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Serotonin: A New Hope in Alzheimer's Disease?

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Abstract

Alzheimer's disease (AD) is the most common form of dementia affecting 35 million individuals worldwide. Current AD treatments provide only brief symptomatic relief. It is therefore urgent to replace this symptomatic approach with a curative one. Increasing serotonin signaling as well as developing molecules that enhance serotonin concentration in the synaptic cleft have been debated as possible therapeutic strategies to slow the progression of AD. In this Viewpoint, we discuss exciting new insights regarding the modulation of serotonin signaling for AD prevention and therapy.

Subjects

what are subjects

- Agonists
- Neurophysiology
- Peptides and proteins
- Receptors
- Rodent models

Keywords

what are keywords

- Serotonin
- neuroprotection

- 5-HT4 receptors
- 5-HT6 receptors

SPECIAL ISSUE

This article is part of the Serotonin Research special issue.

Alzheimer's disease is the most common neurodegenerative disorder and a major public health concern. Given the growing aging population worldwide, societal costs to treat AD patients will increase tremendously in the next decades. Currently available treatments, based on acetylcholinesterase inhibition (donepezil, rivastigmine, galantamine) or NMDA receptor blockade (memantine), provide only symptomatic relief, underscoring an urgent need for disease modifying drugs. In this Viewpoint, we focus on recent data from several groups showing that serotonergic system modulation may present a promising strategy for slowing AD progression and improving cognition.

Main Features of AD

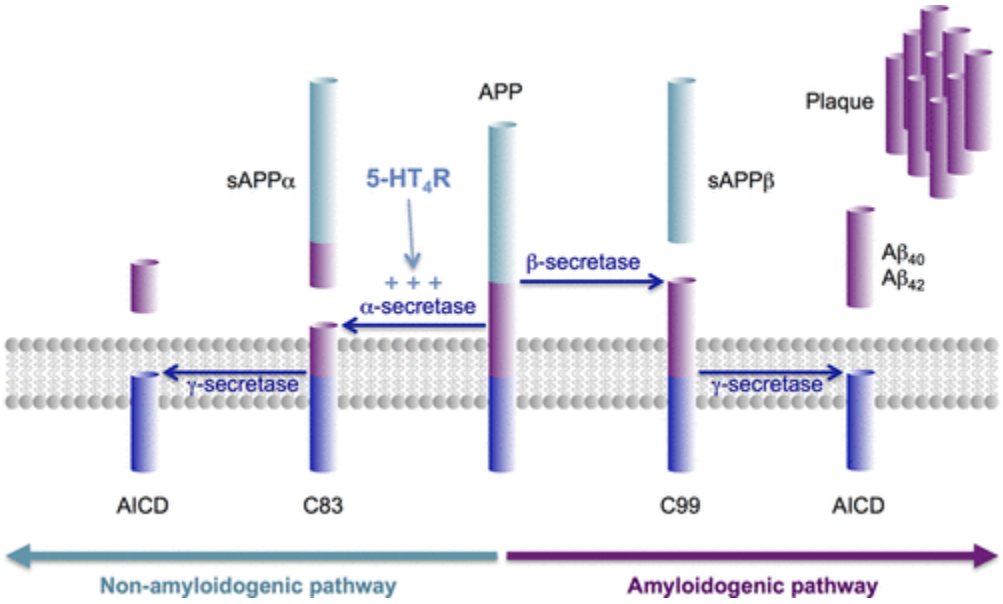
Alzheimer's disease is characterized by irreversible neurodegeneration, which slowly spreads over the brain and causes progressive memory loss, cognitive decline, and finally dementia. The histological hallmarks of the disease are neurofibrillary tangles composed of hyperphosphorylated tau protein and amyloid plaques, insoluble aggregates of hydrophobic β-amyloid peptide (Aβ). The formation of Aβ peptides results from the amyloidogenic degradation of transmembrane precursor, the amyloid precursor protein (APP), by β- and γ-secretases. Amyloidogenic processing occurs mainly in early/sorting and late endosomes (see Box). The nonamyloidogenic proteolysis of APP within the Aβ sequence by α-secretase releases the extracellular fragment of APP (sAPPα), which is neurotrophic and increases long-term potentiation. As the underlying causes of AD remain unknown, clinicians diagnose the disease by considering the results of a series of cognitive tests, sometimes in combination with brain imaging (e.g., amyloid imaging, functional, and volumetric analysis) and/or biomarker dosage (e.g., Aβ species ratios, phosphorylated tau protein levels in cerebrospinal fluid). Incontrovertible AD diagnosis is obtained by postmortem identification of neurofibrillary tangles and amyloid plaques.

1

Metabolism of the Amyloid Precursor Protein (APP)

Two APP pathways coexist. The amyloidogenic pathway leads to production of the amyloid-β peptide (Aβ) following the cleavage of APP by β-secretase (BACE1) and γ-secretase. The

Aβ peptides form oligomeric toxic species, which aggregate into extracellular senile plaques. An alternative nonamyloidogenic pathway relies on the cleavage of APP by α-secretase (ADAM10 in neurons). The α-cleavage site located within the Aβ sequence precludes formation of the Aβ species and releases the soluble sAPPα fragment, which has neurotrophic and neuroprotective properties. Stimulation of 5-HT_4 receptors promotes the nonamyloidogenic cleavage of APP by activating the α-secretase ADAM10.



No therapeutic agents with long-term efficacy currently exist for the treatment of AD. For many years, research and clinical trials have focused on developing antiamyloid agents. However, during the last 10 years, immunotherapy trials against Aβ as well as β-secretase inhibitor clinical studies have produced disappointing results. These outcomes have motivated a shift toward a research focus on the tau protein, the other culprit in AD pathology. Nevertheless, recent findings refocus efforts on β-amyloid in connection with serotonergic system modulators.

Evidence from SSRI Studies

Studies by John Cirrito and Yvette Sheline have demonstrated that activation of serotonergic neurotransmission might be beneficial in AD. In a first study, these authors showed that acute administration of selective serotonin reuptake inhibitors (SSRIs) reduced production of toxic Aβ proteins (a hallmark of AD) in the brains of amyloid protein precursor/presenilin-1 (APP/PS1) overexpressing mice, an AD mouse model. (1) This effect began 12–14 h after treatment, with a 25% reduction in Aβ still detectable 24 h after drug injection. Consistent with this finding, these authors further demonstrated that serotonin

infusion into the hippocampus of APP/PS1 mice, via reverse microdialysis, also reduced Aβ in the brain. This reduction occurred via activation of signaling pathways involving extracellular regulated kinase (ERK) and without alteration of Aβ clearance. Moreover, chronic SSRI administration was also able to reduce Aβ plaque loads in APP/PS1 mice. Together these preclinical findings suggest that increasing extracellular serotonin is a viable means to reduce Aβ plaque formation.

Clinical studies further support this idea. In humans, Aβ imaging via positron emission tomography with the Pittsburgh Compound B (PIB) revealed lower cortical amyloid levels in study participants who had taken SSRIs within the past five years versus those who had not been treated with SSRIs. (1) This first demonstration that SSRIs could have an impact on parameters involved in AD pathogenesis was reinforced by the recent demonstration that chronic administration of the SSRI citalopram blocked plaque growth in APP/PS1 mice. (2) More importantly, citalopram reduced Aβ production and concentration in cerebrospinal fluid of healthy human volunteers. (2)

Rather than removing amyloid plaques, reducing production of Aβ species has been demonstrated as key to the rescue of cognitive and synaptic deficits in AD mouse models. (3) Today, plaques are often viewed as a way by which damaged cells try to diminish Aβ toxicity; namely, plaques may be an amyloid “dump”. Transient Aβ species that form oligomers have been identified as affecting neuronal structure and function. Consequently, lowering Aβ production is a promising strategy to slow AD progression in humans. However, results of recent clinical trials have led to the conclusion that antiamyloid treatments (e.g., solanezumab), should be administered in the very early stages of the disease and for decades to have an impact on slowing AD progression. The safety of the long-term use of such drugs needs to be investigated. In the case of SSRIs, it has already been established that they are safe and globally well tolerated with chronic use, even if they induce some relatively minor side effects. Given this knowledge, clinical trials exploring the protective action of SSRIs in AD will be an exciting area of investigation in the coming years. Nonetheless, demonstrating a protective or disease modifying action of a drug-class like SSRIs will involve long follow-up trials (3–5 years).

5-HT_4 Receptor Activation

The observation that activation of serotonergic neurotransmission may have beneficial effects in the context of AD led us to investigate which serotonin receptor subtypes might mediate this action. Among the 14 different receptors that respond to serotonin, all but 5-HT_3 receptors are G-protein-coupled receptors (GPCRs). More than 30% of currently

marketed drugs target GPCRs and some already target serotonin receptors. Several of these serotonergic GPCRs modulate processing of the amyloid protein precursor (APP) including 5-HT_{2A}, 5-HT_{2C}, and 5-HT_4 receptors. Among them, the latter is an interesting candidate as 5-HT_4 receptor activation induces the nonamyloidogenic cleavage of APP (see Box) and release of the soluble sAPPα fragment, which possesses neurotrophic and neuroprotective properties.

Chronic administration of a 5-HT_4 receptor (5-HT_4R) agonist (i.e., RS 67333, twice a week for 2 to 3 months) slowed amyloid pathology and cerebral inflammation. This treatment also prevented cognitive deficits in an early onset AD mouse model, 5XFAD mice (4) (Figure 1). By promoting α-secretase cleavage of APP, 5-HT_4R activation precluded formation of Aβ (Box). Decreases in amyloid plaque load in mouse brains after chronic administration of the 5-HT_4R agonist (Figure 1) can be seen as an indicator that Aβ has not been produced. Moreover, acute administration of a 5-HT_4R agonist induced a transient increase in sAPPα in CSF of 5XFAD mice (4) (Figure 1). This sAPPα is known to have a neuroprotective effect against various types of brain injury such as stroke or ischemic toxicity. The precise mechanism by which the soluble APP fragment exerts its actions has not yet been resolved. The receptor for sAPPα (if there is one) is still unknown.

Figure 1

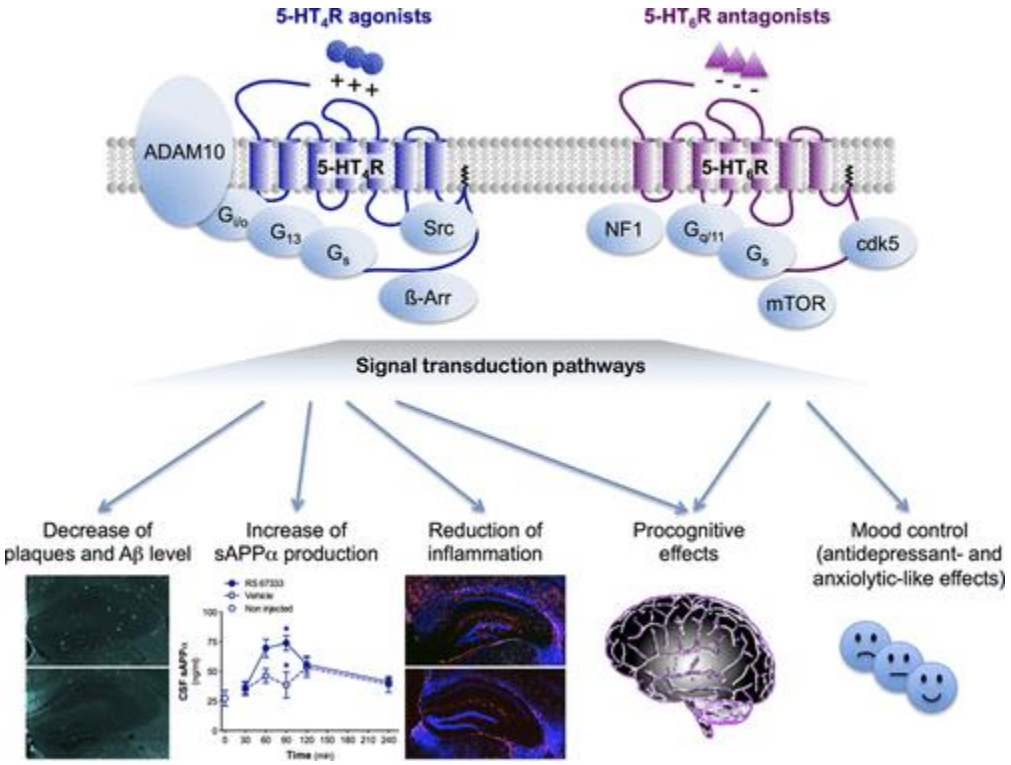


Figure 1. Major positive actions of 5-HT_4R agonists and 5-HT_6R antagonists in the context of Alzheimer's disease. Principal transduction interactions of these two receptors subtypes are indicated and beneficial pharmacological responses are illustrated. Representative results are taken from ref 4.

Chronic administration of the 5-HT_4 receptor agonist RS 67333 markedly reduced cerebral astrogliosis and microgliosis in 5XFAD mouse brains, cerebral inflammation processes associated with AD progression (4) (Figure 1). This effect could be a consequence of lowering plaque burden or a direct action of 5-HT_4R activation leading to the production of cAMP, which is known to have an anti-inflammatory action. Finally, this study demonstrated that the protective action of 5-HT_4R stimulation is effective when the treatment is administrated during the prodromal stage of the disease and is sustained for at least 2 months in 5XFAD mice. (4)

Translating these results to the clinic will be challenging. The first issue will be to identify and to treat patients in the very early stages of the disease. Ideally, treatments should start at the prodromal stage, or in people identified as having mild cognitive impairment (MCI), even if it is impossible to know if their symptoms will evolve and if they will develop AD. Such preventive clinical trials are already underway for genetic forms of AD. As an example, the Dominantly Inherited Alzheimer Network (DIAN) enrolls asymptomatic children of parents carrying a mutated gene known to cause dominantly inherited AD. Preventive treatment with anti-Aβ antibodies (gantenerumab or solanezumab) will be administered to study participants to validate the preventive action of these drugs for developing AD.

To conduct similar clinical trials using 5-HT_4R agonists, the safety of these drugs must first be demonstrated. Several agonists of 5-HT_4 receptors have been developed to stimulate motility of the gastrointestinal tract. However, the 5-HT_4 agonists cisapride and tegaserod have been restricted in use or withdrawn from the market for adverse cardiac effects. Nevertheless, prucalopride, a highly specific 5-HT_4R agonist, has been commercialized for use for 5 years now in Europe and Canada for the treatment of chronic constipation in women. Safety studies on this molecule did not show an increase in QT interval or other severe adverse reactions, which is encouraging for clinical studies to evaluate the ability of prucalopride to slow AD pathology.

5-HT_6 Receptor Inhibition

Another serotonin receptor subtype that has received attention in the AD field is the 5-HT_6 receptor. This GPCR is coupled to G_s similar to 5-HT_4R. However, unlike 5-HT_4R, several reports indicate that beneficial effects on cognition arise from *inactivation* of 5-

HT_6 receptors via mechanisms that may not involve primary G_s coupling (Figure 1). Administration of 5-HT_6R antagonists to rodents improves cognitive performance in numerous behavioral tests through stimulation of glutamate, acetylcholine, and catecholamine release in cortical and limbic areas. Inhibition of the mTOR pathway or stimulation of neurite outgrowth may also be involved in the positive action of 5-HT_6R antagonists on cognitive processes.

More recently, the phase II clinical trial of idalopirdine, a 5-HT_6R antagonist, found cognitive improvement in donepezil-treated patients with moderate AD who received idalopirdine as a combination therapy. (5) Interestingly, the authors of this study pointed out that while some monotherapies administered with 5-HT_6 antagonists failed to show positive effects in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) compared to placebo at the completion of the 2 year study, the combined action of idalopirdine and donepezil revealed a clear improvement in the cognitive indicators compared to the group treated with placebo and donepezil.

Nevertheless, many questions remain. For example, is improvement due to idalopirdine or to the combination therapy? Is it possible that the combination therapy accelerates procognitive effects so that differences between the two treatment groups are amplified and visible earlier? Would treatment with a 5-HT_6R antagonist alone have been beneficial if administered earlier or for a longer period of time? A phase III trial will try to answer these questions and hopefully confirm the promise of using 5-HT_6R antagonists for AD therapy.

Multitarget Action

As mentioned, combination therapy modulating the serotonergic system and simultaneously inhibiting acetylcholine degradation is promising for the treatment of AD. Here, we develop the concept of multitarget action for AD therapy.

For a number of years now, 5-HT_4R agonists have been considered nootropics due to their ability to enhance learning and memory in rodents. Moreover, 5-HT_4R stimulation induces release of acetylcholine, an action that can compensate for the loss of cholinergic neurons, a cellular population that is one of those affected by neurodegeneration in AD and whose loss impairs memory processes. Combination of subthreshold doses of 5-HT_4R agonists with acetylcholinesterase inhibitors has shown synergistic effects on memory performance in rodents (SL 65.0155/rivastigmine, RS 67333 or VRX-03011/galanthaminium, RS 67333 or prucalopride/donepezil).

Donecopride, a new molecule combining 5-HT_4R agonism and acetylcholinesterase (AChE) inhibition was recently released. (6) This compound exerts symptomatic actions (inhibition

of ACh degradation via blockade of the AChE catalytic site and release of ACh via activation of 5-HT_4Rs) that could restore cholinergic neurotransmission (Figure 2). Moreover, donecopride has disease-modifying properties (i.e., inhibition of Aβ aggregation via the blockade of the AChE peripheral anionic site and promotion of nonamyloidogenic processing of APP via 5-HT_4R activation) that could help to slow AD progression. Combining several beneficial actions at different targets via a single drug facilitates pharmacokinetic studies, decreases the risk of drug interactions, and simplifies therapeutic dose and treatment compliance. Preclinical follow-up of donecopride will be needed to verify whether this single molecule acting simultaneously on two targets produces beneficial action beyond coadministration of two active substances directed toward the same two targets.

Figure 2

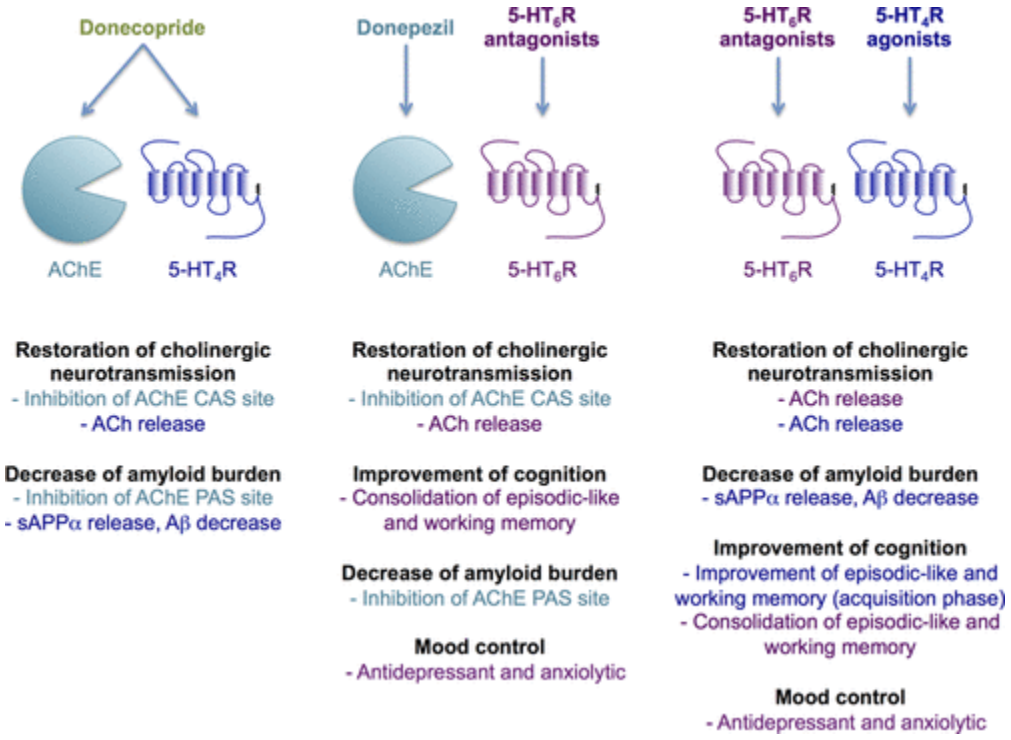


Figure 2. Multitarget-directed action that could be beneficial to slow AD pathology. Names of the different compounds and their targets are depicted. Putative types of effects are indicated with a color code corresponding to the target engaged. AChE, acetylcholinesterase; CAS, catalytic active site of AChE; PAS, peripheral anionic site of AChE.

It may also be of interest to target several serotonin receptors at the same time. In this context, SSRI treatment is relevant. However, activation of all serotonin receptors is not necessarily the best route since stimulating some receptor subtypes may be beneficial

(e.g., 5-HT_4Rs), whereas activating others (e.g., 5-HT_6Rs) may be deleterious. Thus, combining 5-HT_4R activation and 5-HT_6R inhibition may produce greater therapeutic benefit than SSRIs alone. Such a pharmacological combination has yet to be investigated (Figure 2).

In sum, there appears to be support for the idea of modulating the serotonergic system as a promising therapeutic strategy for treatment of AD. Moreover, combination therapy is an approach to be considered for treating complex illnesses such as AD.

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- Notes

The authors declare no competing financial interest.

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