

Treatment of Dementia in Parkinsonian Patients

Felix-Martin Werner^{1,2*} and Rafael Coveñas²

¹Higher Vocational School of Elderly Care and Occupational Therapy, Euro Academy Pößneck, Germany

²Laboratory of Neuroanatomy of the Peptidergic Systems, University of Salamanca, Spain

*Corresponding author: Felix-Martin Werner, University of Salamanca, Instituto de Neurociencias de Castilla y León, Spain, Tel: +34923294400; E-mail: felixm-werner@versanet.de

Rec date: Jul 21, 2016; Acc date: Aug 04, 2016; Pub date: Aug 06, 2016

Copyright: © 2016 Werner FM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Among the patients with Parkinson's disease, 85% show symptoms of a mild cognitive impairment and 40% develop criteria of dementia. Increased levels of glutamate, noradrenaline and serotonin can be found. Diagrams of neural pathways in the extrapyramidal system and hippocampus and temporal cortex are described and compatible treatments for both syndromes are derived. Besides a conventional treatment with the cholinesterase inhibitor, NMDA antagonists, in combination with a decarboxylase inhibitor and selegiline could be administered additionally.

Keywords: Acetylcholine; Dementia; Dopamine; Dopamine agonist; Extrapyramidal system; Glutamate; Hippocampus; l-dopa; Parkinson's disease; Rivastigmine

Introduction

Parkinson's disease is a neurodegenerative disease with movement disturbances and mental dysfunction [1]. Among the patients with Parkinson's disease, 85% show symptoms of a mild cognitive impairment and 40% develop criteria of dementia [2]. A lack of dopamine in the pars compacta of the substantia nigra leads to the Parkinsonian motor-symptoms, while an acetylcholine decline, which begins in the nucleus basalis of Meynert, can be the cause of the dementia symptoms [2]. The alteration in neurotransmitters is associated with a major formation of fibrillary tangles and senile plaques [3]. In Parkinsonian patients showing dementia a neurotransmitter alteration occurs in the hippocampus and temporal cortex. In this syndrome, an acetylcholine and gamma-aminobutyric acid deficiency and a noradrenaline and glutamate surplus can be found in the mentioned brain areas. Diagrams of neural pathways in the extrapyramidal system and hippocampus and temporal cortex are described and compatible treatments for both syndromes are derived from the alterations of classical neurotransmitters [4]. The purpose of this mini-review is to review neurotransmitter alterations acting at specific receptors and the possible neural pathways in the involved brain regions in Parkinson's disease and dementia. From these findings, it will be concluded which anti-Parkinsonian drugs can be administered in Parkinsonian patients showing symptoms of dementia.

Pathophysiology of Parkinson's Disease

In Parkinson's disease, a neurotransmitter imbalance in the extrapyramidal system (EPS) between hypoactivity of D2 dopaminergic and GABAergic neurons and hyperactivity of M4 muscarinic cholinergic and NMDA glutaminergic neurons occurs. In order to stabilize the neural network described above, l-dopa, dopamine agonists, anticholinergics, which act at the M4 receptor, and NMDA antagonists can be given. In the next chapter, the diagrams of neural pathways in the EPS will be discussed.

Pathophysiology of Parkinson's Disease Dementia

In patients with Parkinson's disease who show criteria of dementia, apoptosis occurs as a consequence of the hypo- or hyper-activities of classical neurotransmitters, i.e. dopamine and acetylcholine hypo-activities [4]. In the Landscape study carried out in Denmark, 269 Parkinsonian patients with mild cognitive impairment were included. An anamnestic mild cognitive impairment was more frequent, and altered executive functions were the most detectable symptom. These patients, showing a mild cognitive impairment, have a different risk to develop dementia [5].

Diagrams of Neural Pathways in the Extrapyramidal System

The diagram of neural pathways in the EPS could be the following: dopaminergic neurons in the pars compacta of the substantia nigra with a progradient deficiency transmit a weak postsynaptic excitatory potential via D1 and D2 receptors to other dopaminergic neurons located in the caudate nucleus (Figure 1). D1 dopaminergic neurons located in the caudate nucleus transmit a weak activating potential to dynorphin neurons, which presynaptically inhibit via mu opioid receptors substance P neurons located in the same nucleus. Substance P neurons transmit a weak postsynaptic excitatory potential via NK1 receptors to GABAergic neurons located in the internal globus pallidus. Other dopaminergic neurons in the caudate nucleus transmit a weak activating potential via D2 receptors to GABAergic neurons in the external globus pallidus, and the latter neurons weakly presynaptically inhibit subthalamic NMDA glutaminergic neurons. The latter neurons strongly inhibit D2 dopaminergic neurons in the substantia nigra and enhance dopamine deficiency. Besides, these neurons inhibit via NMDA receptors GABAergic neurons in the internal globus pallidus. The latter neurons inhibit glutaminergic neurons in the thalamus, which transmit an activating potential to other glutaminergic neurons in the cortex. The glutaminergic neurons in the cortex transmit a postsynaptic excitatory potential via NMDA receptors to D1 and D2 dopaminergic neurons in the caudate nucleus and to other glutaminergic neurons located in the subthalamic nucleus. In the internal globus pallidus, GABAergic neurons with a

weak activity transmit a presynaptic inhibitory potential via GABA_A receptors to muscarinic cholinergic and serotonergic neurons in the putamen, which transmit a strong activating potential respectively via M4 and 5-HT_{2A} receptors to glutaminergic neurons. The latter neurons with a high activity presynaptically inhibit dopaminergic neurons in the putamen. The latter neurons receive an activating impulse from nicotinic cholinergic neurons via $\beta 2$ nACh receptors. Dopaminergic neurons in the putamen transmit a weak postsynaptic excitatory potential via D2 receptors to other dopaminergic neurons in the caudate nucleus.

Diagram of Neural Pathways in the Temporal Cortex and Hippocampus in Parkinson's Disease Dementia

Diagrams of neural pathways could be the following: in the nucleus basalis of Meynert, muscarinic cholinergic neurons, which present a progradient lack of acetylcholine, send an activating projection via M1 receptor to other muscarinic cholinergic neurons located in the hippocampus (Figure 2). These neurons send a weak activating potential via M1 receptors to GABAergic neurons, which weakly affect noradrenergic neurons through a presynaptic inhibitory influence via GABA_A receptors. The noradrenergic neurons with a high activity at the beginning of the disease, which decreases constantly [6], transmit a strong postsynaptic excitatory impulse via alpha 1 receptor to glutaminergic neurons, which strongly presynaptically inhibit muscarinic cholinergic neurons via NMDA receptors. In the hippocampus, an antagonistic interaction occurs also between muscarinic cholinergic and serotonergic neurons [3]. Muscarinic cholinergic neurons send a weak activating potential via M1 receptor to GABAergic neurons which weakly affect serotonergic neurons through a presynaptic inhibitory influence via GABA_A receptors. These neurons, the activity of which also decreases, send an activating potential via 5-HT_{1A} receptors to glutaminergic neurons, which strongly presynaptically inhibit muscarinic cholinergic neurons via NMDA receptors [7]. In the temporal cortex, muscarinic cholinergic neurons with a decreasing activity send a weak post-synaptic excitatory potential, via M1 receptors to GABAergic neurons which affect noradrenergic neurons through a weak presynaptic inhibitory influence via GABA_A receptors. GABAergic neurons in the hippocampus send projections to noradrenergic neurons in the temporal cortex. The noradrenergic neurons transmit an activating potential via alpha 1 receptors, the activity of which decreases constantly [3], to glutaminergic neurons, which affect muscarinic cholinergic neurons in the hippocampus through a strong presynaptic inhibitory influence.

Treatment of Parkinson's Disease Dementia

For the treatment of Parkinson's disease dementia the following drugs can be administered:

L-dopa in combination with a decarboxylase inhibitor, because increased dopamine levels exert an anti-apoptotic effect.

Dopamine agonists, for example rotigotine, applicable as a therapeutic plaster.

Selegiline, a monoamine oxidase inhibitor.

NMDA antagonists, which regulate dopamine levels in the extrapyramidal system and acetylcholine levels in the temporal cortex [8].

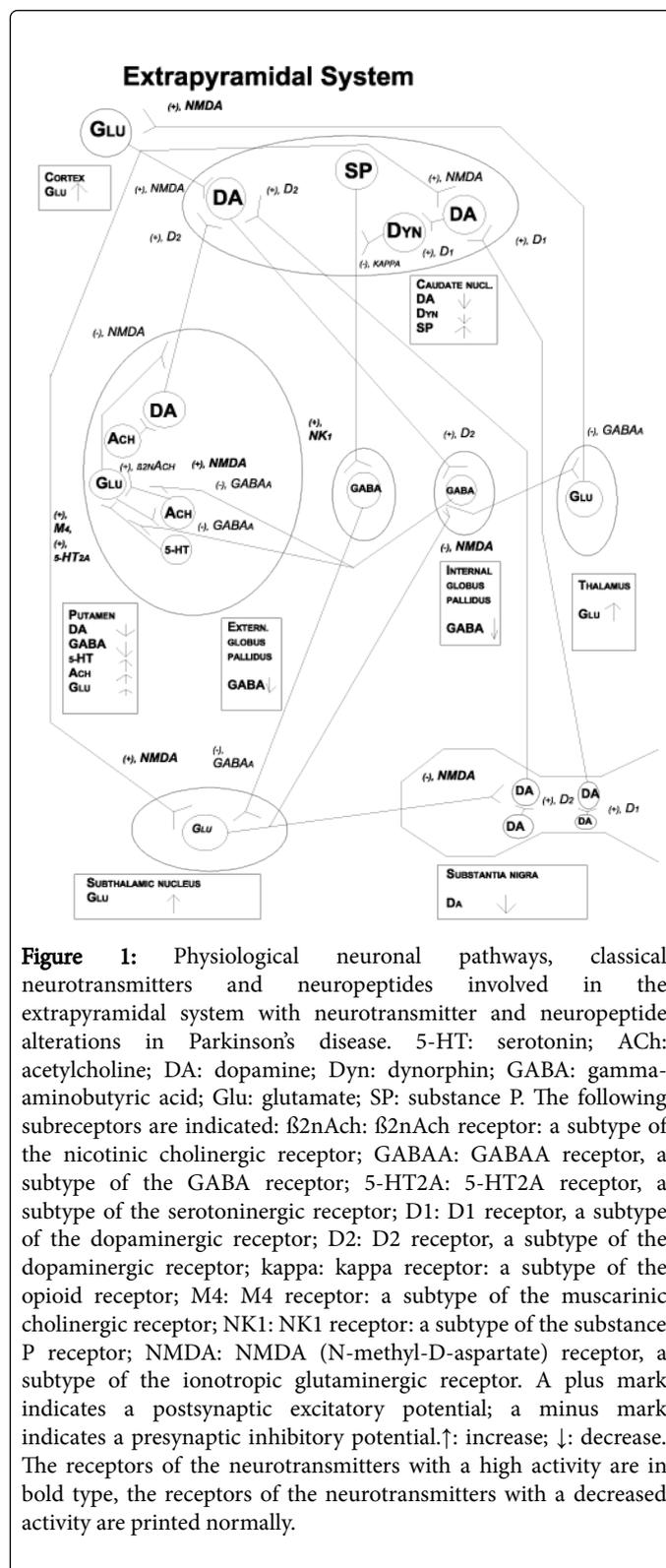
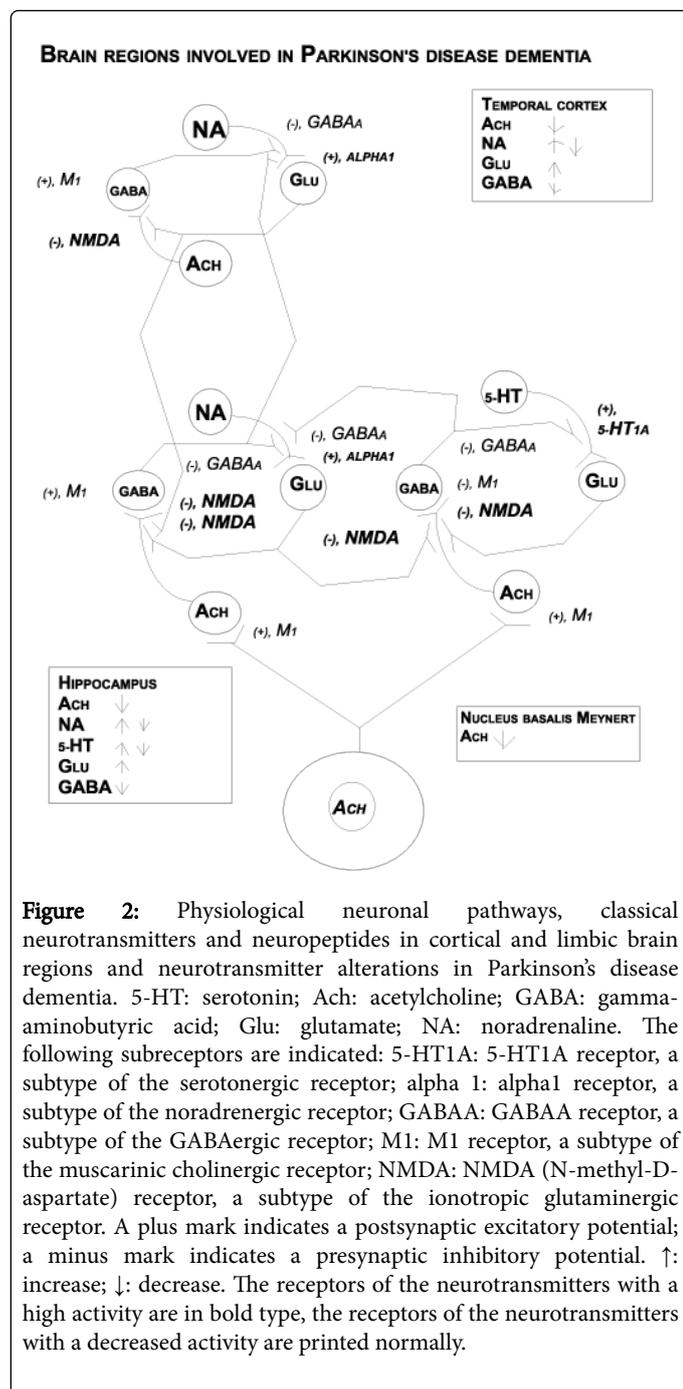


Figure 1: Physiological neuronal pathways, classical neurotransmitters and neuropeptides involved in the extrapyramidal system with neurotransmitter and neuropeptide alterations in Parkinson's disease. 5-HT: serotonin; ACh: acetylcholine; DA: dopamine; Dyn: dynorphin; GABA: gamma-aminobutyric acid; Glu: glutamate; SP: substance P. The following subreceptors are indicated: $\beta 2$ nACh: $\beta 2$ nACh receptor: a subtype of the nicotinic cholinergic receptor; GABA_A: GABA_A receptor, a subtype of the GABA receptor; 5-HT_{2A}: 5-HT_{2A} receptor, a subtype of the serotonergic receptor; D1: D1 receptor, a subtype of the dopaminergic receptor; D2: D2 receptor, a subtype of the dopaminergic receptor; kappa: kappa receptor: a subtype of the opioid receptor; M4: M4 receptor: a subtype of the muscarinic cholinergic receptor; NK1: NK1 receptor: a subtype of the substance P receptor; NMDA: NMDA (N-methyl-D-aspartate) receptor, a subtype of the ionotropic glutaminergic receptor. A plus mark indicates a postsynaptic excitatory potential; a minus mark indicates a presynaptic inhibitory potential. ↑: increase; ↓: decrease. The receptors of the neurotransmitters with a high activity are in bold type, the receptors of the neurotransmitters with a decreased activity are printed normally.



Cholinesterase inhibitors, i.e. rivastigmine, which do not activate cholinergic neurotransmission in the extrapyramidal system [4].

Anticholinergics have no therapeutic effect, because they enhance cognitive deficits [1].

Aim of an appropriate treatment of Parkinson's disease dementia is to find a treatment, which improves motor symptoms and cognitive deficits at the same time. It is important to maintain an anti-Parkinsonian pharmacotherapy, for example to combine rotigotine, a dopamine agonist with rivastigmine, a cholinesterase inhibitor. Both drugs can be applied as therapeutic plasters.

Conclusion

Among the patients with Parkinson's disease, 85% show symptoms of a mild cognitive impairment and 40% develop criteria of dementia. In the concerned brain areas, acetylcholine and dopamine deficiencies are anti-apoptotic. In the hippocampus, acetylcholine and GABA deficiencies and a surplus of glutamate, noradrenaline and serotonin occur. In order to deduce compatible treatments for both syndromes, diagrams of neural pathways are pointed in the involved brain areas. In addition, the cholinesterase inhibitor rivastigmine, NMDA antagonists, l-dopa in combination with a decarboxylase inhibitor and selegiline could be administered. In the treatment of Parkinsonian patients who show symptoms of dementia, it is important to continue the anti-Parkinsonian pharmacotherapy and to improve cognitive deficits. It can be recommended to combine rotigotine, a dopamine agonist with rivastigmine, a cholinesterase inhibitor. Both drugs are applicable as therapeutic plasters. Further research should be undertaken in order to improve the therapeutic and maybe prophylactic pharmacotherapy of this form of dementia.

References

1. Werner FM, Coveñas R (2015) Classical neurotransmitters and neuropeptides involved in Parkinson's disease: focus on anti-Parkinsonian drugs. *Curre Drug Ther* 10: 66-81.
2. Yamal A, Rochester L, Burm DJ (2011) The interplay of cholinergic function, attention, and falls in Parkinson's disease. *Mov Disord* 26: 2496-2503.
3. Werner F-M (2007) Classical neurotransmitters involved in Parkinson's disease. *J Neural Transm* 114: I-XXXI.
4. Werner FM, Coveñas R (2009) How to treat dementia in Parkinson's disease? *J Neural Transm* 116: 233.
5. Kalbe E, Rehberg SP, Heber I, Kronenbuerger M, Schulz JB, et al. (2016) Subtypes of mild cognitive impairment with Parkinson's disease: evidence from the LANDSCAPE study. *J Neurol Neurosurg Psychiatry* 313838.
6. Harrell LE, Parsons DS, Kolasa K (2005) Pro- and anti-apoptotic evidence for cholinergic denervation and hippocampal sympathetic ingrowth in rat dorsal hippocampus. *Exp Neurol* 194: 182-190.
7. Kepe V, Barrio JR, Huang SC, Ercoli L, Siddarth P, et al. (2006) Serotonin 1A receptors in the living brain of Alzheimer's disease patients. *Proc Natl Acad Sci USA* 103: 702-707.
8. Olivares D, Deshpande VK, Shi Y, Lahiri DK, Greig NH, et al. (2012) N-Methyl-D-Aspartate (NMDA) receptor antagonists and memantine treatment for Alzheimer's disease, vascular dementia and Parkinson's disease. *Curr Alzheimer Res* 9: 746-758.