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The Role Of Serotonin In The Cognitive Function Of The Elderly : A Literature Review

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Abstract. *The last few decades have seen an increase in the number of elderly populations around the world. One consequence of an aging population is an increased incidence of impaired cognitive function. Serotonin, or 5-hydroxytryptamine (5-HT), is found to be involved in many physiological or pathophysiological processes including cognitive function. Alterations in serotonin (5-HT) function have been hypothesized to underlie a range of physiological, emotional, and cognitive changes in eldery. This paper provide reviews and references that a serotonin plays a role in the cognitive function of the elderly.*

Keyword: *Serotonin, Elderly, Cognitive function*

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1 Introduction

Many studies report that the population of elderly people is growing, and as the number of elderly persons increases, an increase in the number of people showing cognitive function decline is to be expected[1]. Cognitive functions represent a spectrum of mental abilities and complex processes related to attention, memory, judgment and evaluation, problem-solving and decision

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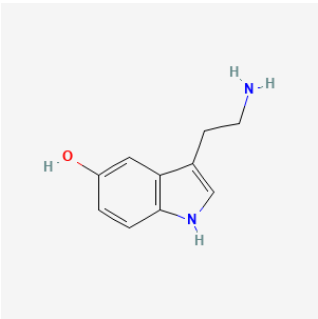
making, as well as to comprehension and language synthesis[2]. The aging process entails various biochemical changes in brain. The recent research has identified a number of neurotransmitters, as well as their receptors which exhibit alterations in various regions of the brain with the aging process. The major neurotransmitter systems include the noradrenaline (norepinephrine) system, the dopamine system, the serotonin system, and the cholinergic system, among others[3]. More recently, studies have focused on serotonin (5-HT) as one of the possible cognition-related biomarkers[2]. In the past decade, experimental studies with animals and humans have revealed that 5-HT may also play an important role in normal and disturbed cognitive function[4]. Serotonin has an influence on cognition, sensory perception, motor activity, temperature regulation, nociception, appetite, sexual behaviour and hormone secretion[5]. A decrease in serotonin levels impacts increases health disorders, such as depression, cognitive function decline, and increase anxiety[6]. Enhanced brain serotonin activity has been shown to improve cognitive performance in animals and human[7].

2 Serotonin (5-HT, 5-hydroxytriptamine)

Serotonin is neurotransmitter acting in the central nervous system (CNS), blood factor, and neurohormone controlling the function of several peripheral organs[8]. Serotonin is found high concentration in enterochromaffin cells throughout gastronintestinal (GI) tract, and enhances platelet aggregation. Serotonin is widely distributed in the animal and plant kingdoms. Several important laboratory invertebrate models have serotonergic system including fruit, fly and nematode[8].

2.1 Source and Chemistry

5-HT [3-(β-anonoethyl)-5-hydroxyindole) is present in vertebrates, tunicates, mollusks, arthropods, coelenterates, fruits and nuts. It it also a component of venoms, including those of the common stinging nettle and wasps and scorpions. Numerous synthetic or naturally occurring congeners of 5-HT have pharmacological activity. Many of the N- and O-methylated indolamines, such as N,N-dimethyltryptamine, are hallucinogens. Because these compounds are behaviorally active and might be synthesized by known metabolic pathways, they have long been considered candidates for endogenous psychotomimetic substances, potentially responsible for some psychotic behaviors[8].



Chemical structure of serotonin

(Source : Serotonin | C10H12N2O - PubChem (nih.gov))

Serotonin (5-HT) is synthesized in the human body from the naturally occurring essential amino acid tryptophan. Once ingested, tryptophan is converted to serotonin (5-HT) via a series of reactions (see Figure). First, L-tryptophan is hydroxylated to 5-hydroxy-L-tryptophan (5-HTP) via the enzyme tryptophan hydroxylase. This enzyme occurs in two isoforms, tryptophan hydroxylase 1 and tryptophan hydroxylase 2, which are responsible for the non-neuronal and neuronal synthesis of serotonin, respectively. This reaction constitutes the rate-limiting step in the synthesis of serotonin. The cofactors oxygen and tetrahydropteridine are required for this reaction to occur. 5-HTP is in turn converted to 5-HT via the enzyme L-amino acid decarboxylase. Necessary cofactors for this reaction are vitamin B6, vitamin B3, and magnesium. The blood–brain barrier is impermeable to peripheral 5-HT, but not to 5-hydroxy-tryptophan. Therefore, the amount of 5-HT that is produced centrally is dependent on the amount of tryptophan that is available peripherally to cross the blood–brain barrier. A carrier protein is required for tryptophan-active transport across the blood–brain barrier. Tryptophan competes with other large neutral and branched-chain amino acids such as valine, leucine, and isoleucine for this carrier protein. Unlike tryptophan, 5-HTP easily crosses the blood–brain barrier as it does not require a specific transport protein[9].

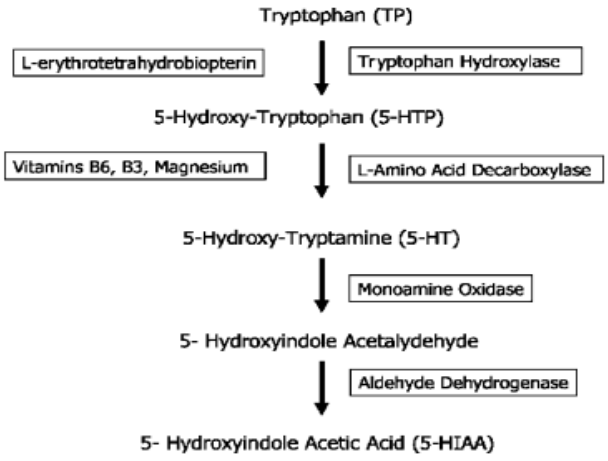


Figure : Biosynthesis and metabolism of serotonin. Cofactors left of arrows, enzymes right of arrows

2.2 Storage and Metabolism

About 95% of peripheral serotonin is synthesized and stored in the enterochromaffin cells found in the gastrointestinal tract crypts with only a small fraction of total body serotonin produced in the brain-stem neurons of the raphe nuclei. Serotonin released into circulation from the enterochromaffin cells is rapidly taken up by platelets via either the 5-HT transporter (5-HTT) or the serotonin transporter (SERT) and stored in platelet dense granules which constitutes almost all total body circulating serotonin. In the central nervous system, serotonin is stored in secretory

granules and released from serotonergic neurons into a synapse. Here, the action of serotonin is terminated by uptake via the 5-HTT located in the membrane of serotonergic axon terminals and returned to presynaptic terminals where it is metabolized. Serotonin is metabolized by the monoamine oxidase (MAO) enzyme (Fig. 1) to 5-hydroxyindole acetic acid (5-HIAA) via oxidative deamination. Two isoforms of monoamine oxidase (MAO-A and -B) exist. Both MAO-A and -B exist in neurons but only MAO-B exists in platelets. Circulatory serotonin enters the portal vein and is metabolized primarily in the liver. Any serotonin escaping liver metabolism is metabolized in the endothelium of lung capillaries. Brain 5-HIAA is actively transported to the periphery where along with peripheral 5-HIAA it is excreted in urine[9].

3 Serotonin receptors and transporter

At least 14 different serotonin classes of receptors (5-HT1A, 1B, 1D, 1E, 1F; 2A, 2B, 2C, 3, 4, 5A, 5B, 6 and 7) and a serotonin transporter (SERT) in the serotonergic system [11]. All serotonin receptors are G-protein-linked except 5-HT3 receptors, which are ionotropic (Table 1). As shown in tables 1 and 2, 5 HT receptors are divided according to distribution, molecular structure, cell response and function into seven group[12][13]. Most 5-HT receptors are present in brain regions associated with learning and memory. However, within any particular region, they may be expressed on different neuronal subtypes and in different layers of the region as heteroreceptors [14]. This diversity allows for complex cellular and regional mechanisms for regulation of receptor activity. Generally, it is has been suggested that effects of 5-HT receptor subtype manipulation on learning and memory are exerted through alterations in the release of neurotransmitters such as acetylcholine and glutamate, which have been more directly implicated in cognitive function than 5-HT itself[15]. Although selective agonists and antagonists have been developed for many 5-HT receptor subtypes, agents tested in healthy humans tend to be relatively non-selective. Nonetheless, evidence supports the potential therapeutic value of targeting one or more 5-HT receptors to enhance learning and memory in humans.

Table 1. Classification, distribution and function of 5-HT receptors

No	Receptor Family	Subtype	Distribution	Mechanism	Cellular respons
1	5-HT1	1A, 1B, 1D, 1E, 1F	CNS, blood vessels	Adenylate cyclase	Inhibitory
2	5-HT2	2A, 2B, 2C	CNS,PNS,plateles, blood vessels, smooth muscle	Phospolipase C	Exitatory
3	5-HT3	3A , 3B	CNS, PNS ; GI tract	Ligand-gated ion channel	Exitatory
4	5-HT4		CNS , PNS	Adenylate cyclase	Exitatory
5	5-HT5		CNS	Adenylate cyclase	Inhibitory
6	5-HT6		CNS	Adenylate cyclase	Exitatory
7	5-HT7			Adenylate cyclase	Exitatory

Abbreviations: CNS = central nervous system; PNS = peripheral nervous system, GI tract = gastrointestinal tract.

Table 2. 5-HT receptors in the brain

No	Receptor family	Distribution in the brain
1	5-HT1	Pituitary gland, rostral raphe nuclei, hippocampus, prefrontal cortex cerebellum, basal ganglia, amygdala, globus pallidus, putamen, caudate nucleus
2	5-HT2	Cerebral cortex, basal ganglia, amygdala, choroid plexus, hypothalamus, hippocampus, caudate nucleus, putamen, globus pallidus, substantia nigra
3	5-HT3	Area postrema, tractus solitarius, limbic system, hippocampus, cerebral cortex
4	5-HT4	Prefrontal cortex, caudate nucleus, putamen, globus pallidus, hippocampus, substantia nigra
5	5-HT5	Cerebral cortex, amygdala, cerebellum, hypothalamus, hippocampus
6	5-HT6	Dentate gyrus, hippocampus, olfactory tubercle, nucleus accumbens, amygdala, cerebellum
7	5-HT7	Thalamus

The serotonin transporter (SERT) is a protein high affinity transporter, located on the plasma membrane from pre-synaptic nerve endings [16]. SERT catalyzes movement of serotonin (5HT)

across cellular membranes[17]. In the brain, SERT clears serotonin from space extra cellular, modulating strength and duration serotonergic signaling.

4 Serotonin in aging and cognition

Alterations in serotonin (5-HT) function may account for behavioural disturbances commonly observed in the elderly. The neuromodulatory action of 5-HT on cognitive functions in both physiological and pathological states largely depends on the action of enzymes, transporters, and specific subtypes of expressed receptors (5-HTR), and their localization, which regulate local 5-HT concentration and neurotransmission[12]. Decrease in serotonin receptors and the serotonin transporter occur with age[13]. The Positron Emission Tomography (PET) studies in human subjects show that with age the number of the serotonin receptors in the caudate nucleus, putamen and frontal cerebral cortex decrease. There is also a decreased binding capacity for serotonin transporter in the thalamus and midbrain [14]. Pre-clinical and clinical studies suggest that the activity of the serotonergic system is associated with short- and long-term memory and cognitive performance, during aging[15] as well as in many psychiatric (schizophrenia, depression, alcoholism) and neurological (Alzheimer disease, epilepsy) disorders[2]. Several postmortem human studies have reported a reduction in the number of cortical 5-HT1A, 5-HT 1B/D and 5-HT2A binding sites with age in the frontal lobe, occipital lobe and hippocampus. There is, however, scant literature on the effect of aging on the 5-HT transporter. Geriatric depression carries an increased risk of suicide, higher mortality, and the potential for future development of dementia[5]. In older aged people, cognitive decline is often accompanied by the development of signs of depression. A meta-analysis of several clinical trials observed a procognitive effect of antidepressants in patients with major depressive disorder. Accordingly, antidepressants have a significant positive effect on psychomotor speed and delayed recall[16].

In the past decade, experimental studies with animals and humans have revealed that serotonin (5-HT) may also play an important role in normal and disturbed cognitive function[4] Recent research shows that serotonin affects cognitive function in the elderly including the essential amino acid tryptophan, which is a precursor to serotonin, a neurotransmitter involved in mood, information processing and cognitive function. For example, bioavailable tryptophan dietary supplements improved cognition in healthy middle-aged women[17]. A diet high in tryptophan as a precursor serotonin has been shown to improve learning and memory in these test animals because it prevents the decreased synthesis of 5-hydroxytryptamine (5-HT) or serotonin and 5-HIAA[18].

5 The ways of increasing serotonin in the body without drugs

A decrease in serotonin levels impacts increases health disorders, such as depression, cognitive function decline, and increase anxiety which are commonly experienced by the elderly. Therefore, it takes the right ways to prevent lower serotonin levels. There has been a lot written and research done on ways to increase serotonin in the body without drugs considering the many side effects

caused by the drugs in long term use. The following four suggestions have been best researched [25]:

1. Alterations in thought – self-induced changes in mood can influence the synthesis of serotonin in the body.

2. Exposure to bright light – more than 3000 lux.

3. Exercise – the most consistent effect is seen when regular exercisers undertake aerobic exercises at a level with which they are familiar.

4. Diet – the ingestion of food containing tryptophan[26]. The following foods naturally boost serotonin availability in the body: salmon, poultry, eggs, spinach, seeds, milk, soy products and nuts. These foods contain tryptophan in adequate quantities to increase serotonin in the body.

Conclusion

Based on literature above, neurotransmitter serotonin plays a role in cognitive function of elderly. Therefore, it is important to maintain serotonin levels in our bodies from decreasing, especially in the elderly to prevent cognitive decline.

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