Published in final edited form as:

Brain Res Bull. 2012 January 4; 87(1): 1–9. doi:10.1016/j.brainresbull.2011.09.013.

The interhemispheric connections of the striatum: implications for Parkinson's disease and drug-induced dyskinesias

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Abstract

Parkinson's disease (PD) is characterized by loss of nigrostriatal neurons and depletion of dopamine. This pathological feature leads to alterations to basal ganglia circuitry and subsequent motor disability. Pharmacological dopamine replacement therapy with medications such as levodopa ameliorates the symptoms of PD but can lead to motor complications known as drug-induced dyskinesias. We have recently shown that clinically hemiparkinsonian rhesus monkeys do not develop levodopa-induced dyskinesias despite chronic intermittent exposure and significant unilateral loss of nigrostriatal neurons and dopamine. It is currently unclear what mechanisms prevent the onset of dyskinesias in these animals. However, based on our study and results from previous lesioning studies in both the rat and monkey models of PD, we hypothesize that one potential mechanism that may prevent the genesis of dyskinesias in these animals is interhemispheric inhibition. Two potential interhemispheric connections that may modulate dyskinesias are the interhemispheric nigrostriatal and corticostriatal pathways. Few investigators have examined the interhemispheric nigrostriatal and corticostriatal connections and the functional role they may play in drug-induced dyskinesias in PD. Therefore, in the following review, we assess the neuroanatomical, electrophysiological and behavioral properties of these interhemispheric connections. Future studies evaluating these interhemispheric striatal pathways and the pathophysiological changes that occur to these pathways in the dyskinetic state are warranted to further develop treatments that prevent or mitigate drug-induced dyskinesias in PD.

Keywords

basal ganglia; nigrostriatal degeneration; movement disorders; dopamine replacement therapy

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in America affecting > 1 million people. PD is characterized by loss of dopaminergic nigrostriatal neurons (neurons originating in the substantia nigra pars compacta (SNc) and terminating in the striatum), which subsequently causes dopamine depletion to the basal ganglia, a set of interconnected nuclei that play a role in the selection and inhibition of movement. This dopamine depletion leads to pathophysiological alterations to the basal ganglia leading to

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the cardinal symptoms of PD: bradykinesia, muscle rigidity and tremor. Dopamine replacement therapy with levodopa (the precursor of dopamine) is currently the best available pharmacological treatment for PD. However, many advanced PD patients develop choreiform and dystonic abnormal involuntary movements known as drug-induced dyskinesias after chronic treatment (Deogaonkar and Subramanian, 2005). Although it is clear that a number of mechanisms affect the onset and severity of dyskinesias, the prevailing hypothesis for the development of dyskinesias is extensive nigrostriatal degeneration and non-physiological pulsatile stimulation of striatal dopamine receptors causing supersensitivity (Mouradian et al., 1989).

The MPTP-treated hemiparkinsonian rhesus monkey has been used in numerous pathophysiological and preclinical studies of PD (Benazzouz et al., 1992; Benazzouz et al., 1996; Collier et al., 2005; Collier et al., 2007; Emborg et al., 2006; Gilmour et al., 2011; Kordower et al., 2000; Kordower et al., 2006; Lieu et al., 2011; Miletich et al., 1994; Schneider et al., 1992; Starr et al., 1999; Subramanian et al., 1997; Subramanian et al., 2005; Subramanian et al., 2010; Xu et al., 2010). The advantages and disadvantages of this model has been extensively reviewed elsewhere, see (Emborg, 2007). While this model does not recapitulate all the classic features of idiopathic PD, the MPTP-treated monkey does model many aspects of PD including bradykinesia, rigidity, therapeutic response to dopaminergic medications, and drug-induced dyskinesias (bilateral models). Most preclinical studies of experimental therapeutics in PD have required safety and efficacy evaluations in the MPTP-treated non-human primate model of PD before regulatory approval for human use of the experimental therapeutic. Currently, the MPTP-treated monkey is perhaps the best model to mimic choreiform and dystonic movements seen in advanced PD patients (Bezard et al., 2003; Bibbiani et al., 2005; Langston et al., 2000; Liang et al., 2008; Papa et al., 1999; Pearce et al., 1995; Quik et al., 2007). It is also well known that the hemiparkinsonian rhesus model is easier to maintain because of its limited disability, and is a preferred model for electrophysiology studies, studies for cell transplantation and gene therapy, and studies designed to explore new therapeutic strategies. In this context, we recently showed in a retrospective study that strictly unilateral MPTP-treated hemiparkinsonian rhesus monkeys do not develop levodopa-induced dyskinesias. In our study, we treated animals chronically with levodopa for up to 12 months (Lieu et al., 2011). Interestingly, none of the animals displayed choreoathetoid or dystonic drug-induced dyskinesias. Post-mortem, histological analysis demonstrated that these animals had extensive unilateral nigrostriatal degeneration with > 90% loss. Based on the prevailing hypothesis for the development of dyskinesias described above, these animals should display dyskinesias at least on the affected side. However, this was not evident in our study. The mechanisms by which these animals do not develop dyskinesias are currently unclear. We had hypothesized in our study that one possible mechanism that prevents dyskinesias in hemiparkinsonian rhesus monkeys is via interhemispheric inhibition, more specifically the interhemispheric nigrostriatal pathway.

The human relevance of our report (Lieu et al., 2011) is the notion that idiopathic PD also begins unilaterally (Hoehn and Yahr stage 1), and such patients in stage 1 disease never develop any dyskinesias. We are unaware of any known reports of unilateral PD (H&Y stage I) patients developing any drug-induced dyskinesias. Published literature to date in which early stage I patients were given large doses of levodopa as part of placebo-controlled randomized studies did not exhibit drug-induced dyskinesias while they were in stage I disease (Fahn, 2006). It is well known that in patients with idiopathic PD at the time of initial onset of symptoms, > 50% of the nigrostriatal dopaminergic neurons have succumbed to neurodegeneration. However, this neurodegeneration is asymmetric and the onset to disease symptoms of PD on one side of the body is a well established diagnostic criterion for PD. Therefore, despite the lack of disease progression in the hemiparkinsonian MPTP-treated monkey model, there are many phenomenological similarities between the

hemiparkinsonian rhesus monkey model and stage 1 idiopathic PD. As a corollary, the MPTP-treated bilateral animal faithfully develops in all cases levodopa-induced dyskinesias that is virtually identical to dyskinesias seen in PD patients. Thus, the MPTP-treated monkey model of PD, despite its static nature, allows adequate modeling of the human disease at different stages and investigation of pathophysiological questions regarding the origin of dyskinesias. Most interestingly, as MPTP doses are increased in the creation of the hemiparkinsonian model, the animal develops bilateral disease despite the deliberate injection of the toxin unilaterally via a single internal carotid artery. This finding further supports the notion that the loss of interhemispheric nigrostriatal connections, as hypothesized in our study, is mandatory to cause drug-induced dyskinesias. The observation that stage I PD patients remain resistant to drug induced dyskinesias while stage II (bilateral) disease patients begin to exhibit drug-induced dyskinesias may be the clinical correlate to the dyskinesia symptoms seen in the MPTP-treated monkey models of PD.

As shown in Figure 1, we retrospectively reviewed the literature to support this interhemispheric inhibition theory in both the monkey and rat model of PD based on data from various lesioning studies. In the rat, we suggested that the dyskinetic Ungerstedt model of PD which causes > 95% unilateral nigrostriatal degeneration by 6-hydroxydopamine (6-OHDA) neurotoxin injection into the medial forebrain bundle leads to loss of interhemispheric nigrostriatal neurons (Lieu et al., 2010; Ungerstedt and Arbuthnott, 1970). In contrast, the non-dyskinetic striatal lesioned model (Sauer and Oertel, 1994; Winkler et al., 2002) with approximately 50–70% nigrostriatal loss by 6-OHDA injection into the striatum retains these interhemispheric nigrostriatal neurons. Similarly in our non-dyskinetic hemiparkinsonian rhesus monkey model, we suggested that interhemispheric nigrostriatal neurons are retained but lost in the bilateral parkinsonian rhesus monkey that readily develops dyskinesias (Liang et al., 2008; Papa et al., 1999).

In this context, it is worthwhile to explain the differences between the unilateral 6-OHDA lesioned hemiparkinsonian rat and MPTP-treated hemiparkinsonian monkey. The injection of the neurotoxin in the case of 6-OHDA (Ungerstedt model) is adjacent to the site of crossing of the interhemispheric nigrostriatal fibers (see discussion below under tracer studies) in the mesencephalon. This location causes the lesioning of the interhemispheric nigrostriatal fibers and its neurodegeneration. In addition, most 6-OHDA-treated rats have near complete lesion of virtually all dopaminergic nigrostriatal neurons in the ipsilateral nigra. On the other hand, injection of MPTP to create the hemiparkinsonian rhesus monkey model of PD is performed via a substantially different technique of neurotoxin administration. MPTP is injected intracarotid unilaterally repeatedly on the same side. MPTP administered in this manner predominantly remains in the ipsilateral hemisphere and to a lesser extent crosses over into the contralateral hemisphere via the Circle of Willis. The effects of MPTP (MPP+) is primarily at the level of the striatum where it is taken up via the dopamine transporter into the nigrostriatal fibers and retrogradely transported to cause delayed toxicity of the cell bodies located in the SN. Due to this very different route of administration, the nigrostriatal degeneration is predominantly ipsilateral, and as noted in our paper (Lieu et al., 2011), the lesion is about 90% complete. We hypothesize that in this scenario, the interhemispheric nigrostriatal fibers are spared, allowing the animal to be resistant to levodopa-induced dyskinesias.

In the following review, we closely examine the previous literature that has used neuroanatomical, neurochemical, electrophysiological, and behavioral techniques to highlight the interhemispheric connections. Although we hypothesize that the most likely candidate for interhemispheric inhibition in drug-induced dyskinesias is by the nigrostriatal pathway, it is also possible that interhemispheric corticostriatal neurons play a role in dyskinesias, which we also describe below. These interhemispheric connections could

provide important information about the pathophysiological basis of PD, and may prove to be a novel target for future anti-PD and anti-dyskinetic treatments.

2. Interhemispheric connections in the normal state

2.1 Interhemispheric nigrostriatal connections

2.1.1 Tracer Studies in the Rat—A number of investigations have examined the presence and topographic organization of interhemispheric nigrostriatal projections using various labeling techniques in the rat. Most studies have used retrograde tracing techniques to identify the presence of these projections using horse-radish peroxidase (HRP). In 1980, Veening and colleagues note the presence of retrogradely labeled cells in the contralateral SNc after unilateral microiontophoretic injections of HRP into the striatum (Veening et al., 1980). Similarly, unilateral injection of wheat germ agglutinin-HRP into two anterior regions of rat striatum lead to sparsely labeled nigral neurons in the opposite hemisphere at the middle rostrocaudal regions of the SN (Consolazione et al., 1985). Additional experiments in adult Long-Evans rats with unilateral striatal injections of HRP confirm these findings. This study suggested that these interhemispheric nigrostriatal connections account for approximately 3% of the ipsilateral pathway (Douglas et al., 1987). Control injections in the cortex and nucleus accumbens did not label contralateral SN, validating the presence of specific crossing nigrostriatal projections. To further delineate the topography of these projections, it has been suggested that these neurons originate mainly in the middle and caudal parts of the SN (Morgan et al., 1986), whereas the ipsilateral nigrostriatal projections are distributed more in the rostral SN. This suggests that there is an inverse distribution between ipsilateral and contralateral projecting nigrostriatal neurons in the rostrocaudal plane. In another study using 10 normal male Wistar rats, investigators only found 1–5 contralaterally HRP-labeled SN neurons after unilateral striatal injection of HRP in 6 out of 10 rats (Pritzel et al., 1983a). These differences in results found with HRP striatal injection and the presence of contralaterally labeled SN neurons may be attributed to site of injection and survival period of the animal.

Anterograde tracer [^3H]leucine injected unilaterally into the SNc in male albino rats leads to the presence of interhemispheric nigrostriatal axonal projections discretely terminating in the medial and lateral portions of the contralateral striatum (Morgan and Huston, 1990). With infusion of Evans Blue (a retrograde fluorescent tracer) unilaterally into the striatum of Sprague-Dawley rats, Fass and Butcher report 2–14 neurons positively labeled in the contralateral SN per brain (Fass and Butcher, 1981). Similar to studies with HRP, control injections with this fluorescent tracer to the cortical regions directly above the striatum did not cause contralateral SN labeling, and thus confirm that the presence of contralateral SN labeling is entirely due to crossing interhemispheric nigrostriatal projections. In another study, nuclear yellow was injected into one striatum and granular blue into the opposite striatum (Loughlin and Fallon, 1982). One to two retrogradely labeled neurons of each tracer were found in the SN and ventral tegmental area (VTA) contralateral to injection through each SN section examined. Investigators did not observe any double-labeled cells. These results were further confirmed using striatal injections of either propidium iodide or Granular Blue and demonstrate that SN contralateral projections to the striatum account for 1–2% of the ipsilateral projections (Fallon et al., 1983). Similar findings were observed in young rats (6 and 30 day old) that had received Nuclear Yellow into one striatum and granular blue in the contralateral striatum, finding that crossed cells approximated 1% of ipsilateral cells with 6-day old rats having slightly more crossed cells than the 30 day old group (Altar et al., 1983). However, dispersion of dyes was more extensive in 6 day old than 30 day old, and thus may account for differences in number of crossing cells observed in the two groups. In a different study, neonatal rats received striatal lesion in one striatum then subsequent retrograde tracer in the opposite hemisphere in adulthood and found neurons

retrogradely-labeled in the contralateral nigra. The authors suggest that these projections are most likely not branching since they were not affected by contralateral striatal lesion (Jaeger et al., 1983), and that ipsilateral and contralateral projecting nigrostriatal neurons are two distinct separate populations. However, this finding is different to those found by Pritzel and colleagues (Pritzel et al., 1983b). Injection of Nuclear Yellow in one striatum and Fast Blue into the other striatum lead to both contralaterally labeled SNc neurons at 5% of ipsilaterally labeled neurons with a small number of nigral neurons double-labeled with both tracer. This particular observation demonstrates bifurcation of single nigrostriatal neurons between the two striatum. Differences in these studies may be due to procedural differences such as tracer used, survival time and analysis of tissue. Nonetheless, these studies validate the presence of interhemispheric nigrostriatal neurons in the rat which approximate < 1–10% of the ipsilateral nigrostriatal connections. Table 1 summarizes the tracer studies in the rat.

Furthermore, investigators have examined the location of where these interhemispheric nigrostriatal neurons decussate as well as the neurochemical properties of these cells. One group of investigators suggests that these fibers cross in the diencephalon, specifically near the thalamus, based on unilateral, striatal injection of HRP (Pritzel et al., 1983b). However, others have more convincingly shown that the interhemispheric nigrostriatal neurons most likely cross near the ventral tegmental region. In these studies, transection of the corpus callosum and thalamic region in rats does not prevent labeling of contralateral neurons after unilateral striatal injection of HRP or Evans Blue, whereas midsagittal transection at the ventral mesencephalon prevents contralateral labeling of interhemispheric nigrostriatal projections (Douglas et al., 1987; Fass and Butcher, 1981; Mintz et al., 1985). Additionally, there is evidence that most of these interhemispheric nigrostriatal neurons are dopaminergic neurons based on their morphological similarities to ipsilateral projecting nigrostriatal neurons and as demonstrated through various techniques such as tyrosine hydroxylase immunocytochemistry (Altar et al., 1983; Consolazione et al., 1985; Jaeger et al., 1983; Pritzel et al., 1983b).

Vibrissae usage in the rat is important for sensorimotor function. Using HRP injections, removal of vibrissae in the rat has shown to induce plastic asymmetrical changes to the number of HRP-positive ipsilateral and crossing nigrostriatal projections (Steiner et al., 1989; Steiner et al., 1992). On the other hand, the nigrostriatal interhemispheric connections do not seem to undergo plastic changes during other types of sensorimotor behavior, such as the reinforcement of operant turning movement (Morgan et al., 1985). These results demonstrate that the interhemispheric nigrostriatal connections are subject to plasticity changes in response to sensorimotor alterations.

2.1.2 Tracer Studies in the Cat—Early cat studies have also been utilized to characterize the presence of interhemispheric SNc neurons to the caudate/striatum. Injection of HRP (ranging from 0.05–0.6µl) into the caudate of cats found dense staining in the ipsilateral SNc in addition to labeling in the SNc contralateral to the injection site (Royce, 1978). Similarly, a double-labeling study using Nuclear Yellow or bisbenzamide into one caudate and HRP in the opposite caudate demonstrate interhemispheric nigrostriatal neurons at < 1% of labeled SN neurons (Fisher et al., 1984). According to the authors, double labeling (SNc neurons labeled with two different tracers) was minor and to a lesser extent than singly labeled interhemispheric nigrostriatal neurons. They argue that the results of double-labeled neurons may be due to technical issues. However, these findings indicate sparse divergent, branched projections of the interhemispheric nigrostriatal projections in the cat, similar to results found in the rat.

2.1.3 Tracer Studies in the Primate—Data from primates has also shown the existence of crossing nigrostriatal neurons. Studying multiple projections from the SN, Francois and

associates injected HRP in the putamen and rostral caudate nucleus of one macaque (Francois et al., 1984). They found that 13% of all labeled neurons were located in the SN of the opposite hemisphere. Another macaque in that study received HRP in the head of the caudate and the superior portion of the rostral putamen and showed similar labeling results in the contralateral nigra.

Taken together, these animal studies confirm the presence of interhemispheric nigrostriatal neurons in different species using a variety of retrograde and anterograde tracer techniques. They have also characterized the topography of these projections and demonstrated that they are dopaminergic in phenotype, indicating potential significance to PD.

2.1.4 Neurophysiological and neurochemical functionality studies of the interhemispheric nigrostriatal projections—Additional studies using electrophysiological and chemical techniques validate the functional coupling properties of the interhemispheric nigrostriatal pathway. Striatal stimulation in one hemisphere can antidromically activate a small proportion of nigral neurons in the contralateral hemisphere as demonstrated by extracellular recordings in albino rats. Furthermore, these interhemispheric neurons exhibit electrophysiological properties similar to dopaminergic neurons (Collingridge, 1982). Also, these cells can demonstrate collision cancellation with a timed action potential before stimulation. Castellano and Diaz similarly suggest that the SN can influence crossing nigrostriatal dopaminergic cells via stimulation (Castellano and Rodriguez Diaz, 1991), specifically the electrophysiological action of A9 cells being influenced by the contralateral substantia nigra. When these interhemispheric connections are transected in the rat, firing rates and discharge patterns change, with a more regular firing pattern and decrease in burst firing when compared to normal animals (Castellano et al., 1993). In terms of chemical modulation, unilateral lesion to the nigra can affect dopamine levels in the contralateral striatum (Nieoullon et al., 1977). Additionally, unilateral administration of dopaminergic drugs in the SN can cause alterations in the release of dopamine in the opposite caudate in the cat (Nieoullon et al., 1979). Taken together, these studies demonstrate that there is neurophysiological and neurochemical coupling of the two nigrostriatal systems and that the nigra in one hemisphere can modulate the electrophysiological and neurochemical activity of the contralateral striatum.

2.2 The interhemispheric corticostriatal connections

Cortical connections to the striatum are known to play an important role in modulating the activity of striatal medium spiny neurons. The neuroanatomical morphology and topography of intrahemispheric corticostriatal connections have been extensively studied. However, a number of labeling studies have identified the presence of interhemispheric corticostriatal connections.

2.2.1 Tracer Studies in the Rat—Similar labeling studies in the rat have found interhemispheric corticostriatal connections originating in the sensorimotor/primary motor regions of the cortex and projecting to the dorsolateral striatum (Alloway et al., 2006; Alloway et al., 2009; Cospito and Kultas-Ilinsky, 1981). Cheng and colleagues have identified that lesion sprouting occurs from the contralateral cortex to the deafferented striatum, indicating the presence of interhemispheric corticostriatal connections (Cheng et al., 1998). Moreover, Neuropeptide Y in the striatum seems to be influenced by the contralateral cortex (Salin and Nieoullon, 1996). These studies further suggest a discrete corticostriatal connection that spans between the two hemispheres.

2.2.2 Tracer Studies in the Cat—An early study in the cat demonstrated that single cortical neurons from the sensorimotor region send decussated projections to the

contralateral striatum or collaterals to both the ipsilateral and contralateral striatum (38% of corticostriatal projections) (Fisher et al., 1986). Single cortical neurons can send collaterals to up to three different areas; the contralateral cortex, ipsilateral striatum and contralateral striatum. However, these only accounted for 2% of all labeled cells. These pyramidal corticostriatal neurons originate in laminae III – V. Further findings in the cat demonstrate that there is topographic collateralization of interhemispheric corticostriatal connections from the motor, cingulate and prefrontal cortex using other types of retrograde labels, such as Fast Blue and Diamidino Yellow (Rosell and Gimenez-Amaya, 2001).

2.2.3 Tracer Studies in the Primate—An early study by Fallon and Ziegler using silver staining identified that prefrontal cortical regions project to the contralateral striatum in the rhesus monkey through the corpus callosum (Fallon and Ziegler, 1979). To our knowledge, we are unaware of any studies that have examined the relative density of intrahemispheric and interhemispheric corticostriatal connections in response to dopamine denervation in animal models of PD.

3. Interhemispheric connections in the dopamine depleted state

3.1 Interhemispheric nigrostriatal labeling studies in lesioned animals

It has been suggested that lesions to the nigrostriatal dopaminergic pathway can induce a short-term compensatory increase of interhemispheric nigrostriatal neurons (Pritzel et al., 1983a). In this study using kainic acid or 6-OHDA before unilateral labeling with HRP in rats, an increase in interhemispheric nigrostriatal neurons at 7 and 21 days was found when compared to controls. However, the number of interhemispheric nigrostriatal neurons 90 days after lesion was decreased, similar to that of control normal animals. A similar increase in interhemispheric nigrostriatal projections after nigral lesioning was also found using the retrograde fluorescent tracers Fast Blue and Nuclear Yellow. In another study, 6-OHDA injected at the region of the ventral tegmental region and SN in rats prevented HRP labeling of interhemispheric nigrostriatal neurons (Douglas et al., 1987). Similarly, a decrease in fluorescent retrograde-labeled crossing nigrostriatal cells was found in young rats after exposure to 6-OHDA (Altar et al., 1983) when compared to normal controls. These two studies demonstrate that the interhemispheric nigrostriatal neurons are susceptible to degeneration via dopaminergic neurotoxin, providing further evidence that these neurons are dopaminergic and their potential role in PD. The variations in results in terms of increase/decrease of interhemispheric nigrostriatal projections in response to 6-OHDA may arise from differences in neurotoxin injection site and type of tracer used. However, these changes to interhemispheric nigrostriatal connections in response to neurodegeneration warrant further research as they may provide further insight into patterns of nigrostriatal degeneration in PD and onset of dyskinesias.

3.2 6-OHDA behavioral studies and interdependence of the nigrostriatal pathways

A study comparing behavioral deficits in the unilateral striatal lesioned rats to bilaterally lesioned rats with 6-OHDA suggest that there is interdependence between the two nigrostriatal systems (Roedter et al., 2001). Animals with bilateral striatal lesions had significantly more behavioral deficits than unilateral striatal lesions. For example, using a food-picking task, unilateral striatal lesioned animals showed no deficit in taking and eating food pellets. However, the bilateral striatal lesioned animals were able to take food pellets to a lesser degree than unilaterally lesioned animals. The bilaterally lesioned animals also had significant difficulty eating food pellets due to additional deficits in voluntary motor function when compared to unilateral lesioned animals. Bilaterally lesioned animals showed other behavioral problems in spontaneous activity not evident in the unilateral lesioned animals. These findings are interesting since both groups of animals had similar partial

hemispheric nigrostriatal degeneration. Thus, it would be expected that bilateral lesioned animals would show similar behavioral deficits to the unilateral animals but in a bilateral manner. However, this was not the case. In another study, intrastriatal 6-OHDA in rats caused a decrease motor function in the contralateral forelimb (Faraji and Metz, 2007). However, subsequent exposure to 6-OHDA into the opposite striatum worsened the functionality of the same forelimb that was initially impaired due to the unilateral lesion. This suggests pathways from not only ipsilateral but interhemispheric contralateral nigrostriatal connections may control a single forelimb. These findings support the hypothesis that the functioning of both nigrostriatal systems is important for movement. These findings also support our hypothesis that interhemispheric nigrostriatal connections may play an important role in the behavioral aspects parkinsonism and perhaps in the prevention of dyskinesias in the hemiparkinsonian rhesus monkey and striatal lesioned rat.

3.3 Dissociation of interhemispheric connections in 6-OHDA-lesioned animals

Hemispheric transection studies in rats have been used to examine if interhemispheric connections play a role in 6-OHDA nigrostriatal lesioning and rotational behavior, a test utilized to examine nigrostriatal asymmetry. In an early study, Mintz and colleagues severed callosal connections located at the thalamic region in hemiparkinsonian 6-OHDA lesioned rats. They found that transection did not influence amphetamine-induced rotations in these lesioned animals (Mintz et al., 1985). Although cutting the connections near the thalamus does not influence amphetamine-induced rotations, transection of the corpus callosum after 6-OHDA lesioning has been shown to significantly alter behavioral open field exploration, turning behavior and apomorphine-induced rotations (Sullivan et al., 1993). Another study dissecting interhemispheric connections in the forebrain region found that transection at this region did not prevent apomorphine-induced rotations in 6-OHDA treated animals (Steiner et al., 1985). Another lesion study identified changes in striatal DA receptor activity after transection of the corpus callosum. The authors suggest that these changes may be through the regulation of interhemispheric connections (Lawler et al., 1995). Taken together, these transection studies demonstrate that interhemispheric connections can influence behavioral responses to nigrostriatal lesioning as well as affect response to DA therapies for PD. Future studies that correlate these behavioral changes to transection/inhibition of specific interhemispheric nigrostriatal or corticostriatal connections are warranted to validate the role that interhemispheric connections play in parkinsonism.

3.4 Neurophysiological changes in the hemiparkinsonian rhesus monkey with levodopa: implications for interhemispheric connections

PD is accompanied by alterations to basal ganglia electrophysiology. Previous studies in the levodopa-treated bilateral parkinsonian monkey show that neuronal activity from the globus pallidus interna (GPi) is almost entirely suppressed during dyskinesias (Papa et al., 1999). Based on this data and our current understanding of the classical rate model of the basal ganglia, it would be hypothesized that levodopa would have a similar effect on the neuronal firing properties of the subthalamic nucleus (STN) and substantia nigra reticulata (SNR) in hemiparkinsonian non-dyskinetic monkeys. We had recently demonstrated that levodopa treatment in the hemiparkinsonian rhesus monkey does not completely normalize basal ganglia electrophysiology in the STN and SNR (Gilmour et al., 2011). We found SNR firing rate decreased with levodopa treatment while firing pattern showed a trend towards increased burstiness. Interestingly, in the STN, we found no significant changes in firing rate or pattern between the hemiparkinsonian state and levodopa-treated state. These findings suggest that intermittent levodopa treatments, while providing sufficient behavioral benefits in ameliorating parkinsonism, does not provide “normalization” of basal ganglia neurophysiology in terms of the discharge rates or discharge patterns. Further, in the case of the SNR we found that levodopa treatments in the hemiparkinsonian monkey caused a trend

towards increased burstiness of discharge patterns. These findings in one sense are the exact opposite of “electrophysiological silence or suppression”, a proposed electrophysiological “hallmark” of drug-induced dyskinesias. We hypothesize that the intact interhemispheric dopaminergic innervation from the “less affected” hemisphere is instrumental in “preventing” the downstream neurophysiological “suppression/silence” in the STN/SNR and GPi. Future neurophysiological studies in the hemiparkinsonian rhesus monkey with and without the intact interhemispheric fibers (with and without dyskinesias) are warranted to further evaluate our hypothesis.

4. Conclusion

This review identifies the existence of the interhemispheric connections of the striatum and some of their functional properties in the normal and dopamine depleted state (Pelled et al., 2002; Rohlf et al., 1997). The progressive nigrostriatal degenerative properties of PD and the onset of dyskinesias have been associated with multiple pathological changes to the basal ganglia system at molecular, chemical and electrophysiological levels (Deogaonkar and Subramanian, 2005). The classic pathophysiological explanation for the genesis of levodopa-induced dyskinesias is the notion that nigrostriatal dopaminergic neuronal degeneration and striatal denervation is associated with upregulation of dopaminergic sensitivity of D₁ subtype and D₂ subtype receptors in the striatum. Such supersensitivity of D₁ and D₂ receptors are potentiated by pulsatile stimulation of these receptors via infrequent dosing of dopaminergic medications. This combination of nigrostriatal D₁ and D₂ receptor supersensitivity combined with pulsatile dopaminergic oral medications is the hypothesized mechanism for drug-induced dyskinesias. Additional mechanisms that have been postulated are the lack of dopamine buffering capacity and alterations in non-dopaminergic neurotransmitter systems in response to pulsatile dopaminergic stimulation in PD. A few studies in the non-human primate have suggested that pulsatile stimulation with levodopa even in the intact striatum can provoke “dyskinesias”. However, it is clear upon review of these studies that choreiform dyskinetic movements and dystonia as seen in humans do not occur in the unlesioned intact non-human primate. Further, we recently reported that the strictly unilateral HP monkey model of PD does not show drug-induced dyskinesias despite >90% loss of ipsilateral nigrostriatal neuronal connectivity and prolonged high-dose dopaminergic treatment. By contrast, the bilaterally parkinsonian monkey model is observed to exhibit classic choreiform dyskinesias and dystonia similar to dyskinesias seen in PD patients. The human correlate to this experimental primate finding is the notion that stage I disease patients also remain resistant to drug-induced dyskinesias until they reach stage II (bilateral) disease, when they begin to exhibit drug-induced dyskinesias. These findings suggest that the interhemispheric nigrostriatal dopaminergic fibers have a significant influence on the genesis of dyskinesias.

We hypothesize two possible mechanisms for the role of interhemispheric pathways to influence the genesis of drug-induced dyskinesias in PD. The first possibility is that the synaptic connectivity between the crossed interhemispheric nigrostriatal neurons to host striatal medium spiny neurons are more robust than that of ipsilateral nigrostriatal pathway. The experimental result that interhemispheric nigrostriatal dopaminergic fibers resist early neurotoxicity from both 6-OHDA (Sauer and Oertel Model) and MPTP (unilateral intracarotid model); acting via striatal dopamine transporter mediated uptake and retrograde transport to the SN argue in support of such a hypothesis. Additional histological studies are warranted to explore this hypothesis, such as electron microscopic techniques using specific labels that identify various connections between the interhemispheric nigrostriatal and corticostriatal pathways and the striatum (Meredith et al., 1999; Soderstrom et al., 2008; Soderstrom et al., 2010). The second possibility is that there is synaptic and biochemical plasticity in the connections between the interhemispheric fibers and the partially denervated

striatum. In this scenario, we hypothesize that when there is unilateral neurodegeneration, the interhemispheric nigrostriatal pathway originating from the contralateral SN become upregulated, providing partial amelioration of dopamine deficiency until more advanced stages of the disease ensues. Studies in the 6-OHDA rat that suggest that SN dopaminergic cell counts are increased in the contralateral SN following unilateral lesioning indicate that such plasticity may be at play in the interhemispheric pathways. Additional studies to measure the levels of dopamine secreted by the interhemispheric pathways at various stages of parkinsonism are warranted to prove this hypothesis. Alternately, the interhemispheric pathways may exhibit synaptic plasticity in response to hemiparkinsonism resulting in increased synaptic connectivity between the partially denervated striatum and crossed interhemispheric fibers. Thus, we hypothesize that the role of interhemispheric fibers in the genesis of drug-induced dyskinesias is complementary to existing pathophysiological hypothesis of D₁/D₂ subtype receptor supersensitivity and pulsatile dopaminergic stimulation. Our hypothesis requires the additional step of the loss of interhemispheric nigrostriatal pathway besides the need for D₁/D₂ receptor supersensitivity and pulsatile dopaminergic stimulation for the genesis of drug-induced dyskinesias. As a corollary, we hypothesize that the preservation of the interhemispheric connections will prevent the genesis of drug-induced dyskinesias.

It is expected that the interhemispheric nigrostriatal fibers that originate on the side that is lesioned in the 6-OHDA rat and the MPTP treated monkey will undergo a near complete lesioning and subsequent neurodegeneration. We hypothesize that the loss of interhemispheric nigrostriatal fibers going from the lesioned nigra to the less affected striatum should have no consequence for the genesis of drug-induced dyskinesias until the less affected striatum itself undergoes neurodegeneration to reach the appropriate threshold for developing D₁/D₂ subtype receptor supersensitivity (Fig. 1). In other words, our hypothesis predicts that unilateral lesioning or natural loss of ipsilateral nigrostriatal fibers and the associated crossed interhemispheric fibers that originate in the SN that is primarily affected in itself is insufficient to cause drug-induced dyskinesias, and there needs to be additive loss of interhemispheric nigrostriatal fibers that originate in the opposite hemisphere for the genesis drug-induced dyskinesias. Future experiments that allow targeted lesioning of the interhemispheric nigrostriatal pathway along with unilateral lesioning of the nigrostriatal pathway, we believe, would readily cause levodopa-induced dyskinesias. By contrast, our hypothesis predicts that any animal with intact interhemispheric nigrostriatal fibers would remain resistant to dyskinesias.

In summary, data from our laboratory demonstrating that hemiparkinsonian rhesus monkeys do not develop dyskinesias after chronic levodopa treatment (Lieu et al., 2011) in combination with earlier reports from the literature suggests that interhemispheric inhibition may account for the prevention of dyskinesias in PD. Future studies that examine this interhemispheric phenomenon will increase our understanding of PD and aid in the development of more superior treatments for dyskinesias in PD.

Acknowledgments

Supported in part by the National Institutes of Health National Center for Complementary and Alternative Medicine R21AT001607 and National Institute of Neurological Disorders and Stroke R01NS42402, Health Resources and Services Administration DIBTH0632 and the Pennsylvania Tobacco Settlement Funds Biomedical Research Grant to T.S. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions. Additional funding was provided by Penn State University Brain Repair Fund.

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Highlights

- Interhemispheric nigrostriatal and corticostriatal connections are present in the rat, cat and primate as demonstrated by tracer studies
- There is interhemispheric functional coupling between the nigra and striatum as demonstrated by electrophysiological, neurochemical and behavioral studies.
- We hypothesize that loss of interhemispheric nigrostriatal connections leads to drug-induced dyskinesias in Parkinson's disease.

Figure 1.

(A) Retention of the interhemispheric nigrostriatal pathway in the striatal 6-OHDA lesioned non-dyskinetic rat which is lost in the medial forebrain bundle 6-OHDA lesioned dyskinetic rat (B). Similarly, retention of the interhemispheric nigrostriatal pathway in the non-dyskinetic hemiparkinsonian (lesioned by intracarotid MPTP) rhesus monkey (C) which is lost in the bilateral parkinsonian dyskinetic rhesus monkey (lesioned by systemic MPTP) (D). Black represents intact nigrostriatal pathway and gray represents degenerated nigrostriatal pathway

Table 1

Summary of interhemispheric nigrostriatal studies in the rat

Reference	Tracer	Injection Site	Survival Period	# of Contralateral Nigral Cells
Retrograde Studies				
Veening et al., 1980	HRP	Striatum - Unilateral	1–3 days	N/A
Fass and Butcher, 1981	Evans Blue	Striatum - Unilateral	2 days	2–14/brain
Loughlin and Fallon, 1982	Granular Blue	Striatum - Unilateral	24 h	
	Nuclear Yellow	Striatum - Unilateral	24 h	5 to 10% of ipsilateral
Altar et al., 1983	Granular Blue	Striatum - Unilateral		
	Nuclear Yellow	6-day old rats: AP, +1.2; ML, +2.4; DV, -3.4	20–28 h	~1% of ipsilateral
		30-day old rats: AP, +7.2; ML, +2.6; DV, -4.2	20–28 h	
Pritzel et al., 1983a	HRP	Striatum	24 h	1 to 5
		AP: 8.3, L: 2.1, H: 4.4		
Pritzel et al., 1983b	Fast Blue	Striatum		
	Nuclear Yellow	AP, 8.3; L, 2.1; H, 4.4	1–7 days (dependent upon tracer transport)	~5% of ipsilateral
Fallon et al., 1983	Propidium Iodide	Medially and Laterall in Anterior 2/3rds of Striatum	24–30 h	1–2% of ipsilateral
	Granular Blue			
Jaeger et al., 1983	HRP	Striatum - Unilateral	1 day	2 to 12
	Fast Blue		3 days	
Mintz et al., 1985		AP78, L2.5, V45	2–3 days	3 to 5/section
Consolazione et al., 1985	WGA-HRP	Striatum - Unilateral (bregma and pial surface)	18–24 h	0 to 2
		Site 1 - AP, 1.2; L, 3.2; V, 4.3		
		Site 2 - AP, 3.0; L, 2.5; V, 5.0		
Morgan et al., 1986	HRP	Striatum - Unilateral		
		A, 8.3; L, 3.1; V, -4.4	24 h	See table in article
Douglas et al., 1987	HRP	AP, 7.8; L, 2.1–2.5; D, 4.5	2–3 days	~3% of ipsilateral
Anterograde Studies				
Morgan and Huston, 1990	[3H]leucine	SNpc - Unilateral (interaural line)		
		R, 2.2; L, 1.7; D, 1.9; toothbar, 2.4 below interaural line	7 days	