compartment-specific modulation of GABAergic synaptic transmission by mu-opioid receptor in the mouse striatum with green fluorescent protein-expressing dopamine islands. J Neurosci. 2007; 27:9721–9728. [PubMed: 17804632]

Moss J, Bolam JP. A dopaminergic axon lattice in the striatum and its relationship with cortical and thalamic terminals. J Neurosci. 2008; 28:11221–11230. [PubMed: 18971464]

Muenter MD, Sharpless NS, Tyce GM, Darley FL. Patterns of dystonia (“I-D-I” and “D-I-D-”) in response to l-dopa therapy for Parkinson's disease. Mayo Clin Proc. 1977; 52:163–174. [PubMed: 839864]

Nanda B, Galvan A, Smith Y, Wichmann T. Effects of stimulation of the centromedian nucleus of the thalamus on the activity of striatal cells in awake rhesus monkeys. Eur J Neurosci. 2009; 29:588–598. [PubMed: 19175404]

Naudon L, Delfs JM, Clavel N, Lorden JF, Chesselet MF. Differential expression of glutamate decarboxylase messenger RNA in cerebellar Purkinje cells and deep cerebellar nuclei of the genetically dystonic rat. Neuroscience. 1998; 82:1087–1094. [PubMed: 9466432]

Naumann M, Pirker W, Reiners K, Lange KW, Becker G, Brucke T. Imaging the pre-and postsynaptic side of striatal dopaminergic synapses in idiopathic cervical dystonia: a SPECT study using [123I] epidepride and [123I] beta-CIT. Mov Disord. 1998; 13:319–323. [PubMed: 9539347]

Nelson AB, Hammack N, Yang CF, Shah NM, Seal RP, Kreitzer AC. Striatal cholinergic interneurons Drive GABA release from dopamine terminals. Neuron. 2014; 82:63–70. [PubMed: 24613418]

Neychev VK, Fan X, Mitev VI, Hess EJ, Jinnah HA. The basal ganglia and cerebellum interact in the expression of dystonic movement. Brain. 2008; 131:2499–2509. [PubMed: 18669484]

Niethammer M, Carbon M, Argyelan M, Eidelberg D. Hereditary dystonia as a neurodevelopmental circuit disorder: Evidence from neuroimaging. Neurobiol Dis. 2011; 42:202–209. [PubMed: 20965251]

Niittykoski M, Ruotsalainen S, Haapalinna A, Larson J, Sirvio J. Activation of muscarinic M3-like receptors and beta-adrenoceptors, but not M2-like muscarinic receptors or alpha-adrenoceptors, directly modulates corticostriatal neurotransmission in vitro. Neuroscience. 1999; 90:95–105. [PubMed: 10188937]

O'Donnell P, Grace AA. Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. J Neurosci. 1995; 15:3622–3639. [PubMed: 7751934]

O'Neill HC, Laverty DC, Patzlaff NE, Cohen BN, Fonck C, McKinney S, McIntosh JM, Lindstrom JM, Lester HA, Grady SR, Marks MJ. Mice expressing the ADNFLE valine 287 leucine mutation of the Beta2 nicotinic acetylcholine receptor subunit display increased sensitivity to acute nicotine administration and altered presynaptic nicotinic receptor function. Pharmacol Biochem Behav. 2013; 103:603–621. [PubMed: 23123803]

Oberlin SR, Konakova M, Pulst S, Chesselet MF. Development and anatomic localization of torsinA. Adv Neurol. 2004; 94:61–65. [PubMed: 14509655]

Oleas J, Yokoi F, Deandrade MP, Pisani A, Li Y. Engineering animal models of dystonia. Mov Disord. 2013; 28:990–1000. [PubMed: 23893455]

Olson L, Seiger A, Fuxe K. Heterogeneity of striatal and limbic dopamine innervation: highly fluorescent islands in developing and adult rats. Brain Res. 1972; 44:283–288. [PubMed: 4403485]

Ondo WG, Desaloms JM, Jankovic J, Grossman RG. Pallidotomy for generalized dystonia. Mov Disord. 1998; 13:693–698. [PubMed: 9686777]

Ostrem JL, Starr PA. Treatment of dystonia with deep brain stimulation. Neurotherapeutics. 2008; 5:320–330. [PubMed: 18394573]

Page ME, Bao L, Andre P, Pelta-Heller J, Sluzas E, Gonzalez-Alegre P, Bogush A, Khan LE, Iacovitti L, Rice ME, Ehrlich ME. Cell-autonomous alteration of dopaminergic transmission by wild type and mutant (DeltaE) TorsinA in transgenic mice. Neurobiol Dis. 2010; 39:318–326. [PubMed: 20460154]

Pan WX, Mao T, Dudman JT. Inputs to the dorsal striatum of the mouse reflect the parallel circuit architecture of the forebrain. Front Neuroanat. 2010; 4:147. [PubMed: 21212837]

Pancani T, Bolarinwa C, Smith Y, Lindsley CW, Conn PJ, Xiang Z. M4 mAChR-Mediated Modulation of Glutamatergic Transmission at Corticostriatal Synapses. ACS Chem Neurosci. 2014; 5:318–324. [PubMed: 24528004]

Paquet M, Smith Y. Group I metabotropic glutamate receptors in the monkey striatum: subsynaptic association with glutamatergic and dopaminergic afferents. J Neurosci. 2003; 23:7659–7669. [PubMed: 12930805]

Parent A, Hazrati LN. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Brain Res Rev. 1995; 20:91–127. [PubMed: 7711769]

Parent M, Parent A. Single-axon tracing and three-dimensional reconstruction of centre median-parafascicular thalamic neurons in primates. J Comp Neurol. 2005; 481:127–144. [PubMed: 15558721]

Pawlak V, Kerr JN. Dopamine receptor activation is required for corticostriatal spike-timing-dependent plasticity. J Neurosci. 2008; 28:2435–2446. [PubMed: 18322089]

Pazos A, Probst A, Palacios JM. Beta-adrenoceptor subtypes in the human brain: autoradiographic localization. Brain Res. 1985; 358:324–328. [PubMed: 3000516]

Peller M, Zeuner KE, Munchau A, Quartarone A, Weiss M, Knutzen A, Hallett M, Deuschl G, Siebner HR. The basal ganglia are hyperactive during the discrimination of tactile stimuli in writer's cramp. Brain. 2006; 129:2697–2708. [PubMed: 16854945]

Perlmutter JS, Mink JW. Dysfunction of dopaminergic pathways in dystonia. Adv Neurol. 2004; 94:163–170. [PubMed: 14509670]

Perlmutter JS, Tempel LW, Black KJ, Parkinson D, Todd RD. MPTP induces dystonia and parkinsonism. Clues to the pathophysiology of dystonia. Neurology. 1997; 49:1432–1438. [PubMed: 9371934]

Peterson DA, Sejnowski TJ, Poizner H. Convergent evidence for abnormal striatal synaptic plasticity in dystonia. Neurobiol Dis. 2010; 37:558–573. [PubMed: 20005952]

Pettigrew LC, Jankovic J. Hemidystonia: a report of 22 patients and a review of the literature. J Neurol Neurosurg Psychiatry. 1985; 48:650–657. [PubMed: 4031909]

Picconi B, Centonze D, Hakansson K, Bernardi G, Greengard P, Fisone G, Cenci MA, Calabresi P. Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia. Nat Neurosci. 2003; 6:501–506. [PubMed: 12665799]

Pisani A, Bernardi G, Ding J, Surmeier DJ. Re-emergence of striatal cholinergic interneurons in movement disorders. Trends Neurosci. 2007; 30:545–553. [PubMed: 17904652]

Pisani A, Martella G, Tscherter A, Bonsi P, Sharma N, Bernardi G, Standaert DG. Altered responses to dopaminergic D2 receptor activation and N-type calcium currents in striatal cholinergic interneurons in a mouse model of DYT1 dystonia. Neurobiol Dis. 2006; 24:318–325. [PubMed: 16934985]

Pisani A, Bonsi P, Centonze D, Martorana A, Fusco F, Sancesario G, De Persis C, Bernardi G, Calabresi P. Activation of beta1-adrenoceptors excites striatal cholinergic interneurons through a cAMP-dependent, protein kinase-independent pathway. J Neurosci. 2003; 23:5272–5282. [PubMed: 12832552]

Poewe WH, Lees AJ, Stern GM. Dystonia in Parkinson's disease: clinical and pharmacological features. Ann Neurol. 1988; 23:73–78. [PubMed: 3345068]

Preston RJ, Bishop GA, Kitai ST. Medium spiny neuron projection from the rat striatum: an intracellular horseradish peroxidase study. Brain Res. 1980; 183:253–263. [PubMed: 7353139]

Prudente CN, Pardo CA, Xiao J, Hanfelt J, Hess EJ, Ledoux MS, Jinnah HA. Neuropathology of cervical dystonia. Exp Neurol. 2013; 241:95–104. [PubMed: 23195594]

Puttfarcken PS, Jacobs I, Faltynek CR. Characterization of nicotinic acetylcholine receptor-mediated [(3)H]-dopamine release from rat cortex and striatum. Neuropharmacology. 2000; 39:2673–2680. [PubMed: 11044737]

Quartarone A, Hallett M. Emerging concepts in the physiological basis of dystonia. Mov Disord. 2013; 28:958–967. [PubMed: 23893452]

Quartarone A, Morgante F, Sant'angelo A, Rizzo V, Bagnato S, Terranova C, Siebner HR, Berardelli A, Girlanda P. Abnormal plasticity of sensorimotor circuits extends beyond the affected body part in focal dystonia. J Neurol Neurosurg Psychiatry. 2008; 79:985–990. [PubMed: 17634214]

Raike RS, Jinnah HA, Hess EJ. Animal models of generalized dystonia. NeuroRx. 2005; 2:504–512. [PubMed: 16389314]

Raike RS, Pizoli CE, Weisz C, van den Maagdenberg AM, Jinnah HA, Hess EJ. Limited regional cerebellar dysfunction induces focal dystonia in mice. Neurobiol Dis. 2012; 49C:200–210. [PubMed: 22850483]

Raiteri M, Marchi M, Paudice P, Pittaluga A. Muscarinic receptors mediating inhibition of gamma-aminobutyric acid release in rat corpus striatum and their pharmacological characterization. J Pharmacol Exp Ther. 1990; 254:496–501. [PubMed: 2384883]

Raju DV, Shah DJ, Wright TM, Hall RA, Smith Y. Differential synaptology of vGluT2-containing thalamostriatal afferents between the patch and matrix compartments in rats. J Comp Neurol. 2006; 499:231–243. [PubMed: 16977615]

Raju DV, Ahern TH, Shah DJ, Wright TM, Standaert DG, Hall RA, Smith Y. Differential synaptic plasticity of the corticostriatal and thalamostriatal systems in an MPTP-treated monkey model of parkinsonism. Eur J Neurosci. 2008; 27:1647–1658. [PubMed: 18380666]

Rapier C, Lunt GG, Wonnacott S. Stereoselective nicotine-induced release of dopamine from striatal synaptosomes: concentration dependence and repetitive stimulation. J Neurochem. 1988; 50:1123–1130. [PubMed: 3346670]

Reiner A, Jiao Y, Del Mar N, Laverghetta AV, Lei WL. Differential morphology of pyramidal tract-type and intratelencephalically projecting-type corticostriatal neurons and their intrastriatal terminals in rats. J Comp Neurol. 2003; 457:420–440. [PubMed: 12561080]

Reynolds JN, Hyland BI, Wickens JR. A cellular mechanism of reward-related learning. Nature. 2001; 413:67–70. [PubMed: 11544526]

Reynolds JN, Hyland BI, Wickens JR. Modulation of an afterhyperpolarization by the substantia nigra induces pauses in the tonic firing of striatal cholinergic interneurons. J Neurosci. 2004; 24:9870–9877. [PubMed: 15525771]

Ribak CE, Vaughn JE, Roberts E. The GABA neurons and their axon terminals in rat corpus striatum as demonstrated by GAD immunocytochemistry. J Comp Neurol. 1979; 187:261–283. [PubMed: 226567]

Rice ME, Cragg SJ. Dopamine spillover after quantal release: rethinking dopamine transmission in the nigrostriatal pathway. Brain Res Rev. 2008; 58:303–313. [PubMed: 18433875]

Rivera A, Alberti I, Martin AB, Narvaez JA, de la Calle A, Moratalla R. Molecular phenotype of rat striatal neurons expressing the dopamine D5 receptor subtype. Eur J Neurosci. 2002; 16:2049–2058. [PubMed: 12473072]

Rudkin TM, Sadikot AF. Thalamic input to parvalbumin-immunoreactive GABAergic interneurons: organization in normal striatum and effect of neonatal decortication. Neuroscience. 1999; 88:1165–1175. [PubMed: 10336127]

Sadikot AF, Parent A, Francois C. Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a PHA-L study of subcortical projections. J Comp Neurol. 1992a; 315:137–159. [PubMed: 1372010]

Sadikot AF, Parent A, Smith Y, Bolam JP. Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneity. J Comp Neurol. 1992b; 320:228–242. [PubMed: 1619051]

Sanberg PR, Shytle RD, Silver AA. Treatment of Tourette's syndrome with mecamylamine. Lancet. 1998; 352:705–706. [PubMed: 9728992]

Sato K, Sumi-Ichinose C, Kaji R, Ikemoto K, Nomura T, Nagatsu I, Ichinose H, Ito M, Sako W, Nagahiro S, Graybiel AM, Goto S. Differential involvement of striosome and matrix dopamine systems in a transgenic model of dopa-responsive dystonia. Proc Natl Acad Sci U S A. 2008; 105:12551–12556. [PubMed: 18713855]

Sciamanna G, Tassone A, Martella G, Mandolesi G, Puglisi F, Cuomo D, Madeo G, Ponterio G, Standaert DG, Bonsi P, Pisani A. Developmental profile of the aberrant dopamine D2 receptor response in striatal cholinergic interneurons in DYT1 dystonia. PLoS One. 2011; 6:e24261. [PubMed: 21912682]

Sciamanna G, Hollis R, Ball C, Martella G, Tassone A, Marshall A, Parsons D, Li X, Yokoi F, Zhang L, Li Y, Pisani A, Standaert DG. Cholinergic dysregulation produced by selective inactivation of the dystonia-associated protein torsinA. Neurobiol Dis. 2012; 47:416–427. [PubMed: 22579992]

Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H. Hereditary progressive dystonia with marked diurnal fluctuation. Adv Neurol. 1976; 14:215–233. [PubMed: 945938]

Shafrir Y, Levy Y, Beharab A, Nitzam M, Steinherz R. Acute dystonic reaction to bethanechol--a direct acetylcholine receptor agonist. Dev Med Child Neurol. 1986; 28:646–648. [PubMed: 2877910]

Sharma N, Baxter MG, Petravicz J, Bragg DC, Schienda A, Standaert DG, Breakefield XO. Impaired motor learning in mice expressing torsinA with the DYT1 dystonia mutation. J Neurosci. 2005; 25:5351–5355. [PubMed: 15930383]

Shashidharan P, Sandu D, Potla U, Armata IA, Walker RH, McNaught KS, Weisz D, Sreenath T, Brin MF, Olanow CW. Transgenic mouse model of early-onset DYT1 dystonia. Hum Mol Genet. 2005; 14:125–133. [PubMed: 15548549]

Shen W, Hamilton SE, Nathanson NM, Surmeier DJ. Cholinergic suppression of KCNQ channel currents enhances excitability of striatal medium spiny neurons. J Neurosci. 2005; 25:7449–7458. [PubMed: 16093396]

Shen W, Tian X, Day M, Ulrich S, Tkatch T, Nathanson NM, Surmeier DJ. Cholinergic modulation of Kir2 channels selectively elevates dendritic excitability in striatopallidal neurons. Nat Neurosci. 2007; 10:1458–1466. [PubMed: 17906621]

Shepherd GM. Corticostriatal connectivity and its role in disease. Nat Rev Neurosci. 2013; 14:278–291. [PubMed: 23511908]

Sidibe M, Smith Y. Differential synaptic innervation of striatofugal neurones projecting to the internal or external segments of the globus pallidus by thalamic afferents in the squirrel monkey. J Comp Neurol. 1996; 365:445–465. [PubMed: 8822181]

Sidibe M, Smith Y. Thalamic inputs to striatal interneurons in monkeys: synaptic organization and co-localization of calcium binding proteins. Neuroscience. 1999; 89:1189–1208. [PubMed: 10362307]

Silver AA, Shytle RD, Sanberg PR. Mecamylamine in Tourette's syndrome: a two-year retrospective case study. J Child Adolesc Psychopharmacol. 2000; 10:59–68. [PubMed: 10933116]

Smith AD, Bolam JP. The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurones. Trends Neurosci. 1990; 13:259–265. [PubMed: 1695400]

Smith Y, Villalba R. Striatal and extrastriatal dopamine in the basal ganglia: an overview of its anatomical organization in normal and Parkinsonian brains. Mov Disord. 2008; 23(Suppl 3):S534–547. [PubMed: 18781680]

Smith Y, Surmeier DJ, Redgrave P, Kimura M. Thalamic contributions to Basal Ganglia-related behavioral switching and reinforcement. J Neurosci. 2011; 31:16102–16106. [PubMed: 22072662]

Smith Y, Bennett BD, Bolam JP, Parent A, Sadikot AF. Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey. J Comp Neurol. 1994; 344:1–19. [PubMed: 7914894]

Smith Y, Galvan A, Ellender TJ, Doig N, Villalba RM, Huerta-Ocampo I, Wichmann T, Bolam JP. The thalamostriatal system in normal and diseased states. Front Syst Neurosci. 2014; 8:5. [PubMed: 24523677]

Somogyi P, Bolam JP, Smith AD. Monosynaptic cortical input and local axon collaterals of identified striatonigral neurons. A light and electron microscopic study using the Golgi-peroxidase transport-degeneration procedure. J Comp Neurol. 1981; 195:567–584. [PubMed: 6161949]

Song CH, Bernhard D, Hess EJ, Jinnah HA. Subtle microstructural changes of the cerebellum in a knock-in mouse model of DYT1 dystonia. Neurobiol Dis. 2014; 62:372–380. [PubMed: 24121114]

Song CH, Fan X, Exeter CJ, Hess EJ, Jinnah HA. Functional analysis of dopaminergic systems in a DYT1 knock-in mouse model of dystonia. Neurobiol Dis. 2012; 48:66–78. [PubMed: 22659308]

Song CH, Bernhard D, Bolarinwa C, Hess EJ, Smith Y, Jinnah HA. Subtle microstructural changes of the striatum in a DYT1 knock-in mouse model of dystonia. Neurobiol Dis. 2013; 54:362–371. [PubMed: 23336980]

Standaert DG. Update on the pathology of dystonia. Neurobiol Dis. 2011; 42:148–151. [PubMed: 21220015]

Stephens B, Mueller AJ, Shering AF, Hood SH, Taggart P, Arbuthnott GW, Bell JE, Kilford L, Kingsbury AE, Daniel SE, Ingham CA. Evidence of a breakdown of corticostriatal connections in Parkinson's disease. Neuroscience. 2005; 132:741–754. [PubMed: 15837135]

Surmeier DJ, Ding J, Day M, Wang Z, Shen W. D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. Trends Neurosci. 2007; 30:228–235. [PubMed: 17408758]

Suzuki T, Miura M, Nishimura K, Aosaki T. Dopamine-dependent synaptic plasticity in the striatal cholinergic interneurons. J Neurosci. 2001; 21:6492–6501. [PubMed: 11517238]

Tabbal SD, Mink JW, Antenor JA, Carl JL, Moerlein SM, Perlmutter JS. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced acute transient dystonia in monkeys associated with low striatal dopamine. Neuroscience. 2006; 141:1281–1287. [PubMed: 16766129]

Tanabe LM, Kim CE, Alagem N, Dauer WT. Primary dystonia: molecules and mechanisms. Nat Rev Neurol. 2009; 5:598–609. [PubMed: 19826400]

Tashiro Y, Sugimoto T, Hattori T, Uemura Y, Nagatsu I, Kikuchi H, Mizuno N. Tyrosine hydroxylase-like immunoreactive neurons in the striatum of the rat. Neurosci Lett. 1989; 97:6–10. [PubMed: 2563908]

Tassone A, Sciamanna G, Bonsi P, Martella G, Pisani A. Experimental models of dystonia. Int Rev Neurobiol. 2011; 98:551–572. [PubMed: 21907100]

Teper Y, et al. Nicotine-induced dystonic arousal complex in a mouse line harboring a human autosomal-dominant nocturnal frontal lobe epilepsy mutation. J Neurosci. 2007; 27:10128–10142. [PubMed: 17881519]

Tepper JM, Tecuapetla F, Koos T, Ibanez-Sandoval O. Heterogeneity and diversity of striatal GABAergic interneurons. Front Neuroanat. 2010; 4:150. [PubMed: 21228905]

Thomas TM, Smith Y, Levey AI, Hersch SM. Cortical inputs to m2-immunoreactive striatal interneurons in rat and monkey. Synapse. 2000; 37:252–261. [PubMed: 10891862]

Threlfell S, Lalic T, Platt NJ, Jennings KA, Deisseroth K, Cragg SJ. Striatal dopamine release is triggered by synchronized activity in cholinergic interneurons. Neuron. 2012; 75:58–64. [PubMed: 22794260]

Threlfell S, Clements MA, Khodai T, Pienaar IS, Exley R, Wess J, Cragg SJ. Striatal muscarinic receptors promote activity dependence of dopamine transmission via distinct receptor subtypes on cholinergic interneurons in ventral versus dorsal striatum. J Neurosci. 2010; 30:3398–3408. [PubMed: 20203199]

Toth E, Sershen H, Hashim A, Vizi ES, Lajtha A. Effect of nicotine on extracellular levels of neurotransmitters assessed by microdialysis in various brain regions: role of glutamic acid. Neurochem Res. 1992; 17:265–271. [PubMed: 1352387]

Tsui JK, Eisen A, Stoessl AJ, Calne S, Calne DB. Double-blind study of botulinum toxin in spasmodic torticollis. Lancet. 1986; 2:245–247. [PubMed: 2874278]

Uca AU, Kozak HH, Uguz F. Varenicline-induced acute dystonic reaction: a case report. Gen Hosp Psychiatry. 2014; 36:361 e361–362. [PubMed: 24576987]

Ulug AM, Vo A, Argyelan M, Tanabe L, Schiffer WK, Dewey S, Dauer WT, Eidelberg D. Cerebellothalamocortical pathway abnormalities in torsinA DYT1 knock-in mice. Proc Natl Acad Sci U S A. 2011; 108:6638–6643. [PubMed: 21464304]

Valjent E, Bertran-Gonzalez J, Herve D, Fisone G, Girault JA. Looking BAC at striatal signaling: cell-specific analysis in new transgenic mice. Trends Neurosci. 2009; 32:538–547. [PubMed: 19765834]

van Vulpen EH, van der Kooy D. Striatal cholinergic interneurons: birthdates predict compartmental localization. Brain Res Dev Brain Res. 1998; 109:51–58.

Vandermaelen CP, Kitai ST. Intracellular analysis of synaptic potentials in rat neostriatum following stimulation of the cerebral cortex, thalamus, and substantia nigra. Brain Res Bull. 1980; 5:725–733. [PubMed: 7470942]

Villalba RM, Smith Y. Striatal spine plasticity in Parkinson's disease. Front Neuroanat. 2010; 4:133. [PubMed: 21179580]

Villalba RM, Lee H, Smith Y. Dopaminergic denervation and spine loss in the striatum of MPTP-treated monkeys. Exp Neurol. 2009; 215:220–227. [PubMed: 18977221]

Vo A, Sako W, Niethammer M, Carbon M, Bressman SB, Ulug AM, Eidelberg D. Thalamocortical Connectivity Correlates with Phenotypic Variability in Dystonia. Cereb Cortex. 2014

Wang F, Gerzanich V, Wells GB, Anand R, Peng X, Keyser K, Lindstrom J. Assembly of human neuronal nicotinic receptor alpha5 subunits with alpha3, beta2, and beta4 subunits. J Biol Chem. 1996; 271:17656–17665. [PubMed: 8663494]

Wang Z, Kai L, Day M, Ronesi J, Yin HH, Ding J, Tkatch T, Lovinger DM, Surmeier DJ. Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons. Neuron. 2006; 50:443–452. [PubMed: 16675398]

Wichmann T. Commentary: Dopaminergic dysfunction in DYT1 dystonia. Exp Neurol. 2008; 212:242–246. [PubMed: 18513716]

Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol. 1996; 6:751–758. [PubMed: 9000030]

Wickens JR. Synaptic plasticity in the basal ganglia. Behav Brain Res. 2009; 199:119–128. [PubMed: 19026691]

Wilson BK, Hess EJ. Animal models for dystonia. Mov Disord. 2013; 28:982–989. [PubMed: 23893454]

Wilson CJ, Goldberg JA. Origin of the slow afterhyperpolarization and slow rhythmic bursting in striatal cholinergic interneurons. J Neurophysiol. 2006; 95:196–204. [PubMed: 16162828]

Wilson CJ, Chang HT, Kitai ST. Firing patterns and synaptic potentials of identified giant aspiny interneurons in the rat neostriatum. J Neurosci. 1990; 10:508–519. [PubMed: 2303856]

Wu Y, Parent A. Striatal interneurons expressing calretinin, parvalbumin or NADPH-diaphorase: a comparative study in the rat, monkey and human. Brain Res. 2000; 863:182–191. [PubMed: 10773206]

Xu M, Mizobe F, Yamamoto T, Kato T. Differential effects of M1-and M2-muscarinic drugs on striatal dopamine release and metabolism in freely moving rats. Brain Res. 1989; 495:232–242. [PubMed: 2765928]

Yan Z, Song WJ, Surmeier J. D2 dopamine receptors reduce N-type Ca2+ currents in rat neostriatal cholinergic interneurons through a membrane-delimited, protein-kinase-C-insensitive pathway. J Neurophysiol. 1997; 77:1003–1015. [PubMed: 9065864]

Yan Z, Flores-Hernandez J, Surmeier DJ. Coordinated expression of muscarinic receptor messenger RNAs in striatal medium spiny neurons. Neuroscience. 2001; 103:1017–1024. [PubMed: 11301208]

Yokoi F, Dang MT, Zhou T, Li Y. Abnormal nuclear envelopes in the striatum and motor deficits in DYT11 myoclonus-dystonia mouse models. Hum Mol Genet. 2012; 21:916–925. [PubMed: 22080833]

Yokoi F, Dang MT, Mitsui S, Li J, Li Y. Motor deficits and hyperactivity in cerebral cortex-specific Dyt1 conditional knockout mice. J Biochem. 2008; 143:39–47. [PubMed: 17956903]

Yokoi F, Dang MT, Li J, Standaert DG, Li Y. Motor deficits and decreased striatal dopamine receptor 2 binding activity in the striatum-specific Dyt1 conditional knockout mice. PLoS One. 2011; 6:e24539. [PubMed: 21931745]

Yoshor D, Hamilton WJ, Ondo W, Jankovic J, Grossman RG. Comparison of thalamotomy and pallidotomy for the treatment of dystonia. Neurosurgery. 2001; 48:818–824. discussion 824-816. [PubMed: 11322442]

Zackheim J, Abercrombie ED. Thalamic regulation of striatal acetylcholine efflux is both direct and indirect and qualitatively altered in the dopamine-depleted striatum. Neuroscience. 2005; 131:423–436. [PubMed: 15708484]

Zaja-Milatovic S, Milatovic D, Schantz AM, Zhang J, Montine KS, Samii A, Deutch AY, Montine TJ. Dendritic degeneration in neostriatal medium spiny neurons in Parkinson disease. Neurology. 2005; 64:545–547. [PubMed: 15699393]

Zhang L, Yokoi F, Parsons DS, Standaert DG, Li Y. Alteration of striatal dopaminergic neurotransmission in a mouse model of DYT11 myoclonus-dystonia. PLoS One. 2012; 7:e33669. [PubMed: 22438980]

Zhang W, Yamada M, Gomeza J, Basile AS, Wess J. Multiple muscarinic acetylcholine receptor subtypes modulate striatal dopamine release, as studied with M1-M5 muscarinic receptor knock-out mice. J Neurosci. 2002; 22:6347–6352. [PubMed: 12151512]

Zhao Y, DeCuypere M, LeDoux MS. Abnormal motor function and dopamine neurotransmission in DYT1 DeltaGAG transgenic mice. Exp Neurol. 2008; 210:719–730. [PubMed: 18299128]

Zhou FM, Wilson CJ, Dani JA. Cholinergic interneuron characteristics and nicotinic properties in the striatum. J Neurobiol. 2002; 53:590–605. [PubMed: 12436423]

Zoli M, Moretti M, Zanardi A, McIntosh JM, Clementi F, Gotti C. Identification of the nicotinic receptor subtypes expressed on dopaminergic terminals in the rat striatum. J Neurosci. 2002; 22:8785–8789. [PubMed: 12388584]

Abbreviations

GPi	globus pallidus internus
STN	subthalamic nucleus
MSN	medium spiny neurons
SNpr	substantia nigra pars reticulata
CM/Pf	centromedian/parafascicular complex
vGluT	vesicular glutamate transporter
TAN	tonically active neurons

DTI	diffusion tensor imaging
FS	fast-spiking
PLTS	persistent and low-threshold spike
ChI	cholinergic interneurons
ChAT	choline acetyltransferase
AHP	afterhyperpolarization
SK	small-conductance calcium-activated potassium channels
GPe	globus pallidus externus
DARPP-32	dopamine- and cAMP-regulated phosphoprotein Mr 32kDa
DBS	deep brain stimulation
IP3	inositol trisphosphatase
DAG	diacyl-glycerol
PKC	protein kinase C
PKA	protein kinase A
LTP	long-term potentiation
STDP	spike-timing-dependent plasticity
LTD	long-term depression
SD	synaptic depotentiation
MS	medial septal nucleus
nBM	nucleus basalis of Meynert
DB	diagonal band of Broca
PPT	pedunculopontine tegmental nucleus
LDT	laterodorsal tegmental nucleus

Highlights

- Cholinergic interneurons (ChIs) play a central role in striatal function.
- Impairment of ChIs produces dystonic movements.
- ChIs are paradoxically excited by dopamine D2 receptor agonism.
- Deficits in striatal synaptic plasticity are improved by muscarinic antagonists.
- ChI alterations may be a common endophenotype useful for investigations in dystonia.

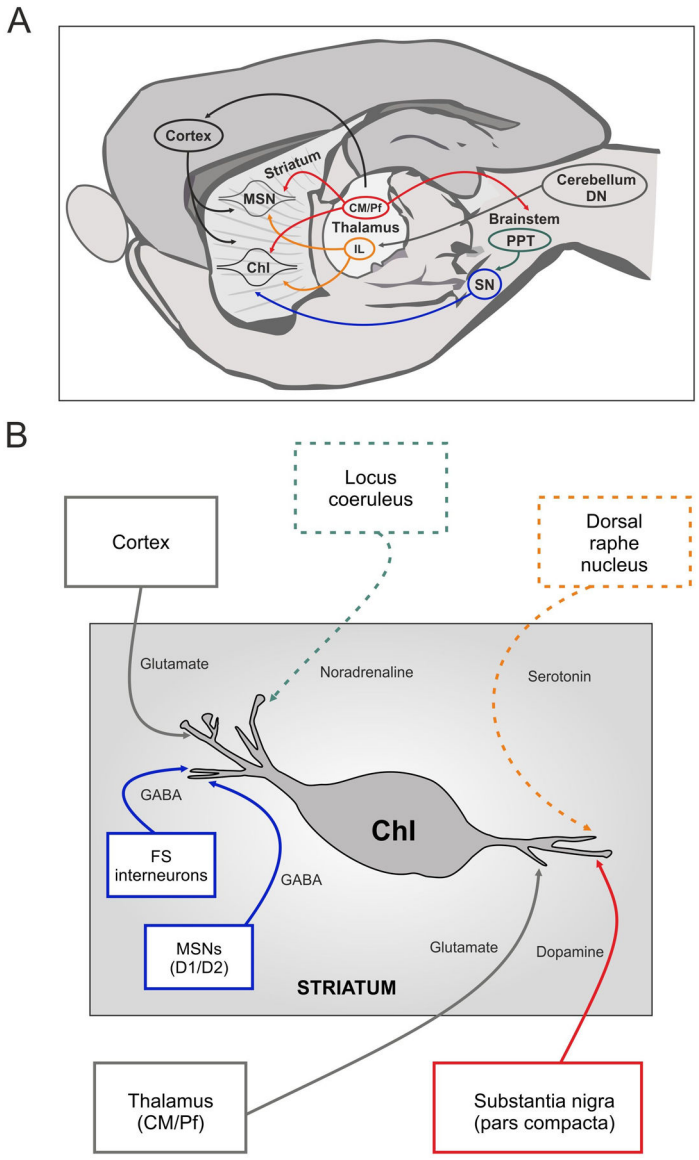

Figure 1. Simplified connectivity of the striatum

A. Glutamatergic inputs to striatal neurons (both MSNs and ChIs) arise from either cortical regions or thalamic nuclei (centromedian-parafascicular, CM-PF and intralaminar nuclei, IL). Sinilarly, both neuron subtypes receive dopaminergic afferents from substantia nigra (SN). Other afferents from cerebellum (dentate nuclei, DN) and brainstem (peduncolopontine nucleus, PPN) may modulate the activity of thalamic nuclei. **B.** Cortical, thalamic and nigral afferents to ChIs are shown. Intrastriatal GABAergic afferents arise from both MSNs and FS interneurons. Dotted lines show inputs to ChIs that are less abundantly represented.

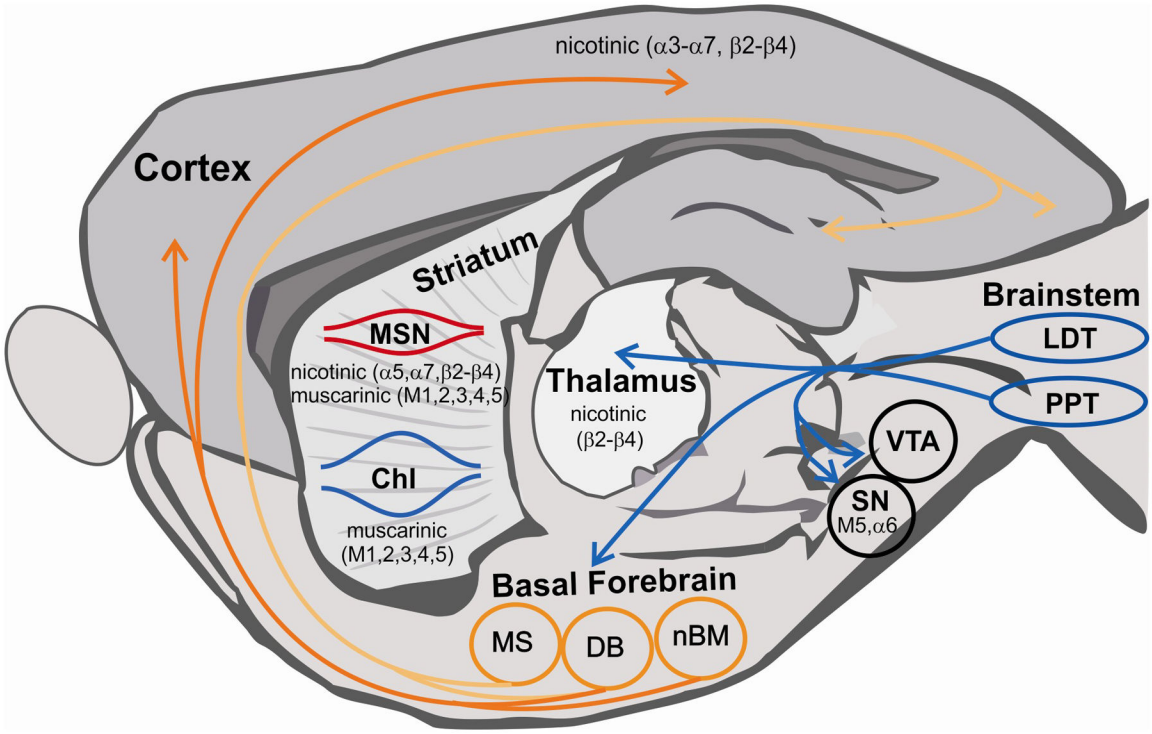

Figure 2. Schematic representation of the central cholinergic systems

Simplified scheme of the main cholinergic systems of the mammalian brain, their area of innervation, and the distribution of muscarinic and nicotinic receptors. Cholinergic neurons are widely distributed throughout the mammalian central nervous system, and they exist as both projection neurons and interneurons. The two most prominent cell groups projecting to several brain areas are: the magnocellular basal forebrain cholinergic system and the brainstem cholinergic system. The basal forebrain cholinergic system includes the medial septal nucleus (MS), the vertical and horizontal limbs of the diagonal band of Broca (DB), and the nucleus basalis of Meynert (nBM). The horizontal limb of the DB and nBM provide extensive projections to neocortex. The MS and vertical limb of the DB project to hippocampus and entorhinal cortices. The brainstem cholinergic system includes the pedunculopontine tegmental nucleus (PPT) and laterodorsal tegmental nucleus (LDT) and projects predominantly to the thalamus but also to the basal forebrain region. Moreover, the striatum is densely innervated by cholinergic interneurons (ChIs). Abbreviations: SN, substantia nigra; VTA, ventral tegmental area, MSN, medium spiny neuron.

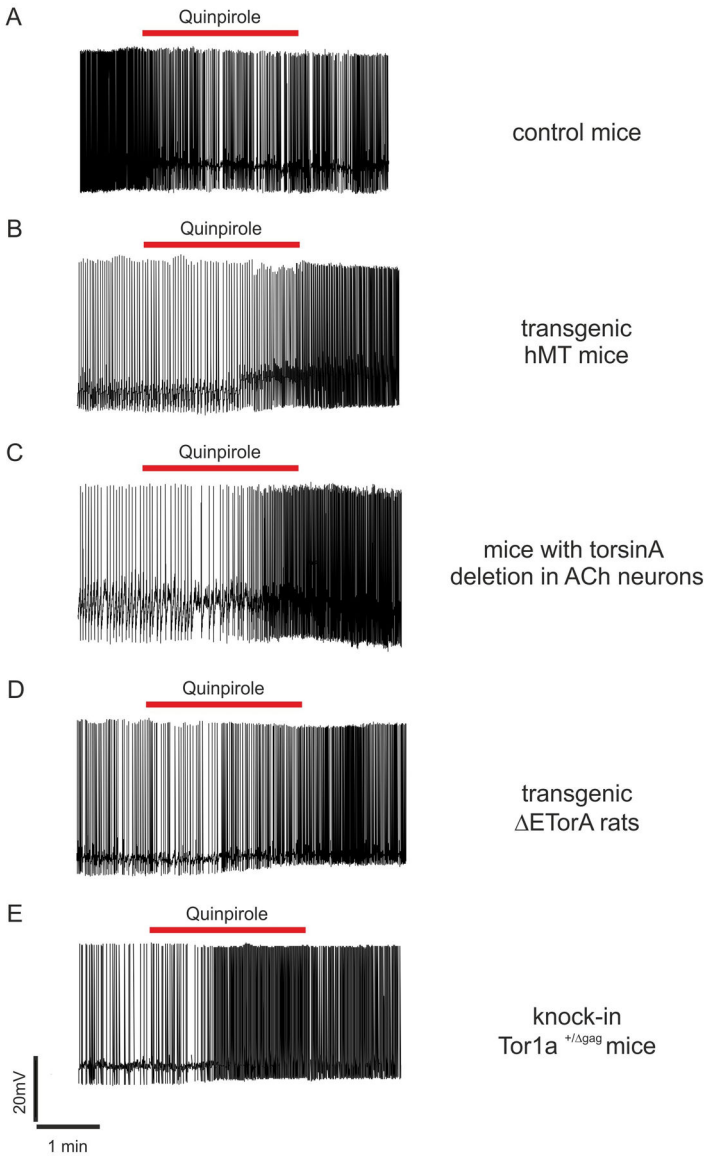

Figure 3. D2 receptor responses are altered in striatal ChIs from different DYT1 dystonia mouse models

Representative traces from patch recordings show an abnormal excitatory effect induced by D2 receptor activation by quinpirole in ChIs from rodent models of DYT1 dystonia. **A.** Quinpirole induces a slightly inhibitory effect on the spontaneous firing activity of ChIs from control mice. **B.** Conversely, the D2 receptor agonist causes a long-lasting increase of firing frequency in ChIs from transgenic hMT1 mice overexpressing human ΔE-torsinA. **C.** A similar alteration of D2 receptor function is observed in mice with selective deletion of torsinA in cholinergic neurons, as well as in ChIs from transgenic rats overexpressing human ΔE-torsinA (**D). E.** Notably, the quinpirole-induced increase in ChI firing frequency was observed also in knock-in mice carrying the ΔGAG mutation in one allele of the murine Tor1a gene.

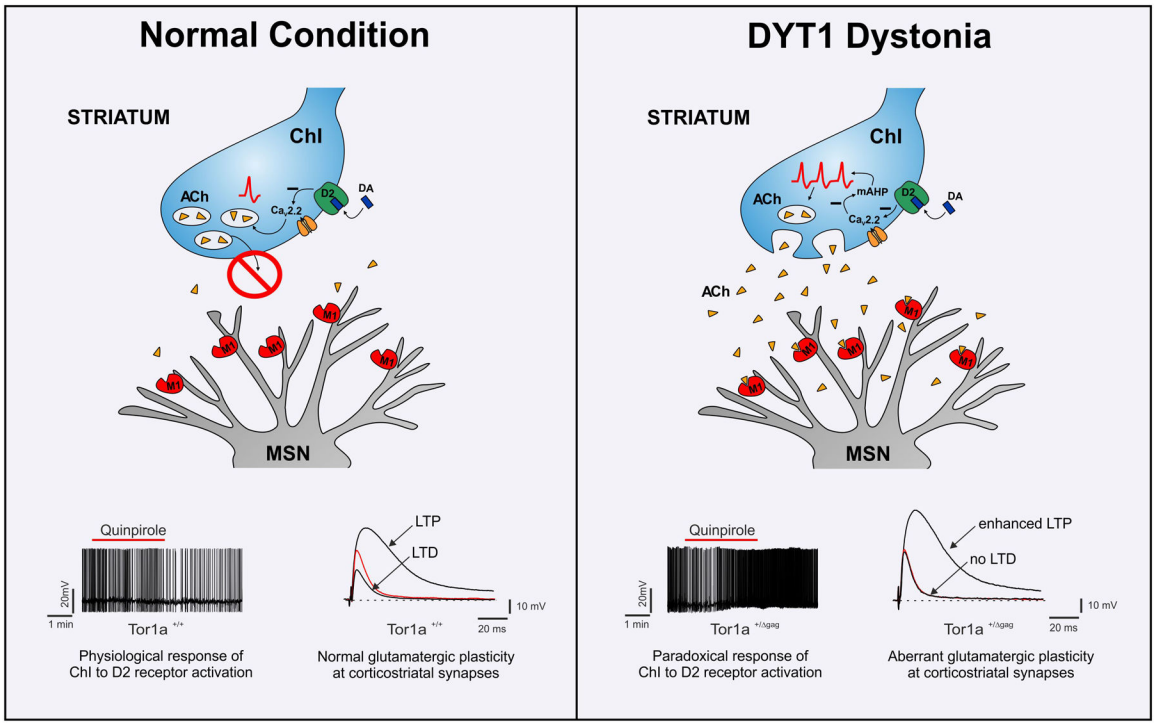

Figure 4. Striatal circuit dysfunction in DYT1 dystonia

In normal condition, endogenous dopamine, by activating D2 dopamine receptors on striatal ChIs reduces calcium influx through $Ca_V2.2$ channels, thereby inhibiting acetylcholine release. Activation of postsynaptic M1 muscarinic receptors on medium spiny neurons (MSN) is therefore reduced, allowing the expression of a physiological bidirectional synaptic plasticity. In DYT1 dystonia, activation of D2 receptors causes an abnormal inhibition of $Ca_V2.2$ channels and of the Ca^{2+}-dependent K^+ currents controlling afterhyperpolarization. Consequently, the pacemaking activity of ChIs is altered, resulting in an increase of their firing activity and of acetylcholine release. Overactivation of M1 receptor on MSNs prevents the induction of long-term depression (LTD) and causes the expression of an enhanced long-term potentiation (LTP).