

Assessments in Primary Parkinson Syndrome for comparison between Mono-dopaminergic and Multi-target Anti-parkinsonian Pharmacotherapies

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Abstract

In this review, the altered functions of neurotransmitters and neuropeptides in the extrapyramidal system in primary Parkinson syndrome are pointed out. In this syndrome, an altered neurotransmitter balance in the nuclei of the extrapyramidal system with hypoactivity of the dopaminergic and GABAergic neurotransmitter systems and hypoactivity of the muscarinic cholinergic and glutamatergic neurotransmitter systems occurs. Serotonin counteracts dopamine deficiency in the putamen via 5-HT_{2A} receptors. Neuropeptides have a modulating function and influence the mentioned neurotransmitter systems. Neurotensin antagonists, at NTS₁ receptors, and antagonists, at the mu opioid receptor, could have a therapeutic function in the anti-Parkinsonian pharmacotherapy. A scheme including the possible neural combinations in the neuronal system and considering the mentioned alterations of the neuroactive substances is described.

A scientific problem to be investigated is, whether a multi-target pharmacological treatment, i.e. add-on drugs such as agonists of the β_2 nicotinic cholinergic receptor, A_{2A} adenosine antagonists, 5 metabotropic glutamatergic receptor antagonists and/or NTS₁ receptor antagonists could exert a neuroprotective effect on dopaminergic neurons and may be slow down the progression of the disease. In clinical studies with Parkinsonian patients, a main goal must be to compare a cohort of Parkinsonian patients receiving a mono-dopaminergic pharmacotherapy with patients receiving multi-target anti-Parkinsonian pharmacotherapy. The motor and cognitive functions could be assessed by assessment tools, and imaging examination techniques should be applied in order to assess the generally progressive course of the illness.

Keywords: Parkinson's disease; Pharmacotherapy; Antagonists; Dopamine

Introduction

Primary Parkinson syndrome is a progressive neurological disease. The prevalence among the persons older than 60 years is about 1%. It has been described that 80% of patients suffering from this disease showed dementia symptoms and 40% of these patients have altered cognitive functions [1,2]. An anti-Parkinson pharmacotherapy is prescribed when the main symptoms, i.e. bradykinesia, rigidity and tremor, can be observed after a neurological examination.

Parkinson's disease is the primary Parkinson syndrome, the causes of which have not yet been identified. To a small extent, susceptibility genes cause the disease. The secondary Parkinson syndrome, which may be reversible, can occur after the administration of first-generation antipsychotic drugs [2].

In primary Parkinson syndrome, dopamine depletion in the dopamine containing nuclei of the extrapyramidal system occurs, and when dopamine deficiency is more than 80%, the main motor symptoms appear [1]. In the basal ganglia, hypoactivity of dopamine and hyperactivity of acetylcholine can be found. Besides, an altered neurotransmitter balance with hypoactivity of GABAergic neurons, via GABAA receptors, and hyperactivity of glutamatergic neurons via NMDA receptors exists [3]. Moreover, neuropeptides have a

modulating function in this illness, neurotensin and cholecystokinin are found to be increased, and other neuropeptides such as substance P and dynorphin showed decreased levels [1,2]. Dopamine depletion is correlated with increased levels of alpha-synuclein in Lewy-bodies [4].

Pharmacotherapy of primary Parkinson syndrome consists in the administration of l-dopa, in combination with benserazide, a decarboxylase inhibitor, agonists of the dopamine receptors, for example rotigotine, antagonists of the muscarinic cholinergic M₄ receptor and NMDA (N-methyl-D-aspartate) antagonists [1]. Besides, agonists of the nicotinic cholinergic receptor (nACh receptor agonists), antagonists of the M₅ metabotropic glutamatergic receptor (m5Glu receptor antagonists) and antagonists of the A_{2A} adenosine receptor have an anti-Parkinsonian effect [5,6]. Moreover, 5-HT_{2A} receptor antagonists could exert a therapeutic function [7].

Analogues, agonists or antagonists of specific receptors of neuropeptides, for example pituitary adenylate cyclase-activating polypeptide (PACAP) agonists or neurotensin (NTS₁) antagonists could be administered in patients with primary Parkinson syndrome in order to know whether they improve Parkinsonian symptoms or not [8]. In patients suffering from this disease, clinical trials must be carried out to know whether a multi-target pharmacological treatment is better than the mono-dopaminergic pharmacotherapy currently used [9].

Altered functions of neurotransmitters and neuropeptides in the basal ganglia in primary Parkinson syndrome

In primary Parkinson syndrome, an altered neurotransmitter balance exists in the basal ganglia with an imbalance between dopaminergic and muscarinic cholinergic systems as well between GABAergic and glutamatergic neurons. In this section, the altered functions of the above-mentioned neuroactive substances, serotonin, adenosine and some neuropeptides are pointed out [9].

Dopamine

In primary Parkinson syndrome, cardinal symptom appear when dopamine depletion in some nuclei of the basal ganglia has a reduced activity of at least 80% [4]. Although the gold-standard in the pharmacological treatment of this illness is l-dopa, for example combined with benserazide, drugs interfering with muscarinic cholinergic, GABAergic and glutamatergic receptors exert also a therapeutic function [10]. Dopamine depletion in the basal ganglia is accompanied with hyperactivity of glutamatergic neurons in the subthalamic nucleus [11]. The neural combination between the single nuclei belonging to the extrapyramidal system will be described in the section about neural networks.

Acetylcholine

In primary Parkinson syndrome, an altered balance between the dopaminergic and the cholinergic neurotransmitter systems can be found in the basal ganglia. The interaction between the two neurotransmitter systems occurs via D₂ and D₅ receptors and via GABAergic neurons with a presynaptic inhibitory function [12].

Consequently, Parkinsonian patients can be treated with antagonists of the M₄ muscarinic cholinergic receptor and alternatively with a subcutaneous injection of scopolamine, a muscarinic cholinergic receptor antagonist [13]. In the putamen, nicotinic cholinergic neurons activate dopaminergic neurons and it has been described that β₂ nicotinic cholinergic receptor agonists (β₂ nAChR agonists) exert a postsynaptic excitatory input upon D₂ dopaminergic neurons [14]. Consequently, β₂ nAChR agonists could exert a therapeutic function [14].

Serotonin

Serotonin (5-HT), which mainly exerts an excitatory effect on different serotonin receptors, shows alterations in the basal ganglia in primary Parkinson syndrome [15]. It has been shown that dopamine deficiency is compensated by increased levels of 5-HT in the nucleus caudatus and putamen and that l-dopa induced dyskinesia is associated to an increased activity of serotonin [16]. In the putamen, an antagonism can be found between dopaminergic and serotonergic neurons. The specific 5-HT subreceptor is the 5-HT_{2A} receptor. Consequently, 5-HT_{2A} antagonists could exert anti-Parkinsonian properties and maybe improve l-dopa induced dyskinesia [17].

Glutamate

Glutamate, which acts mainly as a postsynaptic excitatory substance, i.e. excitatory neurotransmitter and partly as a presynaptic inhibitor, exerts its effect upon ionotropic receptors, for example NMDA (N-methyl-D-aspartate) receptors and metabotropic receptors. In the basal ganglia, an altered balance between the GABAergic and glutamatergic neurotransmitter systems can be found. In the putamen,

glutamatergic neurons exert a strong presynaptic inhibition upon D₂ dopaminergic neurons, via NMDA receptors.

Consequently, the increased presynaptic glutamatergic inhibition via NMDA receptors enhances dopamine deficiency [18]. In the putamen, there is a synergistic interaction between 5-HT_{2A} serotonergic and NMDA glutamatergic neurons. Consequently, 5-HT_{2A} antagonists could reduce glutamate hyperactivity [7].

A scientific problem to be investigated is whether agonists or antagonists of the metabotropic glutamatergic (mGlu) receptors might have anti-Parkinsonian effects. In animal experiments, the m5Glu receptor antagonist (2-chloro-4-((2,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1H-imidazol-4-yl)ethynyl)pyridine) CTEP exerted a therapeutic function and neuroprotective effects on the dopaminergic neurotransmitter system in the nigrostriatal system and on the noradrenergic neurotransmitter system in the locus coeruleus [19]. In the section about possible neural pathways in the basal ganglia, it will be pointed out that glutamatergic neurons exert an increased presynaptic effect via NMDA receptors on the dopaminergic neurons placed in the putamen [9].

Gamma-aminobutyric acid (GABA)

Gamma-aminobutyric acid is the main presynaptic inhibitory neurotransmitter in the central nervous system. The two corresponding receptors are GABAA and GABAB. In primary Parkinson syndrome, an imbalance occurs between the GABAergic and glutamatergic neurotransmitter systems. GABA can be found above all in the internal and external globus pallidus. It is important to know whether drugs exerting an activating effect on the GABAA receptor have a therapeutic function in this illness [20].

Other neuroactive substances: adenosine

Adenosine can be found in nuclei of the extrapyramidal system and interferes with GABAergic and muscarinic cholinergic neurons. Adenosine exerts its effects upon A_{1A} and A_{2A} receptors.

A_{2A} adenosine receptor antagonists have been shown to improve motor symptoms in Parkinson's disease without aggravating dyskinesia. A_{2A} adenosine and D₂ receptors are co-localized in the putamen showing an antagonistic interaction, via two presynaptic inhibitory receptors, namely GABAA and m5Glu receptors [21]. The neural combination between these neurons will be explained in the section of neural networks.

Dynorphin

Dyskinesia in primary Parkinson syndrome is correlated with an increased opioid neurotransmission via mu or delta receptors. Consequently opioid receptor antagonists, which bind to mu opioid receptors, might be administered as add-on drugs to treat l-dopa induced dyskinesia [22]. In the section about neural networks, it will be pointed out that dopaminergic neurons in the nucleus caudatus transmit an activating impulse via D₁ receptors to dynorphin containing neurons, which presynaptically inhibit substance P-containing neurons via mu opioid receptors [9].

Neurotensin

In primary Parkinson syndrome, it has been shown that neurotensin levels are raised in the putamen and that an increased neurotensin

activity enhanced glutamate hyperactivity and excitotoxicity and dopamine deficiency [23]. It is crucial to know whether neurotensin antagonists which act at the NTS₁ receptor could be administered as add-on drugs [24].

Substance P

Substance P is a neuropeptide which mainly acts at the NK-1 receptor. *In vitro* studies have shown that increased substance P concentrations enhanced dopamine depletion in the basal ganglia [25]. Substance P-containing neurons in the nucleus caudatus transmit an activating impulse to GABAergic neurons placed in the globus pallidus externus, via NK-1 receptors [9].

Basal ganglia neuronal circuits in primary Parkinson syndrome

According to the literature on Parkinson's disease and on the interactions of the involved neuroactive substances in the extrapyramidal system, the possible neural pathways are shown in Figure 1: dopaminergic neurons originating in the substantia nigra pars compacta, showing a low activity, transmit a weak activating potential, via D₁ and D₂ receptors, to other dopaminergic neurons placed in the nucleus caudatus. In this nucleus, dopaminergic neurons transmit a weak activating potential via D₁ receptors to dynorphin neurons, which exert a weak presynaptic inhibition via mu opioid receptors upon substance P-containing neurons. The latter neurons exert an activating potential upon GABAergic neurons in the globus pallidus externus via NK-1 receptors.

The GABAergic neurons weakly affect glutamatergic neurons in the subthalamic nucleus by an inhibitory influence. In the nucleus caudatus, dopaminergic neurons exert a weak postsynaptic excitatory potential via D₂ receptors to GABAergic neurons placed in the globus pallidus internus. Glutamatergic neurons in the nucleus subthalamicus exert a strong presynaptic inhibition via NMDA receptors upon dopaminergic neurons in the substantia nigra and upon GABAergic neurons in the globus pallidus internus.

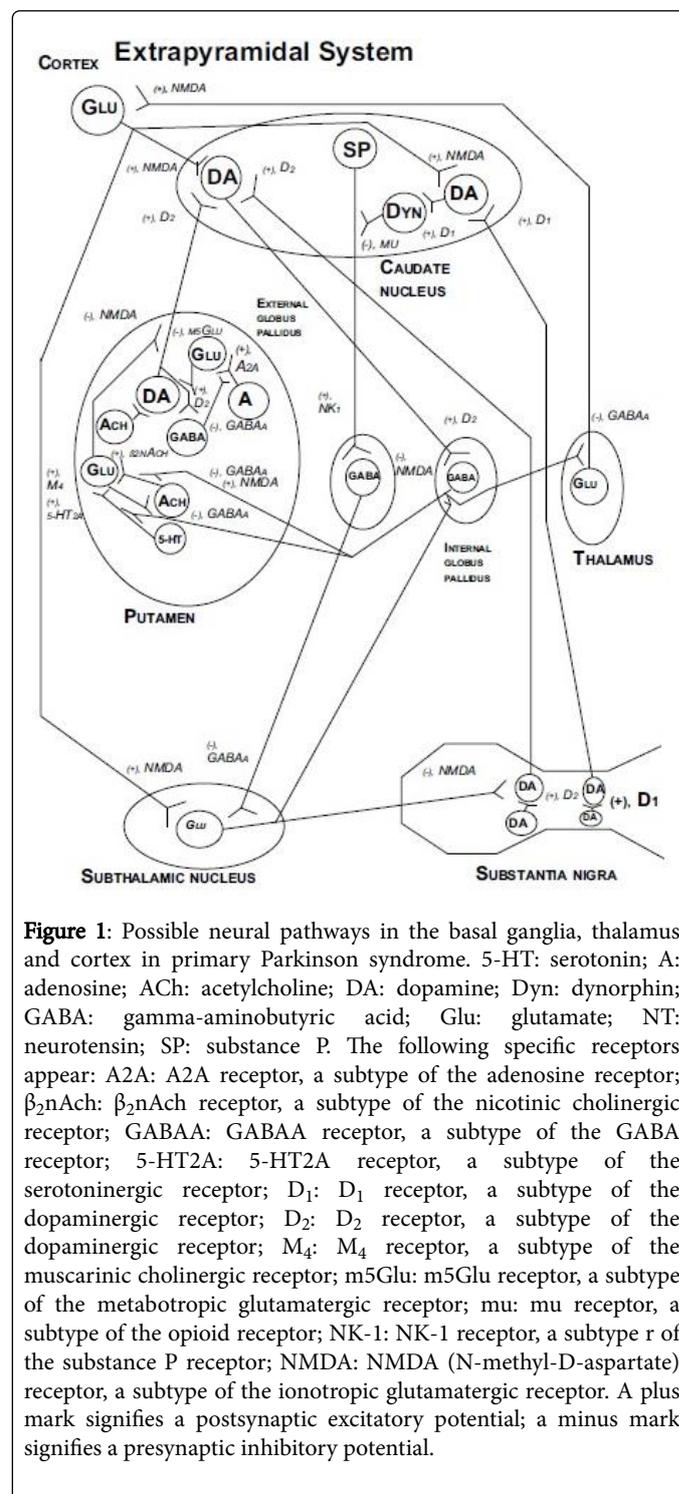
GABAergic neurons, in the latter nucleus, presynaptically inhibit glutamatergic neurons in the thalamus, which transmit a postsynaptic excitatory potential to cortical glutamatergic neurons. The latter neurons exert a postsynaptic excitatory potential upon dopaminergic neurons in the nucleus caudatus. In the globus pallidus internus, GABAergic neurons exert a weak presynaptic inhibition upon muscarinic cholinergic and serotonergic neurons placed in the putamen.

Muscarinic cholinergic and serotonergic neurons, in their turn, send a strong activating potential, respectively via M₄ and 5-HT_{2A} receptors to glutamatergic neurons, which exert a strong presynaptic inhibition upon dopaminergic neurons.

Nicotinic cholinergic neurons transmit a postsynaptic excitatory potential via β₂ nicotinic cholinergic receptors to dopaminergic neurons. In the putamen, dopaminergic neurons transmit a weak activating potential via D₂ receptor to GABAergic neurons, which exert a weak presynaptic inhibition upon adenosine neurons.

Adenosine neurons send a strong postsynaptic excitatory potential, via A_{2A} receptor to glutamatergic neurons, which exert a strong presynaptic inhibition upon dopaminergic neurons via m5Glu receptors. Dopaminergic neurons in the nucleus caudatus send a

postsynaptic excitatory potential to dopaminergic neurons in the nucleus caudatus, via D₂ receptors.



Conventional and newer anti-Parkinsonian drugs

Conventional pharmacotherapy to treat patients with primary Parkinson syndrome consists in the administration of l-dopa, combined with benserazide, a decarboxylase inhibitor or with agonists of the dopamine receptors (e.g., pramipexole). In some cases, these

anti-Parkinsonian drugs are combined with COMT or MAO-B inhibitors, which inhibit dopamine degradation [26]. Additionally, prescribed NMDA antagonists (e.g., amantadine) improve motor symptoms but have side effects such as depression and psychosis [27].

According to the neural pathways described, the following add-on drugs could be administered to treat patients with primary Parkinson syndrome:

- Antagonists of m5Glu receptors, which augment dopamine contents by reducing the presynaptic glutamatergic inhibition [19].
- A2A adenosine antagonists, which decrease the activity of glutamatergic neurons inhibiting the dopaminergic neurons [21].
- β_2 nACh receptor agonists, which activate dopaminergic neurotransmission [14].
- Antagonists of the 5-HT_{2A} receptor, which decrease the presynaptic glutamatergic inhibition of dopaminergic neurons [17].
- Antagonist of the NTS₁ receptor, which activate dopaminergic neurotransmission by decreasing the presynaptic glutamatergic inhibition [24].

Multi-target anti-Parkinsonian pharmacotherapy

It should be examined in clinical trials whether a multi-target pharmacological treatment of Parkinsonian patients is better than the exclusive dopaminergic treatment. Could the administration of add-on drugs such as β_2 nACh receptor agonists, antagonists of the m5Glu receptor, antagonists of the A2A receptor or NTS₁ receptor antagonists exert a neuroprotective effect on dopaminergic neurons? Could a multi-target pharmacological treatment of primary Parkinson syndrome stabilize altered activities of neurotransmitters in the basal ganglia and slow down the disease process? It might be possible to combine dopaminergic drugs with antagonists of the A2A receptor, with antagonists of the m5Glu receptor, with antagonists of the NMDA receptor and/or with antagonists of the 5-HT_{2A} receptor. In addition, 5-HT_{2A} antagonists exert a light antipsychotic effect.

Assessments of Parkinsonian symptoms

Our aim was to compare a dopaminergic pharmacotherapy, for example administering l-dopa (combined with an inhibitor that blocks the dopamine degradation, with agonists of the dopamine receptor or with COMT inhibitors) with a multi-target anti-Parkinsonian pharmacotherapy. Some assessment procedures to examine motor functions, quality of life, cognitive functions and neuropsychiatric symptoms are described.

Altered motor functions are already diagnosed in the stage I of Parkinson's disease. The following assessment procedures, gait speed, Berg balance assessment, functional gait assessment, and unified Parkinson's disease rating scale motor section can be evaluated in the case that motor functions can be kept stable with a combined pharmacotherapy-physical therapy. Millage et al. [28] examined nine patients showing the stage I of Parkinson's disease and showed that a specific physical therapy achieved an improvement of motor functions at a minimal clinical level in eight of these patients.

A total of 34% of the Parkinsonian patients with a stage 1 show a mild cognitive impairment. It is of importance to administer an objective assessment to examine cognitive functions. The Montreal Cognitive Assessment (MoCA) shows a big specificity and a reduced sensitivity in detecting mild cognitive impairment in Parkinsonian

patients. Nevertheless, patients with a stage 1 Parkinson's disease should be performed in order to diagnose, a mild cognitive impairment [29].

Some imaging examination techniques are available in order to detect alterations of brain metabolism in early Parkinson's disease. Different magnetic resonance imaging can perform morphometric analyses. Single photon emission computed tomography can detect alterations of the dopaminergic neurotransmitter system in the extrapyramidal system. Positron emission tomography can analyse nigrostriatal functions, glucose metabolism, amyloid and tau molecular imaging and neuroinflammation. Transcranial sonography can examine echogenicity in the basal ganglia [30]. It is essential to control the development of the dopamine reduction in the basal ganglia in Parkinsonian patients in the course of the disease.

Comparison of a mono-dopaminergic pharmacotherapy and a multi-target anti-Parkinsonian pharmacotherapy

We suggest to compare cohorts of patients suffering from primary Parkinson syndrome: the first group could be administered dopaminergic drugs, for example l-dopa in combination with an enzyme inhibitor, dopamine agonists or with inhibitors of the COMT enzyme, whereas the second group should obtain a combination of different anti-Parkinsonian drugs, for example l-dopa combined with m5Glu or A2A receptor antagonists or l-dopa combined with antagonists of the NMDA or 5-HT_{2A} receptors. Assessment tools should be used to examine motor functions, cognitive function, and imaging examination techniques should be performed in order to control the development of the disease [28-30]. In the second cohort of Parkinsonian patients, l-dopa with benserazide could be combined with amantadine, an NMDA receptor antagonist and M100907, a 5-HT_{2A} receptor antagonist [7]. An alternative to this multi-target anti-Parkinsonian pharmacotherapy could be the combination of l-dopa and benserazide with 2-chloro-4-((2,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1H-imidazol-4-yl)ethynyl)pyridine (CTEP), a m5Glu receptor antagonist and ST1535, an A2A adenosine antagonist [19,31]. It might be possible to administer the dopaminergic and non-dopaminergic drugs alternatively at different times of the day, for example, the dopaminergic drugs at 8 am and at 5 pm and the non-dopaminergic drugs at 12 am and at 9 pm. Assessment procedures to examine motor functions and imaging examination techniques, for example single photon emission computed tomography, which examines the dopaminergic neurotransmitter system in the basal ganglia, should be performed in order to examine the course of the disease in both groups [28,30].

Conclusion

We summarized the altered activities of the neuroactive substances in the basal ganglia. In this neural system a disturbed neurotransmitter balance between the dopaminergic and muscarinic cholinergic neurotransmitter systems, on one hand, and the GABAergic and glutamatergic neurotransmitter systems, on the other hand, can be found. In the putamen, serotonin hyperactivity via 5-HT_{2A} receptor enhances dopamine depletion. Neuropeptides have a modulating function in this illness. Neurotensin hyperactivity is found in the putamen via NTS₁ receptors. A neural network is described in the extrapyramidal system, in which the agonistic or antagonistic effects on neurotransmitters and neuropeptides are considered. Might the administration of add-on drugs, for example β_2 nACh receptor agonists, m5Glu receptor antagonists, antagonists of the A_{2A} receptor

and/or NTS₁ receptor antagonists exert an activating effect on dopaminergic neurotransmission and influence the course of the disease? In clinical trials, one study goal could be whether an add-on pharmacotherapy in patients with primary Parkinson syndrome could improve physical and cognitive symptoms in comparison to the standard pharmacotherapy with exclusive dopaminergic drugs. The development of the disease should be controlled, for example by assessment tools to examine motor and cognitive functions and by imaging examination techniques.

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