

# Specific Agonists and Antagonists of Serotonergic Receptors in the Treatment of Cognitive Symptoms in Alzheimers Disease

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## Abstract

In Alzheimer's disease, decreasing activity of acetylcholine and GABA in the hippocampus and prefrontal cortex are combined with cognitive deficits and with the formation of beta-amyloid. Neurotransmitter alterations in these brain regions are described, while a neurotransmitter imbalance with hypoactivity of muscarinic cholinergic, serotonergic and GABAergic neurons and hyperactivity of noradrenergic and glutamatergic neurons can be found. Serotonin including some specific receptors play an essential role in cognitive symptoms in Alzheimer's disease. Neural networks in the hippocampus and prefrontal cortex are described. Animal experiments and clinical trials about the pro-cognitive effect of 5-HT4 and 5HT7 agonists and of 5-HT3 and 5-HT6 antagonists are mentioned. The question should be investigated, whether a hybrid of a GABAA agonist and an NMDA antagonist is of a therapeutic value in mild Alzheimer's disease.

**Keywords:** Acetylcholine; Alzheimer's disease; Beta-amyloid; Cognitive deficit; Dopamine; GABA; Glutamate; Hippocampus; Noradrenaline; Prefrontal cortex; Serotonin

## Introduction

Alzheimer's disease is a neurodegenerative disease which is associated with cognitive symptoms such as memory loss, disturbances of orientation and neuropsychological symptoms, for example aphasia, agnosia and apraxis. Alzheimer's disease is combined with brain atrophy especially in the hippocampus and the temporal cortex, in these brain areas, amyloid plaques and fibrillary tangles can be found. In the temporal cortex, neurotransmitter alterations (acetylcholine deficiency and hyperactivity of the excitotoxic glutamate) have been described [1]. In this context, acetylcholine deficiency is correlated with the formation of beta-amyloid [2]. However, other neurotransmitters such as dopamine, GABA, noradrenaline and serotonin play an essential role. Dysfunction of the presynaptic inhibitory neurotransmitter GABA acting at GABAA receptors is involved in the formation of cognitive deficits. A multi-neurotransmitter system in the hippocampus, the prefrontal cortex and the temporal cortex including the neurotransmitters acetylcholine, dopamine, noradrenaline and serotonin and the presynaptic inhibitory neurotransmitters GABA and glutamate are involved in cognitive symptoms [3]. Moderate Alzheimer's disease is treated with cholinesterase inhibitors, which increase acetylcholine levels, and severe Alzheimer's disease is treated with N-methyl-D-aspartate antagonists [3]. Serotonin is of importance in cognitive functions, and the question should be answered whether agonists or antagonists at specific serotonergic receptors might ameliorate cognitive symptoms [4].

## Neurotransmitter Alterations in the Brain Regions Involved in Cognitive Symptoms in Alzheimer's Disease

Here, the neurotransmitter alterations in the hippocampus and prefrontal cortex are described. The postsynaptic excitatory neurotransmitters acetylcholine, dopamine, noradrenaline and serotonin and the presynaptic inhibitory neurotransmitters GABA and glutamate are considered.

### Acetylcholine

In Alzheimer's disease, acetylcholine deficiency is associated with cognitive deficits and the formation of beta-amyloid [2]. In a clinical study, patients, who were detected to suffer from beta-amyloid formation, had worse cognitive functions after administration of scopolamine, an M1 muscarinic cholinergic antagonist [5]. An allosteric modulator of the M1 muscarinic cholinergic receptor might improve cognitive symptoms in Alzheimer patients [6]. Not only agonism at muscarinic cholinergic receptors, but also agonism at alpha4beta2 nicotinic and alpha7 nicotinic cholinergic receptors can improve cognitive symptoms in Alzheimer's disease [7].

### Dopamine

Dopamine alterations play a role in depressive and psychotic symptoms in Alzheimer's disease [8]. Polymorphisms of the dopaminergic receptors were examined in Alzheimer patients with aggression. Polymorphisms of polymorphisms of the D3 and D4 receptors could be found in Alzheimer patients with aggression [9].

### GABA

Cognitive deficits in Alzheimer's disease are combined with GABA dysfunction at GABAA receptors. An agonism at GABAA receptors prevents the neuronal death and the formation of beta-amyloid

[10,11]. In the hippocampus and the prefrontal cortex, GABAergic neurons could presynaptically inhibit, via GABAA receptors, dopaminergic, noradrenergic and serotonergic neurons [11]. In animal experiments, the combination of acamprosate, a partial agonist of the NMDA receptor and of baclofen and a GABAB agonist improves cognitive functions [10].

### Glutamate

Glutamate excitotoxicity via ionotropic glutamatergic receptors and the dysfunction of the glial glutamate transporter EEAT2 impair cognitive functions in Alzheimer's disease. NMDA antagonists and an EEAT2 translational activator improve cognitive functions in Alzheimer's disease [12].

### Norarenaline

Noradrenaline has increased levels in the cerebrospinal fluid at the beginning of the disease. The noradrenaline levels decrease more and more in the course of the disease [8]. Noradrenaline can activate tropomyosin related kinase B (TrkB), which has a neuroprotective effect against beta-amyloid [12,13].

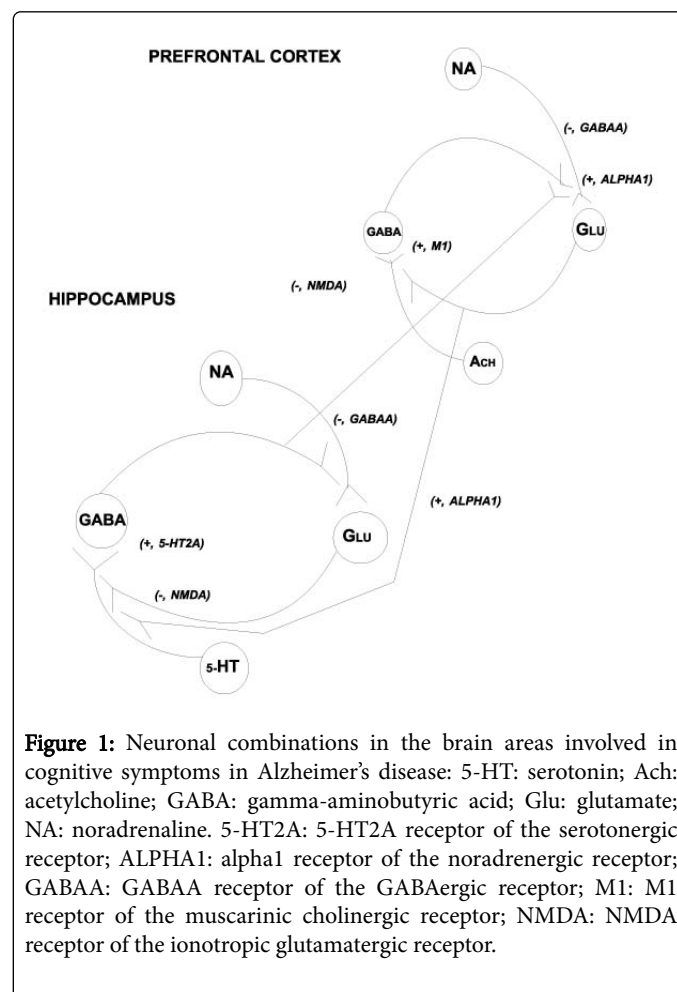
### Serotonin

Currently no prophylactic drug in preventing the formation of beta-amyloid is available. Tropicisetron which has alpha7 nACh (nicotinic cholinergic) agonistic and 5-HT3 antagonistic effects has a superior effect in improving cognitive functions in Alzheimer's disease in comparison to cholinesterase inhibitors and NMDA antagonists. Memantine, an NMDA receptor antagonist which has at the same time alpha7 nACh and 5-HT3 antagonistic effects has a contradictory therapeutic effect, because the alpha7 nACh antagonistic effect has no pro-cognitive effect [14]. 5-HT6 receptors are found in the hippocampus and the prefrontal cortex and are associated with cognitive functions. Idalopirdine, a 5-HT6 antagonist, improves cognitive functions in mild Alzheimer's disease better than placebo [4]. 5-HT4 agonists prevent the formation of beta-amyloid by activating the alpha-secretases and by cleaving the amyloid precursor protein (APP). In clinical trials, these pharmacological agents improve cognitive functions [15].

### Neural Networks in the Brain Areas Involved in Cognitive Symptoms in Alzheimer's Disease

The neural networks in the hippocampus and the prefrontal cortex in cognitive symptoms in Alzheimer's disease can be described in the following way (Figure 1) in the hippocampus, 5-HT2A serotonergic neurons with a decreasing activity weakly activate GABAergic neurons, which weakly affect alpha1 noradrenergic neurons by an inhibitory influence via GABAA receptors. The latter neurons, the activity of which first is high and decreases more and more in the course of the disease, transmit a postsynaptic excitatory impulse to glutamatergic neurons, which strongly presynaptically inhibit, via NMDA receptors, 5-HT2A serotonergic neurons. In the prefrontal cortex, M1 muscarinic cholinergic neurons with a decreasing activity transmit a weak activating impulse to GABAergic neurons, which, via GABAA receptors, weakly affect alpha1 noradrenergic neurons by an inhibitory influence. The latter neurons activate glutamatergic neurons, which exert a strong inhibitory impulse via NMDA receptor upon M1 muscarinic cholinergic neurons. GABAergic neurons in the hippocampus weakly presynaptically inhibit noradrenergic neurons in

the prefrontal cortex. In this brain area, glutamatergic neurons strongly inhibit 5-HT2A serotonergic neurons in the hippocampus.



**Figure 1:** Neuronal combinations in the brain areas involved in cognitive symptoms in Alzheimer's disease: 5-HT: serotonin; Ach: acetylcholine; GABA: gamma-aminobutyric acid; Glu: glutamate; NA: noradrenaline. 5-HT2A: 5-HT2A receptor of the serotonergic receptor; ALPHA1: alpha1 receptor of the noradrenergic receptor; GABAA: GABAA receptor of the GABAergic receptor; M1: M1 receptor of the muscarinic cholinergic receptor; NMDA: NMDA receptor of the ionotropic glutamatergic receptor.

### Specific Agonists and Antagonists of Serotonergic Receptors in Cognitive Symptoms in Alzheimer's Disease

Drugs interacting with specific serotonergic receptors could be used to improve cognitive impairment in Alzheimer's disease. Tropicisetron, which has alpha7 nACh agonistic and 5-HT3 antagonistic properties, has dual functions. It prevents the formation of beta-amyloid and improves cognitive functions [14]. 5-HT6 antagonists, which exert their function in the hippocampus and prefrontal cortex, improved cognitive functions in Alzheimer's disease in clinical trials [4]. 5-HT4 agonists are of therapeutic value in the treatment of Alzheimer's disease, because they inhibit the formation of beta-amyloid and because they increase acetylcholine concentrations [16]. Drugs interfering with the 5-HT7 receptor modulate cognitive functions. 5-HT7 antagonists improve cognitive functions in schizophrenia. It should be examined whether an agonistic or antagonistic effect at the 5-HT7 receptor enhances cognitive functions [17].

## Combined GABAA agonists and NMDA antagonists as a prophylactic and therapeutic treatment of Alzheimer's disease

In Alzheimer's disease, a neurotransmitter imbalance in the hippocampus and the prefrontal cortex with a hypoactivity of presynaptic inhibitory GABAergic neurons via GABAA receptors and a hyperactivity of excitotoxic glutamatergic neurons via NMDA receptors can be found [18]. It should be examined whether combined GABAA agonists and NMDA antagonists could have a therapeutic effect. In animal experiments, the combination of acamprostate, a partial agonist at the NMDA receptor with baclofen, a GABAB agonist improved cognitive functions [10].

## Conclusion

In the brain regions involved in cognitive symptoms in Alzheimer's disease, a multi-neurotransmitter system is described. A neurotransmitter imbalance with hypoactivity of muscarinic cholinergic, serotonergic and presynaptic GABAergic neurons and hyperactivity of noradrenergic and excitotoxic glutamatergic neurons is described. Serotonergic neurons play an important role in cognitive functions in the hippocampus and prefrontal cortex. In this context, it should be investigated in clinical trials, whether 5-HT4 and 5-HT7 agonists and 5-HT3 and 5-HT6 antagonists improve cognitive deficits in mild Alzheimer's disease. Furthermore, it should be examined whether a hybrid of a GABAA agonist and an NMDA antagonist might be of therapeutic value in the treatment of cognitive symptoms in Alzheimer's disease.

## Conflict of Interest

The author confirms that he has no conflict of interest.

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