INTRODUCTION

Parkinson’s disease (PD) is a progressive, neurodegenerative disorder, in which the capacity to execute voluntary movements is gradually lost. The clinical picture of PD includes tremor, rigidity and bradykinesia. The pathologic hallmark of the disease is the degeneration of melanine-containing, dopaminergic neurons of the substantia nigra pars compacta, which leads to severe dopaminergic denervation of the corpus striatum. The dopaminergic deficit of the nigrostriatal system is accompanied by functional modifications of the other basal ganglia nuclei, which constitute the neural substrate for the expression of PD motor symptoms. In the context of this alteration of the basal ganglia circuitry activity, the subthalamic nucleus – the only excitatory nucleus of the circuit – plays a prominent role.

THE BASAL GANGLIA CIRCUITRY

Proper execution of voluntary movements results from the correct processing of sensorimotor information by a complex neural network, which includes the cerebral cortex, the motor thalamus and the basal ganglia nuclei. The basal ganglia circuit, which is functionally interposed between the cortex and the thalamus, plays the major role in this process. The basal ganglia nuclei process the inputs flowing from the cortex to produce an output signal that returns – via the motor thalamus – to the cortex, to modulate movement execution (1).
The basal ganglia circuit consists of four nuclei: **corpus striatum (or striatum), globus pallidus, substantia nigra and subthalamic nucleus** (Fig. 1). The basal ganglia nuclei are interconnected, and their functional organization has been extensively investigated over the past decade. According to a very popular model (2,3), the striatum – the main input nucleus of the circuit – transmits the flow of information received from the cortex to the basal ganglia **output nuclei**, substantia nigra pars reticulata and medial globus pallidus, via a **direct** and an **indirect** pathway originating from different subsets of striatal neurons. In the **direct pathway**, striatal GABAergic neurons containing dynorphin as a co-transmitter and expressing D$_1$ dopamine receptors, project monosynaptically to the substantia nigra pars reticulata and medial globus pallidus. In the **indirect pathway**, a subset of GABAergic neurons containing enkephaline and expressing D$_2$ receptors project to the lateral globus pallidus, which sends GABAergic projections to the STN. In turn, the STN sends its glutamatergic (excitatory) efferents to the output nuclei and to the lateral globus pallidus. From the output nuclei, inhibitory, GABAergic projections reach the ventral lateral and ventral anterior nuclei of the motor thalamus. Thalamic nuclei then send glutamatergic projections to the motor cortex, thus closing the loop (Fig. 1).

---

Fig. 1 - Simplified representation of the functional organization of the basal ganglia nuclei. **SNC**: substantia nigra pars compacta; **SNR**: substantia nigra pars reticulata; **STN**: subthalamic nucleus; **LGP**: lateral globus pallidus; **MGP**: medial globus pallidus.
From the model, it follows that the subthalamic nucleus occupies a strategic position in the circuitry. As repeatedly demonstrated by experimental studies, the subthalamic nucleus can modulate the neuronal activity of both basal ganglia output nuclei (4-6). In addition, recent studies have shown that the subthalamic nucleus receives direct excitatory projections from the primary motor cortex (7) and, more importantly, that the nucleus receives dopaminergic projections from the substantia nigra pars compacta (8-10). The description of this additional connectivity has further increased the importance of the subthalamic nucleus in the functional architecture of the basal ganglia, suggesting a more independent role for this nucleus with respect to the other components of the circuitry.

**Functional changes associated with Parkinson’s disease: role of the subthalamic nucleus**

As mentioned above, the degeneration of nigrostriatal neurons that underlies PD causes a cascade of changes, leading to a functional rearrangement of the basal ganglia circuitry. The ultimate consequence of this phenomenon is the increased activity of the subthalamic nucleus and/or the basal ganglia output nuclei, which receive subthalamic projections. Enhanced activity of the output nuclei results in increased inhibitory control over the motor thalamus and subsequent reduction of the thalamic, glutamatergic output to the motor cortex. These changes are likely to constitute the neural substrate for parkinsonian motor symptoms (1).

Numerous experimental studies have shown that the subthalamic nucleus is central to the PD-related enhancement of the basal ganglia output. In animals, it is possible to replicate the anatomical damage of PD using pharmacological agents. The two most popular techniques involve the intracerebral injection of 6-hydroxydopamine (6-OHDA), in rodents (11), and the systemic (intracarotid) administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (MPTP) to monkeys (12). Both toxins produce, via different mechanisms, selective lesions of the nigrostriatal pathway. Using these animal models of PD, various groups have found increased levels of neuronal firing rate (13,14), glucose metabolism (15), and mitochondrial enzyme activity (16,17) in the subthalamic nucleus and in its projection nuclei. In rodents, the metabolic and electrophysiological changes that affect the output nuclei, as a consequence of the nigrostriatal lesion, are prevented by lesioning the subthalamic nucleus (18,19).

Human studies also support the primary role of subthalamic hyperactivity in PD pathophysiology. For example, it has been reported that the occurrence of a subthalamic hematoma caused the disappearance of parkinsonian symptoms in a PD patient (20). Furthermore, Lange et al. (21) have reported down-regulation of NMDA receptors in the medial globus pallidus of PD patients, which has been interpreted as a consequence of the increased activity of subthalamic projections to the medial globus pallidus. All these findings have led to the introduction of a new, electrophysiological technique in the therapy of PD, known as “deep brain stimulation” (22). This technique relieves PD motor symptoms by stimulating subthalamic neurons at high frequencies through locally implanted electrodes. The procedure induces the functional blockade (depolarization) of the nucleus and, as shown recently, consistent changes in residual dopaminergic transmission at nigrostriatal level (23,24).

**Hypotheses on PD-related subthalamic overactivity: the role of dopaminergic mechanisms**

According to the classical model of basal ganglia organization, subthalamic hyperactivity results from reduction of the inhibitory control exerted by the lateral globus pallidus, possibly inhibited by overactive striato-pallidal, GABAergic, neurons (2). This is one of the controversial points of the model. In fact, instead of showing a reduction, recent studies have found increased pallidal activity in both rodent (16,25) and pri-
mate models of PD (17). In addition, Hassani et al. (26) have demonstrated that complete lesioning of the globus pallidus causes a slight increase in the firing rate of subthalamic neurons, which is far less pronounced than the increase observed in animals with nigrostriatal damage. These data suggest that an additional, if not alternative, explanation for the PD-related subthalamic hyperactivity should be considered.

As mentioned above, emerging evidence shows that dopamine plays an important role at subthalamic level. In addition to receiving dopaminergic projections from the substantia nigra pars compacta (8-10), subthalamic neurons have dopamine receptors that mediate their response to a variety of dopaminergic drugs (14,27-31). Consequently, it is likely that subthalamic dopaminergic mechanisms are directly involved in the basal ganglia functional changes associated with PD. Indeed, the density of subthalamic, dopamine D2 receptors increases in rats bearing a nigrostriatal lesion (28,32), while marked loss of dopaminergic innervation has been reported in MPTP-treated monkeys (33). As a consequence, neuronal and motor responses to intra-subthalamic administration of dopaminergic agonists change dramatically after a nigrostriatal lesion (14,30,34). Moreover, Mukhida et al. have recently shown that the use of intra-subthalamic, dopaminergic transplants enhances the sensorimotor behavioral recovery in hemiparkinsonian rats (35).

Taken together, these data indicate that dopamine plays a central role in the regulation of subthalamic activity and that degeneration of the dopamine neurons of the substantia nigra affects subthalamic activity directly, inducing a dopaminergic “denervation” of the nucleus.

**SUBTHALAMIC OVERACTIVITY AND NIGRAL DEGENERATION: IS THERE A LINK?**

Although the substantia nigra pars compacta is not considered a typical target of subthalamic projections, there is solid evidence that subthalamic neurons send glutamatergic fibers to nigral dopaminergic neurons, too (36). Through this excitatory pathway, the subthalamic nucleus is able to affect the activity of nigral neurons (37). Therefore, the subthalamic hyperactivity occurring in PD also has repercussions on residual neurons of the substantia nigra pars compacta.

In addition to being a neurotransmitter, glutamate can also be a toxin. Excessive stimulation of the glutamate receptor, particularly the N-methyl-D-aspartate subtype, causes cell death, which can be of the necrotic (38) or apoptotic (39) type, or both (40). Glutamate toxicity has been evoked in the pathogenesis of PD, although via an indirect mechanism. In fact, although glutamate is likely to play a direct role in acute neurological disorders, such as hypoxic/ischemic brain damage – which is accompanied by massive release of glutamate (41) – this is unlikely to happen in a chronic, slowly evolving disorder, such as PD. However, glutamate can become neurotoxic – even at physiological concentrations – in the presence of a state of cellular energetic impairment, through a mechanism known as *indirect excitotoxicity* (42,43). This mechanism may very well occur in the nigral neurons of PD patients, which are exceedingly vulnerable to toxic insults due to a number of specific conditions, the most important being mitochondrial enzyme complex I deficiency (44). The increase in glutamatergic inputs to the substantia nigra pars compacta, originating from the subthalamic nucleus, may therefore interact with the bioenergetic defects, thus triggering or – more likely – aggravating the progression of the degenerative process (45). A vicious circle may ensue, with the nigrostriatal damage causing subthalamic hyperactivity that, in turn, could sustain nigrostriatal degeneration. Indeed, in rats, a subthalamic nucleus lesion protects neurons of the substantia nigra pars compacta against the toxicity of 6-OHDA (46) and prevents transneuronal degeneration of the substantia nigra pars reticulata (47). More recently, Nakao et al. (48) have shown that previous ablation of the subthalamic nucleus attenuates the loss of nigral dopaminergic neurons.
by intrastriatal administration of neurotoxin 3-nitropropionic acid.

Thus, in addition to the role it plays in the development of PD motor symptoms, the subthalamic nucleus may also be directly involved in the mechanisms underlying the progression of the neurodegenerative process.

PHARMACOLOGICAL BLOCKADE OF SUBTHALAMIC OVERACTIVITY: A NEUROPROTECTIVE TOOL?

From what has been discussed so far, it follows that, in addition to the symptomatic effects (amelioration of PD motor symptoms), the blocking of PD-related subthalamic hyperactivity might also have a neuroprotective effect. Reduction of enhanced glutamatergic transmission has been recently suggested as an alternative approach to the treatment of PD (49,50). Indeed, the use of glutamate antagonists – as both symptomatic and neuroprotective agents – has proved beneficial in numerous experimental studies (49,50). However, the general limitation of the use of these drugs is that glutamate receptors are widespread in the brain. Thus, if a glutamate antagonist is given systemically, it will affect glutamatergic transmission outside the basal ganglia circuitry as well (even if the drug targets a specific glutamate receptor subtype), which is not desirable. For these reasons, we have recently studied the effects of selective blockade of glutamatergic transmission, at subthalamic level, on the development of a nigrostriatal lesion and the associated functional changes in the basal ganglia nuclei (25). Using permanent cannulas connected to subcutaneous pumps, we infused – directly into the subthalamic nucleus – two glutamate antagonists acting on different receptor subtypes, MK-801 (NMDA antagonist) and NBQX (AMPA antagonist), in rats with an evolving nigrostriatal lesion induced by 6-OHDA (Fig. 2). Subthalamic infusion of MK-

---

Fig. 2 - Drawing illustrating the experimental design followed in the study (ref. 25). Six-hydroxydopamine (2.5 µg/µl) was injected into the striatum, so as to induce a progressive, retrograde lesion in the substantia nigra pars compacta (SNc), which is connected to the striatum by the medial forebrain bundle (mfb). At the same time, a permanent cannula connected to a sub-cutaneous, osmotic mini-pump, was lowered into the subthalamic nucleus (STN). Pumps were loaded with MK-801 (NMDA antagonist), or NBQX (AMPA antagonist), or saline and delivered the solutions – continuously – for four weeks. After three weeks, animals were tested with systemic amphetamine (3 mg/kg, i.p.) for the presence of rotational behavior. At the fourth week, animals were sacrificed and brains were analyzed to determine cytochrome oxidase activity (functional evaluation) and Nissl staining (anatomical evaluation).
801, but not of NBQX, prevented the increase in metabolic activity of basal ganglia output nuclei and reduced the amphetamine-induced rotational behavior associated with nigrostriatal lesions. In addition, animals treated with MK-801 showed a marked reduction of the nigral cell loss caused by the toxin.

CONCLUDING REMARKS

The subthalamic nucleus plays a central role in the functional changes affecting the basal ganglia circuitry in PD. The pathological hyperactivity of subthalamic neurons, which develops as a consequence of the nigrostriatal degeneration, constitutes the neural substrate for PD motor symptoms. Subthalamic hyperactivity is also likely to contribute to the progression of the degenerative process. Therefore, manipulation of the subthalamic activity – possibly through selective pharmacological agents – may constitute a valuable tool to achieve both symptomatic improvement and neuroprotection in PD patients.

REFERENCES

7. Smith Y, Bevan MD, Shink E, Bolam JP. Microcircuity of the direct and indirect pathways of the basal ganglia. Neuroscience 1998;86:353-387


33. Francois C, Savy C, Jan C, Tande D, Hirsch EC, Yelnik J. Dopaminergic innervation of...
the subthalamic nucleus in the normal state, in MPTP-treated monkeys, and in Parkinson’s disease patients. J Comp Neurol 2000;425:121-129


47. Saji M, Blau AD, Volpe BT. Prevention of transneuronal degeneration of neurons in the substantia nigra reticulata by ablation of the subthalamic nucleus. Exp Neurol 1996;141:120-129


49. Blandini F, Greenamyre JT, Nappi G. The role of glutamate in the pathophysiology of Parkinson’s disease. Funct Neurol 1996;1:3-15