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Anatomy of a songbird basal ganglia circuit essential for vocal learning and plasticity

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Abstract

Vocal learning in songbirds requires an anatomically discrete and functionally dedicated circuit called the anterior forebrain pathway (AFP). The AFP is homologous to cortico-basal ganglia-thalamo-cortical loops in mammals. The basal ganglia portion of this pathway, Area X, shares many features characteristic of the mammalian striatum and pallidum, including cell-types and connectivity. The AFP also deviates from mammalian basal ganglia circuits in fundamental ways. In addition, the microcircuitry, role of neuromodulators, and function of Area X are still unclear. Elucidating the mechanisms by which both mammalian-like and unique features of the AFP contribute to vocal learning may help lead to a broad understanding of the sensorimotor functions of basal ganglia circuits.

Keywords

Area X; dopamine; striatum; pallidum; thalamus; anterior forebrain pathway

Introduction

The discovery that the “anterior forebrain pathway” (AFP; Fig. 1A) as well as surrounding brain areas in songbirds are homologous to mammalian basal ganglia circuits creates several opportunities and challenges (Doupe et al., 2005). This relationship allows the wealth of information gained from study of primate and rodent basal ganglia circuits to guide research on the songbird AFP and the role it plays in vocal learning. For instance, the anatomy of mammalian basal ganglia circuits was informative in predicting the neurotransmitter used by the projection from Area X, a large nucleus of the AFP, to its thalamic target and the physiological properties of these Area X projection neurons (see below; Luo and Perkel, 1999a,b; Farries and Perkel, 2002). The organization of mammalian basal ganglia circuits continues to provide a framework for forming predictions about the unknown microcircuitry and neurochemistry of Area X. Of course, unanswered questions about the anatomy and function of mammalian basal ganglia circuits persist as well. The fact that the AFP is a basal ganglia circuit composed of discrete brain regions devoted to a single behavior makes it a

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promising model for understanding at least some aspects of how basal ganglia circuits work in general, including those in mammals during health and disease.

Although mammalian basal ganglia circuits and the AFP exhibit a number of striking similarities, it is important to continue asking precisely how similar they are. The last common ancestor of mammals and birds lived greater than 300 million years ago (Kumar and Hedges, 1998). The degree to which a mechanistic understanding of the AFP might apply to understanding basal ganglia circuits in mammals and their role in motor learning hinges upon how much and in what ways the organization of songbird and mammalian basal ganglia circuits have diverged during this time of independent evolution. In this review we compare the anatomy of the AFP in songbirds to basal ganglia circuits in mammals. We describe several shared features and discuss some potentially important differences. We also consider whether there are any functional parallels between the AFP and mammalian basal ganglia circuits.

We first review the basic organization of mammalian basal ganglia circuits (see also Smith et al., 1998) before describing how it compares with that of the avian basal ganglia and in particular songbird Area X. The largest basal ganglia structure is the striatum, which receives glutamatergic input from much of the cerebral cortex and part of the thalamus. Most striatal neurons are medium spiny neurons. These cells are GABAergic and are the only cells that project out of the mammalian striatum. One class of spiny neuron projects to basal ganglia output structures—the internal segment of the globus pallidus (GPi; the rodent homologue of primate GPi is called the entopeduncular nucleus) and the substantia nigra pars reticulata (SNr). These structures contain tonically active GABAergic neurons that project to the thalamus or other structures outside of the basal ganglia (Fig. 1A). This “direct pathway” through the basal ganglia inhibits basal ganglia output. A second group of striatal spiny neurons initiates an “indirect pathway” by projecting to the external segment of the globus pallidus (GPe, or GP in rodents; Fig. 1B). GPe neurons are GABAergic and inhibit basal ganglia output (GPi and SNr) neurons via a direct connection and by inhibiting glutamatergic neurons in the subthalamic nucleus (STN) that project to the GPi and SNr. The STN also receives direct input from the cortex (the “hyperdirect pathway”). The net effect of activating the indirect or hyperdirect pathway is to increase the firing rate of basal ganglia output neurons. Similar basal ganglia pathways traverse the ventral striatum (nucleus accumbens) and the ventral pallidum (VP). The striatum receives dense dopaminergic innervation from the midbrain cell groups the substantia nigra pars compacta SNc and the ventral tegmental area (VTA), and the SNc and VTA receive basal ganglia input from striatal spiny neurons, GPe, VP, and STN (Fig. 1C).

The avian basal ganglia and where Area X fits in

Most of the avian telencephalon consists of various regions of pallium (Reiner et al., 2004a). In mammals, the pallium develops into the cerebral cortex and non-layered structures, including the claustrum and the amygdala, whereas in birds nearly the entire pallium lacks laminar organization. In both mammals and birds, the remaining telencephalon is called the subpallium and consists mainly of basal ganglia structures. The anatomical, neurochemical, electrophysiological, and developmental evidence that birds contain basal ganglia structures homologous to those in mammals is abundant and extensively reviewed elsewhere (Reiner et al., 1998; Reiner, 2002; Reiner et al., 2004a). This homology is reflected by shared terminology (Reiner et al., 2004a). In summary, a large, ventral portion of the avian telencephalon receiving dense dopaminergic innervation (Fig. 1B) is homologous to mammalian striatum. The vast majority of neurons in the avian striatum are GABAergic and have small somata, spiny dendrites, and physiological properties like those of mammalian medium spiny neurons. Near the striatum are dorsal and ventral pallidal regions (referred to as GP and VP, respectively), which receive less dense dopaminergic innervation and contain large, aspiny GABAergic neurons. Little is known about the detailed properties of VP in birds, and chicken VP appears

comparable to only a portion of mammalian VP (Abellán and Medina, 2009). We use the term “ventral” to refer to location and not necessarily to imply any other similarity to mammalian VP other than characteristics general to the pallidum as a whole.

The lateral striatum (LSt) and GP in birds are part of a basal ganglia circuit remarkably similar to the classical description of mammalian basal ganglia circuits (Reiner, 2002; Person et al., 2008). Spiny neurons in LSt receive glutamatergic input from pallial areas and project to GP. GP, in turn, projects to ventral thalamus and is reciprocally connected with glutamatergic neurons in STN. LSt and GP also project to the substantia nigra pars reticulata (SNr), though the projection from LSt is sparse.

LSt and GP display some differences from mammalian basal ganglia. For example, GP neurons projecting to STN and SNr are intermingled with those projecting to thalamus. Thus, there is no clear evidence for segregated anatomical structures corresponding to GPe and GPi in primates or GP and the entopeduncular nucleus in rodents. In addition, the avian LSt appears to lack cholinergic interneurons, though such neurons are found in the medial striatum (MSt) (Medina and Reiner, 1994; Carrillo and Doupe, 2004; Person et al., 2008).

In songbirds, Area X is a discrete nucleus within the MSt that is visible in Nissl-stained sections and connected with other discrete nuclei, which are together called the song system (Fig. 1). Electrophysiological and neurochemical studies demonstrated that Area X contains all four classes of neurons found in mammalian striatum. These include spiny neurons, fast-spiking interneurons, low-threshold spiking interneurons, and tonically active cholinergic interneurons (Farries and Perkel, 2002; Carrillo and Doupe, 2004; Reiner et al., 2004b). However, unlike spiny neurons in mammalian striatum, spiny neurons in Area X do not project to the pallidum or SNr (Person et al., 2008). Instead, Area X has a GABAergic projection to the thalamus (Fig. 2A), which is a property expected of pallidum rather than striatum (Luo and Perkel, 1999a). This paradox was resolved following the discovery that Area X contains a fifth cell type not found in mammalian striatum or avian LSt (Farries and Perkel, 2002). These neurons have large somata, aspiny dendrites, a high spontaneous firing rate, and project to the thalamus; they are the only cells known to project out of Area X (Carrillo and Doupe, 2004; Reiner et al., 2004b; Farries et al., 2005; Person et al., 2008). We refer to these cells as pallidal-like neurons because they reside in the striatum but have several features similar to those of neurons in the mammalian and avian pallidum.

This spatial mixing of striatal and pallidal-like neurons and other differences between Area X and mammalian basal ganglia could reflect the evolution of unique features as the AFP arose in songbirds. In this scenario, the MSt surrounding Area X and the MSt in non-songbirds might be more similar to the mammalian basal ganglia than Area X is. To the contrary, nearly all of the differences between the Area X and mammalian basal ganglia are shared by the MSt surrounding Area X (Person et al., 2008). In the next section, we discuss these differences in detail.

Differences between Area X and mammalian basal ganglia circuits

Pallidal-like cells, but no pallidum

In the direct pathway through the mammalian basal ganglia, cortical inputs excite spiny neurons in the striatum, which inhibit spontaneously active neurons in the pallidum (or SNr) that project to the thalamus (Fig. 2A). Similarly in songbirds, spiny neurons in Area X receive glutamatergic input from the pallium and make GABAergic synapses on the pallidal-like neurons that project to thalamus (Fig. 2A; Farries et al., 2005). Hence, a fundamental basal ganglia pathway in mammals differs in Area X only in that the pallidal and striatal cells coexist in one structure. Functionally, at least, this difference seems minor. However, as noted above,

the pallidum in both mammals and birds has functionally important connections with the STN (Jiao et al., 2000). If the pallidal-like neurons in Area X that project to thalamus are like thalamus-projecting neurons in mammalian pallidum (e.g. GPi) and SNr, then they should receive glutamatergic input from the STN (Fig. 2B). And if Area X contains neurons like those of rodent and avian GP (primate GPe), then these should project to the STN (Fig. 2B). In fact, Area X neither receives input from, nor projects to the STN (Person et al., 2008). Thus, Area X contains pallidal-like cells but does not contain both striatum and pallidum; its pallidal-like neurons resemble mammalian and avian pallidum only to a degree.

One function of the STN in mammals is to provide an excitatory relay from cortex to pallidal neurons (Nambu et al., 2000). This “hyperdirect” pathway, along with the indirect pathway that extends through the striatum, GPe, and STN, are both expected to increase the firing rate of pallidal and SNr neurons that project to the thalamus (Fig. 2 A, B). Indeed, increased firing during movement or in response to sensory stimuli is commonly observed in pallidal and SNr neurons in primates (Anderson and Horak, 1985; Schultz, 1986; Turner and Anderson, 1997; Wichmann and Kliem, 2004). Interestingly, pallidal-like neurons in Area X also increase their firing rate during singing or in response to playback of song (Doupe, 1997; Hessler and Doupe, 1999a; Person and Perkel, 2007). This activity is likely driven, at least in part, by direct excitatory input to Area X pallidal-like neurons from the pallidum (Fig. 2A; Farries et al., 2005). Thus, although Area X pallidal-like neurons lack excitatory drive from the STN, they are excited by a “STN-less” analogue of the hyperdirect pathway and possibly by indirect pathway analogues as well (see below). The direct pathway involving Area X spiny neurons presumably shapes the magnitude and temporal pattern of Area X pallidal-like neuron excitation. Future studies will clarify how these anatomical differences relate to any differences in information processing between Area X and mammalian basal ganglia circuits.

Giant, one-to-one axon terminals in the thalamus and the mechanism of basal ganglia-thalamic transmission

The axons of Area X pallidal-like neurons form enormous, calyceal-like terminals covering much of the soma of thalamic target neurons (Luo and Perkel, 1999a). Each thalamic neuron receives input from one, or at most two, Area X pallidal-like neurons (Luo et al., 1999b). In contrast, thalamic terminals of basal ganglia output (SNr) neurons in rats and monkeys are smaller and primarily contact proximal dendrites rather than somata, and each thalamic neuron probably receives input from several SNr neurons (Bodor et al., 2008). On the other hand, the axon terminals of basal ganglia inputs to the thalamus in mammals and songbirds are similar in that both appear to be specialized, probably to a greater degree in songbirds, for strong and reliable inhibition of thalamus by the basal ganglia. For instance, mammalian pallidal neurons form dense terminal clusters in the thalamus and each terminal bouton formed by mammalian SNr neurons makes multiple, closely-spaced synapses on its thalamic target (Parent et al., 2001; Bodor et al., 2008).

Does the exaggerated terminal morphology and one-to-one connectivity of Area X pallidal-like neurons projecting to thalamus reflect a specialized mode of information transfer between basal ganglia and thalamus in the AFP? The dominant model in mammals is that inhibition of rapidly-firing basal ganglia output neurons allows glutamatergic inputs from elsewhere to drive thalamic neuron firing (Chevalier and Deniau, 1990). Evidence supporting this model is strong in an oculomotor basal ganglia circuit in monkeys (Hikosaka and Wurtz, 1983; Hikosaka, 2007). However, many pallidal and SNr neurons, as well as Area X pallidal-like neurons, increase firing during movement or sensory responses. One hypothesis is that increased firing of a subset of basal ganglia output neurons enhances inhibition of thalamo-cortical circuits that functionally oppose disinhibited circuits, facilitating the selection of a specific action to perform. This hypothesized role of increased firing rates in basal ganglia output neurons is not

supported in the AFP, where it is possible to simultaneously record the response of a thalamic neuron and its single Area X afferent (its entire basal ganglia input). In the AFP, both thalamic neurons and their GABAergic, pallidal-like afferents are excited during song playback (Person and Perkel, 2007). Further analysis, however, reveals that thalamic neuron spikes are preceded by a rapid (~20 ms) deceleration of pallidal-like neuron firing (Person and Perkel, 2007). Therefore, although the overall firing rate of the pallidal-like afferent increases during song playback, the spike trains possess finer temporal features that fit broadly into a disinhibition model; these features correlate with thalamic firing. Such responses of thalamic neurons in the AFP might be driven by postinhibitory rebound. In brain slices, random, high-frequency stimulation of an Area X axon drives firing in the postsynaptic thalamic neuron by postinhibitory rebound even while glutamatergic excitatory synaptic transmission is blocked (Person and Perkel, 2005). Mammalian thalamic neurons also possess intrinsic membrane mechanisms that can generate postinhibitory rebound (Jahnsen and Llinás, 1984; Llinás and Steriade, 2006). Unlike thalamic neurons in the AFP, however, they appear to receive input from multiple basal ganglia output neurons and it is not known whether they reliably respond to a brief (on the timescale of few interspike intervals or less) disinhibiting “pause” in the firing of any single input. Further, there is little spike-timing correlation between primate SNr neurons during sensorimotor responses (Nevet et al., 2007). The respective roles and interaction of inhibitory input from the basal ganglia and excitatory inputs will be critical to understanding the function of basal ganglia output to thalamus in mammals and songbirds (Kojima and Doupe, 2009).

Relationship with midbrain dopaminergic neurons

A crucial property of mammalian striatum is its dense dopaminergic innervation, which degenerates in Parkinson’s disease. Similarly, Area X receives dense dopaminergic input from the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA; Lewis et al., 1981; Bottjer et al., 1993; Person et al., 2008). Further, in both Area X and the mammalian striatum, dopamine can increase or decrease the intrinsic excitability of spiny neurons, regulate the strength of their glutamatergic input, and contribute to long-term changes in synaptic strength (Nicolar et al., 2000; Ding and Perkel, 2002, 2004; Ding et al., 2003; Kreitzer and Malenka, 2008). The functional role of dopamine in Area X is not known, but one important question is whether the AFP or other brain circuits involved in song learning can influence dopaminergic signals in Area X.

Mammalian basal ganglia circuits do play a role in shaping their dopaminergic input. Some striatal spiny neurons, pallidal neurons, and SNr neurons project to the SNc or VTA (Fig. 2C; Smith and Bolam, 1990; Kalivas et al., 1993; Tepper et al., 1995; Joel and Weiner, 2000). These projections are GABAergic, but can increase or decrease dopaminergic neuron firing via a decrease or increase in their own activity, respectively, or by interacting with GABAergic neurons within the SNc and VTA that contact dopaminergic neurons (Tepper and Lee, 2007). The avian striatum and pallidum also project to the SNc and VTA (Kitt and Brauth, 1981; Székely et al., 1994; Medina and Reiner, 1997). However, Area X does not make such a projection to the midbrain (Gale et al., 2008). The fact that MSt contains spiny neurons that project to the SNc/VTA (but not the pallidum or SNr), whereas Area X spiny neurons do not project outside of Area X at all, is the only known qualitative difference between Area X and surrounding MSt (Person et al., 2008).

Despite the lack of a direct projection, Area X might still be able to regulate its dopaminergic input. The thick axons of Area X pallidal-like neurons projecting to the thalamus make thinner, branching collaterals that form terminals in the ventral pallidum (VP). The same region of VP that receives this input projects to parts of SNc and VTA that project to Area X (Fig. 2C; Gale et al., 2008). Thus, the output of Area X could provide feedback to its dopaminergic input.

The functional impact of Area X output on dopaminergic neuron firing is difficult to predict. Area X pallidal-like neurons, which are spontaneously active and increase their firing rate during singing, are GABAergic and likely inhibit VP neurons. In mammals, pallidal neurons that project to midbrain dopaminergic regions are GABAergic and, like pallidal cells in general, are probably spontaneously active. It is not known whether this is also true in songbirds, or whether VP neurons contact dopamine neurons directly or indirectly via non-dopaminergic neurons in the SNc and VTA. Hence, there is still much to discover about the circuitry and function of basal ganglia control of dopaminergic neuron firing in songbirds as well as in mammals.

Area X pallidal-like neurons are striatal-like, too

The collateral pathway from thalamus-projecting, pallidal-like neurons in Area X to VP is different from any known mammalian basal ganglia pathway (Fig. 2C). The axons of some mammalian pallidal neurons make collateral projections to several basal ganglia targets, but the axons of thalamus-projecting pallidal neurons do not (Parent et al., 2000,2001). Further, the axons of Area X pallidal-like neurons contain the neuropeptide enkephalin, which is a characteristic of striatal spiny neurons that project to the pallidum but not pallidal neurons in mammals (Carrillo and Doupe, 2004).

Another reported difference between pallidal-like neurons in Area X and mammalian pallidal neurons is that the thalamus projecting neurons in Area X in adult zebra finches do not appear to express the pallidal marker Nkx2.1 (Carrillo and Doupe, 2004). Nkx2.1 is important in specifying the development of pallidal structures (Sussel et al., 1999) and is expressed in avian pallidal regions (Puelles et al., 2000; Carrillo and Doupe, 2004). The lack of expression of Nkx2.1 in Area X neurons that project to thalamus suggests at a minimum that it is not essential for maintenance of their cellular phenotype, and is consistent with the hypothesis that they are not truly of pallidal origin. Another possibility is that pallidal-like neurons in Area X and surrounding MSt migrate from pallidal regions during development and then lose their expression of Nkx2.1 in adulthood. Recent findings in developing chickens are consistent with this possibility (Abellán and Medina, 2009). Further studies will be necessary to address the developmental origin of pallidal-like neurons in Area X.

The direct, glutamatergic input from pallidum to Area X pallidal-like neurons is also characteristic of striatal but not pallidal neurons in mammals (Fig. 2A; Farries et al., 2005). This might be just one of several consequences of pallidal-like neurons residing in the striatum rather than the pallidum. For instance, these neurons have access to the dense dopaminergic innervation of striatum and the opportunity to interact with all classes of striatal interneurons.

Together, these observations suggest that the pallidal-like neurons in Area X are “striatal” not only in location, but also in some of their anatomical and neurochemical properties as well.

Unresolved anatomical questions

Are there distinct spiny neuron populations forming “direct” and “indirect” pathways through Area X?

In mammals, cortical input to the striatum excites direct pathway spiny neurons that in turn inhibit pallidal or SNr neurons projecting to the thalamus (Fig. 2A). The indirect pathway from striatum to thalamus originates in a second population of striatal spiny neurons. Cortical activation of indirect pathway spiny neurons increases the activity of thalamus-projecting pallidal and SNr neurons by inhibiting their pallidal, GABAergic input and disinhibiting their glutamatergic input from the STN (Fig. 2B). Area X contains a pathway from spiny neurons to pallidal-like neurons that corresponds to the direct pathway in mammals (Farries et al., 2005). In addition, the presence of connections between Area X pallidal-like neurons allows

the possibility of an indirect pathway in Area X whereby spiny neurons inhibit pallidal-like neurons that in turn inhibit other pallidal-like neurons, thereby increasing firing in the latter (Fig. 2B; Farries et al., 2005). This could occur solely as lateral interactions between pallidal-like neurons that project to the thalamus, or it is possible that some pallidal-like neurons inhibit thalamus-projecting pallidal-like neurons but do not themselves project outside of Area X (Fig. 2B).

A first step in identifying a mammalian-like indirect pathway through Area X is to determine whether there are two different subtypes of spiny neurons. In mammals, most direct pathway spiny neurons express D1-dopamine receptors as well as the neuropeptide substance P, while indirect pathway spiny neurons express D2-dopamine receptors and enkephalin (Smith et al., 1998). These spiny neuron populations further differ in their electrophysiological properties and dendritic tree size (Kreitzer and Malenka, 2007; Cepeda et al., 2008; Gertler et al., 2008). Is a similar pattern of dopamine receptor and neuropeptide expression present in Area X spiny neurons? Receptor autoradiography indicates that D1 receptors are abundantly expressed in Area X, but the identity of the cells expressing these receptors is not known (Casto and Ball, 1994). Electrophysiological evidence suggests that many Area X spiny neurons have both D1 and D2 receptors, but that some spiny neurons express more of one than the other receptor (Ding and Perkel, 2002). Further, substance P is expressed in Area X spiny neurons (Carrillo and Doupe, 2004; Reiner et al., 2004), and enkephalin is as well (Carrillo and Doupe, 2004), but it is not known whether they are expressed in the same or separate populations of spiny neurons. Experiments that quantify the coexpression of D1 and D2 receptors along with substance P and enkephalin will help illuminate the complex microcircuitry within Area X.

Is there a thalamic projection to Area X?

In addition to its substantial excitatory input from cerebral cortex, the mammalian striatum receives a similar number of glutamatergic terminals from the thalamus (Smith et al., 2004; Lacey et al., 2005). The thalamostriatal projection arises mainly from the intralaminar nuclei, which receive direct input from the cerebellum. Is there a similar thalamostriatal projection to Area X? Tracer injection in Area X retrogradely labels neurons in the thalamic target of Area X and nearby thalamic nuclei (Bottjer et al., 1989; Castelino et al., 2007; Person et al., 2008). These regions of thalamus receive input from the cerebellum (Person et al., 2008). However, the axons of these thalamic neurons pass near and through Area X before terminating in the pallidum dorsal to Area X, and it is not known whether they make any terminals in Area X. Resolving this issue conclusively is important. A functional pathway from thalamus to Area X could mediate cerebellar input to the AFP. Alternatively, a lack of thalamic input to Area X is another potentially important difference between Area X and mammalian striatal circuits.

Examining expression of vesicular glutamate transporters (VGluTs) in Area X could be informative in addressing whether Area X receives glutamatergic input from the thalamus. Such experiments have been key in differentiating cortical and thalamic terminals in the striatum of rats (Lacey et al., 2005; Moss and Bolam, 2008). In mammals, glutamatergic terminals made by telencephalic neurons express VGluT1, whereas glutamatergic terminals made by thalamic (and other subtelencephalic neurons) express VGluT2 (Fremeau et al., 2001). If this relation is the same in songbirds, VGluT2 expression might reveal the extent of any subpallial glutamatergic projection to Area X.

Functional roles of Area X and its catecholaminergic input

One way the vocalizations of young songbirds might progress from variable, structureless “babbling” to a stereotyped sequence of structured syllables is by trial-and-error reinforcement learning. In this model, juvenile songbirds produce substantial trial-to-trial variability as they practice and selectively reinforce patterns of motor related neural activity that result in sounds

resembling internal (genetically encoded) and learned (memorized song of an adult) auditory templates. It is clear that one role of the AFP is to generate much of this trial-to-trial song variability. Lesions of the AFP output nucleus LMAN (Fig. 1A) dramatically reduce song variability in juvenile zebra finches and prevent further changes to song (Scharff and Nottebohm, 1991). Reversible inactivation of LMAN has a similar effect (Ölveczky et al., 2005). LMAN lesions also prevent song plasticity in adult zebra finches caused by deafening or damage to the tracheosyringeal nerve (Williams and Mehta, 1999; Brainard and Doupe, 2000).

It is less clear how the basal ganglia component of the AFP, Area X, contributes to song learning and variability. Area X lesions in juvenile zebra finches result in unusually variable song that persists into adulthood (Scharff and Nottebohm, 1991). This is consistent with a role for Area X in controlling the variability generated by the AFP in a manner that promotes normal song development. For instance, Area X might regulate the magnitude and variability of AFP output (overall or during specific portions of song) or play a role in the development of repeated patterns of LMAN neuron activity that could serve as an instructive signal (Kao et al., 2008). However, the long-term effects of Area X lesions on LMAN neuron activity (AFP output) are not known. Area X projection neurons are spontaneously active and strongly inhibit neurons in their thalamic target, DLM (Fig. 1A). DLM also receives excitatory input (Luo and Perkel, 1999b) arising from the premotor nucleus RA (Fig. 1A) and/or unknown anatomical sources (Vates et al., 1997). Releasing DLM from tonic inhibition by lesioning Area X might dramatically increase excitatory drive to LMAN (Kojima and Doupe, 2009), resulting in abnormally high and sustained activity of LMAN neurons during singing. Hence, it would be informative to block the glutamatergic input to Area X with glutamate receptor antagonists or otherwise alter the input-output relation of Area X without suppressing its tonic inhibition of DLM.

Catecholamines in Area X might modulate AFP output and song variability during both song learning in juveniles and sexually-motivated singing in adults. Although the song of adult zebra finches is substantially less variable from trial to trial than juvenile vocalizations, some amount of AFP-dependent variability persists. Song is more variable when an adult zebra finch sings alone (undirected song) than when he sings to a female (directed song). LMAN lesions reduce the variability of undirected song to that of directed song (Kao et al., 2005). During directed singing, the magnitude and variability of singing-related activity is reduced in both Area X and LMAN (Hessler and Doupe, 1999b), and extracellular dopamine concentration is increased in Area X (Sasaki et al., 2006). Area X also appears to contain noradrenergic axons, which are comparatively sparse (Castelino et al., 2007). However, systemic injection of a noradrenergic neurotoxin, but not lesions of SNc/VTA dopaminergic neurons, eliminates social-context dependent differences in the magnitude of singing-related immediate early gene expression in Area X (Castelino and Ball, 2005; Hara et al., 2007). It is not yet known whether these noradrenergic or dopaminergic lesions alter neural activity in the AFP or song variability. Tonic and phasic dopamine release both play critical roles in striatal function in mammals (Schultz, 2007), and dopamine has several physiological effects on Area X neurons (see above). Hence, regardless of whether there are any functionally important dopamine signals during song learning, removing dopamine or blocking its receptors is likely to alter information processing in Area X. Any corresponding behavioral effects could provide clues to the function of Area X.

Given the broad anatomical similarities between the AFP and mammalian basal ganglia circuits, are there any corresponding functional parallels? AFP output generates variability in song that is essential for vocal plasticity. The role of the basal ganglia structure Area X may be to adaptively constrain or release motor variability and perhaps also to promote particular patterns of AFP output that produce successful vocal variants. This is not unlike the function

of mammalian basal ganglia in promoting rewarded behaviors and suppressing other movements. For instance, inactivating the ventral striatum in rats increases the frequency of several non-reinforced behaviors during operant tasks (Yun et al., 2004), and inactivation of basal ganglia output (SNr) neurons in a circuit controlling eye movements in primates prevents visual fixation and precise saccades to rewarded targets, which are instead replaced with frequent spontaneous saccades to non-target locations (Hikosaka and Wurtz, 1985). In both mammals and songbirds, changes in striatal neuron activity might be important in the transition from variable, exploratory behavior to more stereotyped “habits” that utilize learned contingencies between movements and their sensory consequences (Graybiel 2005, 2008).

Other neuromodulators of Area X

While we focus in this review on catecholamine modulation of Area X and functional processing through this basal ganglia pathway, it is important to note the presence of a variety of potential neuromodulators and/or their receptors in Area X. These studies have been conducted in a variety of different songbird species, complicating any direct comparison. Moreover, much of this work addresses simply the presence of the candidate modulator or its receptor rather than its functional role. We nonetheless describe these data to note the broad spectrum of potential mechanisms for neuromodulation in this circuit.

Several peptides or their receptors are present in Area X. As noted above, substance P and enkephalin immunoreactivity were reported in somata and/or terminals in Area X (Ryan et al., 1981; Bottjer and Alexander, 1995; Reiner et al., 2004; Carrillo and Doupe, 2005). The Area X neurons that project to DLM express enkephalin (Carrillo and Doupe, 2005). Gullledge and Deviche (1995, 1999) reported mu, delta, and kappa opioid receptor binding in Area X. In addition, Area X is immunoreactive for somatostatin and CGRP (Bottjer et al., 1997) and is sparsely innervated by VIP positive fibers (Bottjer and Alexander, 1995).

Interestingly, while binding sites for the nonpeptide neuromodulator melatonin are present at high levels in many song-control nuclei, the density of binding sites within Area X is quite low in male zebra finches (Gahr and Kosar, 1996). Levels are higher in house sparrows (Whitfield-Rucker and Cassone, 1996) and are modulated with photoperiod in starlings (Bentley and Ball, 2000; Bentley, 2003). Area X also expresses high levels of the endocannabinoid receptor CB1 (Soderstrom and Johnson, 2000, 2001). Systemic treatment of birds with cannabinoids affects song learning (Soderstrom and Johnson, 2003), consistent with an action through Area X or other song-control regions. There are thus a number of additional neuromodulators that could alter information processing in Area X and the anterior forebrain pathway.

Conclusions

Mammalian and avian basal ganglia circuits, including the songbird AFP, are remarkably similar, yet differ in several intriguing ways. In many instances, conspicuous anatomical differences found in an avian basal ganglia circuit appear as if they might be functionally offset to some degree by other deviations from the mammalian plan. For example, spiny neurons in much of the MSt, including songbird Area X, do not project to the pallidum or SNr, but this is “remedied” by the presence of pallidal-like neurons within the striatum itself. These pallidal-like neurons lack excitatory drive from the STN; instead, they are driven by direct palliostriatal (corticostriatal) input. And unlike other striatal regions, Area X lacks a direct connection that can control the activity of its dopaminergic input; still, an alternative basal ganglia pathway, unique from any found in mammals, links Area X to its dopaminergic input.

As we gain a better understanding of how the AFP contributes to song learning, what it tells us about basal ganglia function in a broader sense will depend on detailed knowledge of the mechanisms by which both conserved and unique features of the AFP contribute to its function.

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Figure 1.

The song-control system in songbirds includes a basal ganglia circuit. **(A)** Song-control nuclei and their interconnections. A motor pathway (red) is involved in song production. The anterior forebrain pathway (blue) regulates trial-to-trial song variability and is essential for song learning and plasticity. **(B)** Tyrosine hydroxylase immunostaining reveals a region of dense dopaminergic innervation in the songbird telencephalon that corresponds to the striatum, of which Area X is part. Dopaminergic cell bodies projecting to the striatum are located in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA). **(C)** An expanded view of the boxed region in (A) reveals the location of Area X relative to some other basal ganglia structures. HVC (proper name); RA, robust nucleus of the arcopallium; DLM, medial

portion of the dorsolateral nucleus of the thalamus; LMAN, magnocellular nucleus of the anterior nidopallium; VP, ventral pallidum; GP, globus pallidum; MSt, medial striatum.

Figure 2.

Comparison of basal ganglia connectivity in mammals and the songbird anterior forebrain pathway. The schematics of mammalian pathways focus on dorsal striatal and pallidal pathways and use primate terminology for the globus pallidus; internal and external portions (GPi and GPe) correspond to rodent entopeduncular nucleus and globus pallidus, respectively. (A) The direct pathway through the mammalian basal ganglia and songbird Area X (green lines). (B) The indirect pathway in mammals and a putative indirect pathway in Area X (red lines). The indirect pathway in Area X could be mediated via pallidal-like neurons that do not project to thalamus; alternatively, thalamus-projecting pallidal-like neurons could be interconnected (dashed lines). (C) Anatomical pathways between striatum, pallidum, and

midbrain dopaminergic neurons differ in mammals and songbird Area X (blue lines). The SNc in mammals also receives basal ganglia input from the subthalamic nucleus (STN) and collaterals of SNr, but not GPi, neurons (not shown).