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Classical Neurotransmitters and Neuropeptides involved in Parkinson's Disease: A Multi-Neurotransmitter System

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Abstract

Parkinson's disease is a neurodegenerative disease with motor and non-motor symptoms. In Parkinson's disease, a neurotransmitter imbalance occurs in the extrapyramidal system with a dopamine and GABA deficiency and an acetylcholine and glutamate surplus. Other classical neurotransmitters such as serotonin, the neuroactive substance adenosine and neuropeptides such as dynorphin and substance P are also involved in the pathophysiology of the disease. Here, we describe the alterations of the involved neuroactive substances and the relationships between them in the extrapyramidal system. From the findings previously reported in the literature, here a neural network is developed in the extrapyramidal system. Additional anti-Parkinsonian drugs and their actions in the neural network are also pointed out, since a multimodal pharmacotherapy of the disease might improve its outcome.

Keywords: Parkinson's disease; Extrapyramidal system; Neural network; Dopamine; Serotonin; ABA, glutamate; Neuropeptides

Introduction

Parkinson's disease (PD) is a neurodegenerative disease that affects up to 1% of the people older than 60 years, more often men than women [1]. Meanwhile, it is known that 40% of the Parkinsonian patients develop dementia and 80% of them suffer from mild cognitive impairment [2]. An anti-Parkinsonian pharmacotherapy is started when the cardinal symptoms akinesia, rigidity and tremor appear. In PD, the above mentioned symptoms occur if dopamine (DA) deficiency is up to 80% in the substantia nigra pars compacta and in the basal ganglia, i.e. the putamen and the caudate nucleus [2]. However, other classical neurotransmitters such as acetylcholine, glutamate and GABA also play a role in the pathophysiology of the disease. In fact, a neurotransmitter imbalance exists in the extrapyramidal system with a DA and GABA deficiency and an acetylcholine and glutamate surplus. In this sense, DA and acetylcholine act as postsynaptic excitatory neurotransmitters: DA exerts its effect upon D1 and D2 receptors and acetylcholine upon muscarinic and nicotinic cholinergic subreceptors [3]. Besides, via GABAA receptors, GABA exerts a reduced presynaptic inhibitory function and glutamate exerts an excitotoxic effect and a presynaptic inhibitory action via NMDA and metabotropic glutaminergic receptors [3]. Neuropeptides are as well involved in the pathophysiology of PD [4,5]. In this sense, neurotensin and cholecystokinin show increased levels in the extrapyramidal system, and dynorphin and substance P have decreased levels [2]. The relationship between the formation of Lewy bodies containing alpha-synuclein and the development of dementia will be also pointed out [6]. Considering the current available literature, here a neural network in the extrapyramidal system is developed. This network acts as a multi-neurotransmitter system. From the neural network suggested, it can be concluded that a multimodal pharmacotherapy could be efficacious in the treatment of the disease, and that the therapeutic efficacy of additional therapeutic options, such as A_{2A} adenosine antagonists, subtype 5 of metabotropic glutaminergic receptor (m5GluR) antagonists or 5-HT_{2A} antagonists might be taken into consideration [7,8].

Alterations of classical neurotransmitters and neuropeptides in Parkinson's disease

In PD, in the extrapyramidal system, a neurotransmitter imbalance between dopaminergic and muscarinic cholinergic neurons occurs as well as between GABAergic and glutaminergic neurons. Here, in order to develop a neural network, the alterations of adenosine and classical neurotransmitters (e.g., DA, acetylcholine, serotonin (5-HT), GABA, glutamate) are described. Moreover, the alterations of neuropeptides (cholecystokinin, dynorphin, neurotensin, substance P) are described.

Dopamine

In PD, the loss of dopaminergic neurons in the substantia nigra pars compacta is due to the oxidative stress and partly to the susceptibility genes [6]. Alpha-synuclein could be detected in the perikarya and processes of dopaminergic neurons, in which Lewy bodies can be found [6]. In the basal ganglia, it has been reported that not only dopaminergic neurons, but also muscarinic cholinergic neurons, GABAergic neurons and glutaminergic neurons are involved in a neural network [9]. After treatment of PD with l-dopa or dopamine agonists, the Parkinsonian motor symptoms improved, however dyskinesia occurred. An additional administration of MAO-B (monoamine oxidse B) or COMT (catechol O-methyl transferase) inhibitors or of non-dopaminergic agents showed a therapeutic effect upon dyskinesias [10].

Acetylcholine

In PD, a dopaminergic-cholinergic neurotransmitter imbalance occurs between DA deficiency, via D2 receptors, and a surplus of muscarinic cholinergic neurons via M4 receptors [11]. Scopolamine (subcutaneous injection), an antagonist of muscarinic cholinergic receptors was used to treat a Parkinsonian patient who could no longer take an oral medication [12]. Dopaminergic and muscarinic cholinergic neurons exert an antagonistic interaction between each other, which is enabled through presynaptic GABAergic neurons via GABAA receptors and glutaminergic neurons via NMDA receptors. However, nicotinic cholinergic (nAch) neurons partly activate dopaminergic neurons [11]. NAch neurons activate dopaminergic neurons in the putamen via ß2 receptors. Thus, ß2 nAch agonists could be of therapeutic value in the treatment of PD [13]. Forty percent of Parkinsonian patients develop dementia. This could be due to the cholinergic loss in the nucleus basalis of Meynert, where the inputs to the cerebral cortex are originated [14].

Serotonin

In l-dopa treated 6-hydroxy-dopamine lesioned rats, the 5-HT hyperactivity in the striatum and the caudate nucleus is associated with dyskinesias. In this sense, DA loss is compensated by 5-HT hyperactivity [15]. It has been showed a dopaminergic-serotonergic interaction in the putamen through glutaminergic neurons via NMDA receptors and that 5-HT exerts its function via 5-HT_{2A} receptors [16]. A question arises, whether 5-HT_{2A} antagonists could have anti-Parkinsonian properties and could improve l-dopa induced dyskinesias [16]. An additional administration of 5-HT_{2A} antagonists could not only improve dyskinesias, but also improve psychotic symptoms [16].

GABA

GABA exerts a presynaptic inhibitory function in the globus pallidus internus and externus and in the striatum via $GABA_A$ and $GABA_B$ receptors [17]. While the globus pallidus internus is an output nucleus, the globus pallidus externus is an input nucleus [17]. DA deficiency is enhanced by the GABA hypofunction, while there is an antagonistic interaction between AMPA/NMDA glutaminergic neurons and $GABA_A$ receptors [18]. Drugs enhancing GABAergic neurotrasmission with an agonistic effect at $GABA_A$ receptors could be of therapeutic value in the treatment of PD.

Glutamate

In PD exists a GABAergic glutaminergic neurotransmitter imbalance in the extrapyramidal system with a GABA deficiency and a glutamate hyperactivity or excitotoxicity [4]. In the putamen, glutaminergic neurons could strongly inhibit presynaptically D_2 dopaminergic neurons via NMDA receptors and thus these neurons could enhance DA deficiency [3,4]. NMDA antagonists have antidyskinetic effects [19]. Metabotropic glutaminergic neurons are also of importance in the treatment of PD [20]. In this sense, antagonists of m5GluR (e.g., 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl] pyridine) have a protective effect on dopaminergic neurons and ameliorate Parkinsonian motor symptoms [20]. In the putamen, metabotropic glutaminergic neurons, which are strongly activated by adenosine neurons via A2A receptors, could strongly inhibit dopaminergic neurons via m5Glu receptors (Figure 1).

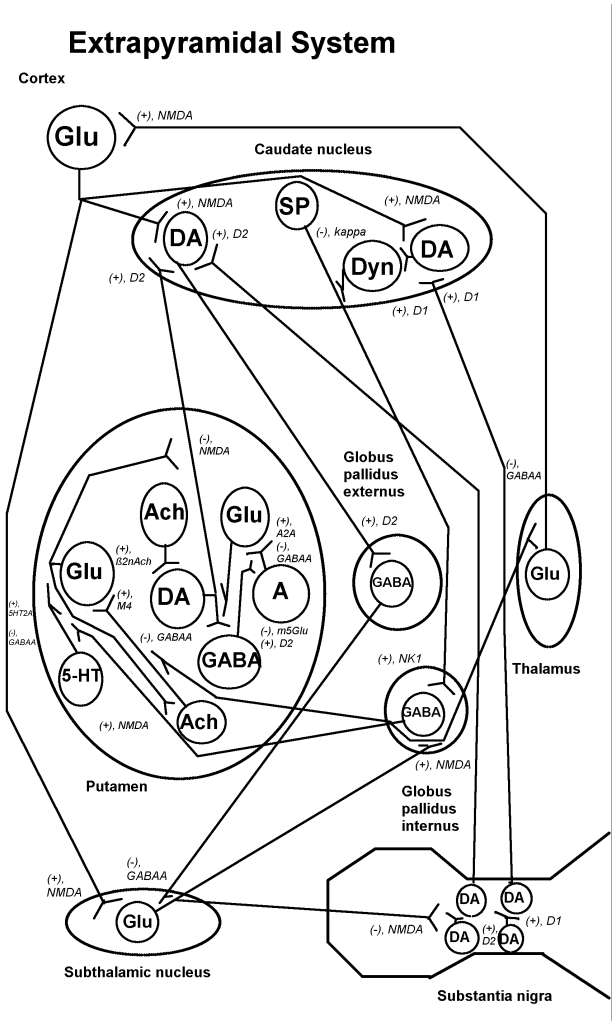

Figure 1: Neural networks, classical neurotransmitters and neuropeptides involved in Parkinson's disease. Ach: acetylcholine; A: adenosine; A2A: a subreceptor of the adenosine receptor; ß2nAch: a subreceptor of the nicotinic cholinergic receptor; DA: dopamine; D1: D_1 receptor, a subreceptor of the dopamininergic receptor; D2: D_2 receptor, a subreceptor of the dopamininergic receptor; Dyn: dynorphin; GABA: gamma-aminobutyric acid; GABAA: $GABA_A$ receptor, a subreceptor of the GABAergic receptor; Glu: glutamate; 5-HT: serotonin; 5-HT2A: 5-HT_{2A} receptor, a subreceptor of the serotonergic receptor; kappa: a subreceptor of the dynorphin receptor; m5Glu: m5Glu receptor, a subreceptor of the metabotropic glutaminergic receptor; NK1: a subreceptor of the tachykinin receptor; NMDA: N-methyl-D-aspartate receptor; SP: substance P. A plus mark indicates a postsynaptic excitatory impulse, and a minus mark indicates a presynaptic inhibitory impulse.

Cholecystokinin

In 6-hydroxy-dopamine lesioned rats, alterations in the level of some neuropeptides have been found. In this sense, cholecystokinin (CCK) levels have been reported to be increased in the striatum [21]. It

is known that, in contrast to CCK_A antagonists, antagonists of the CCK_B receptor could exert beneficial therapeutic effects [22].

Dynorphin

In the substantia nigra exists an inverse correlation between DA deficiency and the increased activity of dynorphin neurons which show a high affinity for both mu and/or delta opioid receptors [23]. In the neural network suggested here, it will be shown that dynorphin neurons in the caudate nucleus receive a weak activating input from the D_1 dopaminergic neurons located in the substantia nigra, and that these dynorphinergic neurons via kappa receptors presynaptically inhibit substance P neurons [5].

Neurotensin

It has been described in PD an increased activity of neurotensin in the striatum which enhances both the excitotoxicity of glutamate, via NMDA receptors, and the DA deficiency [24]. In the future, it should be examined whether NTS_1 receptor antagonists could exert a beneficial therapeutic effect in the treatment of PD [25].

Substance P

Substance P is an undepeptide belonging to the tachykinin family of peptides and mainly exerts its function via the NK_1 receptor. In the substantia nigra, the release of DA and the concentration of substance P are positively correlated [26]. In the neural network presented here, substance P-containing neurons in the caudate nucleus, which are inhibited by dynorphin neurons via kappa receptors, weakly activate GABAergic neurons located in the globus pallidus internus [27].

Other neuroactive substances: adenosine

Adenosine is a neuroactive substance located in the basal ganglia which influences the release of GABA and acetylcholine [28]. Adenosine A_{2A} antagonists have been proved to ameliorate motor symptoms in PD without worsening dyskinesias [28]. In the putamen, an antagonistic interaction between D_2 dopaminergic neurons and A_{2A} adenosine neurons occurs: A_{2A} adenosine neurons strongly activate glutaminergic neurons which strongly inhibit D_2 dopaminergic neurons via m5GluR. The D_2 dopaminergic neurons weakly activate GABAergic neurons which, via $GABA_A$ receptors, inhibit adenosine neurons [29].

Alpha-synuclein formation and dementia in Parkinson's disease

In PD, Lewy bodies containing A53T alpha-synuclein have been described [30]. It has been reported that reduced DA levels are correlated with the overexpression of alpha-synuclein [30]. Mice with an overexpression of A53T alpha-synuclein showed a reduced neurogenesis in the olfactory bulb and the substantia nigra [31].

Forty percent of the patients with PD develop dementia and 85% of these patients show a mild cognitive impairment [14]. DA deficiency in the substantia nigra pars compacta causes the motor symptoms, whereas acetylcholine deficiency which starts in the nuclues basalis of Meynert can induce dementia symptoms [14]. The appropriate treatment of dementia in Parkinson's disese is the administration of rivastagmine, a cholinesterase inhibitor which increases acetylcholine levels [32].

Neural networks in the extrapyramidal system

The basal ganglia are characterized by their complex neural networks. The following nuclei, namely the striatum (caudate nucleus and putamen), the subthalamic nucleus, the external and internal globus pallidus and the substantia nigra are involved in these neural networks [33]. According to the available literature [3,4,11,13,16,19,20,26-28,33,34], the neural networks can be described as follows (see Figure 1). In the substantia nigra pars compacta, dopaminergic neurons via D_1 and D_2 receptors send projections to dopaminergic neurons located in the caudate nucleus. The D_1 dopaminergic neurons weakly activate dynorphin neurons which presynaptically inhibit via kappa receptors substance P neurons. The latter neurons transmit a weak activiting impulse via NK_1 receptor to GABAergic neurons in the globus pallidus internus [26]. The D_2 dopaminergic neurons located in the caudate nucleus weakly activate GABAergic neurons in the globus pallidus externus which weakly inhibit, via $GABA_A$ receptors, glutaminergic neurons located in the nucleus subthalamicus [34]. The latter neurons strongly inhibit dopaminergic neurons in the substantia nigra and thus enhance DA deficiency. Besides, they activate GABAergic neurons in the globus pallidus internus. The GABAergic neurons in this nucleus inhibit presynaptically glutaminergic neurons in the thalamus which activate other glutaminergic neurons located in the cortex. The cortical glutaminergic neurons activate, via NMDA receptors, D_1 and D_2 dopaminergic neurons located in the caudate nucleus and glutaminergic neurons located in the nucleus subthalamicus [19]. The GABAergic neurons in the globus pallidus internus inhibit presynaptically, via $GABA_A$ receptors, muscarinic cholinergic and serotonergic neurons in the putamen. These muscarinic cholinergic and serotonergic neurons transmit a strong activating impulse via M_4 and 5-HT_{2A} receptors to glutaminergic neurons which strongly inhibit D_2 dopaminergic neurons via NMDA receptors [11,16]. Nicotinic cholinergic neurons weakly activate dopaminergic neurons via $ß_2$ receptors, and adenosine neurons activate via A_{2A} receptors glutaminergic neurons which, via the subtype 5 of metabotropic glutaminergic neurons, strongly inhibit D_2 dopaminergic neurons [13, 20,28]. The D_2 dopaminergic neurons in the putamen are connected to other D_2 dopaminergic neurons located in the caudate nucleus.

Additional therapeutic options in the treatment of Parkinson's disease

In addition to l-dopa combined with a decarboxylase inhibitor, the following anti-Parkinsonian drugs could also be administered according to the neural networks described: DA agonists, inhibitors of enzymes degrading DA (e.g. MAO(B) and COMT inhibitors), M_4 antagonists and NMDA antagonists.

In the future, it should be also examined whether additional anti-Parkinsonian pharmacotherapies could be applied, for example:

- m5GluR antagonists, which increase DA levels through a reduced presynaptic inhibition [20].
- A_{2A} adenosine antagonists, which reduce the glutaminergic presynaptic inhibition of dopaminergic neurons via m5Glu receptors [28].
- $ß_2$nAch agonists, which stimulate the $ß_2$ subreceptor of nicotinic cholinergic receptors and also activate dopaminergic neurons in the putamen [13].
- 5-HT_{2A} antagonists, which block the 5-HT_{2A} subreceptor of serotonergic neurons in the putamen, reduce the glutaminergic

presynaptic inhibition of dopaminergic neurons via NMDA receptors and ameliorate dyskinesias by counteracting D_2 DA deficiency. Besides 5-HT_{2A} antagonists have a slight antipsychotic effect [16].

Conclusion

We have focused our review on the alterations of classical neurotransmitters (DA, acetylcholine, 5-HT, GABA, glutamate), adenosine and neuropeptides (cholecystokinin, dynorphin, neurotensin, substance P) in PD and we have also reported the functional relationships between them. In the extrapyramidal system, neural networks have been developed and the relationships between the mentioned neuroactive substances and the existing dopaminergic-cholinergic and GABAergic-glutaminergic neurotransmitter imbalances have been taken into consideration. The neural networks suggested here have been taken from the results published in laboratory animals and they still need to be confirmed in humans. In the neural networks, 5-HT hyperactivity via 5-HT_{2A} receptors, glutamate excitotoxicity via m5Glu receptors, adenosine hyperactivity via A_{2A} receptors and acetylcholine hypoactivity via nAchß$_2$ receptors are included. Since a multimodal pharmacotherapy can improve the course of the disease, some additional pharmacological options are mentioned and justified according to the suggested neural networks. Two examples of a multimodal anti-Parkinsonian pharmacotherapy could be given: It could be possible to combine l-dopa or dopamine agonists with A_{2A} adenosine antagonists and m5GluR antagonists or to combine l-dopa or dopamine agonists with NMDA antagonists and 5-HT_{2A} antagonists. In the second example, these combined anti-Parkinsonian drugs have a synergistic effect. NMDA antagonists could cause psychotic symptoms as an adverse effect, while 5-HT_{2A} antagonists exert a slight antipsychotic effect. It remains to be examined the clinical efficacy of such drugs and to investigate in-depth the neural networks suggested in the extrapyramidal system.

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