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Basal ganglia circuits underlying the pathophysiology of levodopa-induced dyskinesia

Pedro Barroso-Chinea and Erwan Bezard*

Centre National de la Recherche Scientifique UMR 5227, Bordeaux Institute of Neuroscience, Université Victor-Segalen Bordeaux 2, Bordeaux, France

Edited by:
Jose L. Lanciego, University of Navarra, Spain

Reviewed by:
Jose L. Lanciego, University of Navarra, Spain
Marco Aurelio M. Freire, Federal University of Rio Grande do Norte, Brazil

***Correspondence:**
Erwan Bezard, CNRS UMR 5227, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France.
e-mail: erwan.bezard@u-bordeaux2.fr

Involuntary movements or dyskinesia, represent a debilitating complication of levodopa therapy for Parkinson's disease. Dyskinesia is, ultimately, experienced by the vast majority of the patients. Despite the importance of this problem, little was known about the cause of dyskinesia, a situation that has dramatically evolved in the last few years with a focus upon the molecular and signaling changes induced by chronic levodopa treatment. Departing from this, we here review the progress made in functional anatomy and neuroimaging that have had a tremendous impact on our understanding of the anatomo-functional organization of the basal ganglia in Parkinsonism and dyskinetic states, notably the demonstration that dyskinesia are linked to a pathological processing of limbic and cognitive information.

Keywords: Parkinson's disease, levodopa, basal ganglia, abnormal involuntary movements

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, which neuropathological hallmark is the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc). The loss of dopaminergic input to the striatum results in the depletion of dopamine that causes a cascade of functional modifications that involves all components of the basal ganglia circuitry. These changes are thought to represent the neural substrate for parkinsonian motor symptoms such as bradykinesia (slowness of movement), rigidity (stiffness), and tremor. However, other neurotransmitter systems (e.g., cholinergic, adrenergic, serotoninergic) also degenerate and cell loss is seen in other brain stem nuclei and the cortex (Braak et al., 2002; Chaudhuri et al., 2006). This non-dopaminergic degeneration is thought to be the major cause of the non-motor symptoms of PD (e.g., cognitive decline, autonomic dysfunction). Dopaminergic drugs (e.g., dopamine precursor drug, L-3,4-dihydroxyphenylalanine – levodopa), dopamine agonists and the inhibitors of dopamine catabolism are the main therapeutic options for alleviating the parkinsonian motor symptoms.

INCIDENCE AND PHENOMENOLOGY OF DYSKINESIA

However, as PD patients receive chronic treatment with levodopa upon a progressive disease, they gradually develop two clinical phenomena requiring changes in their clinical management: fluctuations in motor response and a variety of abnormal involuntary movements, known as levodopa-induced dyskinesia (LID) (Yahr et al., 1968). The frequency of these motor complications has been estimated between 40 and 50%, after 4–6 years of levodopa treatment (Ahlskog and Muenter, 2001) but increases to 90% after 10 years of treatment (Rascol et al., 2000). Despite its frequency and clinical significance, the pathophysiology and the clinical risk factors causing dyskinesia in PD are not understood. The incidence is estimated at about 10% per year after initiating levodopa therapy. Some people exhibit severe dyskinesia very rapidly, whereas others do not develop this complication despite many years of levodopa treatment. The phenomenology of dyskinesia encompasses various forms: chorea, athetosis, dystonia, stereotypy, ballismus, or a combination of these. In addition to levodopa-induced motor fluctuations, PD patients can frequently experience affective, motivational, and cognitive disorders (Ahlskog and Muenter, 2001). The development of dyskinesia has been reported to depend on several clinical risk factors, such as duration of disease, severity of disease, duration of levodopa treatment and actual, or cumulative levodopa dose. Numerous important advances have been made in understanding of the etiopathogenesis, pathology and clinical phenomenology of PD and LID over the past 10 years.

BASAL GANGLIA ANATOMICAL ORGANIZATION

The basal ganglia comprise a group of interconnected subcortical nuclei located at the base of the cerebral hemispheres, with parts belong to the forebrain, diencephalon, and midbrain. The basal ganglia nuclei include the striatum (caudate and putamen), the globus pallidus pars externa (GPe) and pars interna (GPi), the subthalamic nucleus (STN) and the substantia nigra, divided into its pars compacta (SNc) and pars reticulata (SNr). Current knowledge suggests that the basal ganglia constitute a highly organized network, whose functional organization is complex. There is a clear consensus in considering that input to the basal ganglia from different cortical areas terminates within specific basal ganglia territories, which are connected to similarly specific portions of the thalamus.

Abbreviations: CM, centromedian nucleus; 2-DG, 2-deoxyglucose; D1 dopamine receptor; D2R, D2 dopamine receptor; FDG, fluorodeoxyglucose; GABA, g-amino-butyric acid; GAD, glutamic acid decarboxylase; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; IT, intratelencephalic corticostriatal neurons; LID, levodopa-induced dyskinesia; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSN, medium spiny neurons; 6-OHDA, 6-hydroxydopamine, PD, Parkinson's disease; PDRP, Parkinson's disease-related pattern; PET, positron emission tomography; Pf, parafascicular nucleus; PPE-A, preproenkephalin A; PPE-B, preproenkephalin-B; PPT, pedunculopontine tegmental nucleus; PT, pyramidal tract; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; SPECT, single photon emission computed tomography; STN, subthalamic nucleus.

These thalamic areas, in turn, project back to the same areas of the cortex from which the circuit originates (Alexander et al., 1986; Kelly and Strick, 2004; DeLong and Wichmann, 2007). Numerous data suggest that the basal ganglia nuclei are involved in movement control, as well as associative learning, planning, working memory, and emotion (Hikosaka et al., 2002; Pasupathy and Miller, 2005; Yin and Knowlton, 2006).

At present, there is a classical model of movement disorders in basal ganglia disease, developed in the late 1980s (Alexander et al., 1986; Crossman, 1987; Albin et al., 1989), both describing the neural mechanisms underlying parkinsonian akinesia and explaining the appearance of abnormal involuntary movements (dyskinesia). These represent two diametrically opposed mechanisms. However, the limitations and pitfalls of these models have also been discussed extensively on several occasions (Wichmann and DeLong, 1996; Obeso et al., 1997; Rodriguez-Oroz et al., 2009). The classical box and arrows basal ganglia model (Crossman, 1987; Albin et al., 1989; DeLong, 1990) proposes a motor circuit consisting of two input structures, comprising the striatum and STN, two output structures (GPi and SNr) and two intrinsic structures, including GPe and SNc (Mink, 1996). The striatum and the STN receive topographically organized input from the cerebral cortex (Monakow et al., 1979; Nambu et al., 1997; Lei et al., 2004) whereas the GPi and the SNr provide basal ganglia output to the thalamus and brainstem (Carpenter et al., 1976; Parent and De Bellefeuille, 1982; Francois et al., 1984; Oertel and Mugnaini, 1984).

The striatum receives massive cortical excitatory inputs (Kemp and Powell, 1970; Kitai et al., 1976; McGeer et al., 1977; Cherubini et al., 1988) and is densely innervated by dopamine from the SNc (Faull and Mehler, 1978; Beckstead et al., 1979). In the striatum, the major neuronal population is represented by medium spiny neurons (MSNs), accounting for almost 95% of total striatal cells (Kemp and Powell, 1971). MSNs use g-amino-butyric acid (GABA) as a inhibitory neurotransmitter (Kita and Kitai, 1988). They form two main populations of projection neurons (striatofugal system) that differ in their expression of the receptors that mediate the effect of dopamine. The striatonigral MSNs that monosynaptic project to GPi and the SNr (direct pathway) express preferentially dopamine D1 receptors (D1R) and produce the neuropeptides dynorphin and substance P whereas the striatopallidal MSNs that project to GPe (indirect pathway) express dopamine D2 receptors (D2R) and enkephalin (Gerfen et al., 1990). Although this strict "segregation" was supported by previous studies, a significant number of D1R and D2R-coexpressing neurons (about 5–10%) were found in rat (Le Moine and Bloch, 1995) and primate (Aubert et al., 2000) using double *in situ* hybridization technique. In this same line, anatomical studies clearly show that single striatofugal axons arborize in both pallidal segments in rodents (Kawaguchi et al., 1990; Castle et al., 2005) and in primates (Parent and Hazrati, 1995; Levesque and Parent, 2005; Nadjar et al., 2006). These data indicate that the striatofugal system is not as functionally segregated in rodents and primates as previously considered in the current model of basal ganglia. Dopamine modulates glutamatergic effects on corticostriatal inputs by exerting a dual effect on striatal neurons, exciting D1R neurons in the direct pathway and inhibiting D2R neurons in the indirect circuit. Within this general context, activation of direct-pathway circuits has been proposed to facilitate or select appropriate movements, whereas activity in the indirect pathway may inhibit unwanted or inappropriate movements (Albin et al., 1989; Alexander et al., 1990). Clearcut demonstration of such roles has just been released using optogenetic approaches (Kravitz et al., 2010).

The GPe and the STN are classically viewed as part of the so-called indirect pathway (Parent and Hazrati, 1995). The GPe, principally sends GABAergic projections to the STN (Albin et al., 1989; Alexander et al., 1990; DeLong, 1990) but anatomical studies have revealed the existence of new efferent projections of the GPe to the two output structures of the basal ganglia (Hazrati et al., 1990; Kincaid et al., 1991). The STN is an important control structure of basal ganglia circuits, being the only glutamatergic nucleus of the network (DeLong and Wichmann, 2007). The STN, like the other components of the basal circuit, is subdivided into different territories, motor, oculomotor, associative, and limbic, each with different connections and functions (Parent and Hazrati, 1995; Bevan et al., 2006). The large dorsolateral portion of the STN corresponds to the motor territory; the ventromedial portion to the associative territory and the medial tip to the limbic territory of the STN.

Most STN neurons are glutamatergic projection neurons and provide a powerful excitatory input to the GPe (Van Der Kooy and Hattori, 1980; Kita and Kitai, 1987; Parent et al., 2000; Castle et al., 2005) and to the two output structures of the basal ganglia (Parent and Smith, 1987; Smith et al., 1990). Additionally a subpopulation of efferent STN neurons innervate directly the ventral motor thalamic nuclei (Nauta and Cole, 1978; Rico et al., 2010). The STN also has important reciprocal connections with the pedunculopontine tegmental nucleus (PPT) (Hammond et al., 1983; Jackson and Crossman, 1983; Kita and Kitai, 1987; Granata and Kitai, 1989; Steininger et al., 1992) as well as the cerebral cortex (Jackson and Crossman, 1981; Nambu et al., 2002; Degos et al., 2008). Furthermore, as inputs to both striatum and STN arise from the intralaminar thalamic nuclei, the centromedian nucleus (CM), and the parafascicular nucleus (Pf) (Wilson et al., 1983; Sadikot et al., 1992; Feger et al., 1994; Lanciego et al., 2004; Castle et al., 2005), the STN is now viewed as a key entry to the basal ganglia circuit, probably as important as the striatum itself.

The GPi and SNr share many histological characteristics, as well as similar afferent and efferent connections. Although the projection neurons of the basal ganglia output nuclei are generally considered to be GABAergic (Penney and Young, 1981; Rajakumar et al., 1994), there is evidence that projection neurons within the entopeduncular nucleus (ENT, the rodent homolog of GPi) also express other markers such as markers of cholinergic (Parent et al., 1981) and glutamatergic neurons (Kha et al., 2000), as well as peptides like somatostatin and substance P (Murakami et al., 1989a,b). Both nuclei project to the ventral motor thalamus, caudal intralaminar nuclei (Sidibe et al., 1997, 2002) and PPT (Steininger et al., 1992; Grofova and Zhou, 1998). Finally the thalamic nuclei then send glutamatergic projections to the motor cortex, thus closing the loop.

THE STRIATUM, FOCUS OF MOST STUDIES

Dyskinesia in PD seems to be mediated by alterations in basal ganglia activity that are the opposite of those occurring in PD (Vidailhet et al., 1999; Obeso et al., 2000; Boraud et al., 2001). Current

models of LID suggest that excessive decrease in GPi activity in turn disinhibits the motor thalamus and the cortex, giving rise to abnormal increase in cortical drive and consequent excessive motor movements (Wichmann and DeLong, 1996; Bezard et al., 2001a).

The first site of interest is of course the striatum with a particular emphasis upon the MSNs. Over the past few years, LID have been associated with a number of molecular changes, including regulation of striatal dopamine receptors, downstream changes in striatal proteins and genes, abnormalities in non-dopaminergic transmitter systems, etc., all changes that go beyond the topic of the present review (Bezard et al., 2001a; Jenner, 2008). Changes are not simply the consequence of chronic treatment since the first levodopa dose would induce expression changes of numerous proteins in the dopamine depleted striatum that equate those induced by chronic exposure as evidenced using a proteomic approach in the MPTP macaque model (Scholz et al., 2008).

DENDRITIC SPINE PRUNING OCCURS ON D2-EXPRESSING MSNs

A simple but long ignored question was the possible changes in the connections in the basal ganglia circuit in both the parkinsonian and dyskinetic states. Recently, Nadjar et al. (2006) showed that both the phenotype and the targets of striatofugal neurons, and therefore their relative influence on target structures, is preserved after dopamine denervation in the parkinsonian state and after additional chronic levodopa treatment in both non-dyskinetic and dyskinetic groups (Nadjar et al., 2006). This suggests that the phenotypic plasticity of the striatofugal system is not affected by the experimental condition. It does not mean however that plastic changes do not occur in the striatum. For instance, it has been shown that the size of the dendritic tree and the density of dendritic spines of MSNs is significantly reduced in the caudate nucleus and the putamen of PD patients compared with controls (Stephens et al., 2005), confirming previous data in rodents (Ingham et al., 1998). Such pruning was observed in MPTP-primates as well (Scholz et al., 2008; Villalba et al., 2009). The MSNs submitted to this dramatic plastic change were recently characterized as the D1R-immunonegative neurons, i.e., the D2R-expressing neurons (Day et al., 2006). Unfortunately, the impact of such spine pruning on MSN physiology is still unclear. These data nevertheless support the idea of plastic changes in the corticostriatal network but with no consequence on the phenotype and organization of projections of striatal neurons. Thus, loss of cortical afferents appears unlikely to affect the phenotypic pattern of striatal neurons, but rather might alter their activity or mRNA processing (Day et al., 2006). Altogether, these changes contribute in the development of adverse events related to levodopa therapy, because they would alter information flow through the striatum and rest of the basal ganglia nuclei.

IS THE DIRECT/INDIRECT PATHWAY IMBALANCE CAUSED BY DIFFERENTIAL CORTICOSTRIATAL INPUT?

Many studies have investigated the pathophysiology of the basal ganglia after dopamine denervation. Imbalances between neural activity in the two major output pathways of striatum have been proposed to underlie the profound motor deficits observed in PD, such as the hypokinesia (Albin et al., 1989; DeLong, 1990; Bezard et al., 2001b). This imbalance was first documented in anatomo-functional studies (Gerfen et al., 1990; Gerfen, 2000) and, surprisingly, only very recently confirmed with an electrophysiological approach (Mallet et al., 2006). Such an imbalance could be generated locally within the striatum or caused by a complex interaction with the corticostriatal excitatory. Retrograde tract-tracing experiments in the rat have shown that striatonigral neurons are preferentially innervated by cortical neurons that project inside the telencephalon (intratelencephalic (IT)-type), in both the ipsilateral and contralateral striatum, whereas striatopallidal neurons receive a greater input from cortical neurons that send their main axon into the pyramidal tract (PT) and their collateral axons only in the ipsilateral striatum (Lei et al., 2004). Although such a clearly segregated corticostriatal organization has recently been challenged (Ballion et al., 2008), a deficit in specific cortical inputs might also contribute to selectively depress the activity of striatonigral neurons (Mallet et al., 2006). Both the spontaneous activity and the sensitivity to cortical stimulation of striatonigral neurons were reduced by the lesion, whereas the reverse effects were observed for striatopallidal neurons (Mallet et al., 2006). However, elegant electrophysiological studies have shown that the decreased IT neuron activity associated with the dopaminergic depletion does not contribute to the striatal imbalance (Ballion et al., 2008).

STRIATAL GLUTAMIC ACID DECARBOXYLASE mRNA LEVELS IN PD AND LID

While electrophysiological investigations are scarce, anatomo-functional studies have documented the specific changes in the transcriptional activity of subpopulations of striatal GABA neurons in PD and LID conditions. Outside the scope of this review, a number of studies have indirectly confirmed the anatomo-functional organization of the striatal territories. Immediate-early genes have been extensively studied and expression patterns of c-fos and FosB proteins clearly relate a given behavioral phenotype with an increased expression/signal in a sub-territory of the striatum (Saka et al., 1999; Cenci, 2002; Jenner, 2008).

For instance, a number of studies using *in situ* hybridization studies have unraveled changes in glutamic acid decarboxylase (GAD) mRNA levels, the rate-limiting enzyme in the synthesis of GABA, in parkinsonian and dyskinetic animal models. Studies carried out during the last 25 years have shown the existence of two GAD isoforms, GAD_{65}, and GAD_{67}, each encoded by a different gene, and differing in molecular size and intraneuronal distribution (Denner and Wu, 1985; Kaufman et al., 1991; Martin et al., 1991; Martin and Rimvall, 1993). In MPTP-treated primates, GAD_{65} mRNA and GAD_{67} mRNA are increased in the striatum (Pedneault and Soghomonian, 1994; Soghomonian et al., 1994; Levy et al., 1995). Levodopa treatment significantly normalizes GAD_{67} mRNA expression in the putamen and caudate nucleus to levels similar to those found in control monkeys (Levy et al., 1995). Other studies, however, showed not significant changes in the distribution of both isoforms in the cortex, caudate, and putamen of parkinsonian and dyskinetic primates (Stephenson et al., 2005). In rats bearing a unilateral 6-OHDA lesion, GAD gene expression is increased in the striatum on the side of the lesion (Lindefors et al., 1989; Soghomonian et al., 1992; Consolo et al., 1999; Bacci et al., 2002). By contrast, the administration of levodopa leads to further increases in striatal GAD_{67} mRNA levels (Cenci et al., 1998; Consolo et al., 1999; Carta et al., 2001, 2003; Bacci et al., 2002; Nielsen and Soghomonian, 2004).

OPIOID PEPTIDE PRECURSOR mRNA AND OPIOID RECEPTOR LEVELS IN PD AND LID

Besides GAD, expression levels of precursors of the opioid peptides have been extensively investigated. Investigations in rodents (Gerfen et al., 1990; Engber et al., 1992; Duty et al., 1998), primates (Herrero et al., 1995; Morissette et al., 1999; Tel et al., 2002) and humans (Nisbet et al., 1995; Calon et al., 2002; Henry et al., 2003) have shown that Parkinsonism is associated with an increased expression of the opioid precursor preproenkephalin-A (PPE-A) messenger RNA (mRNA) in striatal neurons projecting to the GPe and a decreased preproenkephalin-B (PPE-B) mRNA expression in striatal neurons projecting to the GPi. In the dyskinetic state, however, the expression of PPE-B mRNA is increased (Cenci et al., 1998; Duty et al., 1998; Henry et al., 1999; Westin et al., 2001; Tel et al., 2002; Winkler et al., 2002; Henry et al., 2003), whereas that of PPE-A mRNA is either unchanged or further increased (Herrero et al., 1995; Morissette et al., 1997; Duty et al., 1998; Henry et al., 1999; Morissette et al., 1999; Zeng et al., 2000; Westin et al., 2001; Calon et al., 2002; Tel et al., 2002). These data suggest a role for enhanced endogenous opioid peptide transmission in striatal output pathways for the generation of LID. However, none of these studies has regarded basal ganglia nuclei other than the striatum as potential sources and those opioid precursors have almost never been quantified, simultaneously with the levels of opioid receptors, at the peak of dyskinesia severity, a quite surprising observation. Recently, Aubert and colleagues, studying a comprehensive brain bank of control, parkinsonian and dyskinetic monkeys terminated at the peak of levodopa-induced antiparkinsonian efficacy and dyskinesia manifestation, found a reduction in κ and μ opioid receptor binding in the GPi correlating with dyskinesia severity. Such decrease also correlated with an enhanced expression of PPE-B mRNA, but not that of PPE-A, in both the striatum and the STN, known to also express peptide precursors (Merchenthaler et al., 1997). This abnormal PPE-B-derived transmission could therefore be involved in LID manifestation with increased peptide levels arising from both the striatum and the STN (Aubert et al., 2007).

TRANSCRIPTOMIC CHANGES AFFECTING PALLIDAL COMPLEX AND STN IN PD AND LID

In the 6-OHDA-lesioned rat model of PD, the profound dopamine depletion in the striatum resulted in significant increases in the percentage of GPe neurons that expressed GADs mRNA and in the amount of GADs mRNA per GPe neuron (Kincaid et al., 1992; Soghomonian and Chesselet, 1992). Similar results were described MPTP-treated monkeys, the expression of GAD_{67} but not GAD_{65} was augmented in the GPe, along with a significant increases in number of GAD_{67} neurons, while no significant difference in the number of GAD_{65} neurons was observed (Stephenson et al., 2005). Levodopa treatment did not significantly change the number of GAD_{65} or GAD_{67}-expressing pallidal neurons following MPTP (Stephenson et al., 2005).

In the GPi of MPTP-treated monkeys, i.e., the main output structure, the expression of GAD_{67} and GAD_{65} mRNAs is increased (Pedneault and Soghomonian, 1994; Soghomonian et al., 1994; Herrero et al., 1996). Similar results were described in MPTP-lesioned cats (Schroeder and Schneider, 2001). Interestingly the increase in GAD_{67} mRNA is abolished by levodopa treatment in MPTP-treated monkeys (Herrero et al., 1996). These data fit with the observation that there is no difference in the levels of GAD_{67} mRNA between levodopa-treated PD patients and control subjects (Herrero et al., 1996), i.e. that levodopa treatment normalizes GAD_{67} mRNA levels. In rats, an ipsilateral marked up-regulation of $GAD_{65}/_{67}$ mRNA expression in the ENT nucleus has been reported following 6-OHDA lesion (Soghomonian and Chesselet, 1992; Barroso-Chinea et al., 2008). Continuous or intermittent levodopa administration is equally effective at reversing the lesion-induced increase in GAD_{67} mRNA expression in the ENT nucleus (Nielsen and Soghomonian, 2004). Altogether, these results indicate that the level of GAD_{67} mRNA is increased in the cells of the GPi after nigrostriatal dopaminergic denervation and that this increase can be reversed by levodopa therapy (Herrero et al., 1996).

One should however keep in mind that a transcriptional regulation does not necessarily mean a change in electrical activity. Parallel to these observations, there are evidences of an increase in mitochondrial respiratory chain enzyme activity in ENT nucleus in the lesioned hemisphere of 6-OHDA rats suggesting increased synaptic activity, perhaps due to increased firing of the STN (Porter et al., 1994). The enzymatic activity or the changes in the expression of cytochrome oxidase-I (COI) have indeed been shown to correlate with changes in the firing activity of several structures (Wong-Riley and Welt, 1980; Wong-Riley, 1989). "*In situ*" hybridization of cytochrome oxidase-I (COI) mRNA in the MPTP monkey model of PD has shown increased levels parallel increased firing of the STN (Bergman et al., 1994; Vila et al., 1996; Bezard et al., 1999). Comparably, increased levels in the GPi correlate with an increased firing frequency of GPi neurons (Bezard et al., 1999; Boraud et al., 2000, 2001). As expected, levodopa treatment reversed such COI mRNA overexpression in all affected structures (Vila et al., 1996). Similar results were obtained in the 6-OHDA rat model (Vila et al., 1999). No changes were however detected in levodopa-treated PD patients compared to control subjects, a situation that could either reflect the levodopa-induced normalization of the COI mRNA expression in PD patients or the inescapable poor quality of human post-mortem samples (Vila et al., 1996). In conclusion, these anatomo-functional evidences correlate with the observed hypoactivity of both the STN and GPi during levodopa or apomorphine-induced dyskinesia in MPTP-treated monkeys (Filion et al., 1991; Boraud et al., 2001), in dyskinetic PD patients (Merello et al., 1999) and in patients with generalized dystonia and hemiballismus (Suarez et al., 1997; Vitek et al., 1999).

"PARKINSON'S DISEASE-RELATED PATTERN" IN PD AND LID

Considerable efforts have been devoted to develop neuroimaging methods to study the basal ganglia (Eidelberg and Edwards, 2000; Feigin et al., 2001; Eckert et al., 2005; Asanuma et al., 2006; Trost et al., 2006; Eidelberg, 2009). These techniques have been developed with the hope that they could be used as biomarkers to help the diagnosis, to detect early stages of the disease, later on to grade the disease severity of the disease, and, finally, to serve as a surrogate marker for progression of the underlying disease. Positron emission tomography (PET) and single photon emission computed tomography (SPECT), which is less sensitive but more widely available than PET, are capable to provide an objective measure of PD severity as both techniques depict the loss of neurotransmitter

function and can detect changes in striatal dopamine levels after levodopa administration in relationship with the motor responses. Such investigations of the dopamine transmission have brought extremely important insights, even unraveling the physiological basis for the placebo effect (de la Fuente-Fernandez et al., 2001), but they do not impact our understanding of the functional anatomy of PD and LID. Metabolic PET studies, however, have demonstrated that PD is characterized by a set of reproducible functional brain networks that correlate with its clinical features (Huang et al., 2007). Using [^{18}F] fluorodeoxyglucose (FDG) and PET, changes in a so-called Parkinson's disease-related pattern (PDRP) expression have been observed. Disease progression is associated with increasing metabolism in the STN and GPi, as well as in the dorsal pons and primary motor cortex. Advancing disease is associated with declining metabolism in the prefrontal and inferior parietal regions (Huang et al., 2007). Changes in a cognition-related network paralleled these motor-related changes. At present, there is a clear consensus in considering that the PDRP is characterized by increased pallido-thalamic and pontine activity, associated with relative reductions in cortical motor and premotor areas in PD patients (Carbon et al., 2003; Eidelberg, 2009) although no changes are reported in the thalamus. The impact of dopaminergic therapy upon PDRP has also been investigated (Feigin et al., 2001; Asanuma et al., 2006). The changes in the pallidal metabolism and the overall PDRP network activity correlated significantly with clinical improvement of PD symptoms during dopaminergic treatment (Feigin et al., 2001; Asanuma et al., 2006). Interestingly, a recent study (Hirano et al., 2008) showed a highly significant dissociation between levodopa-mediated PDRP changes in cerebral blood flow and glucose metabolic scans. This phenomenon was accentuated in PD patients with LID, reflecting excessive dopaminergic-induced vasodilatation in these subjects.

What is clear from these studies is that not only the PDRP is affected by dopaminergic treatments but the cognition-related pattern as well. Such findings have lead to dig in the experimental literature when researchers used the then-popular 2-deoxyglucose (2-DG) accumulation technique for studying brain metabolism. Alan Crossman and his colleagues extensively studied the metabolic changes induced by dopamine depletion and further dopaminergic treatments. Of particular interest for this review, they found that the STN showed a dramatic increase in 2-DG uptake in animals exposed to dopamine agonist immediately prior to the terminal procedure, especially in ventromedial "limbic/associative" STN, along with relative greater levels of 2-DG uptake in GPi (Mitchell et al., 1989, 1992). This suggested that a major effect of dopaminergic treatment was to affect the limbic/associative network more than the motor network. Since consistent funneling of information takes place between the sensorimotor, limbic, and associative cortico-basal ganglia domains (Haber et al., 1993, 2000), we hypothesized that non-motor domains play a role in these manifestations and studied the changes in 2-DG accumulation in the sensorimotor, limbic, and associative domains of basal ganglia and thalamic nuclei of four groups of non-human primates (Guigoni et al., 2005): normal, parkinsonian, parkinsonian chronically treated with L-dopa without exhibiting dyskinesia and parkinsonian chronically treated with levodopa and exhibiting overt dyskinesia. While non-dyskinetic animals displayed a rather normalized metabolic activity, dyskinetic animals were distinguished by significant changes in 2-DG accumulation in limbic and associative-related structures and not simply in sensorimotor-related ones, suggesting that dyskinesia are linked to a pathological processing of limbic and cognitive information (Guigoni et al., 2005). These metabolic changes likely reflect the underlying neural mechanisms of not simply motor dyskinesia but also affective, motivational, and cognitive disorders associated with long-term exposure to levodopa.

CONCLUDING REMARKS

The anatomical and functional organization of the basal ganglia circuitry has received considerable attention in the last two decades. This has led to a better understanding of the physiological and pathophysiological aspects involved in PD and LID. To our opinion, the most fundamental consequence of the recent findings is that we cannot continue analyzing LID by investigating the only motor areas, thus rendering unreliable all studies that do not pay attention to the anatomo-functional organization of cortico-basal ganglia loops. Seeing LID as either "caused" by unwanted involvement of associative and limbic areas or simply as having their cognitive and limbic abnormal counterparts ("consequence") as often reported in hyperkinetic disorders might have different clinical consequences. For instance, if electrophysiological investigations support the causative hypothesis, modulating the activity of non-motor regions would reduce LID severity, thereby offering new drug targets for treatment of this debilitating condition.

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