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Implication of the Subthalamic Nucleus in the Pathophysiology and Pathogenesis of Parkinson's Disease

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The subthalamic nucleus (STN) has been shown to play an important role in the control of movement and has been considered as a key structure in the functional organization of the basal ganglia. Several studies postulated that the STN plays a critical role in the pathophysiology of Parkinson's disease and that its inhibition or its lesioning can reverse the cardinal motor symptoms. Nevertheless, the beneficial effect was accompanied by dyskinetic abnormal movements. In order to avoid unpleasant and irreversible side effects we used high-frequency stimulation (HFS) of the STN instead of lesions. We have shown that parkinsonian motor symptoms, akinesia, rigidity, and tremor can be alleviated by HFS of the STN in the nonhuman primate model. Side effects were controllable and appeared only at intensities higher than that inducing the improvement of motor symptoms. In severe parkinsonian patients, bilateral STN-HFS greatly improved parkinsonian motor symptoms. Motor fluctuations were attenuated and patients became independent in most activities of daily living. It appears that STN-HFS mimics the effects of lesions by inhibiting its neuronal activity. In a rat model of parkinsonism, we studied the implication of the STN in the excitotoxicity of nigral dopamine cells. We showed that kainic acid lesioning of the STN can protect nigral dopaminergic cells against 6-hydroxydopamine-induced toxicity. The evidence reviewed in the present article clearly demonstrates that the STN is implicated in the pathophysiology and pathogenesis of Parkinson's disease.

Key words: Parkinson's disease; Subthalamic nucleus; Neuroprotection; High-frequency stimulation

INTRODUCTION

The subthalamic nucleus (STN) is a small structure of the basal ganglia characterized by a high neuronal density. Its neurons are excitatory and use glutamate as a neurotransmitter (77). Several anatomical and electrophysiological studies have shown that the STN receives excitatory glutamatergic projections from the cortex (43,46,66,71) and parafascicular nucleus of the thalamus (61), inhibitory GABAergic afferents from the external part of the globus pallidus (GPe) (1), dopaminergic projections from the pars compacta of the substantia nigra (SNc) (23,56), and cholinergic/glutamatergic afferent projections from the pedunculopontine nucleus (PPN) [for review see (66)]. Concerning its efferents, STN neurons project to different structures according to a specific topography (66). Neurons in the associative part of the STN send efferents to the caudate nucleus of the striatum and to the main output structures of the basal ganglia (66): the internal part of the globus pallidus (GPi) and the pars reticulata of the substantia nigra (SNr). The sensorimotor territory of the nucleus projects to the putamen and GPe and the limbic part sends projections to the ventral globus pallidus (GPv).

The STN has been shown to play an important role in the control of movement. It has been linked with hemiballismus, because vascular accidents in the region including STN were often associated with the appearance of abnormal involuntary movements (AIM) (22,54, 57,85). These AIMs can be reproduced in a nonhuman primate by inhibiting STN activity after in situ injection of GABA agonists or after lesion of the nucleus (26,36,85,86). Recently, several studies have demonstrated that the STN is implicated in the pathophysiology of Parkinson's disease.

THE PLACE OF STN IN BASAL GANGLIA CIRCUITRY

The STN has been considered as a key structure in the functional organization of the basal ganglia. Its place in basal ganglia circuitry has been recently reviewed by Parent and Hazrati (66). In the current accepted model of this circuitry, the striatum and the STN are the two major structures through which cortical signals are transmitted to the output nuclei of the basal ganglia (1,66). The striatum and the STN receive direct excitatory glutamatergic projections from the cortex and exert oppo-

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site effects, inhibitory versus excitatory, on the GPi and SNr, because they receive inhibitory GABAergic projections from the striatum and excitatory glutamatergic inputs from the STN. In the current model, the STN is viewed as a relay nucleus because, in addition to the direct cortico-STN pathway, the cortex influences the STN through an indirect pathway involving the striatum and GPe. Electrophysiological studies have shown that the STN plays an important role in maintaining tonic activity in the output structures of the basal ganglia (34,70).

IMPLICATION OF STN IN THE PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

The manifestation of parkinsonian motor symptoms is the consequence of a progressive degeneration of dopaminergic cells in the SNc, which induces a depletion in dopamine concentration at the striatal level. These abnormalities induce a complete disorganization of neuronal activity in the basal ganglia structures. In monkeys rendered parkinsonian by systemic injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), abnormal activity of STN neurons has been observed. Electrophysiological results have shown a slight but significant increase in neuronal firing rate and an important change in the firing pattern of STN and GPi neurons (17,28,58,82). Compared to the normal situation, the percentage of cells exhibiting burst firing pattern increased after MPTP treatment. In 6-hydroxydopamine (6-OHDA)-lesioned rats, electrophysiological studies have shown different results concerning the firing frequency of STN neuronal activity, but similar changes in the firing pattern have been reported (33,40). The changes reported by electrophysiological studies are in good agreement with the changes in basal ganglia metabolic activity. In MPTP-treated monkeys several studies have shown a significant reduction in 2-deoxyglucose uptake (60) and a significant increase in cytochrome oxidase mRNA and GAD mRNA expression at the STN level (32,84). Similar results were obtained in STN efferent structures (GPi and SNr), showing that these abnormalities can be reversed by levodopa treatment or STN lesion (32,39). From these results, it has been postulated that the STN plays a critical role in the pathophysiology of Parkinson's disease and that its inhibition can be effective in the therapy of the disease.

REVERSAL OF EXPERIMENTAL PARKINSONISM BY STN INACTIVATION

Recently, pharmacological interruption of transmission between STN efferents and their target neurons has been shown to alleviate parkinsonian motor symptoms in experimental MPTP-treated monkeys (20,31). In the same animal model and under similar conditions an STN lesion has been shown to reverse the symptoms (2,16). Nevertheless, this beneficial effect was accompanied by the appearance of abnormal dyskinetic movements. In addition, in the 6-OHDA rat model of parkinsonism, it has been shown that lesions of the STN reduce contralateral rotational behavior induced by apomorphine (21) and reverse increases of reaction time, but at the same time induce multiple deficits in attention tasks (3,4). In the 6-OHDA-lesioned marmoset, an additional unilateral lesion of the STN significantly reversed some, but not all, parkinsonian-like deficits (38). Animals showed a decrease of contralateral hemineglect as evidenced by improved latencies to initiate reaching on the contralateral side on the staircase reaching task; however, deficits in skilled movements persisted. From these data it appears that abnormal STN activity is implicated in the manifestation of parkinsonian motor symptoms, but that lesioning of the STN may not be appropriate as a therapy for Parkinson's disease.

In order to avoid unpleasant and irreversible side effects of STN lesions, we used high-frequency stimulation (HFS) (frequency: 130 Hz, pulse width: 0.06 ms, variable intensities) of this nucleus. This technique is known to induce reversible, gradual, and controllable functional impairment of another brain structure, the ventral intermediate nucleus of the thalamus (VIM). In clinical practice, HFS (>100 Hz) applied to the VIM induces a dramatic suppression of rest tremor in parkinsonian patients (6,7,9) without the adverse effects observed after standard thalamotomy (64,81). Recently, we have shown that parkinsonian motor symptoms, akinesia, and rigidity can be alleviated by HFS of the STN (STN-HFS) in monkeys rendered hemiparkinsonian by unilateral intracarotid injection of MPTP (13,14). In these experiments, we used electromyographic recordings and comparisons of kinetic parameters in trained movements to quantify the impairment induced by the unilateral nigral lesion and the improvement obtained using STN-HFS. A clear decrease in muscle EMG recorded from agonist/antagonist muscles correlated with the decrease in clinical rigidity. Moreover, the animals were able to perform rapid trained flexion and extension movements as in the normal situation, whereas the movements performed before STN stimulation were much smaller (13,14). The amelioration of movement parameters was associated with the normalization of EMG activities recorded in the agonist/antagonist muscles. In addition, the reversal of rigidity and improvement in motor performance induced by STN-HFS were comparable to those obtained after L-dopa treatment (13). These studies were carried out in rhesus monkeys, which developed only akinesia and rigidity after MPTP treatment, but parkinsonian rest tremor has never been observed in this species of primate (12). To study the

effect of STN-HFS on tremor we used another animal model obtained by lesioning the red nucleus and the SNc. The tremor obtained has a frequency close to that observed in parkinsonian patients, and can be suppressed by apomorphine treatment. In this model, STN-HFS induced a dramatic arrest of rest tremor (30). Side effects were controllable and appeared only at intensities higher than that inducing the improvement of motor symptoms. The beneficial effects of STN-HFS obtained in MPTP-treated monkeys and experience with VIM stimulation led us to propose STN-HFS for the improvement of the whole parkinsonian triad.

STN-HFS IN PARKINSONIAN PATIENTS

From 1993, several parkinsonian patients received bilateral implantation of a stimulating electrode in the STN and were chronically stimulated by means of a pulse generator placed subcutaneously in the subclavicular area. The selection criteria of patients were: 1) age under 70 years, 2) clinically diagnosed idiopathic Parkinson's disease, 3) disabling motor fluctuations despite all drug therapies, 4) no severe dementia, and 5) normal MRI of the brain. Bilateral STN-HFS greatly improved parkinsonian motor symptoms and the UPDRS III score was significantly reduced (8,44,45,50–52). Motor fluctuations were attenuated, and patients with sudden on–off fluctuations before surgery had milder or no fluctuations thereafter. As a very important clinical result, all patients became independent in most activities of daily living. Neuropsychological results showed that cognitive functions were unchanged after surgery (50). Adverse effects were controllable, and in general dyskinesias were only induced by increasing the stimulation voltage above the long-term level, inducing the improvement of the three cardinal signs of parkinsonism (akinesia, rigidity, and tremor).

HOW DOES STN-HFS WORK?

Regarding the functional mechanism of STN-HFS, it appears from different studies that STN stimulation at high frequency mimics the effects of lesions in MPTP-treated monkeys (13,14,16) by inhibiting the neuronal activity of this nucleus. Recently, we have demonstrated that high-frequency stimulation of the STN induces a decrease or suppression of neuronal activity in the two main output structures of the basal ganglia (SNr and EP) in normal rats (15). As the SNr and EP receive direct excitatory glutamatergic projections from the STN, the inhibitory responses of these two nuclei to STN-HFS can be due to a direct inhibition of STN neuronal activity, probably by a depolarization blockade phenomenon. The inhibition of these two output structures of the basal ganglia should induce a decrease in the inhibitory action on motor thalamus and consequently an increase of the excitatory input to the cortex, and the results of recent studies support this hypothesis. Gao et al. (29) showed that STN-HFS resulted in an increase of neuronal firing in the majority of neurons recorded in the ventromedial nucleus of the thalamus. In the same way, a positron-emission tomography study in operated parkinsonian patients demonstrated an increase in cortical activity of the supplementary motor area, dorsolateral prefrontal cortex, and cingulate when patients performed movements during STN-HFS (49).

STN AND THE PATHOGENESIS OF DOPAMINERGIC CELL LOSS IN PARKINSONISM

The pathophysiology of Parkinson's disease has been well understood but the pathogenesis of the underlying dopaminergic cell death remains unclear. Some hypotheses have been advanced suggesting a bioenergetic defect in the etiology of Parkinson's disease. Histological and immunohistochemical studies of postmortem brain tissue have shown a reduction in activity of mitochondrial complex I in the substantia nigra pars compacta (SNc) of parkinsonian patients but not in other brain regions (37,67,74). Recently, a defect in the mitochondrial respiratory chain and an increased amount of deleted mitochondrial genome in the nigrostriatal system of patients with Parkinson's disease has been reported (41,42). As shown earlier (62), glutamate becomes neurotoxic via NMDA receptors when intracellular energy levels are reduced. Moreover, several authors have proposed that glutamate excitotoxicity mediated by the activation of NMDA receptors could be implicated in the pathogenesis of Parkinson's disease. Stimulation of excitatory amino acid receptors is known to induce entry of calcium into the cell, leading to increased levels of intracellular free calcium. Some studies have suggested that increased cytoplasmic calcium could lead to excitotoxic cell death by several mechanisms (5,27,65). Several studies reported that NMDA antagonists can be used as neuroprotective agents in animal models of parkinsonism, showing that both competitive and noncompetitive NMDA antagonists protected against methamphetamine-induced dopaminergic neuron degeneration in rats (63, 78,79). The enhanced neurotoxicity of methamphetamine, caused by unilateral administration of NMDA into the striatum, has confirmed the role of NMDA receptors in toxic mechanisms (78). Evidence for the concept of participation of NMDA receptors in 1-methyl-4-phenylpyridinium (MPP^+) neurotoxicity in rats have been reported (83). MPP^+-induced dopamine cell loss was prevented by previous administration of noncompetitive NMDA antagonists [(+)-5-methyl-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine maleate (MK-801), 2-amino-7-phosphonoheptanoic acid (AP7)]. More-

over, it has been shown that intrastriatal MPP^+ lesions were partially blocked by both prior decortication and systemic administration of MK-801 (80). Moreover, MK-801 administered to monkeys, jointly with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) given once daily, prevented degeneration of dopaminergic neurons (87). The same result was observed by Lange et al. (48) with a competitive NMDA antagonist [3-(±)-2-carboxy-piperazin-4-yl)-propyl-1-phosphonic acid (CPP)]. Recently, we have shown that riluzole (2-amino-6-trifluoromethoxy-zothiazole), a compound that interferes with glutamatergic neurotransmission by inhibiting the release of glutamate (10,55), can be neuroprotective when administred before MPTP treatment in monkeys (11). These results complement previous biochemical data obtained in rodents in which riluzole has been shown to partially antagonize the decrease in dopamine levels induced by MPTP in mice (19), while in rats, the MPP^+-induced increase in dopamine release in the striatum in vivo was blocked (18).

It is clearly established that the STN, which has an important role in the clinical manifestations of Parkinson's disease, influences both dopaminergic and nondopaminergic neurons in the substantia nigra. Anatomical and electrophysiological studies have demonstrated the existence of a direct projection from the STN to SNc dopaminergic neurons and that this pathway is glutamatergic (35,66,75,76). Single shock electrical stimulation of the STN induces an excitatory response in the SNc (35) and SNr neurons (15). In addition, STN stimulation results in a marked increase in dopamine release in the substantia nigra (59). Smith and Grace (76) have shown that STN plays a role in the regulation of nigral dopaminergic neuron activity and that its lesioning or inhibition results in a reduction of the burst firing pattern. A similar result was obtained in SNr neurons by Burbaud et al. (21) showing a regularization of the firing pattern in these neurons after lesioning the STN. In contrast, disinhibition of STN by microinjection of bicuculine increased burst firing pattern in SNc neurons, an effect that was reversed by NMDA receptor antagonists (24,25).

Taken together, these data demonstrate the capacity of STN to modulate the activity of SNc dopaminergic neurons through excitatory glutamatergic pathways. This excitatory effect is mediated through activation of NMDA receptors, which can be an important mechanism of neuronal death.

POTENTIAL NEUROPROTECTIVE EFFECT OF STN INACTIVATION

In a rat model of parkinsonism we determined whether STN inactivation could prevent dopaminergic cell loss in the SNc against toxicity induced by a selective dopamine neurotoxin. To avoid an immediate and severe destruction of the dopaminergic nigrostriatal pathway induced by direct infusion of 6-OHDA into the SNc, we used the rat model described by Sauer and Oertel (73). This model is characterized by a progressive loss of dopaminergic neurons in the SNc induced by intrastriatal infusion of 6-OHDA. Animals developed a progressive increase of rotational behavior in response to apomorphine administration, which can be correlated with the progressive dopaminergic cell death (68). In this rat model of parkinsonism, behavioral and immunohistochemical results showed that kainic acid lesion of the STN provided protection of SNc dopaminergic neurons against 6-OHDA toxicity (68). When 6-OHDA was injected into the striatum 1 week after STN lesion, the number of tyrosine hydroxylase immunoreactive (TH-ir) cells in the ipsilateral SNc was not significantly different compared to that on the normal side. Nevertheless, biochemical results showed a reduction of dopamine concentration at the striatal level that was similar to that found in 6-OHDA control rats (69). The quantification of TH-ir cell loss in SNc and dopamine concentration in the striatum was realized in animals killed 15 days after 6-OHDA infusion. Similar results were reported in other studies carried out in MPTP-treated mice previously treated with NMDA antagonists (53) or nimodipine, a selective calcium channel blocker (47). In another experiment, STN ablation has been shown to prevent transneuronal degeneration of SNr neurons (72).

CONCLUSION

From this review, it is clear that the subthalamic nucleus plays a direct and crucial role in the pathophysiology and pathogenesis of dopaminergic cell degeneration in parkinsonism. The manifestation of the three cardinal motor signs—akinesia, rigidity, and tremor—is the consequence of dopamine depletion inducing abnormal neuronal activity in the STN. These symptoms can be alleviated by STN inactivation after lesioning or high-frequency electrical stimulation, both of which result in a decrease of activity in the two main output structures of the basal ganglia, inducing a disinhibition of motor thalamic nuclei and activation of premotor cortical areas. In addition, the ablation of glutamatergic input from the STN to SNc has a neuroprotective effect against 6-OHDA-induced dopamine cell degeneration in a rat model of parkinsonism. This suggests that surgical or pharmacological inactivation of STN, in patients with Parkinson's disease at an early stage of the disease, may arrest or slow down the progression of dopaminergic cell loss.

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