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## Serotonin in The Brain: It's Role in maintaining the Survival of nerve cells in Alzheimer's Disease

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### Abstract.

Serotonin signaling is central to depression and anxiety disorders, but could also play important roles in the pathogenesis of several age-related disorders, including Alzheimer's disease. Alzheimer's disease (AD) is the most common form of dementia affecting 35 million individuals worldwide and this is expected to increase to 115 million by 2050. Therefore, modulation of defined serotonin receptors by specific ligands represents a promising tool for treatments for neurodegenerative diseases like AD. Serotonin neurons located in the raphe nucleus of the hindbrain have crucial roles in regulating brain functions and brain development where it regulates neurite outgrowth, synaptogenesis and cell survival. This paper provides a review the synthesis of serotonin and an overview of the involvement of the serotonergic system in AD

**Keywords:** Serotonin; nerve cell survival; alzheimer's disease

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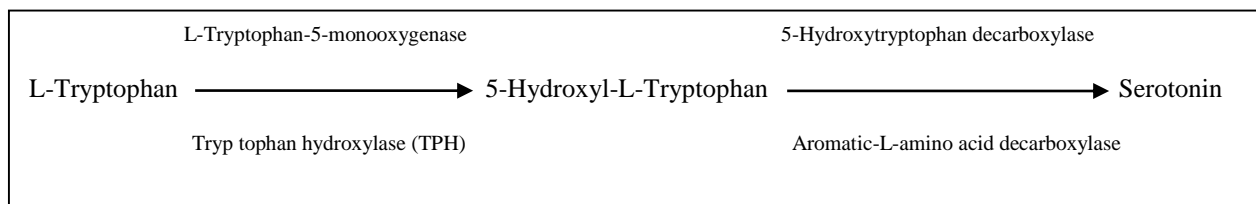
## 1. Introduction

The prevalence of AD is approximately 7–10% in individuals over the age of 65 and increases to about 40% over the age of 80 (Wuwongse et al, 2010). There are now thought to be more than 35 million sufferers worldwide and this is expected to increase to 115 million by 2050 (Hebert et al, 2013). It's related to pregressing death of neurons and loss of synapse, which results from accumulation of pathological protein deposits in the brain namely  $\beta$ -amyloid forming senile plaques and hyperphosphorylated tau protein forming neurofibrillary tangles/NFT (Apollini et al, 2009). Neurotoxic  $\beta$ -amyloid is a product resulting from the activity of  $\beta$ -secretase and  $\gamma$ -secretase, which cleave the Amyloid Precursor Protein (APP) (Delarasse et al, 2011). The activity of  $\alpha$ -secretase leads to the creation of soluble secreted Amyloid Precursor Protein- $\alpha$  (sAPP $\alpha$ ) (Scott and Sam, 2006), which is characterized by neuroprotective and neurotrophic properties (Franke, 2011). Serotonin acts as a neurotransmitter, a type of chemical that helps relay signals from one area of the brain to another. Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter derived from tryptophan (González et al, 2011). That serotonergic system modulation may present a promising strategy for slowing AD progression and improving cognition, named by Rapport et al (M. M. Rapport et al, 1948), is one of the ubiquitous molecules acting as messengers, well known as a neurotransmitter and neuromodulator mostly found outside the central nervous system (M.Berger et al, 2009) it was first identified in enterochromaffin cells and named as “enteramine” by Vialli and Erspamer in 1937 and confirmed to be the same entity with the “clotted blood” vasoconstriction effects in 1952 of animal including humans contributor to feelings of well-being and happiness (V.Erspamer and Asero, 1952; Young SN, 2007). 5-Hydroxytryptamine (5-HT) is produced by neurons located in the brainstem raphe nuclei and is released from the terminals of serotonergic neurons that project from the raphe nucleus. The serotonergic projections innervate multiple cortical brain regions to regulate a wide repertoire of behaviors, as well as cognition and mood. In addition to its prominent role as a neurotransmitter, 5-HT plays an important role in brain development via regulation of neurite outgrowth, synaptogenesis, and cell survival (Gaspar *et al*, 2003). There are a distinct number of serotonin receptors 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6 and 5-HT7 which can be further categorised into subtypes. The 5-HT2 receptor is a Gq linked G-protein coupled receptor, increasing cellular levels of IP3 and DAG, while 5-HT1 and 5-HT5 are Gi -protein coupled, 5HT3 is a ligand-gated Na<sup>+</sup> and K<sup>+</sup> cation channel and 5HT4,-6 and

-7 are Gs-protein coupled. Microglia from primary cultured neonatal mice, as well as freshly isolated microglia from the brains of adult mice, were shown to express mRNA for serotonin receptors. Freshly isolated adult microglia were found to express class 2, 5-HT5a and 7 serotonin receptors but not 5-HT1b, 5-HT3a, 5-HT5b, 5-HT6 (Krabbe et al, 2012). Several 5-HT receptors have been shown to influence processing of the amyloid protein precursor (APP), including 5-HT2AR, 5-HT2CR, and 5-HT4R (Cochet et al., 2013; Thathiah and De Strooper, 2011). The human brain is a large, complex organ that is characterized by communication between its component cells, especially neurons. One neurotransmitter used by many neurons throughout the brain is serotonin, synthesized in serotonergic neurons of the CNS, it has functions the regulation of mood, appetite, sleep, memory and learning. The appearance of 5-hydroxytryptamine in the cerebral cortex coincides with developmental events such as cell proliferation, survival, and differentiation (Dolley AE et al, 1997).

## II. Discussion

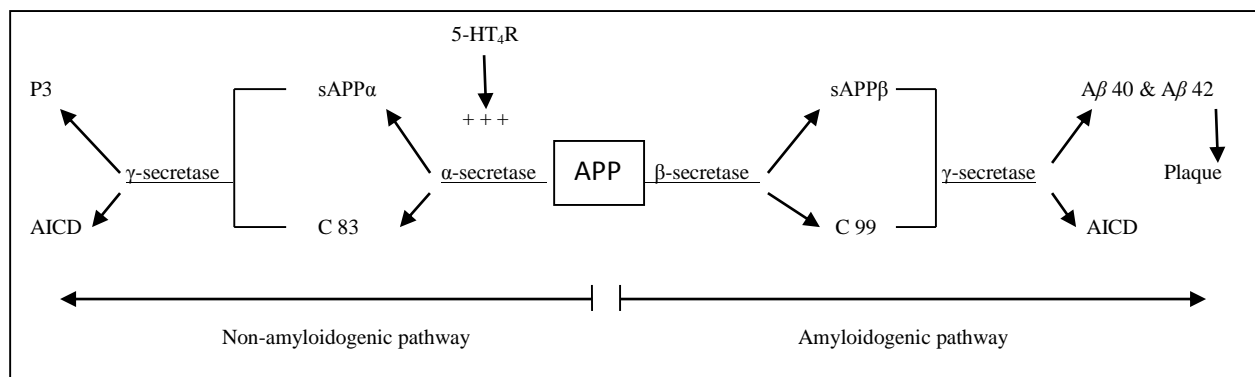
Serotonin is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of three enzymes: Tryptophan Hydroxylase (TPH), aromatic amino acid decarboxylase (DDC) and pyridoxal phosphate. TPH has been shown to exist in two forms: TPH1, found in several tissues, and TPH2, which is a neuron-specific isoform (Côté et al,2003). Tryptophan hydroxylase, a chemical reactor which, when combined with tryptophan, forms 5-hydroxytryptamine (5-HT), otherwise known as serotonin. More pictures can be seen in the following chart below:



The receptors for serotonin, are located on the cell membrane of nerve cells and other cell types in animals, and mediate the effects of serotonin as the endogenous ligand, except for the 5-HT<sub>3</sub> receptor, a ligand-gated ion channel, all other 5-HT receptors are G-protein-coupled receptors that activate an intracellular second messenger cascade (Hannon J et al, 2008). The serotonergic hypothesis of depression holds that 5-HT dysregulation is central to the

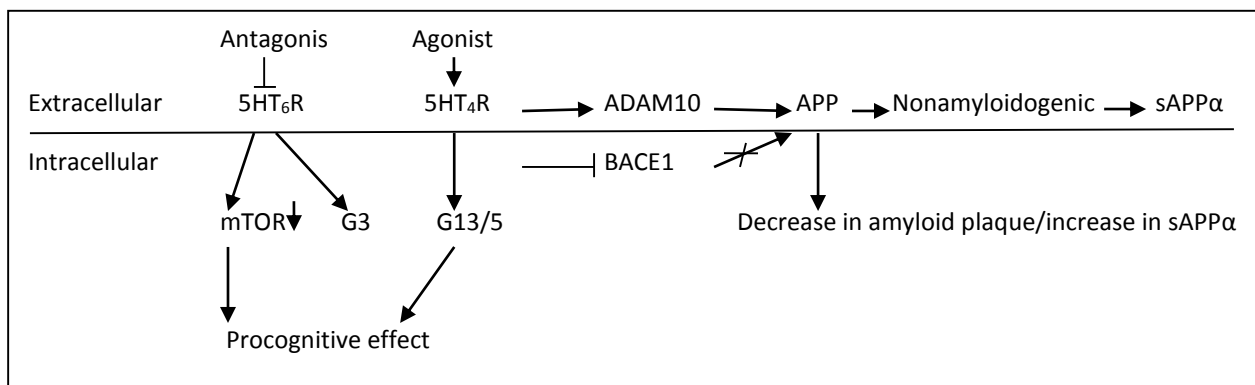
pathophysiology of mood disorders.. The neurons of the raphe nuclei are the principal source of 5-HT release in the brain (Frazer, A et al, 1999).

Activation of serotonergic neurotransmission might be beneficial in AD, acute administration of selective serotonin reuptake inhibitors (SSRIs) reduced production of toxic  $A\beta$  protein (a hallmark of AD) in the brains of amyloid protein precursor/presenilin-1 (AA/PS-1) overexpressing mice, an AD mouse model (Cirrito et al, 2011). The production of new neurons may be required for the behavioral effects of these molecules—it may also indicate that progenitor survival, proliferation, and differentiation are modulated by serotonergic neurotransmission (Banar *et al*, 2004; Brezun and Daszuta, 1999; Jacobs *et al*, 2000; Santarelli *et al*, 2003). The histological hallmarks of the AD are NFT composed of hyperphosphorylated tau protein and amyloid plaques, insoluble aggregates of hydrophobic  $\beta$ -amyloid peptide ( $A\beta$ ). The formation of  $A\beta$  peptide results from the amyloidogenic degradation of transmembrane precursor, the APP by  $\beta$ - and  $\gamma$ -secretase. Amyloidogenic processing occurs mainly in early/sorting and late endosomes. The nonamyloidogenic proteolysis of APP within the  $A\beta$  sequence by  $\alpha$ -secretase releases the extracellular fragment of APP (sAPP $\alpha$ ), which is neurotrophic (Claeysen et al, 2015). Metabolism of the APP: Two APP pathways coexist. The amyloidogenic pathway leads to production of the  $A\beta$  peptide 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 nonamyloidogenic pathway relies on the cleavage of APP by  $\alpha$ -secretase (ADAM10 in neuron). 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 $_4$  receptors promotes the nonamyloidogenic cleavage of APP by activating the  $\alpha$ -secretase ADAM10 (Claeysen et al, 2015). More pictures can be seen in the following chart below:



The latter is an interesting candidate as 5-HT<sub>4</sub> receptor activation induces the nonamyloidogenic cleavage of APP and release of the soluble sAPP $\alpha$  fragment, which possesses neurotrophic and neuroprotective properties (Giannoni et al, 2013). 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 (Giannoni et al, 2013). Another 5-HT receptor that has recently received attention as a potential target for the AD treatment is the 5-HT<sub>6</sub>R. Although, similarly to 5-HT<sub>4</sub>R, this receptor is coupled to the Gs-protein to stimulate AC, several reports suggest that beneficial effects on cognition arise from 5-HT<sub>6</sub>R inactivation. Administration of 5-HT<sub>6</sub>R antagonists to rodent models of AD improves cognitive performance in numerous behavioral tests (Upton et al, 2008). More recently, results obtained in the phase II clinical trial for 5-HT<sub>6</sub>R antagonist idalopirdine demonstrated cognitive improvement in patients with moderate AD who received idalopirdine as a combination therapy with an inhibitor of Acetylcholinesterase donepezil, which is routinely used for a symptomatic AD treatment (Wilkinson et al, 2014). At the cellular level, beneficial effects of 5-HT<sub>6</sub>R inhibition might be evoked due to inhibition of the mTOR pathway, rather than Gs-mediated modulation of proteases involved in A $\beta$  processing (e.g. ADAM10) (Wang et al, 2013). However, detailed molecular mechanisms still remain elusive.

Serotonin receptors and APP processing: The impact of 5HT<sub>4</sub>R and 5HT<sub>6</sub>R mediated signaling on the APP degradation, while stimulation of the 5HT<sub>4</sub>R drives APP processing towards the beneficial non-amyloidogenic path via direct interaction with  $\alpha$ -secretase ADAM10 or  $\beta$ -secretase BACE1. Inhibition of the 5HT<sub>6</sub>R promotes precognitive effects via reduction of mTOR activity (Claeysen et al, 2015) . More pictures can be seen in the following chart below:



### III. Conclusion

Alzheimer's disease (AD) is the most common cause of severe memory loss and cognitive deterioration in the elderly, thus representing a major health concern in the ageing society. The extensive serotonergic denervation obtained in the AD brain, as well as an important role of serotonin (5-hydroxytryptamine; 5-HT) in both cognition and behavioural control. Serotonin is a chemical that is manufactured in the body and acts as a neurotransmitter and neuromodulator, that helps signals cross from one neuron, or nerve cell, to the other and to regulate synaptic plasticity, neurogenesis, neuroprotective, neuroprotective and neuronal survival in the adult brain. This leads to the formation of two amyloidogenic fragments of APP, A $\beta$ 40 and A $\beta$ 42. Amyloidogenic processing occurs mainly in early/sorting and late endosomes, where resulting A $\beta$  peptides form oligomeric toxic species aggregating into extracellular senile plaques. An alternative non-amyloidogenic pathway is based on the cleavage of APP by an  $\alpha$ -secretase (e.g. ADAM10). Cleavage at the  $\alpha$  site located within the A $\beta$  sequence prevents formation of the A $\beta$  species and releases the extracellular soluble fragment of APP (sAPP $\alpha$ ), which possesses neurotrophic and neuroprotective properties and can thus increase a long-term potentiation. The molecular and cellular mechanisms leading to its onset and progression are still far from being completely understood. Thus, general treatment approaches using SSRIs might also be of interest, and combined application of agonists and antagonist from 5HT $_4$ R and 5HT $_6$ R for defined serotonin receptors may result in higher therapeutic benefit, is expected to affect the survival of nerve cells in AD.

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