

Might Combined GABAA Agonists and NMDA Antagonists have a Therapeutic and maybe a Prophylactic Effect in Alzheimer's and Parkinson's Diseases?

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Abstract

Alzheimer's and Parkinson's diseases are neurodegenerative diseases which cannot be cured so far. In both diseases, a GABAergic-glutamatergic neurotransmitter imbalance might occur. Neural networks are suggested for Parkinson's disease in the extrapyramidal system and for Alzheimer's disease in the hippocampus and the temporal cortex. Combined GABAA agonists and NMDA antagonists might have therapeutic and maybe prophylactic properties in Alzheimer's and Parkinson's diseases. It is important to examine the neural networks in the brain areas involved in both diseases. This would offer the possibility to try an early beginning pharmacotherapy of these, up to now, incurable diseases.

Keywords: Alzheimer's disease; Parkinson's disease; Extrapyramidal system; Hippocampus; Dopamine; Acetylcholine; Noradrenalin

Introduction

Alzheimer's and Parkinson's diseases are neurodegenerative diseases which cannot be cured so far [1]. In both diseases, neuronal degeneration is associated with neurotransmitter and neuropeptide alterations. In Alzheimer's disease, a neurotransmitter imbalance (noradrenalin and glutamate hyperactivity and acetylcholine and GABA hypoactivity) occurs in the hippocampus and the temporal cortex [2]. In Parkinson's disease, a neurotransmitter imbalance in the extrapyramidal system with a dopamine and GABA deficiency and an acetylcholine and glutamate hypoactivity occurs [3,4]. In both diseases, neural networks are disturbed in the involved brain regions. The pharmacotherapy of the Alzheimer's disease consists in the administration of cholinesterase inhibitors or NMDA antagonists [5,6]. An anti-Parkinsonian pharmacotherapy is started when the cardinal symptoms akinesia, rigidity and tremor appear [3]. The following question arises, whether an early beginning pharmacotherapy of Alzheimer's and Parkinson's diseases could positively influence the course of both diseases. In this sense, the clinical effect of combined GABAA agonists and NMDA antagonists could exert a therapeutic and maybe a prophylactic effect [3,4].

Pathophysiology of Alzheimer's Disease

In Alzheimer's disease, neurotransmitter and neuropeptide alterations can be found, which have been described previously. At the beginning of the disease, noradrenalin has increasing levels and exerts an anti-apoptotic effect, but during the course of the disease noradrenalin levels decrease more and more [7]. The neurotransmitter alterations are associated with a major formation of fibrillary tangles and senile plaques. The neural networks in the hippocampus and the

temporal cortex can be described as follows: in the nucleus basalis of Meynert muscarinic cholinergic neurons, which develop more and more a hypoactivity, send projections to other M1 muscarinic cholinergic neurons located in the hippocampus. The latter neurons weakly activate GABAergic neurons which weakly presynaptically inhibit, via GABAA receptors, alpha1 noradrenergic neurons located in the hippocampus. Activated by the alpha1 noradrenergic neurons, glutamatergic neurons strongly inhibit M1 muscarinic cholinergic neurons via NMDA receptors and enhance acetylcholine deficiency. GABAergic neurons located in the hippocampus weakly inhibit alpha1 noradrenergic neurons in the temporal cortex with a high activity, which activate glutamatergic neurons. The latter neurons strongly inhibit M1 muscarinic cholinergic neurons located in the temporal cortex and the hippocampus. M1 muscarinic cholinergic neurons weakly activate the GABAergic neurons located in the temporal cortex [3].

Pathophysiology of Parkinson's Disease

In Parkinson's disease, dopamine, acetylcholine, GABA and glutamate alterations can be found, but more classical neurotransmitters (e.g., serotonin), other neuroactive substances (e.g., adenosine) and neuropeptides (e.g., dynorphin) are also involved. In this brain system, the following neural networks can be suggested [3]: in the substantia nigra pars compacta, D1 and D2 dopaminergic neurons activate dopaminergic neurons located in the caudate nucleus [8]. In the caudate, D1 dopaminergic neurons weakly activate dynorphin neurons which presynaptically inhibit, via kappa receptors, substance P neurons. The latter neurons, via NK-1 receptors, transmit a weak postsynaptic excitatory impulse to GABAergic neurons located in the globus pallidus internus. Caudate D2 dopaminergic neurons weakly activate GABAergic neurons located in the globus pallidus externus, which via GABAA receptors, weakly inhibit subthalamic glutamatergic neurons. In this nucleus, glutamatergic neurons, via

NMDA receptors, strongly inhibit dopaminergic neurons located in the substantia nigra, enhancing dopamine deficiency. Moreover, the dopaminergic neurons activate GABAergic neurons located in the globus pallidus internus. The latter neurons weakly inhibit, via GABAA receptors, thalamic glutaminergic neurons which activate, via NMDA receptors, other cortical glutaminergic neurons. Cortical glutaminergic neurons can activate, via NMDA receptors, D1 and D2 dopaminergic neurons located in the caudate nucleus as well as other subthalamic glutaminergic neurons. GABAergic neurons in the globus pallidus internus inhibit, via GABAA receptors, muscarinic cholinergic and serotonergic neurons located in the putamen. These muscarinic cholinergic and serotonergic neurons strongly activate, via M4 and 5-HT_{2A} receptors, glutaminergic neurons which strongly inhibit via NMDA receptors D2 dopaminergic neurons [9,10]. The latter neurons, located in the putamen, are connected to other caudate D2 dopaminergic neurons [3].

Emir et al. (2012) found by examining Parkinsonian patients with a mild to moderate form by 7 proton tesla MRS that GABA concentrations in the pons were augmented at 64% and in the putamen at 32% [11]. It is not clear whether GABA increases in the putamen are primary or due to a Parkinsonian treatment. In the pons, the hyperactive GABAergic interneurons are possibly associated with dysfunction of noradrenergic and serotonergic neurons in the brainstem [11]. It is possible that an inverse interaction between GABAergic and dopaminergic neurons in the putamen might exist [11]. For that reason, GABA levels in Parkinson's disease in the nuclei of the extrapyramidal system, the hippocampus and the cortex should be examined further. It has to be considered that GABAA agonists can cause adverse affects such as a paradoxical reaction, a dependence and that NMDA antagonists can cause confusion and psychotic reactions [12].

Clinical Effect of Combined GABAA Agonists and NMDA Antagonists

In Alzheimer's and Parkinson's diseases occur neurotransmitter alterations which are associated in both diseases with neurodegeneration. [1,3]. The clinical effect of combined GABAA agonists and NMDA antagonists could consist in stabilizing the neural networks in both diseases and hence to slow down the neurodegeneration. This would be a novel pharmacotherapy strategy, because up to now a pharmacological treatment of patients in an early stage of Alzheimer's or Parkinson's diseases has not yet been performed. The meaning of a prophylactic medication is that at the beginning of Alzheimer's and Parkinson's diseases neurotransmitter alterations occur which could be stabilized by an early pharmacotherapy. In clinical trials it should be examined if neurodegeneration could be prevented by such a medication.

Conclusions

Alzheimer's and Parkinson's diseases are incurable neurodegenerative diseases which are treated when symptoms are diagnosed. A question arises, whether an early beginning pharmacotherapy is possible. In the hippocampus and the temporal cortex, in Alzheimer's disease, and in the extrapyramidal system in Parkinson's disease, a GABAergic-glutaminergic neurotransmitter

imbalance might occur with a GABA hypoactivity via GABAA receptors and a glutamate hyperactivity via NMDA receptors [1,4,6]. Combined GABAA agonists and NMDA antagonists might have a therapeutic and maybe a prophylactic effect in both diseases. In Alzheimer's disease, GABAA agonists would activate M1 muscarinic cholinergic neurons, counteracting acetylcholine deficiency. A further glutamate antagonism at NMDA receptors would as well increase acetylcholine levels in the hippocampus and the temporal cortex through a reduced presynaptic inhibition. In Parkinson's disease, GABA agonism at GABAA receptors could reduce acetylcholine and serotonin hyperactivity in the putamen through an increased presynaptic inhibition. Glutamate antagonism at NMDA receptors could enhance dopamine levels in the putamen and the substantia nigra through a reduced presynaptic inhibition. This treatment would counteract the existing neurotransmitter imbalance. In this sense, it is important to examine the suggested neural networks and to investigate whether an early beginning pharmacotherapy of these neurodegenerative diseases could improve the course of both diseases [1].

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