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Dopaminergic Control of the Neurotransmitter Release in the Subthalamic Nucleus: Implications for Parkinson's Disease Treatment Strategies

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1. Introduction

A critical role of the subthalamic nucleus (STN) in the control of movement has been proposed based on the observations that its lesion or high-frequency stimulation, aimed at altering its activity, is effective in alleviating clinical features of Parkinson's disease (Bergman et al,. 1990; Bennazouz et al., 1993; Pollak et al., 1993, Benazzouz et al., 2000). Indeed, overactivity of the subthalamic neurons due to the loss of midbrain dopaminergic neurons is believed to be a key feature in Parkinson's disease. Several studies indicate that the activity of STN neurons can be influenced directly by dopamine and its receptor agonists/antagonists. Indeed, the STN receives a direct dopaminergic input arising in the substantia nigra pars compacta (SNc) and both dopamine D1- and D2-like receptors are present in the STN (Canteras et al., 1990; Hassani et al., 1997; Flores et al., 1999). Understanding the position of the STN within the basal ganglia and the possible direct effects of dopamine and its ligands at the level of this nucleus in normal and parkinsonian states may be important in the development of new therapies for Parkinson's disease. The purpose of this chapter is to give an overview of the current position of the STN in the basal ganglia motorloop and to clarify the role of dopamine at the level of the STN in both normal conditions and in parkinsonian experimental animal models.

2. The subthalamic nucleus and its connections

Despite the small size of this biconvex-shaped structure, the STN has an important role in the modulation of the basal ganglia output and thus movement control (DeLong & Wichmann, 2007; Obeso et al., 2008; Gubbelini et al., 2009). Indeed, together with the striatum, the STN forms the major input to the basal ganglia and is considered an important relay nucleus of the indirect pathway. In this section, the role of the STN within the basal ganglia and its connections are described.

2.1 The subthalamic nucleus as a part of the basal ganglia

The basal ganglia consist of five interconnected nuclei including the caudate nucleus, the putamen [which forms together with the caudate nucleus the striatum], the globus pallidus (pars interna (GPi) and externa (GPe)) the SN (SNc and substantia nigra pars reticulata (SNr))

and the STN (DeLong, 1990; Blandini et al., 2000). Albin and DeLong proposed a schematic view of the basal ganglia organisation which has been used for many years as a reference for understanding their functioning in physiological and pathological conditions (Albin et al., 1989; DeLong, 1990; Gubellini et al., 2009). Currently, this view has been replaced by a more recent representation of the organisation of the basal ganglia based on novel anatomical, neurochemical and physiological data (Levy et al., 1997; Gubellini et al., 2009). In this representation, the striatum and STN are considered as the two major input structures of the basal ganglia. Both nuclei receive input from the cerebral cortex, whereas the GPi and SNr provide output of the basal ganglia to the thalamus and brainstem (DeLong & Wichmann, 2007; Obeso et al., 2008). The striatum is connected with these output structures via a monosynaptic direct pathway and a polysynaptic indirect pathway which includes the GPe and the STN. The striatal direct pathway neurons also receive input from the intralaminar nuclei of the thalamus. The STN is directly connected with the output nuclei.

Besides motor functions, the basal ganglia are involved in cognition and emotion (Alexander et al., 1990; Smith et al., 1998). Indeed, the basal ganglia can be functionally divided into different cortico-subcortical circuits: the motor loop, the associative loop and the limbic loop. Each circuit originates from individual cortical areas, innervates the respective regions of the striatum, GP and SN and, via the thalamus, terminates in their respective cortical areas of origin (Hamani et al., 2004; DeLong & Wichmann, 2007). Like the other structures of the basal ganglia, the STN is subdivided into different major parts: a motor, an associative and a limbic part (Hamani et al., 2004; Benarroch, 2008). The motor part is represented by the large dorsolateral portion of the STN whereas the associative and the limbic part are represented by respectively the ventromedial portion and the medial tip of the STN. Currently, the best characterized cortico-subcortical circuit is the motor circuit.

The motor loop (figure 1) originates from the motor cortex and sends glutamatergic projections to both input nuclei, the striatum and the STN (DeLong & Wichmann, 2007; Obeso et al., 2008). Striatal efferent neurons are γ-aminobutyric acid (GABA)-ergic and are connected, as mentioned before, with the output nuclei, GPi and SNr, by the direct or the indirect pathway. Neurons from the direct pathway, which bear dopamine D1 receptors (excitatory receptors), project directly to the output nuclei. Neurons from the indirect pathway express dopamine D2 receptors (inhibitory receptors) and send GABA-ergic projections to the GPe. The GPe in turn influences the STN by GABA-ergic projections. The STN, which is a glutamatergic structure, provides excitatory input to the output nuclei of the basal ganglia. The balance within the basal ganglia is regulated by the dopaminergic neurons from the SNc. Release of dopamine in the striatum leads to an increase in activity of the direct pathway via the D1 receptors, whereas the activity of the indirect pathway is decreased via the D2 receptors. This dopamine release results in a reduction in the activity of the output nuclei and thus facilitates movement. In Parkinson's disease, nigrostriatal degeneration leads to hyperactivity of the STN and thus to an increase of the output nuclei activity which in turn results in inhibition of ongoing movement.

2.2 Subthalamic nucleus afferents and efferents

As described above, the STN has a pivotal position in the motor circuitry. Indeed, it is part of a complex organisation within the basal ganglia and is connected with a wide range of structures. It is the only glutamatergic nucleus of the basal ganglia (Smith & Parent, 1988; Blandini et al., 2000; Hamani et al., 2004). The STN provides a strong excitatory input to the two output structures, GPi and SNr, but also to the GPe. Via its excitatory input to the SNc, it influences the regulation of the dopamine release (Smith et al., 1990; Parent & Hazrati, 1995; Hamani et al., 2004). Besides the main efferent projections described above, the STN is

connected with the peduncolopontine nucleus and the ventral tegmental area through which it influences the processing of emotional information (Smith et al., 1990; Parent & Hazrati, 1995; Haegelen et al., 2009). Furthermore, the STN sends poor glutamatergic projections to the striatum and the motor cortex (Smith et al., 1990; Blandini et al., 2000).
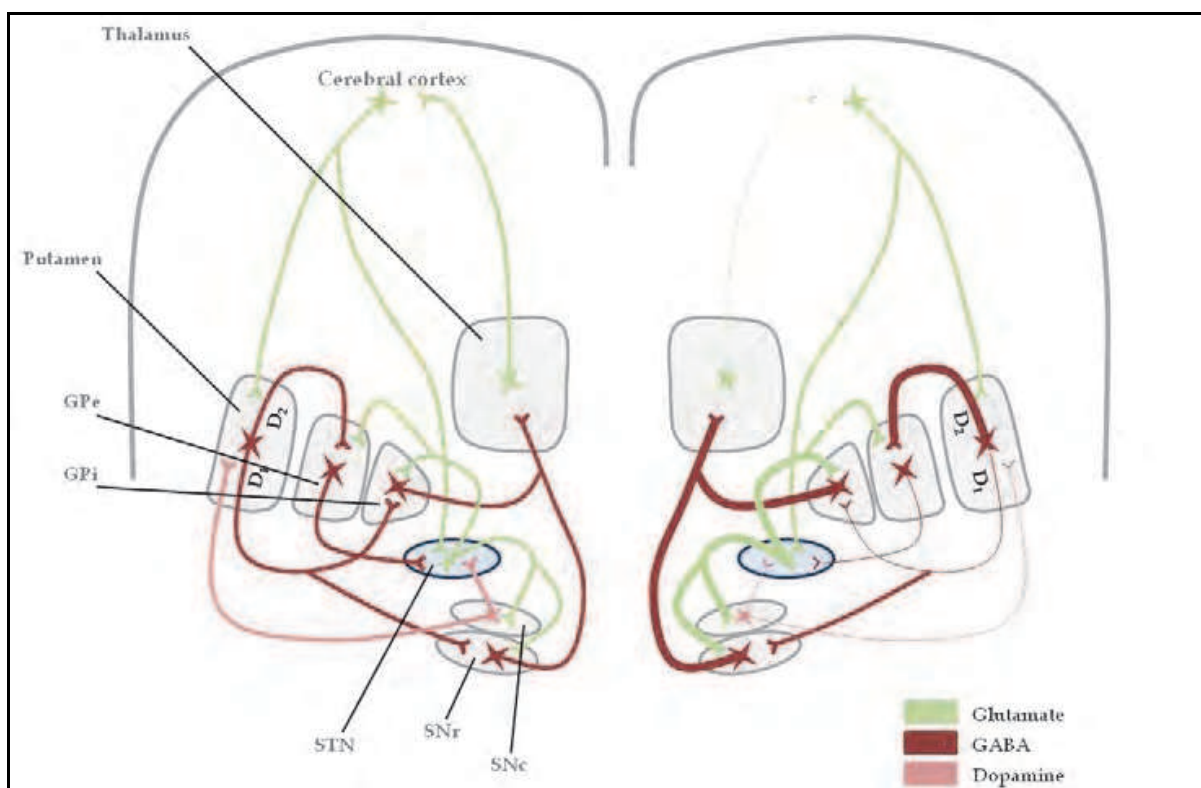

Fig. 1. Left brain hemisphere: motor loop in a normal condition. Right brain hemisphere: motor loop in Parkinson's disease. The motor loop originates from the motor cortex and sends glutamatergic projections to both input nuclei, the striatum and the STN. Striatal neurons from the direct pathway (contain D1 receptors) project directly to the output nuclei whereas neurons from the indirect pathway (contain D2 receptors) send GABA-ergic projections to the GPe. The GPe in turn influences the STN by GABA-ergic projections. The STN provides excitatory input to the output nuclei. Release of dopamine in the striatum leads to an increase in activity of the direct pathway via the D1 receptors whereas the activity of the indirect pathway is decreased via the D2 receptors. Dopamine release results in a reduction in the activity of the output nuclei and, via the thalamus, leads to glutamatergic projections to the cortex which facilitates movement. In Parkinson's disease, dopaminergic degeneration of the SNc leads to hyperactivity of the STN and thus an increase of the output nuclei activity which in turn results in inhibition of ongoing movement. The thickness of the depicted projections reflects their activity.

Neurons of the STN receive two major projections: a direct excitatory glutamatergic input from the cerebral cortex and an important inhibitory GABA-ergic innervation from the GPe (Blandini et al., 2000; Hamani et al., 2004; DeLong & Wichmann, 2007). It also receives inhibitory projections from the GPi, SNr and striatum. Another source of excitatory input to the STN is the centromedian-parafascicular nucleus of the thalamus. Furthermore, glutamatergic and cholinergic projections arise from the pedunculopontine nucleus to the STN. Besides the main glutamatergic and GABA-ergic afferents to the STN, dopaminergic neurons from the SNc also innervate the STN (Campbell et al., 1985; Canteras et al., 1990;

Hassani et al., 1996). These neurons modulate the activity of glutamatergic and GABA-ergic afferents arising from respectively the cortex and the pallidum to the STN. In addition, the STN receives serotonergic projections from the dorsal raphe nucleus which may also be involved in the modulation of the STN activity (Blandini et al., 2000; Hamani et al., 2004; DeLong & Wichmann, 2007). In this chapter, the importance of the dopaminergic input from the SNc to the STN will be described.

3. Dopamine receptors in the subthalamic nucleus

Because of their relevance in Parkinson's disease, large research efforts have been made to investigate the presence and localisation of dopamine receptors in the central nervous system, especially since the mid to late eighties (Wamsley et al., 1989). These receptors consist of a large family of D1-like dopamine receptors, divided into D1 and D5 receptors, and D2-like dopamine receptors, divided into D2, D3 and D4 receptors (Niznik, 1987; Niznik et al., 1992; Sibley et al., 1992; Gingrich et al., 1993). In general, D1 receptors are known to be positively coupled to adenylatecyclase via a Gs protein, whereas D2 receptors are either uncoupled or negatively coupled to adenylatecyclase (Onali et al., 1985; Memo et al., 1986). Both the D1-like and the D2-like dopamine receptors are known to be abundantly expressed and widely distributed throughout different basal ganglia nuclei. A series of experimental studies indicate that functional dopamine receptors are expressed and localised in the STN but there is still debate concerning the receptor subtypes.

The occurance of D1 receptors in the STN has been reported in a number of histological studies (Brown et al., 1979; Dubois et al., 1986; Fremeau et al., 1991; Mansour et al., 1992). However, Johnson et al. reported that D1 receptors are not located within the borders of the STN but are situated in the cerebral peduncles (Johnson et al., 1994). By means of autoradiography in rats, Kreiss et al. confirmed the presence of D1 dopamine receptors along the ventral edge of the STN which borders the cerebral peduncle. This was confirmed in a morphological study showing that the dendrites of STN neurons extend across the ventral STN borders into the peduncles (Kita et al., 1983). D1 receptors were not observed in the dorsal regions of the STN (Kreiss et al., 1996). Another autoradiographic study confirmed the presence of D1 receptors in the STN and found that there was a clear dorsoventral gradient in D1 binding sites at the level of the STN (Flores et al., 1999). Dopamine D2 receptors have also been shown to be present at the level of the rat STN by several groups (Boyson et al., 1986; Bouthenet et al., 1987; Johnson et al., 1994). Flores et al. were able to show the presence of all three subtypes of the D2-like receptors, although the amounts of D3 dopamine receptors were very low (Flores et al., 1999). However, no dopamine D1, D2, D3 nor D4 mRNA was detected by several investigators in both rat and human STN (Fremeau et al., 1991; Mansour et al., 1992; Augood et al., 2000). Nevertheless, Bouthenet et al. showed the presence of both D2 and D3 mRNA at the level of the STN with in situ histochemistry (Bouthenet et al., 1991). Moreover, using reverse transcriptase polymerase chain reaction the presence of D1 receptor mRNA was confirmed (Flores et al., 1999), together with the expression of the mRNA encoding for D2 and D3 receptors. By means of in situ hybridisation, high levels of D5 dopamine receptor mRNA were found at the level of the STN (Svenningson & Le Moine, 2002). However, they were unable to detect mRNA levels for all other dopamine receptor subtypes. Baufreton et al. also showed the presence of D5 dopamine receptors on burst competent STN neurons with single-cell reverse transcription-PCR profiling. They also used an antibody raised against a peptide sequence of cloned D5 receptor and detected immunoreactivity in the STN cell bodies (Baufreton et al., 2003).

Thus, using an array of techniques, all dopamine receptor subtypes have been detected in STN. However, the data remain inconsistent and more research is warranted.

4. Role of dopamine at the level of the subthalamic nucleus

Numerous studies in the past have suggested a direct role of dopamine and its receptor ligands at the level of the STN. As described above, the presence of both D1- and D2-like dopamine receptors in the STN has been demonstrated. Several anatomical studies provided evidence for a direct and substantial nigrosubthalamic dopaminergic projection in rats (Campbell et al., 1985; Canteras et al., 1990; Hassani et al., 1996). Moreover, we and others have shown that dopamine is released within the STN in vivo (Cragg et al., 2004; Ampe et al., 2007). However, despite numerous investigations, many discrepancies still exist with regard to the effect of dopamine and its receptor agonists on the activity of STN neurons. In the classical model of the basal ganglia motorloop, dopamine is widely assumed to exert an inhibitory influence on STN neuronal activity (Albin et al., 1995) and dopamine should reduce excitability of STN neurons in parkinsonian brain (DeLong, 1990; Bergman et al., 1994). A variety of in vitro an in vivo experimental studies have addressed this issue.

Several in vitro electrophysiological studies have shown inhibitory effects of dopamine on STN neuronal activity (Campbell et al., 1985; Hassani et al., 1999). However, others have found dopaminergic agonists to excite the activity of STN neurons. Indeed, Zhu et al. (2002a) showed that a dopamine bath application significantly increased the firing rates of STN neurons in a concentration-dependent fashion in both intact and 6-hydroxydopamine (6-OHDA) lesioned rats. They also showed that this excitatory effect of dopamine was largely mimicked by application of the dopamine D2 receptor agonist quinpirole. The dopamine D1 receptor agonist SKF-38393 showed a trend towards an increase in STN firing rate, but this effect was only significant in the 6-OHDA lesioned group. They concluded that dopamine exerts an excitatory influence on STN neuronal activity and that this effect is likely to be established by stimulation of D2 receptors. They also observed that dopamine, in 6-OHDA lesioned rats, in addition to the firing rates, also changes the irregular firing pattern into a more regular pacemaker pattern at the level of the STN (Zhu et al., 2002a). The same group also demonstrated that dopamine increases the firing rates of action potentials and produces inward currents in STN neurons. Together with the fact that these inward currents persisted when excitatory synaptic transmission was blocked, illustrated that dopamine exerted a direct excitatory effect at the level of the STN (Zhu et al., 2002b). In another in vitro electrophysiological study, Tofighy et al. (2003) showed that dopamine caused modest, but reliable, increases in the firing rates of STN neurons and considered this effect likely to be a direct excitatory action on STN neurons. The dopamine D2 receptor agonists quinpirole and bromocriptine caused concentration-dependent increases in the firing rates of STN neurons, whereas the mixed dopamine D1/D2 receptor agonist apomorphine caused only weak and less reproducible responses in STN firing rates. The dopamine D1 receptor agonist, SKF 38393 was without effect on STN firing rates. These results initially suggested an excitatory effect of dopamine on the STN neurons through a direct D2 receptor mediated mechanism. However, due to the fact that the effective concentration of all agonists was high, the authors stated that the effects could well be non-specific. This, together with the inconsistent effects of apomorphine and the inability of dopamine D2 (nor D1) receptor antagonists to reduce the observed excitatory effects led the authors to conclude that these effects probably cannot be assigned to dopamine receptors but to non-catecholaminergic receptors (Tofighy et al., 2003). Baufreton et al., by means of in vitro electrophysiological recordings, showed that activating D1 and D2 dopamine

receptors with D1 and D2 agonists promotes pace making at the level of the STN by increasing the firing frequency of neurons that exhibit tonic firing capacity and by changing firing in burst-competent and spontaneously burst-firing neurons. Moreover, they also showed that D5 dopamine receptors may potentiate burst-firing in STN neurons by modulating L-type calcium channels in the absence of dopamine (Baufreton et al., 2003; Baufreton et al., 2005). Finally, Loucif et al. showed that dopamine clearly produces subthalamic membrane depolarisation leading towards an increase in firing rate. This effect seemed to be due to action on D1-like dopamine receptor mediated activation of a cyclic-nucleotide gated non-specific cation conductance. This conductance also contributed to the membrane depolarisation changing STN neuronal bursting towards a regular activity (Loucif et al., 2008). Thus, in vitro studies suggest that dopamine at the level of the STN exerts excitatory effects, possibly via D2 receptors. More recent studies, however, suggest D1-like mediated effects.

Several in vivo studies showed an inhibitory effect of dopamine on the activity of STN neurons. Campbell et al., using horseradish peroxidase and microiontophoresis, suggested that dopamine suppresses STN activity (Campbell et al., 1985). Injection of the mixed D1/D2 agonist apomorphine into the STN of intact rats decreased the mean firing rates of STN neurons significantly. However, an increase of firing rates was observed in 6-OHDA lesioned rats (Hassani et al., 1999). The selective D1 dopamine receptor agonist SKF 82958, when injected into the STN, decreased the activity of STN neurons in both intact and 6-OHDA lesioned rats. Injection of the selective D2 dopamine receptor agonist quinpirole decreased the firing rate of STN neurons, whereas in 6-OHDA lesioned animals it significantly increased firing rates. Hassani and colleagues concluded that dopamine receptor agonists probably have an inhibitory effect on STN neurons of intact rats via a D1 dopamine receptor mediated mechanism, whereas in 6-OHDA lesioned animals dopamine receptor agonists stimulate the STN via D2 dopamine receptors and inhibit activity via D1 dopamine receptors (Hassani et al., 1999). On the other hand, several other in vivo studies suggested a facilitatory effect of dopamine at the level of the STN. Glucose utilization was decreased in the STN following systemic administration of the dopamine D1 receptor antagonist SCH23390 (Trugman et al., 1993) whereas it was increased following systemic administration of the mixed D1/D2 dopamine receptor agonist apomorphine or following amphetamine (Brown et al., 1978; Wechsler et al., 1979; Trugman et al., 1993). Kreiss et al. described predominantly D1 mediated excitatory effects since neuronal firing rates in the STN of intact rats was increased following a systemic administration of apomorphine. Systemic administration of the dopamine D2 receptor agonist quinpirole did not alter STN firing rates, whereas the dopamine D1 receptor agonists SKF 38393 and SKF 82958 clearly increased STN firing rates. Local administration of the dopamine D1 receptor agonist SKF 82958 also increased firing rates (Kreiss et al, 1996). Using microiontophoresis, a clear excitatory effect of dopamine on the majority of STN neurons in both intact and 6-OHDA lesioned rats was observed (Ni et al., 2001). The excitatory effect of dopamine in the 6-OHDA lesioned rats was similar to that in intact rats. Their results were in good agreement with previous studies using the same technique also showing that dopamine induced an increase in firing rate of almost all STN neurons of intact rats (Mintz et al, 1986). Selective dopamine depletion by injection of 6-OHDA in the STN resulted in a clear decrease of the firing rate together with a change in firing pattern, reinforcing the evidence of an excitatory effect of dopamine at the level of the STN (Ni et al. 2001). Finally, we were the first to study the in vivo release of dopamine and glutamate in the STN using in vivo microdialysis (Ampe et al., 2007). We were able to establish that perfusion of the STN with NMDA enhanced dopamine and glutamate release in a concentration dependent manner. We

showed that this release was dependent on both D1 and D2 receptors since the NMDA-mediated effects were blocked by local perfusion of both the dopamine D1 receptor antagonist SCH 23390 and the dopamine D2 receptor antagonist raclopride, confirming the presence of this type of receptors in the STN. The importance of the dopaminergic innervation to the STN in these effects was demonstrated by the fact that depletion of dopamine by 6-OHDA lesioning of the SNc resulted in an absence of the effects of NMDA in the STN (Ampe et al., 2007). More recently, we showed that perfusion of the STN with dopamine or its D1 receptor agonist SKF38393 results in excitation of the STN since extracellular glutamate is increased. Again, 6-OHDA lesioning abolished these effects (Ampe et al., submitted elsewhere). Taken together, the majority of the available in vivo data clearly suggest an excitatory effect of dopamine on STN neurons that is mediated via dopamine D1 receptors.

	Intact		6-OHDA	
	STN inhibition	**STN activation**	**STN inhibition**	**STN activation**
In Vitro	**DA** *Campbell et al., 1985* *Hassani et al., 1999*	**DA** *Zhu et al., 2002a* *Zhu et al., 2002b* **D2 - quinpirole** *Zhu et al., 2002a* *Tofighy et al., 2003* **D1/D5-SKF82958;SKF 81297** *Baufreton et al., 2003*		**DA** *Zhu et al., 2002b* **D2 - quinpirole** *Zhu et al., 2002a* *Baufreton et al., 2005* **D1/D5-SKF38393 ; SKF82958; SKF 81297** *Baufreton et al., 2005* *Loucif et al, 2008*
In Vivo	**DA** *Campbell et al., 1985* **amphetamine** *Welchsler et al.,1979* **D1/D2 - apomorphine** *Brown et al., 1978* *Hassani et al., 1999* **D1/D5 – SKF82958** *Hassani et al., 1999* **D2 - quinpirole** *Hassani et al., 1999*	**DA** *Mintz et al., 1986* *Ni et al., 2001* **D1/D2 - apomorphine** *Trugmann et al.,1993* *Kreiss et al., 1996* **D1/D5-SKF38393 ; SKF82958** *Ni et al., 2001* *Kreiss et al., 1996*	**D1/D5 – SKF82958** *Hassani et al., 1999*	**DA** *Ni et al., 2001* **D2 - quinpirole** *Hassani et al., 1999* *Ni et al., 2001* **D1/D5-SKF38393** *Ni et al., 2001*

Table 1. Overview of different publications regarding the effects of dopamine and its agonists on subthalamic activity in both intact and 6-OHDA lesioned rats.

5. Implications for Parkinson's disease treatment strategies

The existence of a direct nigrosubthalamic dopaminergic pathway is nowadays a well established fact. Moreover, dopamine receptors of both D1 and D2 like families have been shown to be present at the level of the STN. Otheiatal level, it is now clear that dopamine exerts direct effects at the level of other basal ganglia nuclei of which the STN plays a pivotal role in Parkinson's disease. Since altered neuronal output from the STN plays a central role in the pathophysiology of Parkinson's disease and overactivity of subthalamic

neurons due to the loss of dopaminergic neurons contributes to increased excitation of the main output nuclei, effects of dopaminergic drugs (still the main drug treatment for Parkinson's disease) on subthalamic neuronal activity is highly important. It has been shown in different studies that dopamine and its agonists can alter subthalamic activity in both intact and parkinsonian animals. However, discrepancies still exist regarding the effects of dopaminergic stimulation. In the pathological state, most in vitro and in vivo studies agree on an excitatory effect of dopamine at the subthalamic level. Surprisingly, this opposes the current hypothesis that dopamine receptor stimulation alleviates symptoms of Parkinson's disease by reducing STN output (DeLong, 1990). The receptor subtypes by which dopamine exerts these excitatory effects differ between studies and different effects are seen depending on the receptor subtype. Moreover, not only effects on firing rates but also effects on subthalamic firing patterns were seen after dopamine application, further strengthening the hypothesis that dopamine clearly alters neuronal output at the subthalamic level. Dopamine replacement therapy remains the standard therapy for Parkinson's disease. Most of the dopamine agonists used to treat the symptoms of Parkinson's disease are non-specific for one or the other receptor subtype. We also know that after the so-called "honeymoon period" the effective response to dopamine wears off, and that undesirable side effects, like dyskinesia, occur. Further investigation towards an even better understanding of the effects of dopamine at the subthalamic level, and the receptor subtypes involved in these effects, can lead towards the development of better targeted drugs for the treatment of Parkinson's disease. Therefore, future studies investigating the effects of selective ligands of different dopamine receptor subtypes in experimental Parkinson's disease models, combining investigation towards electrophysiological effects and effects on neurotransmitter release of these ligands at the level of the STN, are necessary for developing more specific and selective drugs to treat different stages of Parkinson's disease.

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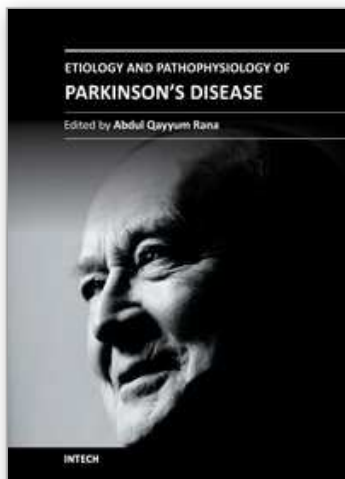
Etiology and Pathophysiology of Parkinson's Disease

Edited by Prof. Abdul Qayyum Rana

This book about Parkinson's disease provides a detailed account of etiology and pathophysiology of Parkinson's disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinson's disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinson's disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinson's disease.

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