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 glutamnergic receptors [3]. Neuropeptides are as well involved in the pathophysiology of PD [4,5]. In this sense, neotensin 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 alphasyneuclein 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 A2A adenosine antagonists, subtype 5 of metabotropic glutaminergic receptor (m5Glur) antagonists or 5-HT2A 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 glutamnergic 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, neotensin, 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 oxidase 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-HT2A receptors [16]. A question arises, whether 5-HT2A antagonists could have anti-Parkinsonian properties and could improve l-dopa induced dyskinesias [16]. An additional administration of 5-HT2A 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 neurotransmission 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 D2 dopaminergic neurons via NMDA receptors and thus these neurons could enhance DA deficiency [3,4]. NMDA antagonists have antidyokinetic 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]ethylnyl] 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).

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].
is known that, in contrast to CCK₂ receptors, antagonists of the CCK₈ 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 D₂ dopaminergic neurons located in the substantia nigra, and that these dynorphinergic neurons via kappa receptors presynaptically inhibit substance P neurons [5].

**GABAergic neurons located in the globus pallidus internus** [27].

**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 NT₁ receptors antagonist could exert a beneficial therapeutic effect in the treatment of PD [25].

**Substance P**

Substance P is an undopeptide belonging to the tachykinin family of peptides and mainly exerts its function via the NK₁ 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 A₂A antagonists have been proved to ameliorate motor symptoms in PD without worsening dyskinesias [28]. In the putamen, an antagonistic interaction between D₂ dopaminergic neurons and A₂A adenosine neurons occurs: A₂A adenosine strongly activate glutaminergic neurons which strongly inhibit D₂ dopaminergic neurons via mGluR. The D₂ 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 nucleus basalis of Meynert can induce dementia symptoms [14]. The appropriate treatment of dementia in Parkinson’s disease 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 D₁ and D₂ receptors send projections to dopaminergic neurons located in the caudate nucleus. The D₂ dopaminergic neurons weakly activate dynorphin neurons which presynaptically inhibit via kappa receptors substance P neurons. The latter neurons transmit a weak activating impulse via NK₁ receptor to GABAergic neurons in the globus pallidus internus [26]. The D₂ 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 located in the cortex. The cortical glutaminergic neurons activate, via NMDA receptors, D1 and D2 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 serotoninergic neurons in the putamen. These muscarinic cholinergic and serotoninergic neurons transmit a strong activating impulse via M₁ and 5-HT₂A receptors to glutaminergic neurons which strongly inhibit D₂ dopaminergic neurons via NMDA receptors [11,16]. Nicotinic cholinergic neurons weakly activate dopaminergic neurons via β₂ receptors, and adenosine antagonists, which block the 5-HT₂A receptors, glutaminergic neurons which, via the subtype 5 of metabotropic glutaminergic neurons, strongly inhibit D₂ dopaminergic neurons [13, 20,28]. The D₂ dopaminergic neurons in the putamen are connected to other D₂ 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), M₄ 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].
- A₂A adenosine antagonists, which reduce the glutaminergic presynaptic inhibition of dopaminergic neurons via m5Glu receptors [28].
- β₂ACh agonists, which stimulate the β₂ subreceptor of nicotinic cholinergic receptors and also activate dopaminergic neurons in the putamen [13].
- 5-HT₂A antagonists, which block the 5-HT₂A subreceptor of serotoninergic neurons in the putamen, reduce the glutaminergic...
References

1. Werner FM, Coveñas R (2005) Classical neurotransmitters and neupeptides involved in Parkinson’s disease. Curr Top Prot Pept Res 4: 75-84.

2. Varanese SI, Birnbaum Z, Rossi R, Di Rocco A (2011) Treatment of advanced Parkinson’s disease. Parkinsons Dis 2010: 480260.

3. Werner FM (2007) Classical neurotransmitters involved in Parkinson’s disease. J Neural Transm 114:1-XXX.

4. Werner FM, Covéñas R (2011) Classical neurotransmitters and neupeptides involved in generalized epilepsy: a focus on antiepileptic drugs. Curr Med Chem 18: 4933-4948.

5. Werner FM, Covéñas R (2012) Possible therapeutic options in Parkinson’s disease according to a neuronal network. Neurologie & Rehabilitation 18: 420-421.

6. Tapia-González S, Giráldez-Pérez RM, Cuartero MI, Casarejos MJ, Mené MÁ, et al. (2011) Dopamine and ß-synuclein dysfunction in Sma23 null mice. Mol Neurodegeneration 6:72.

7. Grégoire L, Morin N, Ouattara B, Gasparini F, Bilbe G, et al. (2011) The acute antiparkinsonian and antidysesthetic effect of AFQ056, a novel metabotropic glutamate receptor type 5 antagonist, in L-Dopa-treated parkinsonian monkeys. Parkinsonism Relat Disord 17: 270-276.

8. Ansah TA, Ferguson MC, Nayyar T (2011) The 5-HT2A(2A) Receptor Antagonist M100907 Produces Antiparkinsonian Effects and Decreases Striatal Glutamate. Front Syst Neurosci 5: 48.

9. Rice ME, Patel JC, Cragg SJ (2011) Dopamine release in the basal ganglia. Neuroscience 198: 112-137.
30. Kurz A, Double KL, Lastres-Becker I, Tozzi A, Tantucci M, et al. (2010) A53T-alpha-synuclein overexpression impairs dopamine signaling and striatal synaptic plasticity in old mice. PLoS One 5: e11464.

31. Peng J, Andersen JK (2011) Mutant α-synuclein and aging reduce neurogenesis in the acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. Aging Cell 10: 255-262.

32. Werner F-M, Covenas R (2009) How to treat dementia in Parkinson's disease?. J Neural Transm 116: 233.

33. Miguelez C, Morera-Herreras T, Torrecilla M, Ruiz-Ortega JA, Ugedo L (2014) Interaction between the 5-HT system and the basal ganglia: functional implication and therapeutic perspective in Parkinson's disease. Front Neural Circuits 8: 21.

34. Gajcy K, Lochyński S, Librowski T (2010) A role of GABA analogues in the treatment of neurological diseases. Curr Med Chem 17: 2338-2347.