

# Efficacy of the Deep-Brain Stimulation in Parkinson's Disease According to a Neural Network

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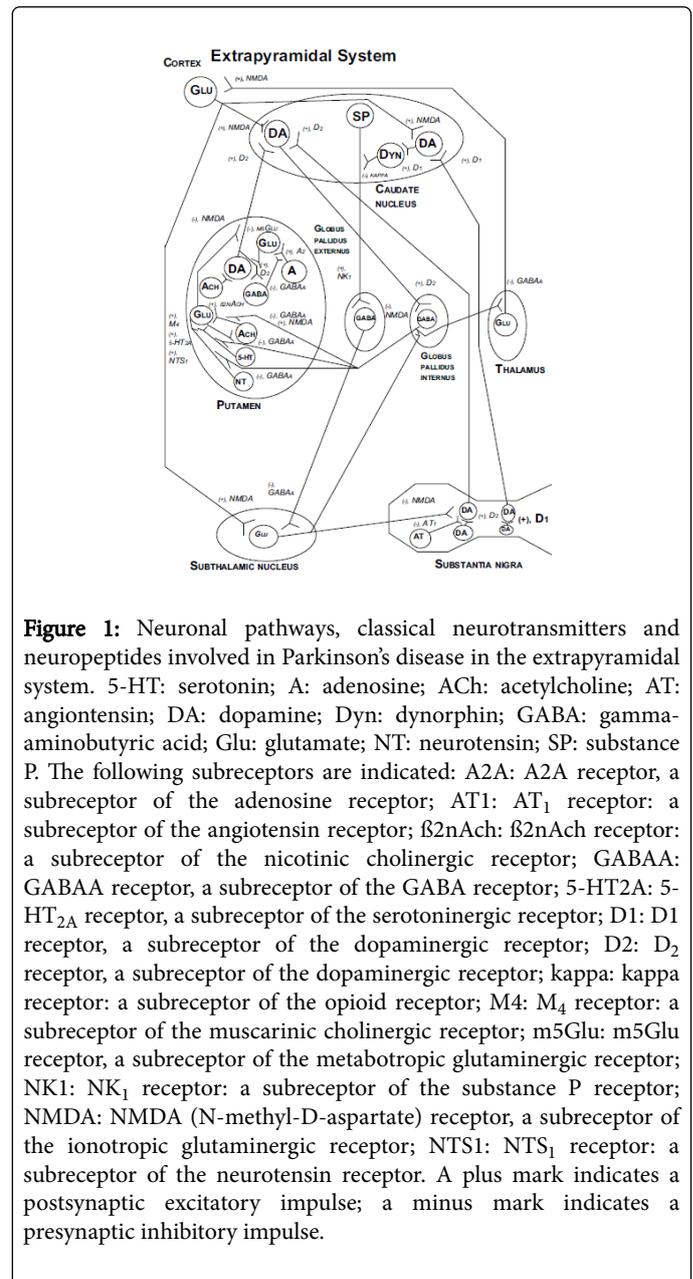
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## Introduction

Parkinson's disease is treated by l-dopa with a decarboxylase inhibitor, dopamine agonists and monoamine oxidase (MAO) or catechol-O-methyl transferase (COMT) inhibitors [1]. The high frequency stimulation of the subthalamic nucleus is a non-pharmacological method to improve motor symptoms in Parkinsonian patients [2].

## Efficacy of the Deep Brain Stimulation in Parkinson's Disease according to the Neural Networks

High frequency stimulation of the subthalamic nucleus is an efficacious treatment of PD. However, a question has not yet been answered: how the high frequency stimulation of this nucleus improves Parkinsonian movement symptoms [2]. This therapy against PD increases the spontaneous spiking and firing activity of the neurons located in the substantia nigra. According to Rosch et al., [2] a balance between NMDA/AMPA glutaminergic and GABA GABAergic neurons exists, which can lead to a net excitation or a net inhibition. A higher excitation rate was observed in 6-OHDA treated rats. According to Lafrenier-Roula et al., [2], who examined the activity of the globus pallidus and the substantia nigra in Parkinsonian patients, after a high-frequency stimulation this technique leads to an inhibition of the subthalamic nucleus and consequently to a stimulation-induced GABA release combined with an activation of the GABAergic afferents in the substantia nigra and globus pallidus internus. How can the effects of the high-frequency stimulation of the subthalamic nucleus be explained according to the neural networks suggested in the extrapyramidal system (Figure 1)? A high frequency stimulation of the subthalamic nucleus inhibits the firing rate of the glutaminergic neurons in this nucleus. Consequently, a GABA release is enabled through a reduced presynaptic inhibition via NMDA receptors occurring in the globus pallidus internus. As a consequence of the increased GABAergic inhibition via GABA<sub>A</sub> receptors in the putamen, the firing rate of M<sub>4</sub> muscarinic cholinergic, 5-HT<sub>2A</sub> serotonergic and NTS<sub>1</sub> neurotensin neurons is decreased. In the substantia nigra, through a reduced glutaminergic presynaptic inhibition via NMDA receptors, the firing rate of dopaminergic neurons is increased. The described neural networks (Figure 1) confirm the alterations of classical neurotransmitters induced by high frequency stimulation, namely a higher firing rate of dopaminergic neurons in the substantia nigra [2] and an increased release of GABA from the GABAergic efferents of the globus pallidus internus [3]. The mentioned alterations of DA, GABA and other classical neurotransmitters improve the movement disturbances in PD [2,3].



**Figure 1:** Neuronal pathways, classical neurotransmitters and neuropeptides involved in Parkinson's disease in the extrapyramidal system. 5-HT: serotonin; A: adenosine; ACh: acetylcholine; AT: angiotensin; DA: dopamine; Dyn: dynorphin; GABA: gamma-aminobutyric acid; Glu: glutamate; NT: neurotensin; SP: substance P. The following subreceptors are indicated: A2A: A2A receptor, a subreceptor of the adenosine receptor; AT1: AT<sub>1</sub> receptor: a subreceptor of the angiotensin receptor; β<sub>2</sub>nACh: β<sub>2</sub>nACh receptor: a subreceptor of the nicotinic cholinergic receptor; GABAA: GABAA receptor, a subreceptor of the GABA receptor; 5-HT<sub>2A</sub>: 5-HT<sub>2A</sub> receptor, a subreceptor of the serotonergic receptor; D1: D1 receptor, a subreceptor of the dopaminergic receptor; D2: D<sub>2</sub> receptor, a subreceptor of the dopaminergic receptor; kappa: kappa receptor: a subreceptor of the opioid receptor; M<sub>4</sub>: M<sub>4</sub> receptor: a subreceptor of the muscarinic cholinergic receptor; m5Glu: m5Glu receptor, a subreceptor of the metabotropic glutaminergic receptor; NK1: NK<sub>1</sub> receptor: a subreceptor of the substance P receptor; NMDA: NMDA (N-methyl-D-aspartate) receptor, a subreceptor of the ionotropic glutaminergic receptor; NTS1: NTS<sub>1</sub> receptor: a subreceptor of the neurotensin receptor. A plus mark indicates a postsynaptic excitatory impulse; a minus mark indicates a presynaptic inhibitory impulse.

The bilateral high-frequency stimulation of the subthalamic nucleus has often neuropsychiatric side effects such as depression which are linked to a decreased 5-HT release [4]. It has been measured the release of 5-HT and *in vivo* the firing rate of serotonergic neurons in DA-depleted rats [4]. The described therapy caused a decrease up to 25% of the extracellular levels of 5-HT in the striatum and in the medial prefrontal cortex, and a decrease of the firing rate of the midbrain raphe 5-HT neurons [4]. As described above, the increased GABAergic presynaptic inhibition via GABAA receptors in the globus pallidus internus, which is due to a reduced action of the glutaminergic neurons via NMDA receptors, reduced the activity of 5-HT<sub>2A</sub> serotonergic neurons in the putamen (Figure 1).

## Conclusion

Werner and Covenas suggest a multimodal pharmacotherapy in the treatment of Parkinson's disease. In clinical studies it has to be demonstrated if this form of pharmacotherapy improves the motor and non-motor symptoms better than the conventional pharmacotherapy. High-frequency stimulation of the subthalamic

nucleus is a method to improve above all motor symptoms in Parkinson's disease. These symptoms can be improved to a great extent in comparison to anti-Parkinsonian pharmacotherapy.

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