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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.

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 comprised of hyperphosphorylated tau protein and amyloid plaques, insoluble aggregates of hydrophobic  $\beta$ -amyloid peptide ( $A\beta$ ). The formation of  $A\beta$  peptides results from the amyloidogenic degradation of transmembrane precursor, the amyloid precursor protein (APP), by  $\beta$ - and  $\gamma$ -secretases. Amyloidogenic processing occurs mainly in early/sorting and late endosomes (See Box 1). The non-amyloidogenic proteolysis of APP within the  $A\beta$  sequence by  $\alpha$ -secretase releases the extracellular fragment of APP ( $sAPP\alpha$ ), 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 biomarkers of  $A\beta$  dosage (e.g.,  $A\beta$  species ratios, phosphorylated tau protein levels in cerebrospinal fluid). Incontrovertible AD diagnosis is obtained by *post mortem* identification of neurofibrillary tangles and amyloid plaques.

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 anti-amyloid agents. However, during the last ten years, immunotherapy trials against  $A\beta$ , as well as  $\beta$ -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  $\beta$ -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  $A\beta$  proteins (a hallmark of AD) in the brains of amyloid protein precursor/presenilin-1 (APP/PS1) overexpressing mice, an AD mouse model<sup>1</sup>. This effect began 12-14 h after treatment, with a 25% reduction in  $A\beta$  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  $A\beta$  in the brain. This reduction occurred via activation of signaling pathways involving extracellular regulated kinase (ERK) and without alteration of  $A\beta$  clearance. Moreover, chronic SSRI administration was also able to reduce  $A\beta$  plaque loads in APP/PS1 mice. Together these preclinical findings suggest that increasing extracellular serotonin is a viable means to reduce  $A\beta$  plaque formation.

Clinical studies further support this idea. In humans,  $A\beta$  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<sup>1</sup>. 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<sup>2</sup>. More importantly, citalopram reduced A $\beta$  production and concentration in cerebrospinal fluid of healthy human volunteers<sup>2</sup>.

Rather than removing amyloid plaques, reducing production of A $\beta$  species has been demonstrated as key to the rescue of cognitive and synaptic deficits in AD mouse models<sup>3</sup>. Today, plaques are often viewed as a way by which damaged cells try to diminish A $\beta$  toxicity; namely, plaques may be an amyloid "dump". Transient A $\beta$  species that form oligomers have been identified as affecting neuronal structure and function. Consequently, lowering A $\beta$  production is a promising strategy to slow AD progression in humans. However, results of recent clinical trials have led to the conclusion that anti-amyloid 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 to 5 years).

## 5-HT<sub>4</sub> 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<sub>3</sub> 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<sub>2A</sub>, 5-HT<sub>2C</sub>, and 5-HT<sub>4</sub> receptors. Among them, the latter is an interesting candidate as 5-HT<sub>4</sub> receptor activation induces the non-amyloidogenic cleavage of APP (see Box 1) and release of the soluble sAPP $\alpha$  fragment, which possesses neurotrophic and neuroprotective properties.

Chronic administration of a 5-HT<sub>4</sub> receptor (5-HT<sub>4</sub>R) 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<sup>4</sup> (Fig. 1). By promoting  $\alpha$ -secretase cleavage of APP, 5-HT<sub>4</sub>R activation precluded formation of A $\beta$  (Box 1). Decreases in amyloid plaque load in mouse brains after chronic administration of the 5-HT<sub>4</sub>R agonist (Fig. 1) can be seen as an indicator that A $\beta$  has not been produced. Moreover, acute administration of a 5-HT<sub>4</sub>R agonist induced a transient increase in sAPP $\alpha$  in CSF of 5XFAD mice<sup>4</sup> (Fig. 1). This sAPP $\alpha$  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 sAPP $\alpha$  (if there is one) is still unknown. Chronic administration of the 5-HT<sub>4</sub> receptor agonist RS 67333 markedly reduced cerebral astrogliosis and microgliosis in 5XFAD mouse brains, cerebral inflammation processes associated with AD progression<sup>4</sup> (Fig. 1). This effect could be a consequence of lowering plaque burden or a direct action of 5-HT<sub>4</sub>R 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<sub>4</sub>R



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<sup>4</sup>.

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-A $\beta$  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<sub>4</sub>R agonists, the safety of these drugs must first be demonstrated. Several agonists of 5-HT<sub>4</sub> receptors have been developed to stimulate motility of the gastrointestinal tract. However, the 5-HT<sub>4</sub> 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<sub>4</sub>R agonist has been commercialized for use for five 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<sub>6</sub> RECEPTOR INHIBITION

Another serotonin receptor subtype that has received attention in the AD field is the 5-HT<sub>6</sub> receptor. This GPCR is coupled to G<sub>s</sub> similar to 5-HT<sub>4</sub>R. However, unlike 5-HT<sub>4</sub>R, several reports indicate that beneficial effects on cognition arise from *inactivation* of 5-HT<sub>6</sub> receptors via mechanisms that may not involve primary G<sub>s</sub> coupling (Fig. 1). Administration of 5-HT<sub>6</sub>R 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<sub>6</sub>R antagonists on cognitive processes.

More recently, the phase II clinical trial of idalopirdine, a 5-HT<sub>6</sub>R antagonist, found cognitive improvement in donepezil-treated patients with moderate AD who received idalopirdine as a combination therapy<sup>5</sup>. Interestingly, the authors of this study pointed out that while some monotherapies administered with 5-HT<sub>6</sub> 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 two-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 pro-cognitive effects so that differences between the two treatment groups are amplified and visible earlier? Would treatment with a 5-HT<sub>6</sub>R 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<sub>6</sub>R antagonists for AD therapy.

### MULTI-TARGET 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 multi-target action for AD therapy.

For a number of years now, 5-HT<sub>4</sub>R agonists have been considered nootropics due to their ability to enhance learning and memory in rodents. Moreover, 5-HT<sub>4</sub>R 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 sub-threshold doses of 5-HT<sub>4</sub>R 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<sub>4</sub>R agonism and acetylcholinesterase (AChE) inhibition was recently released<sup>6</sup>. 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<sub>4</sub>Rs) that could restore cholinergic neurotransmission (Fig. 2). Moreover, donecopride has disease-modifying properties (*i.e.*, inhibition of A $\beta$  aggregation *via* the blockade of the AChE peripheral anionic site and promotion of non-amyloidogenic processing of APP *via* 5-HT<sub>4</sub>R 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. Pre-clinical follow-up of donecopride will be needed to verify whether this single molecule acting simultaneously on two targets produces beneficial action beyond co-administration of two active substances directed towards the same two targets.

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<sub>4</sub>Rs), whereas activating others (*e.g.*, 5-HT<sub>6</sub>Rs) may be deleterious. Thus, combining 5-HT<sub>4</sub>R activation and 5-HT<sub>6</sub>R inhibition may produce greater therapeutic benefit than SSRIs alone. Such a pharmacological combination has yet to be investigated (Fig. 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.

## BOX 1

### Metabolism of the amyloid precursor protein (APP).

Two APP pathways co-exist. The amyloidogenic pathway leads to production of the amyloid- $\beta$  peptide ( $A\beta$ ) following the cleavage of APP by  $\beta$ -secretase (BACE1) and  $\gamma$ -secretase. The  $A\beta$  peptides form oligomeric toxic species, which aggregate into extracellular senile plaques. An alternative non-amyloidogenic pathway relies on the cleavage of APP by  $\alpha$ -secretase (ADAM10 in neurons). The  $\alpha$ -cleavage site located within the  $A\beta$  sequence precludes formation of the  $A\beta$  species and releases the soluble sAPP $\alpha$  fragment, which has neurotrophic and neuroprotective properties. Stimulation of 5-HT<sub>4</sub> receptors promotes the non-amyloidogenic cleavage of APP by activating the  $\alpha$ -secretase ADAM10.

## FIGURE LEGENDS

Figure 1. Major positive actions of 5-HT<sub>4</sub>R agonists and 5-HT<sub>6</sub>R 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<sup>4</sup>.

Figure 2. Multi-target-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.

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### Notes

The authors declare no competing financial interests.

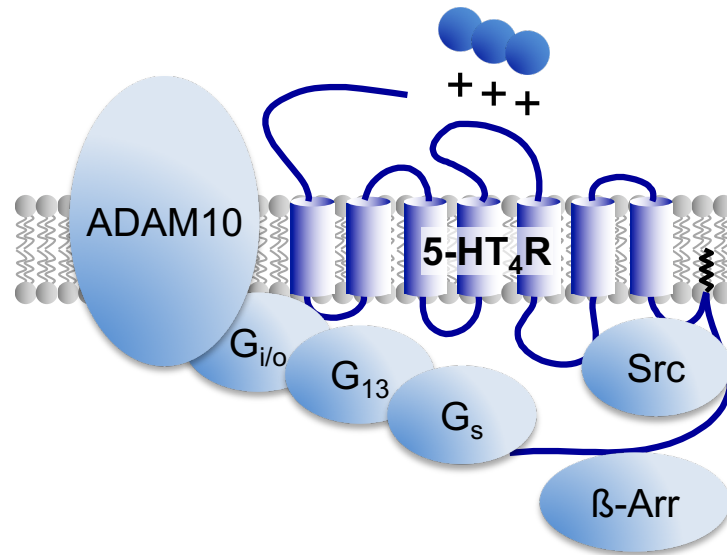
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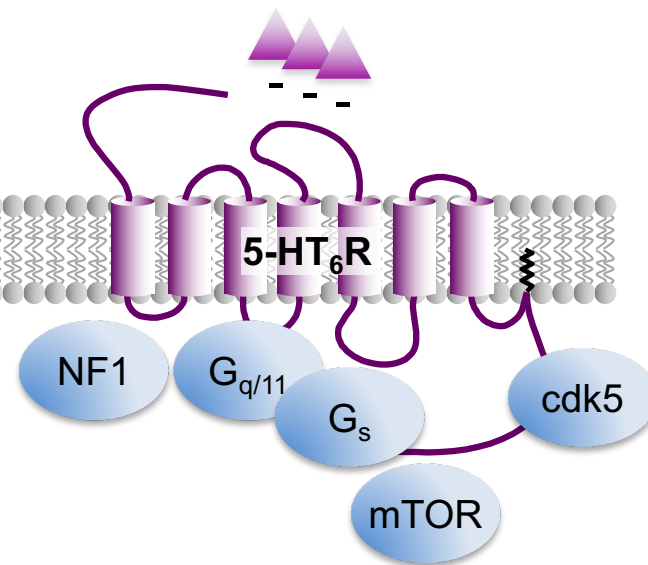
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## 5-HT<sub>4</sub>R agonists

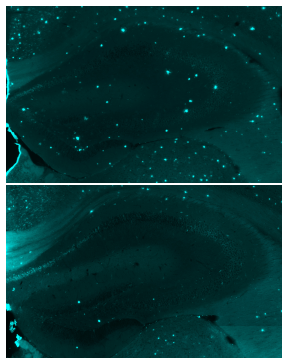


## 5-HT<sub>6</sub>R antagonists

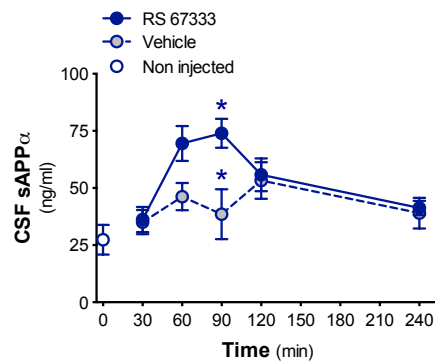


## Signal transduction pathways

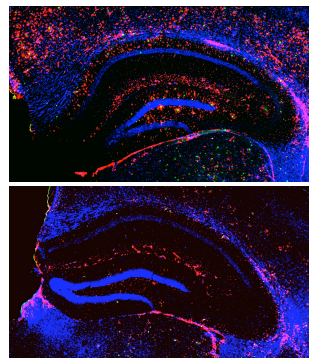
Decrease of  
plaques and Aβ level



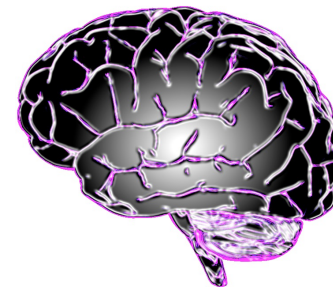
Increase of  
sAPP<sub>α</sub> production



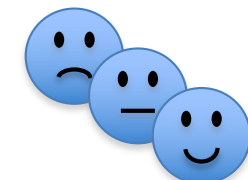
Reduction of  
inflammation

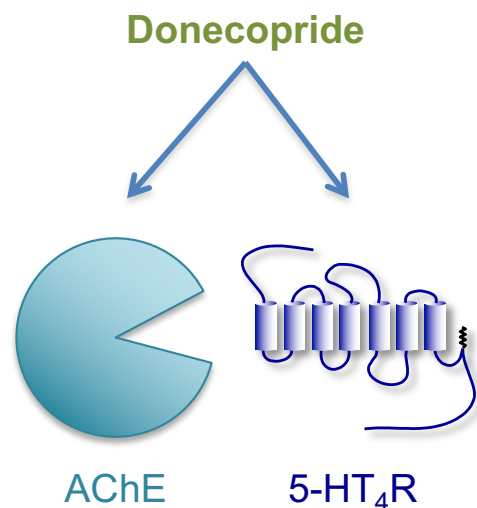


Procognitive  
effects



Mood control  
(antidepressant- and  
anxiolytic-like effects)



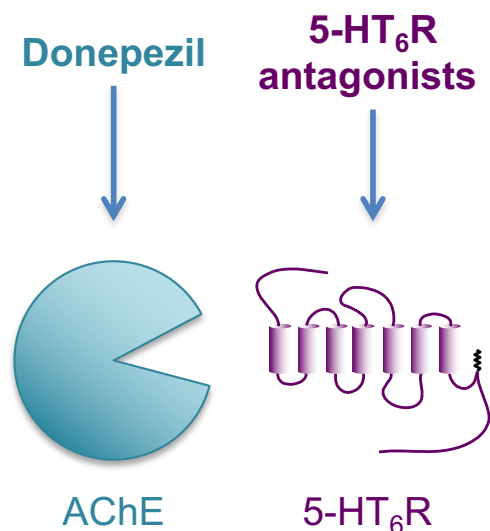


**Restoration of cholinergic neurotransmission**

- Inhibition of AChE CAS site
- ACh release

**Decrease of amyloid burden**

- Inhibition of AChE PAS site
- sAPP $\alpha$  release, A $\beta$  decrease



**Restoration of cholinergic neurotransmission**

- Inhibition of AChE CAS site
- ACh release

**Improvement of cognition**

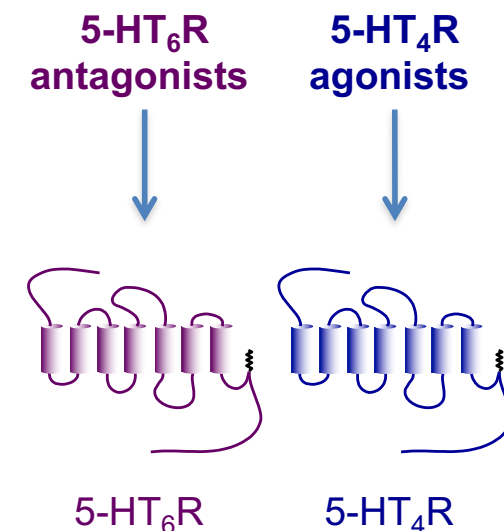
- Consolidation of episodic-like and working memory

**Decrease of amyloid burden**

- Inhibition of AChE PAS site

**Mood control**

- Antidepressant and anxiolytic



**Restoration of cholinergic neurotransmission**

- ACh release
- ACh release

**Decrease of amyloid burden**

- sAPP $\alpha$  release, A $\beta$  decrease

**Improvement of cognition**

- Improvement of episodic-like and working memory (acquisition phase)
- Consolidation of episodic-like and working memory

**Mood control**

- Antidepressant and anxiolytic

