

## Review Article

# Serotonin In Brain: A Cue for Alzheimer's Disease

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Corresponding Author:

**Dr. Vivek Sharma \***

Department of  
Pharmacology, Government College  
of Pharmacy, Rohru, Distt. Shimla-  
171207 (Himachal Pradesh) India

Ph.No. +919816532662



\*Email Id-

viveksharma\_pharma@yahoo.co.in

Vivek Sharma\*, Anita, Rajni Sharma, Rajender Guleria

### ABSTRACT

Alzheimer's disease (AD), a common fatal neurodegenerative disorder is manifested by core features of progressive memory impairment, visuospatial decline, aphasia, agnosia, loss of executive function and severe neuropsychiatric changes like hallucinations and depression. AD is characterized by cholinergic dysfunction, but treatments targeting the cholinergic system alone have yielded disappointing results. Present review focuses on the investigation of possible involvement of serotonin (5-HT) in pathogenesis of AD beside its versatile role in brain physiology. Serotonin has been implicated in almost every conceivable physiologic or behavioural function like affect, aggression, appetite, cognition, memory, sleep, emesis, endocrine functions, gastrointestinal functions, motor functions, neurotrophism, perception, sensory functions, sex, and vascular function etc. In addition to its physiological role, growing evidence suggests the neuromodulator serotonin also regulates the connectivity of the brain by modulating developmental cellular migration and cyto-architecture. Pathologically, it is involved in depression, aggression, anxiety and disturbances in food intake. This plethora of roles has consequently led to the development of many compounds of therapeutic value, including various antidepressant, antipsychotic and antiemetic drugs. Investigation of serotonin is encouraged by the fact that there is serotonin loss in normal aging and neuropsychiatric diseases of late life which may contribute to behavioural changes. Continuous researches over the years have found that instead of malfunction of single neurotransmitter, AD is a multineurotransmitter deficit thus role of other neurotransmitter particularly 5HT, beside Ach needs thorough investigation.

**Key-words:** Alzheimer's disease, acetylcholine, serotonin

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## **Introduction**

The human brain is a large, complex organ that is characterized by communication between its component cells, especially neurons. Other bodily organs as pancreas, gut, and adrenal glands excrete hormones to the blood stream and thereby communicate with cells far away. However, the intercellular communication of the brain has a far greater complexity and communication among neurons is the prerequisite for the working brain.<sup>1</sup>

Neurotransmitters are chemicals that allow signal transmission and thus communication, among neurons. One neurotransmitter used by many neurons throughout the brain is serotonin, also known as 5-hydroxytryptamine (5-HT). Serotonin released by the signal-emitting neuron subtly alters the function of the signal-receiving neurons in a process called neuro-modulation.<sup>2</sup>

Serotonin is an ancient biochemical manipulated through evolution to be utilized extensively throughout the animal and plant kingdoms. Specific 5-HT-containing neurons and ascending 5-HT projections probably arose early in phylogeny.<sup>3</sup> In snails, leeches and molluscs, specialized 5-HT containing neurons have been identified.<sup>4</sup> It may appear in vertebrates, tunicates, arthropods, coelenterates and also in edible fruits and nuts. It may occur in diverse venoms, along with the common stinging nettle and in wasps and scorpions.<sup>5</sup>

Mammals employ 5-HT as a neurotransmitter within the central and peripheral nervous systems and also as a local hormone in numerous other tissues, including the gastrointestinal tract, the cardiovascular system and immune cells.

The discovery of serotonin can be traced back to 1868 when it was shown that the serum of clotted blood contained a factor capable of causing vasoconstriction. Eventually the indolamine serotonin was discovered by Rapport et al. and was to have vasoconstrictor properties and to clot blood. Independently Erspamer had discovered a factor (called Enteramine) in gut mucosa that was later shown to be identical to serotonin. Twarog page (1953) finally discovered that serotonin was present in the mammalian brain and this led others to prove the neurotransmitter role for this Indolamine.<sup>6</sup>

5-HT, one of the classes of monoamine neurotransmitters, all of which have a chemical template comprising of a basic amino group separated from an aromatic nucleus by a two carbon aliphatic chain. In mammals, 5-HT is biosynthetically derived by two enzymatic steps: (1) ring hydroxylation of the essential amino acid tryptophan by tryptophan hydroxylase, the rate-limiting step, and (2) side chain decarboxylation by aromatic amino acid decarboxylase.<sup>7</sup>

It is mainly found in the gastrointestinal tract (about 90% in enterochromaffin cells), platelets and in the central nervous system of humans and animals.<sup>8</sup> It is a thoroughly known contributor to feelings of well-being.<sup>9</sup>

While other cells outside the brain, such as blood platelets and some enterocytes, make and/or use serotonin, all serotonin used by brain cells must be made within the neurons, since serotonin cannot cross the blood brain barrier. Therefore, the synthesis of serotonin is heavily dependent upon the availability of L-tryptophan (LT) within the CNS. The production and subsequent transport of LT from the blood stream into the CNS can be compromised by several factors:

- 1) Stress, elevated cortisol levels, vitamin B6 deficiency, and even high dosages (above 2,000 mg) of LT, which all stimulate the conversion of LT to kynurenine, lowering serum LT levels.<sup>10,11</sup>
- 2) Elevated serum levels of kynurenine inhibit transport of LT into the CNS, and reduce CNS serotonin levels.<sup>12</sup>

3) Transport of LT across the blood brain barrier requires binding to a transport molecule, which LT shares with five other amino acids (tyrosine, phenylalanine, valine, leucine and isoleucine). Since LT is present in foods in relatively small amounts in comparison to these other amino acids, as little as one percent of dietary LT may be transported into the CNS.<sup>13</sup>

4) LT is used by the body for other metabolic purposes in addition to serotonin production, including protein synthesis and the creation of niacin<sup>13</sup>

Serotonin's diverse effects are mediated by a number of receptors distributed throughout the body. To date, at least fourteen different serotonin receptor subtypes have been identified in mammals and are grouped into seven families (5-HT<sub>1</sub>–5-HT<sub>7</sub>).<sup>7</sup>

All of the serotonin receptors are G-protein-coupled receptors except the 5-HT<sub>3</sub> ligand gated ion channel.<sup>14</sup> Most of the receptor subtypes are exclusively located postsynaptically on neurons, astrocytes and vascular elements while the 5-HT<sub>1</sub> receptors in the raphe nuclei are located presynaptically on the soma, dendrites, and axon terminals of serotonin neurons. They have an autoregulatory function.<sup>1</sup>

The binding of serotonin to its receptors initiates a series of biochemical events that converts the extracellular, chemical signal into an intracellular signal in the recipient cell. For example, the interaction of serotonin with one type of receptor stimulates the formation of small molecules (i.e., second messengers) within the cell. Second messengers interact with other proteins to activate various cellular functions, such as changes in the cell's electrical activity or in the activity of certain genes. These changes can result either in the inhibition or the excitation of the signal-receiving neuron, depending on the cell affected.<sup>2</sup>

Serotonin, has been implicated in almost every conceivable physiologic or behavioural function— affect, aggression, appetite, cognition, emesis, endocrine function, gastrointestinal function, motor function, neurotrophism, perception, sensory function, sex, sleep, and vascular function.<sup>15</sup>

Although serotonin's effect on individual neurons can be rather modest, its overall effect on the neurons in a given brain area can substantially influence brain functions such as learning and memory, perception of the environment, mood states, and responses to alcohol and other drugs of abuse.<sup>2</sup> The central serotonergic system has also been implicated in many physiological processes including thermoregulation,<sup>16</sup> satiety,<sup>17</sup> neurogenesis<sup>18</sup>, stress response<sup>19</sup> and aggression.<sup>20</sup> In addition, 5-HT has been linked to motor system function,<sup>21</sup> circadian rhythms<sup>22</sup> respiratory stability,<sup>23</sup> embryonic development<sup>24</sup> and reward processing.<sup>25</sup>

Dysfunctional 5-HT transmission has been associated with depression, panic, anxiety, postpartum blues, depression, obsessive-compulsive disorders, attention deficit hyperactivity disorder, autism, eating disorders, schizophrenia and borderline personality disorders.<sup>26,27</sup>

Many drugs that are currently used for the treatment of psychiatric disorders (e.g., depression, mania, schizophrenia, autism, obsessive compulsive disorder, anxiety disorders) are thought to act, at least partially, through serotonergic mechanisms. This versatile role may be attributed to serotonin because of 5-HT cell bodies clustered in the brainstem raphe nuclei are positioned through their vast projections to influence all regions of the neuraxis. Another answer lies in the molecular diversity and differential cellular distribution of the many 5-HT receptor subtypes that are expressed in brain and other tissues.

Pharmacologically, the focus on the serotonin system has increased by the widespread use of the antidepressant medications of the class 'selective serotonin reuptake inhibitor' (SSRI), which block the serotonin transporter (5-HTT) located presynaptically on projecting serotonergic axons,

thereby increasing the interstitial serotonin concentration. In addition, the 5-HT<sub>2A</sub> receptors are targets for medications used to treat conditions such as schizophrenia, anxiety, depression, and Parkinson's disease. Moreover, most hallucinogens mediate their effects through the 5-HT<sub>2A</sub> receptor.<sup>28</sup>

### **Serotonin and Alzheimer's disease**

Alzheimer's disease (AD) is the most common neurodegenerative form of dementia and aging is the most important risk factor for AD. 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. AD is incurable and increases the mortality rate by approximately 40% in men and women. The number of people who have AD is expected to double every 20 years, thereby constituting significant medico- and socioeconomical burden.<sup>29</sup> Alzheimer's disease can occur in people as young as 40, the prevalence increases with age, with up to one in four aged 85 and above suffering from this condition.<sup>30</sup> (WHO, 2002). There are now thought to be more than 35 million sufferers worldwide and this is expected to increase to 115 million by 2050.<sup>31</sup>

AD mainly affects primarily limbic, paralimbic, and neocortical structures. At the molecular level, the primary abnormalities include abnormal processing of amyloid precursor protein (APP), hyperphosphorylation of tau protein, and apoptotic-like cell death.<sup>32</sup> Intraneuronal neurofibrillary tangles containing tau protein, which first appear in the medial temporal lobe and spread to the rest of the cortex as the disease advances.<sup>33</sup>

Neuronal death in specific transmitter source nuclei results in deficiencies of acetylcholine, serotonin, and norepinephrine that contribute to the matrix of pathological changes underlying the clinical syndrome.<sup>34</sup>

In this disease, the capacity to memorize is seriously reduced because of compromised neuronal transmission<sup>35</sup> and multiple neurotransmitter systems have been reported to be altered in the AD brain. Significant pyramidal neuronal loss results in diminished acetylcholine (ACh), epinephrine, and serotonin transmissions in the cortex and hippocampus, accounting for the symptoms in AD.<sup>36</sup>

Although cholinergic and glutamatergic drugs are used for the symptomatic treatment of memory deficits in AD, there is a crucial need to discover new and efficient therapeutic strategies. In this context, serotonin receptors (5-HT<sub>R</sub>) represent promising therapeutic targets since the serotonergic neurotransmission system is implicated in the modulation of learning and memory processes.<sup>37,38</sup>

A well-documented decrease of 5-HT<sub>2A</sub> receptor binding is seen in PET studies of AD<sup>39</sup> whereas normal aging is associated with a decrease of 6–8% per decade.<sup>40</sup>

Symptoms of depression, aggression, anxiety and disturbances in food intake and sleep are common in AD and serotonergic impairment is well documented in that condition.<sup>1</sup> Serotonin has been shown to be linked to emotional behaviour in rat.<sup>41</sup> Thus it may be presumed that the anxiety state in Alzheimer's disease may be linked with disturbed serotonergic activity.<sup>35</sup>

Serotonergic dysfunction in AD appears to reflect a selective process rather than the result of generalized cortical neuronal degeneration, because other neurotransmitter systems, such as opioid,  $\gamma$ -aminobutyric acid (GABA),  $\alpha$ -1,  $\alpha$ -2, and  $\beta$ -adrenergic, are unaltered or less severely affected.<sup>42,43</sup>

Most of the brain 5-HT is localized in the thalamus, hypothalamus, midbrain and raphe nuclei of the lower brain stem.<sup>44</sup> The largest collections of 5-HT neurons are in the dorsal and median raphe nuclei of the caudal midbrain.<sup>45</sup>

The neurons of these nuclei project widely over the thalamus, hypothalamus, basal ganglia, basal forebrain, and the entire neocortex. These innervations result in 5-HT release into the cerebrospinal fluid (CSF) and measurement of 5-HT content in CSF in disease states will largely reflect this pool.<sup>46</sup> This is another interesting aspect of the 5-HT neuron innervations of forebrain. Work by Descarries and colleagues<sup>47</sup> have shown that the terminals of 5-HT neurons in forebrain, unlike terminals from other systems, only infrequently form synaptic complexes. Thus, when 5-HT neurons innervating forebrain are activated, 5-HT will be released into the extracellular fluid, and its action will depend on the location of nearby 5-HT receptors. The organization of the ascending 5-HT neuron projections, the nature of their interaction with postsynaptic elements and the widespread distribution of 5-HT terminals in cortical and limbic areas indicate that these projections are most likely to be involved in the regulation of behavioural state and the modulation of more specific behaviours. The second 5-HT neuron system is comprised of 5-HT neurons in the pontine and medullary raphe with projections principally to brainstem, cerebellum, and spinal cord. This system appears primarily to be involved in modulation of sensory input and motor control.<sup>48</sup>

Additionally, modulation of cholinergic neuronal activity by 5-HT may play a role in higher cognitive processes such as memory and learning.<sup>49,50</sup> Accordingly, alterations in serotonergic function may account for behavioural disturbances commonly observed in the elderly. Indeed, changes in serotonergic activity have been implicated in normal aging, depression, and dementia.<sup>48</sup>

Serotonin receptors are more dense at birth than in the mature brain and may regulate the maturation of cortical neurons.<sup>51</sup>

Several post mortem human studies have reported a reduction in the number of cortical 5-HT<sub>1A</sub>, 5-HT<sub>1B/D</sub>, and 5-HT<sub>2A</sub> binding sites with age in frontal lobe, occipital lobe, and hippocampus.<sup>52,53</sup>

Extra-hepatic catabolism of tryptophan along the oxidative pathway occurs via the enzyme indoleamine 2,3-dioxygenase (IDO). Under normal conditions, IDO activity is minimal, but the enzyme becomes induced through pro-inflammatory cytokines such as interferon.<sup>54</sup> High IDO activity has been observed in activated macrophages of the peripheral immune system and in activated microglia of the brain.<sup>55</sup> In inflammatory brain diseases including Alzheimer's dementia, microglia concomitant with IDO will become activated, leading to an increased degradation of tryptophan, thereby reducing local synthesis of 5-HT.

First, reduction of 5-HT and its metabolites have been reported in post mortem AD brains.<sup>56</sup> The raphe nucleus, and area of high serotonergic neuronal density, is a preferential site for neurofibrillary tangle (NFT) formation and neuronal losses in AD.<sup>57</sup> There is evidence of decreases in cortical 5-HT receptors, with 5-HT<sub>2A</sub> preferentially affected over 5-HT<sub>1A</sub> receptors.<sup>58</sup>

Post mortem brain studies of patients who had AD have consistently found significant loss of serotonergic neurons or reductions in the plasma membrane serotonin transporter (5-HTT) in the raphe nuclei.<sup>59,60</sup>

Further, amyloid- $\beta$  (A $\beta$ ) dysregulation appears to initiate the pathogenesis of Alzheimer's disease (AD) with a cascade of downstream factors that exacerbate and propagate neuronal injury.<sup>61</sup> A $\beta$  can accumulate as toxic plaques and soluble oligomers in the brains of individuals with AD a

decade or more before the initial symptoms are identified.<sup>62</sup> Serotonin signalling acutely reduced brain A $\beta$  levels and chronically reduced A $\beta$  plaques in a mouse model of AD.<sup>63</sup>

The 5-HT<sub>4</sub> receptor has its' highest cerebral density in the basal ganglia and medium density in hippocampus.<sup>64</sup> Animal studies have found procognitive and memory enhancing effects of 5-HT<sub>4</sub> partial agonists<sup>65,66</sup> possibly mediated by a modulation of other neurotransmitter systems<sup>67</sup> such as the dopaminergic,<sup>68</sup>GABAergic<sup>69</sup> and acetylcholinergic systems. Thus, 5-HT<sub>4</sub> agonists are shown to facilitate at least in part the release of the neurotransmitter acetylcholine in frontal cortex<sup>70</sup> and hippocampus.<sup>64</sup>

Clinical trials (phase IIb) with a partial agonist are underway for the treatment of Alzheimer's disease (AD), based on the observation that 5-HT<sub>4</sub> receptor stimulation in a transgenic mouse model<sup>71</sup> increases the cerebral levels of the soluble amyloidprecursor protein (sAPP $\alpha$ ) that is believed to be neuroprotective and enhance memory consolidation.<sup>72</sup> This is achieved by diverting the cleavage pathway of the amyloid precursor protein, which thereby precludes the formation of the pathological and neurotoxic insoluble b-amyloid polypeptide,<sup>73</sup> which is involved in Alzheimer's disease.<sup>1</sup>

## Conclusion

Serotonin shows its involvement in regulation of majority of physiological and metabolic processes. Although its role in pathogenesis of AD is not clear but it's malfunctioning have been reported not only in AD patients but also with normal aging. Thus it become very clear that age associated neurodegeneration (AD) have a direct link with the normal levels of serotonin in our system. Thus it may be safe to conclude that targeting cholinergic system will not suffice, research efforts must be oriented to investigate and explore the exact role of serotonin and its possible therapeutic potential in treatment of Alzheimer's disease.

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