Review

Convergent evidence for abnormal striatal synaptic plasticity in dystonia

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ARTICLE INFO

ABSTRACT

Dystonia is a functionally disabling movement disorder characterized by abnormal movements and postures. Although substantial recent progress has been made in identifying genetic factors, the pathophysiology of the disease remains a mystery. A provocative suggestion gaining broader acceptance is that some aspect of neural plasticity may be abnormal. There is also evidence that, at least in some forms of dystonia, sensorimotor "use" may be a contributing factor. Most empirical evidence of abnormal plasticity in dystonia comes from measures of sensorimotor cortical organization and physiology. However, the basal ganglia also play a critical role in sensorimotor function. Furthermore, the basal ganglia are prominently implicated in traditional models of dystonia, are the primary targets of stereotactic neurosurgical interventions, and provide a neural substrate for sensorimotor learning influenced by neuromodulators. Our working hypothesis is that abnormal plasticity in the basal ganglia is a critical link between the etiology and pathophysiology of dystonia. In this review we set up the background for this hypothesis by integrating a large body of disparate indirect evidence that dystonia may involve abnormalities in synaptic plasticity in the striatum. After reviewing evidence implicating the striatum in dystonia, we focus on the influence of two neuromodulatory systems: dopamine and acetylcholine. For both of these neuromodulators, we first describe the evidence for abnormalities in dystonia and then the means by which it may influence striatal synaptic plasticity. Collectively, the evidence suggests that many different forms of dystonia may involve abnormal plasticity in the striatum. An improved understanding of these altered plastic processes would help inform our understanding of the pathophysiology of dystonia, and, given the role of the striatum in sensorimotor learning, provide a principled basis for designing therapies aimed at the dynamic processes linking etiology to pathophysiology of the disease.

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Contents

Introduction

Dystonia is the third most common movement disorder after Parkinson's disease and essential tremor. It is expressed as involuntary excessive and sustained muscle activity producing abnormal movements and postures. It can be focal, involving only cranial, cervical, or limb musculature, or generalized, involving most of the body. Onset varies from early childhood to late adulthood and the symptoms can be functionally disabling. Although it is not degenerative, it is chronic with a remission rate of less than 5%. Treatments are symptomatic and only partially effective. See Jankovic (2009) for a recent review of how hyperkinetic disorders, including dystonia, are clinically characterized and managed. Over 15 genetic forms have thus far been identified that may predispose one for various forms of dystonia. However, for most of these, the penetrance is low and many forms of the disease still have no identifiable genetic determinant. Furthermore, the specific genes, proteins for which they code, and the functions of those proteins, have only begun to be understood. Thus, despite substantial recent progress (Vidailhet et al., 2009), the genetic and non-genetic factors in the pathophysiology of dystonia remain a mystery.

Plasticity has come to be viewed as one of the most basic of brain functions (Pascual-Leone et al., 2005) and several investigators have suggested that abnormal plasticity is a key factor in the pathophysiology of dystonia (Altenmuller, 2003; Berardelli et al., 1998; Hallett, 1998, 2001, 2006; Quartarone et al., 2009, 2006b; Rosenkranz et al., 2007; Sanger and Merzenich, 2000; Schenk and Mai, 2001; Torres-Russotto and Perlmutter, 2008). More specifically, Quartarone and others (Hallett, 2002; Quartarone et al., 2008, 2006b; Sanger and Merzenich, 2000; Torres-Russotto and Perlmutter, 2008) have suggested that two factors jointly underlie the pathophysiology of dystonia: "use-dependent" environmental factors like peripheral injury or repetitive training and subtly abnormal mechanisms of plasticity. Much of the empirical evidence for abnormal plasticity in dystonia derives from changes in the plasticity of reflexes and changes in the organization of the cortex. Blepharospasm patients, who exhibit involuntary contractions of the periocular musculature, demonstrate an enhanced ability to potentiate the trigeminal blink reflex (Quartarone et al., 2006a). However, the neural substrates for this abnormal reflex plasticity are unclear because reflexes can be modulated by descending signals from suprasegmental sensorimotor areas (Anastasopoulos et al., 2009; Berardelli et al., 1998; Mink, 1996; Rea and Ebner, 1991). The abnormal plasticity in motor cortical areas in dystonia (Edwards et al., 2006) is manifest as enlarged, smeared, or disorganized components of the homunculus in primary motor cortex (Berardelli et al., 1998; Byrnes et al., 1998; Thickbroom et al., 2003). Also, motor evoked potentials (MEPs) are hyperexcitable in dystonia (Chen, 2000; Siebner et al., 1999) and the facilitatory and inhibitory effects of theta burst stimulation transcranial magnetic stimulation (TMS) on the MEP are longer lasting in dystonia patients than in controls (Huang et al., 2005). Somatosensory cortical areas exhibit similar patterns of abnormal plasticity in dystonia, including larger and dedifferentiated somatotopy (Bara-Jimenez et al., 1998; Cuny et al., 2008; Elbert et al., 1998; Meunier et al., 2001). Systems-level associative plasticity involving somatosensory and motor cortical areas, measured with TMS and paired associative stimulation-induced increases in subsequent single-pulse somatosensory-evoked potential

and MEP amplitudes, is enhanced in focal hand dystonia patients (Tamura et al., 2009). Depending on its timing, paired associative stimulation can induce both facilitatory and inhibitory effects on MEPs that are exacerbated in dystonics compared to controls (Quartarone et al., 2003; Weise et al., 2006). Some of these topographic and physiologic abnormalities in cortex are also evident in basal ganglia (Lenz et al., 1998; Vitek et al., 1999) and thalamus (Lenz et al., 1999), so there may be abnormal plasticity throughout the greater basal ganglia thalamocortical network (Quartarone et al., 2009). Abnormal plasticity in reflexes and cortical areas may be modulated by or even secondary to abnormal plasticity in basal ganglia (Berardelli, 2006; Berardelli et al., 1998; Hallett, 2009; Vitek, 2002). Unfortunately plasticity is experimentally more difficult to investigate in basal ganglia than in reflexes or cortex.

There are several reasons why abnormal plasticity in the basal ganglia may also play an important role in dystonia: (1) the basal ganglia have long been considered a nexus of pathophysiology in dystonia (Guehl et al., 2009; Oppenheim, 1911; Sheehy and Marsden, 1982), including interpretations from lesion (Bhatia and Marsden, 1994) and functional imaging studies (Blood et al., 2004; Meunier et al., 2003), (2) basal ganglia dysfunction has been implicated in several models of movement disorder pathophysiology, including dystonia (Albin et al., 1989; DeLong, 1990; Gale et al., 2008; Mink, 1996, 2003; Nambu et al., 2000, 2002; Vitek, 2002), (3) the basal ganglia, and most commonly their primary output structure the globus pallidus internum (GPi), are the most common targets for ablative and deep brain stimulation (DBS) treatment of dystonia, (4) the basal ganglia play a prominent role in procedural and sensorimotor learning (Adamovich et al., 2001; Bar-Gad et al., 2003; Barnes et al., 2005; Berns and Sejnowski, 1998; Frank et al., 2004; Graybiel, 2008; Horvitz, 2009; Krebs et al., 2001; Kreitzer and Malenka, 2008; Messier et al., 2007; Packard and Knowlton, 2002; Pisani et al., 2005; Williams and Eskandar, 2006; Yin and Knowlton, 2006) and sensorimotor integration and learning are impaired in dystonia (Abbruzzese et al., 2001; Doyon, 2008; Ghilardi et al., 2003; Sharma et al., 2005; Tamburin et al., 2002), and (5) sensorimotor learning is associated with neural plasticity in both healthy (Graybiel et al., 2000; Rosenkranz et al., 2007) and dystonic individuals (Quartarone et al., 2006b). Contemporary views of the function of the basal ganglia continue to evolve. The cortical-basal ganglia network has come to be seen as the "fundamental unit of function at the level of behavior" (Yin and Knowlton, 2006, p. 471). Some investigators have even suggested that the classic view of the basal ganglia role in motor modulation may in fact be secondary to a more general purpose role in learning (Wickens, 2009). Thus, the basal ganglia likely play a role not only in the expression of dystonia but also perhaps the process by which dysfunctional motor behavior is implicitly "learned" during the development of dystonia. Nevertheless, the role of basal ganglia plasticity in dystonia remains poorly understood.

Our working hypothesis is that abnormal plasticity in the basal ganglia is a critical link between the etiology and pathophysiology of dystonia. In this review we set up the background for this hypothesis by integrating a large body of indirect evidence that dystonia may involve abnormalities in synaptic plasticity in the primary input nucleus of the basal ganglia, the striatum. After summarizing striatal afferents and efferents in the context of the greater basal ganglia network, we review evidence implicating the striatum in dystonia.

We then turn to the cellular constituents of the striatum and the synapses among them. Two neuromodulatory systems, dopamine (DA) and acetylcholine (ACh), have diffuse and diverse influences throughout the striatum. For both of these neuromodulators, we first describe the evidence for abnormalities in dystonia and then how they may influence striatal synaptic plasticity.

Basal ganglia network

The basic components of the basal ganglia thalamocortical network are depicted in Fig. 1. There are many good reviews of functional neuroanatomy of the basal ganglia (e.g. see the recent review in Utter and Basso (2008)). The main output from the basal ganglia is from the GPi and substantia nigra pars reticulata (SNr) to motor thalamic nuclei (ventral anterior and ventrolateral), which project primarily to frontal cortical areas but also back to striatum (McFarland and Haber, 2001). The striatum is the largest nuclei among the basal ganglia. It is also the primary input gateway to the basal ganglia, and therefore well positioned to play a prominent role in any plastic processes in the basal ganglia. The striatum consists of the caudate, putamen, and nucleus accumbens. As the putamen is the predominant striatal component involved in motor control, subsequent references to "striatum" will generally refer to the putamen. The output ("striatofugal") pathways from the striatum originate from only the medium spiny neurons (MSNs). MSNs, also known as "spiny projection neurons," are so called because of the densely spinous morphology of their dendritic processes. They constitute approximately 95% of the neurons in the primate striatum. Although the striatum forms the primary input structure of the basal ganglia a notable exception is the so-called hyperdirect pathway from cortex to GPi via the subthalamic nucleus (STN). The striatum receives convergent glutamatergic input from two primary sources: the vast majority of cortex and the intralaminar nuclei of the thalamus (nILT). The nILT comprise primarily the centromedian/parafasicular complex. The centromedian portion provides the primary projection to the sensorimotor striatum. In addition to preserving a grossly segregated parallel loop structure for limbic, associative, and motor functions (Alexander et al., 1986; Parent and Hazrati, 1995), the broad convergent cortical input and large MSN dendritic arborizations also provide, within the somatomotor divisions, an anatomical substrate for the integration of abstract sensory representational and motor planning information. The nILT inputs to striatum have been the subject of much less research than the cortical inputs and less is known about their functional significance (for a good review, see Smith et al. (2004)). One hypothesis is that they mediate attention to multimodal sensory information (Kimura et al., 2004; Minamimoto and Kimura, 2002). Regardless of their function at the behavioral level, they probably play an important and underappreciated role in striatal function and plasticity: the nILT inputs have higher glutamate release probability than cortical inputs (Ding et al., 2008) and surgical interventions in nILT, in the form of lesions (Cooper, 1976) and DBS (Caparros-Lefebvre et al., 1999), provide relief to dystonia symptoms.

Another important category of inputs to the striatum are the ascending neuromodulatory projections from multiple brain stem nuclei, including DA from the substantia nigra pars compacta (SNc), ACh from the pedunculopontine nucleus (PPN), and others, such as serotonin (5-HT) from the dorsal raphe nucleus, which will not be discussed here. Although the diffuse projections of these neuromodulatory systems enable them to influence plasticity in many brain regions well beyond the basal ganglia, in the present review we focus on their influence in the striatum. These neuromodulatory systems have differential effects on basal ganglia pathways that originate from MSNs in the striatum. The "direct" pathway from the striatum to the GPi/SNr (usually called the "striatonigral" projection in rodents) is classically thought to involve MSNs expressing predominantly DARs of the G_s-coupled D_1R dopamine receptor family. The "indirect" pathway (usually called the "striatopallidal" projection in rodents, referring to either of two polysynaptic pathways from striatum to GPi/SNr: striatum to globus pallidus externum (GPe) to GPi or striatum to STN to GPe to GPi) is associated with MSNs expressing predominantly DARs of the G_i-coupled D_2R family (Gerfen et al., 1990). There are also striosomal compartments embedded in the striatal matrix which contain D_1R-predominant MSNs projecting not to pallidal structures but to the SNc (Gerfen, 1992).

There is a small but growing body of evidence that D_1Rs and D_2Rs are extensively colocalized on MSNs in the striatum (Aizman et al., 2000; Surmeier et al., 1996). Accordingly, the extent to which the differential expression of D_1Rs and D_2Rs maps to "direct" or "indirect" MSN projections remains unclear. In conjunction with the possibility that MSN axons projecting to GPi might make collateral en passant synapses within GPe, the long-held distinction between "direct" and "indirect" pathways may not be the best way to characterize circuitry and pharmacology through the striatum (Nambu, 2008). Nevertheless, most contemporary research on striatal synaptic physiology
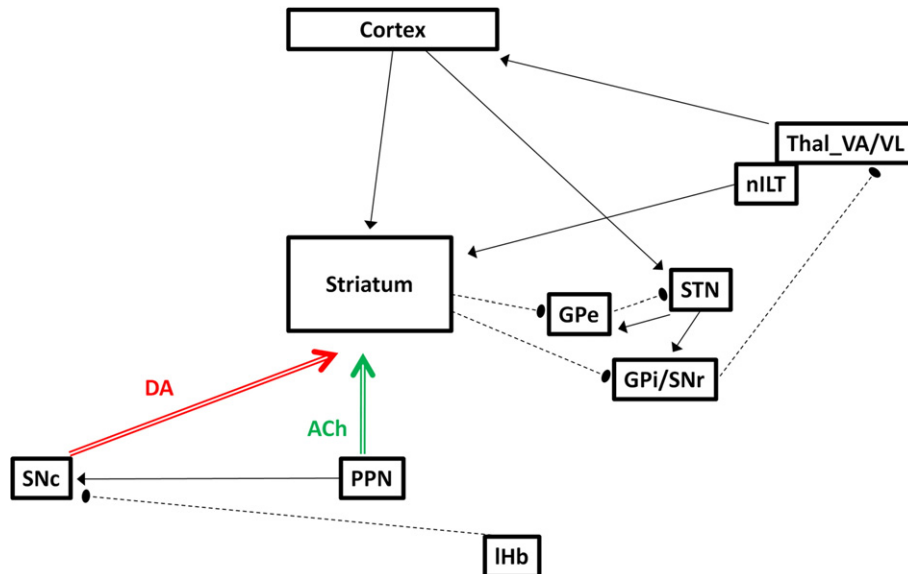

Fig. 1. Simplified schematic of primary network involving the basal ganglia, including extrinsic neuromodulatory inputs. Solid lines with triangular arrowheads depict excitatory projections. Dashed lines with oval arrowheads depict inhibitory projections. (Abbreviations: Thal_VA/VL—thalamic ventral anterior and ventrolateral nuclei).

makes the distinction between the D_1R- versus D_2R-predominant MSN projections, and the present review follows this convention.

The striatum and dystonia

Historically, there is very limited evidence for structural or histological abnormalities in postmortem analyses of brain tissues from patients with primary dystonia (Holton et al., 2008), with only a few case reports of neuronal loss or astrocytic gliosis in striatum (Gibb et al., 1992; Waters et al., 1993). However, dystonia can be secondary to putamenal lesions with (Starostarubinstein et al., 1987) or without Wilson's disease, and the symptomatic expression is proportional to the lesion extent (Bhatia and Marsden, 1994; Palfi et al., 2000). Furthermore, the topographic expression of secondary dystonia symptoms is consistent with lesion localization within putamen (Krystkowiak et al., 1998). Among primary dystonias and secondary dystonias without overt striatal pathology, there is some albeit limited evidence for subtle changes in striatal structure and function. In primary dystonias, there is conflicting data about putamenal volume, some reporting increases (Black et al., 1998; Etgen et al., 2006) and some reporting decreases (Obermann et al., 2007). It is unclear whether changes in putamenal volume are a causal factor or potentially a compensatory result of the disorder. In patients positive for the DYT1 genetic form of dystonia (caused by mutations in TOR1A, the gene that codes for torsinA, and is typically generalized with childhood onset) there is a negative correlation between putamenal volume and dystonic symptoms, i.e. smaller volume corresponds to exaggerated symptoms (Draganski et al., 2009). There may also be network changes involving the putamen: mice expressing human mutant torsinA (Grundmann et al., 2007) and dystonia patients with involvement of the cervical musculature (Colosimo et al., 2005; Fabbrini et al., 2008) exhibit increased fractional anisotropy in diffusion tensor images in putamen bilaterally. Curiously, no such differences from healthy controls were found in blepharospasm patients (Fabbrini et al., 2008). Delmaire et al. (2009) interpreted increased fractional anisotropy in the posterior limb of the internal capsule in focal hand dystonia patients as evidence for abnormalities in corticostriatal projections. Furthermore, the putamen is hyper-echogenic on transcranial sonography images in adult onset primary dystonia (Becker et al., 1997; Naumann et al., 1996). Although interpretation of this measure remains unclear, it may be more sensitive than MRI, because it was abnormal in seven out of ten cervical dystonia patients, compared with only one out of ten abnormalities seen with MRI (Becker et al., 1997). In cases where there is no structural abnormality in striatum, there may be subtle yet functionally significant changes in physiology not detectable with structural assays.

Metabolic measures of striatal activity in dystonia are mixed. There is decreased striatal glucose utilization in (especially manifesting) DYT6 carriers (Carbon et al., 2004). Focal hand dystonia patients show stronger decreases in striatal glucose consumption in response to repetitive TMS than controls (Siebner et al., 2003). Other forms of dystonia exhibit the opposite trend. In the dt^{sz} mutant hamster model of paroxysmal dystonia, an NADH fluorescence measure of striatal metabolism was reversibly increased during dystonic episodes (Hamann et al., 2009). DYT1 carriers exhibit increased glucose utilization in striatum compared to controls (Eidelberg et al., 1998). Importantly, this was not simply a result of motor symptoms, because it was present in both the awake and sleep states. TorsinA is an ATP-binding protein, and the striatum is particularly metabolically active. The plastic changes in response to forebrain ischemia involves an increase in torsinA transcript levels over several days in striatum and, possibly, remodeling of basal ganglia circuits (Zhao et al., 2008b). The striatum is particularly sensitive to metabolic challenge (Nishino et al., 2000) and stroke, vascular malformation, or perinatal asphyxia (Bressman, 2000) can induce secondary dystonias. This has also been demonstrated with animal models using nitropropionic acid (3-NP). 3-NP is a mitochondrial toxin found in moldy sugarcane (Liu et al., 1992). It is commonly used in animal models of Huntington's disease because at sufficient dosage there is cell death in striatum (Beal et al., 1993). However, lower doses provide a model of metabolic challenge and induce a dystonia-like state: a single injection can induce hindlimb dystonia 4 h later in rats (Akopian et al., 2008). The T2-weighted MRI signal intensity in the striatum was correlated with dyskinesias produced in the 3-NP lesion primate model (Palfi et al., 2000). Dyskinesias represent a constellation of generally hyperkinetic clinical features, frequently but not always including dystonic symptoms. When interpreting the delayed onset of dyskinesias produced weeks after terminating the 3-NP treatment, Palfi et al. (2000) suggested that the development of dystonic symptoms may reflect reorganization of the corticostriatal projections. Thus the response to metabolic challenges may involve subtle changes in striatal circuitry.

Striatal abnormalities could impair function throughout the whole cortical–subcortical sensorimotor system (Guehl et al., 2009). The striatum mediates a wide array of sensorimotor mappings and these mappings are plastic. Given the influence of striatum over basal ganglia output (via the GPi/SNr) to thalamus and back to motor cortical areas, the basal ganglia have been attributed a role in "sensory gating," filtering what sensory information is "passed" to the motor system (Kaji, 2001; Murase et al., 2000). Dystonia involves somato-sensory dysfunction (Murase et al., 2000), including spatial acuity deficits proportional to striatal volume (Walsh et al., 2009). The somatotopic disorganization seen in motor and somatosensory cortical areas of dystonia patients is also present in the striatum (Delmaire et al., 2005). The question remains what role striatal synaptic plasticity might play in dystonia. It may be that an abnormally plastic striatum predisposes individuals to dystonia (Martella et al., 2009). In subsequent sections, we introduce the cellular constituents of the striatum and the forms of synaptic plasticity they exhibit before characterizing how they are influenced by the neuromodulators.

Striatal constituents and plasticity

Striatal synaptic plasticity plays an important role in procedural and sensorimotor learning (Graybiel et al., 2000; Horvitz, 2009; Kreitzer and Malenka, 2008; Pisani et al., 2005; Yin and Knowlton, 2006). Much of that research has implicated plasticity specifically in corticostriatal synapses (Kreitzer and Malenka, 2008). Corticostriatal potentiation is correlated with learning rate in an intracranial self-stimulation paradigm involving stimulation of DA neurons in SNc (Reynolds et al., 2001) and this was interpreted as a cellular instantiation of sensorimotor learning, i.e. how context-sensitive motor behavior is shaped (Reynolds et al., 2001; Wickens et al., 2003). This corticostriatal synapse is the best studied of the synapses in the striatum and its modulation by DA is discussed at length in a later section.

There are many types of synapses within the striatum at which plasticity is likely to play a role in the functional forms of learning that the structure putatively subserves. In addition to the MSNs, the striatum contains a few classes of aspiny interneurons shown in Fig. 2: cholinergic neurons that fire autonomously in vivo at 3–9 Hz without synaptic input activity (therefore often referred to as "tonically active" neurons, or "TANs"), and two classes of GABAergic interneurons characterized physiologically and histochemically: "fast-spiking" (FS) cells staining positive for parvalbumin and "low-threshold spiking" cells staining for somatostatin, neuropeptide Y, and nitric oxide synthase (NOS). The striatum receives glutamatergic inputs from two primary sources: the cortex and the thalamus. The cortical inputs to the striatum synapse onto all of the striatal cell classes. Because these cortical afferents activate the cell classes in the order GABAergic
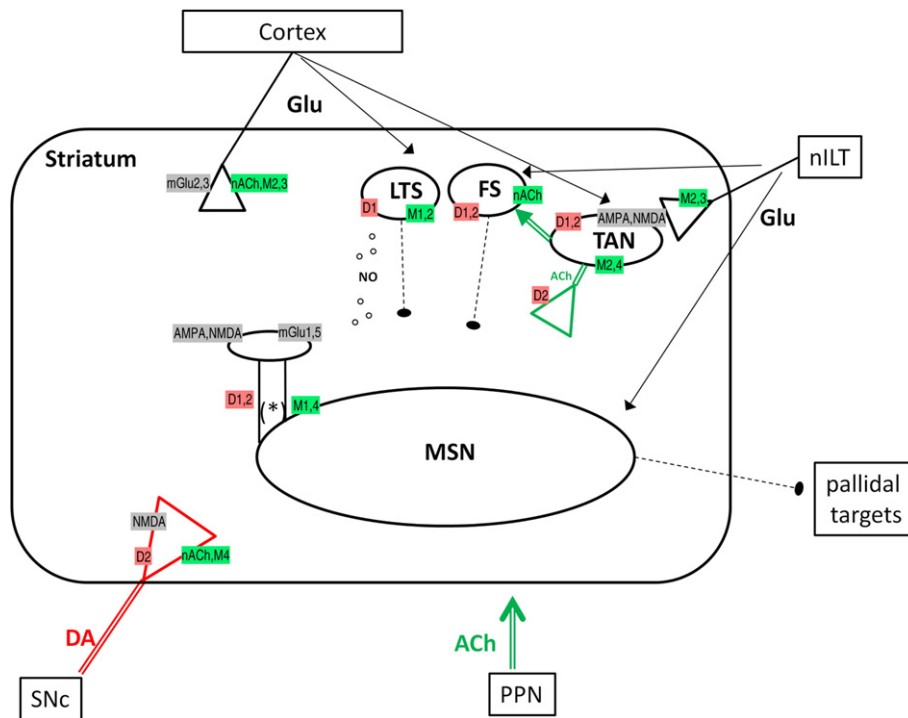
Fig. 2. Schematic of neuromodulatory receptors in striatum. Excitatory and inhibitory projections as depicted in Fig. 1. DARs in red, AChRs in green, and glutamate receptors in grey. (*) denotes pathway-dependent receptor expression, i.e. DARs on MSN spine shafts are primarily D_1Rs on "direct" pathway MSNs and D_2Rs on the "indirect" pathway MSNs and M_1Rs on both "direct" and "indirect" pathway MSNs, but M_4Rs on "direct" pathway MSNs only. Presynaptic processes depicted without specific postsynaptic targets denote incomplete information on these synapses. Omitted for simplicity: GABA receptors as well as myriad intracellular signaling cascades and their downstream effects on ion channel families and receptor expression/trafficking. (Abbreviations: Glu—glutamate; LTS—low-threshold spiking interneuron; NO—nitric oxide). Based in part on figures in (Breakefield et al., 2008; Kreitzer, 2009; Kreitzer and Malenka, 2008; Pisani et al., 2007; Surmeier et al., 2007).

interneurons, TANs, then MSNs (Fino et al., 2008), the local interneurons are likely to play an important modulatory role on how cortical inputs influence MSNs. Indeed this has been demonstrated *in vivo*, whereby FS interneurons in particular exhibit a strong feedforward inhibitory influence on MSNs, especially in the macroscopically desynchronized "awake" state (Mallet et al., 2005). This may explain why, in dt^{sz} hamsters, the slowed development of parvalbumin-positive FS interneurons in striatum (Gernert et al., 2000; Hamann et al., 2007) corresponds to dystonic attacks, because the reduced feedforward inhibition from FS interneurons may disinhibit the MSN cells.

Within the striatum's local circuits, there are not only strong feedforward influences from the GABAergic interneurons (Tepper et al., 2004) but also weaker feedback influences. For example, there is evidence that TAN firing induces polysynaptic GABA$_A$-mediated inhibition of TANs (Sullivan et al., 2008). Also, MSN axon collaterals provide lateral inhibitory feedback connections to other MSNs, with D_2R MSNs exhibiting stronger local inhibition than D_1R MSNs (Taverna et al., 2008). These synapses may be differentially modulated by DARs (e.g. inhibited by D_2Rs) in a fashion consistent with the differential D_1R/D_2R modulation of cortical inputs to MSNs. The synapses exhibit DA-dependent short-term forms of synaptic plasticity (Czubayko and Plenz, 2002; Taverna et al., 2008) and LTP induced by high-frequency stimulation (HFS) (Rueda-Orozco et al., 2009).

Glutamatergic synapses onto MSNs exhibit spike-timing-dependent plasticity (STDP) whereby LTP (requiring metabotropic glutamate receptor (mGluR) activation) is induced by post–pre firing and LTD (requiring NMDAR activation) is induced by pre-post firing order (Fino et al., 2008). This STDP "rule" is opposite that found in the cerebral cortex and hippocampus, perhaps because the MSN is an inhibitory neuron, in which LTP and LTD have the opposite effect on the output (see (Wickens, 2009) for a discussion of the interpretation

of these results). Corticostriatal LTD may require NO (Calabresi et al., 1999), which is released when HFS is used to induce long-lasting depolarizations in NOS+ interneurons (Kawaguchi et al., 1995). Because NOS+ interneurons have axonal arborization fields larger than TANs, they probably have a more topographically diffuse influence on MSNs than TANs. In any case, understanding plasticity in the full complement of feedforward and feedback intrastriatal connections remains an important challenge for the field (Plenz, 2003).

Importantly, as depicted in Fig. 2, there is a wide distribution of neuromodulator receptors of different types on several of the cell classes in striatum. Our understanding of all of the synaptic connections within striatum and the relative contribution of synaptic versus extra-synaptic influence of the neuromodulators remains incomplete. Accordingly, some of the presynaptic processes are intentionally depicted in Fig. 2 without a specific postsynaptic target. Likewise, many constituents of the intracellular pathways in pre- and post-synaptic cells have been omitted. Although their influence on a vast array of ion channel families has already been identified, the complete details are still being resolved and are beyond the scope of this review. Nevertheless, the broad distribution of DA and ACh receptors among all of the striatal cell classes could provide a substrate for many different forms of synaptic plasticity.

The nILT inputs to striatum are the dominant influences on TANs (Lapper and Bolam, 1992), where they facilitate ACh release via NMDA glutamate receptors, not AMPARs (Consolo et al., 1996). The influence of nILT inputs to MSNs is probably quite different from the cortical inputs, because the nILT inputs target dendritic shafts not spines (Smith et al., 2004). Thus, these two glutamatergic sources probably have distinctly different functions in striatal plasticity. The spatial relationship between glutamate and DA afferents onto MSN dendritic processes is also likely important. Unlike the close proximity

between DA terminals and cortical afferents to MSNs, DA terminals and nILT inputs are relatively more spatially segregated on MSN dendritic processes (Smith et al., 1994), consistent with a more diffuse attention-mediating role stipulated for the nILT inputs. Strikingly, there is also evidence for a limited number of DA cells *intrinsic* to the human striatum (Cossette et al., 2005). Although their function remains to be elucidated, the number of such cells may be responsive to extrinsic DA input to the striatum, because it increases after nigral DA lesions (Huot and Parent, 2007; Tashiro et al., 1989).

Several good reviews on synaptic physiology and plasticity in the striatum have been published in the past few years (Centonze et al., 2003c; Kreitzer, 2009; Kreitzer and Malenka, 2008; Pisani et al., 2007; Pisani et al., 2005; Surmeier et al., 2007). In the balance of this review, we will consider in turn evidence that the DA and ACh systems are affected in dystonia and, in both cases, highlight evidence for their influence on synaptic plasticity in the striatum. Because of space limitations, we have intentionally omitted other factors such as serotonin, norepinephrine, and the endocannabinoid and neurotrophic systems, all of which probably make important contributions to striatal synaptic plasticity.

DA in dystonia: general considerations

DA's influence in dystonia is varied, complex, and sometimes paradoxical. Despite some SNc DA cell loss with normal aging (Cruz-Sanchez et al., 1997; Itoh et al., 1996) and unlike Parkinson's disease, there is historically no evidence for abnormal cellular degeneration of nigral DA cells in dystonia. Nevertheless, reduced striatal DA (Perlmutter et al., 1997b; Tabbal et al., 2006), or more commonly a general DA dysfunction (Augood et al., 2004, 1999; Breakefield et al., 2008; Perlmutter and Mink, 2004), have been suggested as factors in dystonia (see also Wichmann (2008) for a recent review). When midbrain strokes produce a dystonia, the severity of the symptoms is correlated with the degree of DA denervation in the striatum (Vidailhet et al., 1999). In a postmortem study of two cases of childhood onset generalized dystonia, one of the cases exhibited below normal levels of DA in the striatum (Hornykiewicz et al., 1986). DAergic control of the trigeminal blink reflex circuit starts to decline in the 40- to 60-year age range (Peshori et al., 2001), perhaps related to the natural age-related decline in DA cells and consistent with the distribution of onset age for blepharospasm (Martino et al., 2005). Deficiencies in the DA system may induce dystonia by changing reflex excitability: the trigeminal blink reflex exhibits increased excitability after SNc DA cell loss (Basso et al., 1993). On the other hand, striatal DA release is increased in the dt^{sz} dystonia model, although only transiently during dystonic attacks (Hamann and Richter, 2004). In healthy basal ganglia, excessive DA has behavioral effects with similarities to involuntary motor functions in dystonia, increasing stereotyped and compulsive behaviors (Graybiel et al., 2000; Ridley, 1994; Voon et al., 2006). Curiously, symptomatic response to modulation of the DA system varies widely: some dystonia patients benefit from DA agonists and some from DA depleting agents (Lang, 1988). It is also worth noting the association of dystonia with both excessive and deficient striatal DA is consistent with the dystonias seen in both "on" and "off" states in L-DOPA treated Parkinson's disease (PD). Thus it may be that either too little or too much DA in striatum, perhaps depending on the developmental life stage of the individual, can have a causal influence on dystonia (Breakefield et al., 2008). In either case, abnormal striatal DA could modify DA's influence on striatal synaptic plasticity.

An important factor in DA's striatal influences is likely to be DAR regulation. Striatal DAR binding is decreased in humans with focal dystonia (Chase et al., 1988; Naumann et al., 1998; Perlmutter et al., 1997a) and, to a large but nonsignificant degree, in DYT1 patients (Augood et al., 2002). The DAR blocker haloperidol ameliorates symptoms in a primate model of cervical dystonia induced by

mesencephalic lesions (Battista et al., 1976). D_1R and D_2R binding are unchanged in a mouse model of DYT1 dystonia (Balcioglu et al., 2007; Zhao et al., 2008a). In the dt^{sz} model of dystonia, however, D_1R and D_2R binding are decreased in dorsal striatum (Nobrega et al., 1996) and corticostriatal LTP is increased (Kohling et al., 2004). In cervical dystonia (Placzek et al., 2001) and blepharospasm (Misbahuddin et al., 2002), a polymorphism has been implicated in the gene coding for the D_5R, which is part of the D_1R family of DARs. There is, however, a larger body of evidence suggesting that D_2R-mediated function in the striatum is preferentially impaired in dystonia (Defazio et al., 2007; Perlmutter et al., 1997a; Tabbal et al., 2006). Mutations in D_2R genes have been associated with DYT11 myoclonus-dystonia (Klein et al., 1999) which, along with dopa-responsive dystonia (DRD) and DYT12, constitutes one of the "dystonia-plus" syndromes. D_2R availability is reduced in striatum in DYT1 patients and carriers (Carbon et al., 2009). Although striatal D_2R binding is increased in DRD (Rinne et al., 2004), it is decreased in several other forms of dystonia (Asanuma et al., 2005; Carbon et al., 2009; Horstink et al., 1997; Naumann et al., 1998; Perlmutter et al., 1998, 1997a). Whether DAR binding effects reflect loss of neurons with DARs, some sort of dysfunction in neurons with DARs, increased DA in synapses, DAR downregulation, or increased DA turnover is not always clear (Carbon et al., 2009). Although there is evidence for increased DA turnover in striatum of DYT1 patients (Augood et al., 2002), the findings in mouse models of DYT1 are mixed, including decreases (Dang et al., 2006), increases (Zhao et al., 2008a), or no change (Balcioglu et al., 2007). Within the striatum, enhanced feedforward inhibition (probably between FS interneurons and MSNs) has also been attributed to D_2R dysfunction in a mouse model of DYT1 dystonia (Sciamanna et al., 2009). Collectively there is more evidence for D_2R- than D_1R-system abnormalities in dystonia. Importantly for the development of dystonia, D_2Rs play a role distinct from D_1Rs in striatal synaptic plasticity, as discussed later. Differential abnormalities in D_1R- versus D_2R-mediated striatal synaptic plasticity may therefore be a determining factor in the clinical expression of different forms of dystonia.

DA in dystonia: specifics

Several distinct forms of dystonia involve modified DA function, including at least four genetically-identified forms of dystonia (DYT1, DYT3, DYT5 and DYT11), tardive dystonia, and two aspects of PD: levodopa-induced dyskinesias (LIDs) and the early phase of the MPTP primate model of PD.

The DYT1 form of dystonia may cause a variety of abnormalities in the nigrostriatal DA system, as summarized in a recent commentary by Wichmann (2008). Human SNc exhibits high levels of the torsinA protein (Augood et al., 1999; Konakova et al., 2001; Shashidharan et al., 2000a). Although generalized dystonia, with or without TOR1A mutations, does not appear to change immunoreactivity to torsinA-like proteins, the SNc DA cells appear to be larger in generalized dystonia patients than in controls (Rostasy et al., 2003). Ubiquitin immunoreactive aggregates are found in the SNc of DYT1 patients (McNaught et al., 2004). TOR1A mutations influence torsinA's distribution and therefore probably also the protein's function (Cao et al., 2005; Torres et al., 2004). TorsinA is colocalized with alpha-synuclein in Lewy bodies (Sharma et al., 2001; Shashidharan et al., 2000b) and there is evidence for Lewy bodies in some dystonia patients (Mark et al., 1994). Thus, because alpha-synuclein couples with the DA transporter (Lee et al., 2001), TOR1A mutations may lead to dysfunctional presynaptic uptake by the transporter and therefore abnormal modulation of nigrostriatal DA transmission. TorsinA may also play a more direct role in the striatum. TorsinA preferentially localizes to neurons in the matrix compartment of the striatum (Konakova et al., 2001), which gives rise to both the direct and indirect pathways from the striatum. In a DYT1 postmortem case study, there was no cellular pathology detected in SNc but

substantially reduced DA in rostral striatum (Furukawa et al., 2000). Also, in mouse models of DYT1 involving TOR1A mutations, symptomatically affected mutants have decreased striatal DA and unaffected mutants have increased striatal DA (Shashidharan et al., 2005). The decreased DA appears to be due to disrupted DA transport or release, but not pre-synaptic transport or post-synaptic DARs (Balcioglu et al., 2007). Other influences of mutant forms of torsinA downstream from DARs remain to be elucidated but they are probably numerous and varied because torsinA regulates protein processing through secretory pathways in the endoplasmic reticulum (Hewett et al., 2008) and cellular trafficking of G-protein coupled receptors and ion channels (Torres et al., 2004). Regardless of the specific mechanisms, abnormalities in the striatal DA system are consistent with the possibility of abnormal striatal synaptic plasticity in DYT1 dystonia, and recent evidence in a DYT1 mouse model (Martella et al., 2009) supports this possibility.

Although more progress has been made in characterizing the DYT1 form of dystonia, there is some evidence for DA abnormalities in DYT3, DYT5, and DYT11 forms of dystonia. In DYT3 (also known as "x-linked recessive dystonia-parkinsonism" or "Lubag"), there is neuronal degeneration specifically in the striosomal compartments of the striatum (Goto et al., 2005) which, given their projection to SNc, modulate DA input back to striatum. In DYT5 (also known as DRD or Segawa's disease (Segawa et al., 1976)), the various genetic subforms result in reduced DA production typically without loss of nigral DA cells by interfering with tyrosine hydroxylase (Knappskog et al., 1995; Sato et al., 2008). This rare form of dystonia responds so dramatically to levodopa (L-DOPA) that an L-DOPA trial is merited in all early onset dystonia without a clear alternative diagnosis (Albanese et al., 2006). DYT11 (myoclonus dystonia) is attributed to deficits in the epsilon-sarcoglycan protein SGCE (Zimprich et al., 2001), which is highly expressed in DA neurons (Chan et al., 2005) and may influence structural morphology of neurons by mediating linkages between cytoskeleton and the extracellular matrix. A mouse model of DYT11 has elevated levels of striatal DA (Yokoi et al., 2006). Whether abnormalities in striatal DA are present in other genetic forms of dystonia remains to be determined. But the myriad abnormalities found thus far in the DYT1, 3, 5, and 11 forms suggest that DA abnormalities may be a common, albeit subtly different, factor in many forms of the disease.

Tardive dystonia can result from the long-term chronic administration of DAR-blocking neuroleptics (Burke and Fahn, 1982; Kiriakakis et al., 1998) including, in some rare cases, second generation neuroleptics (Miller et al., 2008). The slow time course is consistent with a subtle abnormality in striatal synaptic plasticity that induces clinically observable changes only after a protracted period. Curiously, the post-surgical therapeutic response to GPi DBS in tardive dystonia is typically on the order of only a few days, much faster than the typical dystonia response to GPi DBS (Franzini et al., 2005; Trottenberg et al., 2005), suggesting that the modified DAergic system central to tardive dystonia may provide an abnormal plastic substrate that accelerates the normally slow therapeutic response to DBS.

Parkinson's disease offers potentially informative clues about DA's role in both dystonia and striatal synaptic plasticity. Nigrostriatal DA dysfunction is a hallmark of PD and there are at least two "phases" of PD that can exhibit features of dystonia: LIDs and early phases of the MPTP primate. LIDs are a common motor complication of chronic pulsatile L-DOPA treatment in PD patients. They most commonly develop in young onset PD patients (Luquin et al., 1992), perhaps because the system is relatively more plastic than in older patients. They have been characterized as a dysfunctional form of motor learning (Bedard et al., 1999; Calabresi et al., 2000b) likely involving plasticity in the corticostriatal projections (Bezard et al., 2001; Calabresi et al., 2008; Gubellini et al., 2004). One theory is that LIDs develop as an inability to depotentiate from LTP, because among 6-hydroxydopamine (6-OHDA) rats treated with L-DOPA, only those

developing LIDs showed impaired synaptic depotentiation (Picconi et al., 2003). Interestingly, the depotentiation could be prevented by D_1R activation (Picconi et al., 2003). In a separate line of research with 6-OHDA rats, other researchers have shown that chronic L-DOPA treatment increases glutamate sensitivity in corticostriatal synapses by modifying phosphorylations of AMPARs and NMDARs (Chase and Oh, 2000; Oh et al., 2003; Smith et al., 2007). It also appears that L-DOPA treatment may influence the relative synaptic versus extra-synaptic distribution of NMDAR subunits (Gardoni et al., 2006), thereby influencing their efficacy in mediating plasticity of glutamatergic synapses onto MSNs. However, the effects of L-DOPA on striatal function may extend beyond the corticostriatal synapse. For example, the 6-OHDA injections in the rodent modulate the amount of the vesicular GABA transporter in striatum, increasing its expression in MSNs of the indirect pathway and decreasing its expression in MSNs of the direct pathway (Wang et al., 2007). The direct pathway decrease was reversed by systemic L-DOPA administration (Wang et al., 2007). Interestingly, the DA fluctuations inherent to the L-DOPA treated 6-OHDA rat model of PD even result in abnormal changes to the vascularization of the basal ganglia (Westin et al., 2006). Collectively the results suggest that although fluctuating DA has profound effects on plasticity of the corticostriatal synapse, such fluctuations may also induce changes in many other aspects of striatal physiology and function.

Most of the research with MPTP in non-human primates has focused on PD pathophysiology. However, shortly after MPTP injections but before developing a Parkinsonian profile, the animals exhibit dystonic symptoms. The relative contribution of the transient increase in striatal DA caused by the MPTP (Irwin et al., 1990) and the nigral DA cell loss and subsequent decrease in striatal DA is unclear. Interestingly, there is a transient decrease in striatal DA and decrease in D_2R expression in putamen coincident with symptom onset (Perlmutter et al., 1997b; Todd and Perlmutter, 1998). There are also gross changes in relative levels of afferent synaptic activity in striatum, as reflected in increased 2-deoxyglucose uptake (Mitchell et al., 1990). After the PD-like presentation and a period of chronically administering a dopaminergic medication regime, the MPTP animals become dystonic (Crossman et al., 1987; Mitchell et al., 1990). Thus the evidence suggests that chronic striatal DA modulation either by L-DOPA or DA agonists may induce multiple forms of abnormal plasticity in striatal synapses.

In summary, there is a broad base of evidence for abnormalities in the striatal dopamine system in dystonia. As with other movement disorders, most discussions of DA's role in dystonia focus on its steady-state influence on motor activity (hyperkinetic versus hypokinetic, loss of surround inhibition, etc.). Yet DA-mediated synaptic plasticity in striatum may be the key to understanding the dynamic pathophysiology of LIDs (Gubellini et al., 2004) and dystonia. Although it remains unclear which if any of the aforementioned aspects of striatal dopamine function are causative, they are all consistent with an abnormal striatal dopamine system that could induce abnormal plasticity in striatal synapses because of DA's central role in mediating synaptic plasticity.

DA in striatal synaptic plasticity

There is a wealth of evidence that the midbrain DA system mediates many forms of learning (Frank and O'Reilly, 2006; Graybiel et al., 2000; Montague et al., 1996) including sensorimotor learning involving striatal synaptic plasticity (Wickens et al., 2003). Dopamine influences many aspects of striatal local circuit physiology and plasticity. All of the interneurons in the striatum can be modulated by DA, because they all express DARs (Tepper et al., 2004). These dopaminergic influences are modulated by a wide variety of autoreceptors, heteroreceptors, and the DA transporter (Schmitz et al., 2003). The striatum is a dominant recipient of projections from

mesencephalic DA cells: DA markers in the striatum are among the densest in the nervous system (Lavoie et al., 1989). The efficacy and plasticity of the corticostriatal synapse is a factor not only of cortical inputs and MSN outputs, but also modulation by dopaminergic afferents from SNc. Most research to date on DA's role in striatal synaptic plasticity has been on the glutamatergic synapse between cortical afferents and their MSN targets (Arbuthnott et al., 2000). In a triadic arrangement, DA is well positioned to modulate this synapse because the DA terminals are in close proximity to the glutamatergic boutons on MSN dendritic spine heads (Kotter, 1994). DA terminals onto dendrites and spine necks, combined with incomplete DA reuptake (Cragg and Rice, 2004), also strategically position the DA afferents to modulate the impact of cortical inputs (Rice, 2000; Venton et al., 2003). DA plays a significant role even in maintaining corticostriatal synapses, as evidenced by a reduction in the number of dendritic spines after DA denervation of the striatum (Ingham et al., 1989; Nitsch and Riesenberg, 1995).

The steady-state influence of interactions between the D_1R and D_2R systems has been a central tenet of basal ganglia function in motor control. Not surprisingly then, the differential activation of the two DAR families is thought to play an important role in striatal synaptic plasticity (Calabresi et al., 1996; Schultz, 2002; Surmeier et al., 2007), most notably but not exclusively by influencing LTP and LTD of the corticostriatal synapse (Calabresi et al., 2000b; Centonze et al., 2001; Kerr and Wickens, 2001). There is a complex set of intracellular second messenger signaling pathways that are modulated by, and in turn modulate, DARs in the striatum (Centonze et al., 2003c; Greengard, 2001; Tang and Lovinger, 2000). These influences are typically dependent upon the specific type of DAR receptor (Canales and Graybiel, 2000; Vallone et al., 2000). By influencing these intracellular signaling pathways, DAR activations influence the gating and trafficking of a wide array of ligand-gated and voltage-dependent ion channels (Surmeier et al., 2007). The influence on voltage-dependent channels is particularly important, given the sensitivity of MSN physiology to membrane potential and the tendency of MSNs to be in either "up" or "down" states (Gruber et al., 2003; Nicola et al., 2000). In summary, the different types of DARs differentially modulate intracellular signaling pathways that modify the efficacy of synapses onto the cells, and therefore their subsequent responses to afferent activity.

There are several ways in which DARs influence striatal synaptic plasticity. LTD of the corticostriatal synapse, which does not require NMDAR activation (Centonze et al., 2003c), can be induced with the brief application of mGluR1 agonist if D_2R agonist is present (Kreitzer and Malenka, 2007). It can also be induced by 100 Hz HFS of cortical inputs (Calabresi et al., 1992a, 1994) but reversed if the SNc is simultaneously stimulated at 20 Hz (Wickens et al., 1996). D_1R and D_5R activation on NOS interneurons in striatum also facilitates corticostriatal LTD (Centonze et al., 2003a). Curiously, although D_1R and D_5Rs belong to the same "D_1R" family and mediate the "direct" pathway through the basal ganglia, they have distinct influences on corticostriatal synaptic plasticity: LTD depends on D_5Rs yet LTP depends on D_1Rs (Centonze et al., 2003a). LTP requires NMDAR activation (allowing Ca^{2+} influx) (Calabresi et al., 1992b; Centonze et al., 2003c) as well as D_1R activation (Centonze et al., 2003b; Kerr and Wickens, 2001; Kitada et al., 2007). STDP in the corticostriatal synapse requires DAR activation (Pawlak and Kerr, 2008) and can be used to induce LTP in the direct pathway with D_1Rs (Shen et al., 2008). Curiously, DA depletion reverses this effect, such that direct pathway STDP induces LTD instead (Kreitzer and Malenka, 2007; Shen et al., 2008). Thus there is a complex array of mechanisms whereby the striatal DA system can strongly influence synaptic plasticity.

The mesencephalic DA system operates at a multitude of time scales. In the clinical context, there is the notion of steady state DA level (as modified over the course of months and years in PD, for example) and pulsatile DA (as driven by the decay constants of dopaminergic medications, over the course of minutes and hours). However, there is a rapidly growing literature based on the putative "prediction error" signal coded by brief phasic changes in DA cell firing that occur over the course of 10s–100s of milliseconds (Schultz, 2007). An evolving concept is that the slower temporal dynamics in DA set the stage for the influence of relatively faster, phasic DA (Schultz, 2007). Discussion of this "phasic" DA signal is beyond the scope of the present review. However, the role that phasic DA dynamics play in corticostriatal synaptic plasticity is likely a function of its interaction with and dependence upon relatively "tonic" levels of DA (Grace, 1991) and the relative affinities of D_1Rs and D_2Rs (Jaber et al., 1996; Richfield et al., 1989; Trantham-Davidson et al., 2004). D_2R agonists decrease phasic firing of mesencephalic DA cells (Piercey et al., 1996) and reduce phasic DA release (Schmitz et al., 2003), possibly due to D_2R autoreceptor activation (Samuels et al., 2006). As described earlier, LIDs may be the result of dysfunctional plastic changes arising from the pulsatile fluctuations in tonic DA level produced by conventional oral administration of L-DOPA. Thus, interactions among the multiple time scales of DA signaling probably play an important role in striatal synaptic plasticity and merit further attention by the dystonia research community.

If the DA system is so important to striatal synaptic plasticity, and the primary source of DA in the sensorimotor striatum is the SNc, a logical question is: what influences the SNc? The diversity of inputs to the SNc is usually neglected in the dystonia literature. Besides the striatal striosomes, the SNc receives afferents from the STN, the habenula, the raphe nucleus, and the PPN. The striosomal compartment projection to SNc DA cells (Gerfen, 1992) provides a means by which striatum can provide feedback to the SNc and may therefore play an important role in mediating feedback signals to the striatal DA source. Graybiel et al. (2000) have suggested that the differential plasticity in striosomal and matrix-based pathways from the striatum may underlie LIDs and habitual behaviors induced by DAR agonists. The STN input is of particular clinical interest, given the increasing interest in the mechanisms of action of STN DBS not only in PD but also in a limited number of patients with focal dystonia (Ostrem et al., 2008). HFS in STN not only induces synaptic plasticity locally in STN (Shen et al., 2003), but also may be able to indirectly modulate corticostriatal synapses by potentiating DA's influence in striatum (Oueslati et al., 2007). The PPN projections to SNc are excitatory (Futami et al., 1995; Pan and Hyland, 2005; Semba and Fibiger, 1992). Recent trials of DBS in the PPN for some PD patients may provide an opportunity to learn more about PPN modulation of motor system plasticity. Projections from the PPN to SNc may also indirectly mediate some of the influence of extrinsic ACh on striatal synaptic plasticity, as discussed in subsequent sections.

ACh in dystonia

Although central ACh systems have been less well studied than DA, there are now several pieces of evidence for abnormalities in dystonia. Striatal cholinergic terminal density is decreased in cervical dystonia (Albin et al., 2003). There are at least two anatomic sources of ACh input to the striatum: cholinergic neurons in the PPN provide an extrinsic source (Woolf and Butcher, 1986) and TANs provide an intrinsic (and the predominant) source. The PPN can influence striatal plasticity either directly through its projection to striatum (Bevan and Bolam, 1995; Cragg, 2006) or indirectly through its projection to SNc. There is decreased metabolism in brain stem areas including the PPN in DYT1 and DYT6 manifesting patients, although it is unclear whether this is due to modified inputs (Eidelberg et al., 1997). DYT1 patients show perinuclear inclusion body pathology mostly in the brainstem, including cholinergic neurons in the PPN (McNaught et al., 2004). Mouse models of DYT1 exhibit several abnormalities in the ACh system. The animals exhibit formation of perinuclear inclusion bodies in the PPN and striatum and,

interestingly, this evidence of cellular pathology is present 4–5 months before symptom onset (Grundmann et al., 2007). The animals also show evidence of ubiquitin immunoreactive aggregates in the PPN (Dang et al., 2005). In the DYT1 mouse striatum, TANs exhibit altered D_2R responses, whereby D_2R activation increases TAN firing (Pisani et al., 2007, 2006). There is also increased acetylcholinesterase activity in these mice, possibly in response to the increased endogenous ACh (Martella et al., 2009) and consistent with the partial efficacy of anticholinergic medications in generalized dystonia. TorsinA is expressed not only in SNc DA neurons but also in TANs in striatum and in cholinergic neurons of the PPN (Augood et al., 1999; Shahed and Jankovic, 2007). Thus modifications to torsinA function may adversely affect both the extrinsic and intrinsic cholinergic influences on striatal function. Whether forms of dystonia besides DYT1, 6, and cervical exhibit abnormalities in striatal ACh remains to be determined.

ACh in striatal synaptic plasticity

ACh's influence on striatal synaptic plasticity has not been as well studied as that of DA. Despite the proportionally small representation of ACh interneurons in striatum, ACh probably plays a prominent role in striatal function (Izzo and Bolam, 1988). The vesicular ACh transporter, a marker for cholinergic terminals, has its highest CNS expression in the striatum. Striatal ACh appears to be important for sensorimotor learning: the proportion of primate TANs synchronously responding (in the form of a pause and rebound firing) to a conditioned cue increases dramatically over the course of Pavlovian sensorimotor conditioning (Aosaki et al., 1994b). TANs influence MSNs directly via muscarinic ACh receptors (mAChRs), which probably instantiate how TANs are thought to modulate the sensitivity of MSNs to contextual information from cortical inputs (Apicella, 2007). There are several means by which striatal ACh influences corticostriatal synaptic plasticity (Centonze et al., 2003c). M_1Rs on MSNs promote corticostriatal LTP (Calabresi et al., 2000a) and inhibit LTD induction (Wang et al., 2006). Martella et al. (2009) have recently demonstrated in a DYT1 mouse model that the increased cholinergic tone in striatum and correspondingly increased M_1R activation result in several abnormalities of plasticity at the corticostriatal synapse: increased LTP, decreased LTD, and an inability to depotentiate from LTP. Importantly, the animals exhibited normal synaptic physiology, normal pre-HFS AMPAR and NMDAR expressions, and the abnormalities in synaptic plasticity were not present in hippocampus. Interestingly, striatal ACh may have differential influences on direct versus indirect pathway MSNs, because M_1Rs differentially regulate the physiology of D_1 versus D_2 MSNs (Shen et al., 2007). Furthermore, although both types of MSNs express M_1Rs, it appears that only the direct pathway MSNs express M_4Rs (Ince et al., 1997; Yan et al., 2001). ACh may also play a general, indirect modulatory role in corticostriatal synaptic plasticity by regulating voltage-gated Ca^{2+} channels on local inhibitory projections between MSNs (Perez-Rosello et al., 2005). In summary, as with DA, there are several mechanisms by which ACh can influence striatal synaptic plasticity.

Early data on the relationship between TANs and DA inputs to the striatum suggested that the two systems were reciprocally inhibitory (DeBoer and Abercrombie, 1996; Drukarch et al., 1989; Pisani et al., 2000). The basic idea was that they provide an antagonistic balance in normal striatal function (Calabresi et al., 2000a; Zhou et al., 2003). However, subsequent findings have painted a more complex picture. ACh may directly modulate the nigral source of striatal DA, because systemic administration of nicotine increases burst firing of mesencephalic DA cells (Mereu et al., 1987). TANs, which provide most of the ACh in the striatum, project to the presynaptic side of nigrostriatal synapses, where they increase DA release via nAChRs and, with a presumably different time course, decrease DA release via M_4R

(Cragg, 2003; Rice and Cragg, 2004; Zhou et al., 2001; Zoli et al., 2002). On DA terminals, nAChRs may modulate DA release by forming heteromeric complexes with D_2R autoreceptors (Quarta et al., 2007). Given the diverse array of nAChR subunits present, the full complement of AChR function in DA terminals remains far from complete (Salminen et al., 2004). However, an emerging concept is that striatal ACh levels can enhance the saliency of DA inputs to the striatum by effectively amplifying the efficacy of phasic DA firing (Cragg, 2006).

In addition to cholinergic modulation of striatal DA function, DA inputs to striatum also influence TAN function. GABAergic inputs onto TANs can be inhibited by D_2R activation (Bracci et al., 2002). TAN plasticity that occurs during Pavlovian conditioning depends on DA, because it can be prevented by MPTP in the primate (Aosaki et al., 1994a). DARs on TANs can either reduce (via D_2Rs) (Maurice et al., 2004; Wang et al., 2006) or increase (via D_5Rs) TAN activity and even induce LTP in glutamatergic synapses onto TANs (via D_5Rs) (Suzuki et al., 2001). The requirement of D_2R activation for HFS-induced LTD in the indirect pathway may result from the D_2R's inhibitory influence on TANs (Wang et al., 2006). Collectively the evidence suggests that there is a complex yet carefully coordinated interaction between the DA and ACh systems mediating plasticity at several types of striatal synapses. The relative time dynamics of the various DARs, AChRs, and their intracellular signaling pathways may be key to understanding their joint influence on striatal synaptic plasticity.

Discussion

Striatal synaptic plasticity in dystonia

The breadth of indirect but convergent evidence summarized in this review suggests that dysfunctional synaptic plasticity in the striatum may be a pathophysiological feature common to various forms of dystonia with very disparate clinical expressions. There is a large and growing body of evidence for abnormalities in the DA and ACh systems in dystonia and synaptic plasticity in the striatum is heavily influenced by these two neuromodulators, separately and jointly (Lovinger et al., 2003). Both neuromodulatory systems should be considered in concert, as has been the case in studying their impact on functions of the prefrontal cortex, because they interact with each other and jointly influence efferent systems (Briand et al., 2007). There is also limited evidence that both may be simultaneously affected in dystonia: in 2 out of 4 patients examined postmortem, including 1 generalized and 1 focal dystonia, there were neurofibrillary tangles or some neuronal loss in both of the brainstem nuclei (SNc and PPN) giving rise to striatal projections of these neuromodulatory systems (Zweig et al., 1988). Nevertheless, although interactions among neuromodulatory systems may be central to plasticity in striatal synapses, these interactions are relatively neglected in movement disorders and particularly in research on dystonia.

Although the focus of the present review was on mechanisms of synaptic plasticity that putatively involve strengthening or weakening existing synapses, it should be recognized that other forms of neural plasticity may be at work in the striatum, including not only synaptic structure alterations (for which there is evidence from Drosophila that torsinA may play a role (Lee et al., 2009)), synaptic pruning, and synaptogenesis, but also even neurogenesis, for which there is evidence in adult striatum (Luzzati et al., 2007). Further research is needed to achieve a complete understanding of neuromodulatory influences in striatal plasticity, how those influences are affected in dystonia, and the implications for treating the disorder.

The two-factor hypothesis

Although the etiology of dystonia remains a mystery, its varied presentation, the reduced penetrance exhibited by identified genetic

factors, and its use-dependence in some forms, suggest that it may involve the conjunction of multiple factors. Genetic influences are likely an important but not exclusive contributing factor. Single genetic abnormalities can lead to very different clinical expressions in different affected individuals and different single genetic abnormalities can lead to similar clinical expressions (Defazio et al., 2007; Draganski et al., 2009). Although polygenic interactions not yet identified cannot be ruled out, there is a broad array of evidence pointing to the contribution of environmental factors, and in particular use-dependence (Altenmuller, 2003; Byl et al., 1996; Lin and Hallett, 2009; Quartarone et al., 2006b).

The striatum is well positioned in the basal ganglia thalamocortical network to mediate interactions between diffuse neuromodulatory influences and the sensorimotor activations inherent to use-dependence. Thus abnormal plasticity in striatum may be an important aspect of the subtly abnormal plasticity that, in conjunction with use-dependence, constitutes a two-factor mechanism in the pathophysiology of dystonia. This concept is depicted in Fig. 3. Abnormal plasticity in striatum may be a pathophysiological feature common to various forms of dystonia with very disparate clinical expressions. The relative contribution of abnormal plasticity and use-dependence may determine the specific clinical profile of individual patients. For example, abnormal striatal plasticity may play a stronger role in patients with early onset generalized dystonia and a relatively weaker (but still critical) role in patients with adult-onset focal dystonia. This concept is consistent with recent suggestions that inclusion body pathology may be more prominent in early onset generalized forms of dystonia (Holton et al., 2008; Wichmann, 2008), because cellular pathologies in dopaminergic and cholinergic brain stem nuclei could have severe adverse effects on plastic processes throughout the striatum.

Only a few studies have thus far provided empirical evidence in support of a neuromodulatory-mediated version of this two-factor hypothesis. In 1997 Schicatano reported on a rat model of blepharospasm that required reduced striatal DA (via the classic 6-OHDA lesion in SNc) and a peripheral injury induced by weakening the obicularis oculi muscle (Schicatano et al., 1997). Some suggested that

the resultant increased blink reflex was due to plasticity in interneurons in the reflex pathway (Hallett, 2002). However, this may in turn be modulated by plasticity in more central systems that have descending influence on those interneurons, as suggested by basal ganglia influence on reflexes (Rea and Ebner, 1991) and GPi DBS' progressive inhibition of blink and spinal cord reflexes (Tisch et al., 2006a; Tisch et al., 2006b). A more recent study conducted by Kuo et al. (2008) demonstrated that the plasticity induced by a combination of transcranial direct current stimulation and paired associative stimulation TMS depends on DA and is modulated by ACh (Kuo et al., 2007). Although the experimental measures were from cortex, the close interactions between basal ganglia and cortex and the systemic modulation of DA and ACh used in the experiments are consistent with the role stipulated for these neuromodulators in the present review.
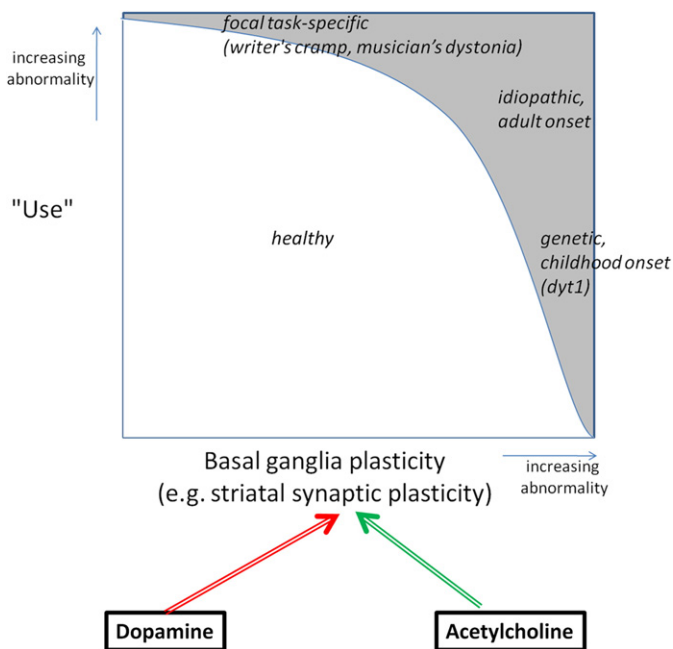
From etiology to pathophysiology

Our working hypothesis is that subtle abnormalities in striatal plasticity, some of which may arise from genetic abnormalities, may be involved in the development of dystonia by facilitating the transition from healthy to dystonic states. If this hypothesis is confirmed, an improved understanding of abnormal plasticity in dystonia may help provide some of the missing links from etiological factors in the disease to the pathophysiology seen at the time of clinical presentation. Defazio et al. (2007) stipulate that genetic factors should lead to detectable biological abnormalities, evident in neurophysiological or imaging measures. Aberrant striatal plasticity may be one such abnormality. The idea that abnormal plasticity can provide a link between genetic factors and phenotype, as has been suggested in autistic and psychotic spectrum disorders (Oberman and Pascual-Leone, 2008), may also be central to dystonia. DA and ACh probably play important roles in mediating not only moment-to-moment expression of motor dysfunction in dystonia, but also in mediating plastic processes potentially involved in its development. A clearer picture of the dynamics that link etiological factors to the pathophysiology of dystonia could open avenues of research toward therapies directed at causal influences in the disease rather than its symptomatic effects.

Confirmation of our hypothesis awaits a better understanding of neural plasticity in the striatum, the basal ganglia thalamocortical circuits within which it operates, and the broader sensorimotor systems they modulate. Basal ganglia plasticity is experimentally more difficult to investigate than plasticity in reflexes or the cerebral cortex. Many questions about basal ganglia plasticity will require the use of animal models, despite the known limitations in correspondence between the animal and human clinical phenotypes (Wichmann, 2008). If as this review suggests striatal plasticity is abnormal in dystonia, it will be imperative to identify and characterize the etiological factors that could adversely affect striatal plasticity, whether behavioral or genetic. It will be interesting, for example, to see whether the recently identified THAP1 gene mutations associated with DYT6 dystonia, which impair DNA binding and may therefore affect transcriptional regulation (Fuchs et al., 2009), might influence the expression of proteins that mediate the influence of neuromodulators on striatal synaptic plasticity. An improved understanding of how these "upstream" factors lead to abnormal plasticity would ultimately facilitate the development of interventions that could not only ameliorate dystonia symptoms but, more importantly, reverse or prevent them in the first place.

Fig. 3. Conceptual framework for two factors in pathophysiology of dystonia. Shaded area corresponds to dystonia, in which various forms involve different relative contributions from the two factors.

Acknowledgments

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