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THE SEROTONERGIC SYSTEM IN ALZHEIMER'S DISEASE

ALZHEİMER HASTALIĞINDA SERATONERJİK SİSTEM

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Abstract

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases throughout the world that impairs brain regions related to learning and memory. Several neurotransmitter systems, especially the serotonergic system take part in cognitive processes, and the neurochemistry of AD patients is affected by AD-associated neurodegeneration. Serotonergic markers are located in diverse brain areas mostly related learning and memory. Therefore the serotonergic neurotransmission is very important in memory. Remarkable changes occur in the serotonergic system because of AD. Since AD is a progressive and irreversible disorder and there is no specific treatment for this disease, the number of patients is rapidly increasing. In this review, the relationship between AD and the serotonergic system is described in general terms. Especially serotonin (5-HT) receptors that take part in cognitive dysfunctions have examined in this study.

Keywords: alzheimer's disease, serotonergic markers, serotonin receptors, serotonin transporter, cognitive impairment

Özet

Öğrenme ve hafıza ile ilişkili beyin bölgelerinde bozulmalara neden olan Alzheimer hastalığı, dünya genelindeki en yaygın nörodejeneratif hastalıklardan biridir. Birçok nörotransmitter sistem, özellikle serotonerjik sistem, bilişsel süreçlerde yer alır ve Alzheimer hastalarının nörokimyası Alzheimer hastalığı ile ilişkili nörodejenerasyondan etkilenir. Serotonerjik belirteçler, çoğunlukla öğrenme ve bellek ile ilişkili çeşitli beyin bölgelerinde bulunur; bu nedenle serotonerjik nörotransmisyon hafızada çok önemlidir. Alzheimer hastalığı nedeniyle serotonerjik sistemde dikkate değer değişiklikler meydana gelir. Alzheimer hastalığı ilerleyici ve geri dönüşümsüz bir hastalık olduğundan ve bu hastalık için kesin bir tedavi yöntemi bulunmadığından, hasta sayısı günden güne hızla artmaktadır. Bu derlemede, Alzheimer hastalığı ile serotonerjik sistem arasındaki ilişki genel hatlarıyla açıklanmaktadır. Bu çalışmada, özellikle bilişsel işlev bozukluklarında rol alan serotonin (5-HT) reseptörleri incelenmiştir.

Anahtar Kelimeler: *alzheimer hastalığı, serotonerjik belirteçler, serotonin reseptörleri, serotonin taşıyıcı, kognitif bozukluk*

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1. Introduction

1.1.Dementia

Dementia is a serious disorder that is qualified by multiple cognitive deficits and presents many challenges to the patients, their families, and caregivers throughout the pathway of care, from early diagnosis to end of life (Logiudice & Watson, 2014). Dementia is a significant health problem in aging populations in which life expectancy has been longer (Toda et al., 2010). At the beginning of the 2010s, there were ~18 million people who had dementia throughout the world, and it was estimated that there would be ~34 million people with dementia in 2025. (Toda et al., 2010)

There are several risk factors of dementia such as older age, hypertension, genetic predisposition, diabetes, loss of consciousness that is caused from head injury, depression, smoking, etc. (Lautenschlager et al., 2003; Logiudice & Watson, 2014). Primary symptoms of dementia are complication in understanding people/finding the right words to say, loss of memory, being incapable of routine jobs and changes of personal characteristics. (Toda et al., 2010) Unfortunately, pharmacological therapies are largely unsuccessful on dementia, and they just provide symptomatic relieving. (Logiudice & Watson, 2014)

1.2. Alzheimer's Disease As The Most Common Cause of Dementia

Alois Alzheimer discovered Alzheimer's disease, the most prevalent cause of dementia in the older adults, in 1907. (Toda et al., 2010; Lai et al., 2011) Alzheimer's disease is one of the significant neurodegenerative diseases that is described by deterioration of memory and cognitive functions, and also it is a progressive and irreversible disorder. (Noristani et al., 2010; Toda et al., 2010; Rodríguez et al., 2012)

Alzheimer's disease (AD) impairs some brain regions such as the basal forebrain, the hippocampus and the neocortex which are associated with learning and memory, including both short- and long-term memory. (Noristani et al., 2010; Rodríguez et al., 2012) Also, it is known that the hippocampus and related structures are one of the earliest and most extensively affected brain regions in AD. (Lai et al., 2011)

Neuropathologically, there are some hallmarks such as amyloid-β plaques, neurofibrillary tangles (NFT), synaptic loss and synaptic plasticity degradation and neuronal impairment in AD. (Noristani et al., 2010; Lai et al., 2011) In addition, AD-associated neurodegeneration severely affects neurochemistry of brains of patients. Characteristically, impairment of cholinergic neurons in the cortex and hippocampus, a loss of the neurotransmitter (acetylcholine (ACh)) in cholinergic neurotransmission and a general decrease in the activity of choline acetyltransferase are linked with the AD. The loss of cholinergic neurotransmission has a critical function in the memory and learning degeneration of AD patients. Likewise, other neurotransmitter systems including serotonin, noradrenaline, and dopamine take part in cognitive processes; for instance, it has been proven that serotonergic impairments cause cognitive deficits in elderly animals and humans. (Toda et al., 2010; Rodríguez et al., 2012)

Drugs that increase cholinergic function have only mild effect in treating the cognitive deficits. Therefore, treating the cognitive deficits is required other neurotransmitters. (Noristani et al., 2010; Rodríguez et al., 2012)

2. Relationship Between Alzheimer's Disease and Serotonin Associated Structures

Serotonin (5-hydroxytryptamine, 5-HT) is a molecule with roles as a hormone, a neurotransmitter, and a mitogen; it has various functions in both central and peripheral nervous systems. (Figure 1) Serotonin has been present in numerous tissues such as kidney, brain, platelets, lung, gastrointestinal tract, etc. (Mohammad-Zadeh et al., 2008) Also, serotonin has various neuronal markers such as serotonin transporter (SERT) and serotonin receptors. (Meneses, 2015)

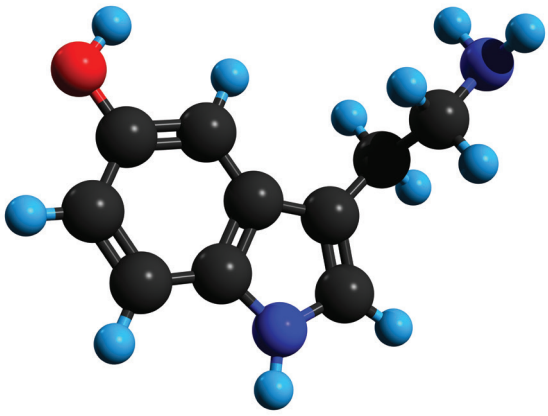

Figure 1: 3D View of the Serotonin Molecule in SPARTAN'14.

The serotonergic system is the most abundant monoaminergic system compared to others such as noradrenergic and dopaminergic systems; it is included in cognition, psychological and emotional states. (Lai et al., 2003; Rodríguez et al., 2012) 5-HT receptors, 5-HT reuptake site/transporter complex, and serotonergic pathways are distributed in various brain regions that are associated with learning, memory, drug addiction, cognitive processes, etc. (Meneses, 1999; Gonzalez et al., 2013; Meneses, 2015)

The serotonergic system works directly and indirectly by activated serotonin receptors as well as modulation of systems of other neurotransmitters such as glutamatergic, cholinergic, GABAergic, etc. (Rodríguez et al., 2012) In addition, the serotonergic system is intensively affected in people with Alzheimer's disease; remarkable changes are observed in the functions of the system because of aging, AD, amnesia, and anti-amnesic effects. (Lai et al., 2011; Gonzalez et al., 2013) One of the reasons of the damage is the reduction of neurons in the dorsal and median raphe nuclei that includes the greater part of the neurons, which synthesize serotonin for supplying essential serotonergic

innervation to the forebrain. (Noristani et al., 2010; Lai et al., 2011; Rodríguez et al., 2012)

One of the biochemical sources of neuropsychiatric, cognitive and non-cognitive behaviors in AD is confusion in serotonin-associated structures. (Lai et al., 2003; Lai et al., 2011) 5-HT neurotransmission has an important role in learning, memory and cognition; deficiency of 5-HT neurotransmission causes cognitive dysfunction in such neuropathological diseases known as schizophrenia, AD, depression, stress etc. (Noristani et al., 2010; Rodríguez et al., 2012; Xu et al., 2012) Both central and peripheral 5-HT neurotransmission decrease in AD patients due to the reduced 5-HT concentrations in the cerebrospinal fluid and platelets. In addition, post-mortem examination studies showed that extracellular levels of 5-HT and its metabolite (5-hydroxyindoleacetic acid, 5-HIAA) and expression of 5-HT receptors in diverse brain regions such as the hippocampus and the neocortex are reduced in AD patients. All of these reductions are interrelated with cognitive and behavioral differences between people with and without AD. (Noristani et al., 2010; Rodríguez et al., 2012) For instance Lai et al. mentioned that neuropsychiatric behaviors of AD patients and patients with psychiatric disorders have pretty same neurochemical features. (Lai et al., 2011)

The serotonergic system takes part in the therapeutic way of cognitive processes; for the treatment of dysfunctions in learning and memory several 5-HT mechanisms are beneficial. (Gonzalez et al., 2013) As stated by Noristani et al. and Rodríguez et al., to increase cognitive functions and of AD patients who have a 5-HT deficit, selective 5-HT re-uptake inhibitors (SSRIs) and specific ligands of 5-HT receptors are of some treatments methods; enhancement of 5-HT neurotransmission with various drugs is effective for cognitive and behavioral impairments of AD. (Noristani et al., 2010; Rodríguez et al., 2012)

2.1. 5-HT Receptors

Generally, there are seven class of 5-HT receptors called 5-HT1, 5-HT2, …, 5-HT7 based upon their primary physiological mechanisms, pharmacological characteristics, connection to intracellular signaling cascades and the protein structure. (Rodríguez et al., 2012; Kusek et al., 2015) 5-HT1,2,4-7 receptors are G-protein coupled receptors, and 5-HT3 receptor is the only ligand-gated cation channel in the 5-HT receptors family. (Bétry et al. 2011; Rodríguez et al., 2012; Xu et al. 2012) Also, Xu et al. and Meneses described that there are at least 16 different types of these receptors (5-HT1A/1B/1D/1E/1F, 5-HT2A/2B/2C, 5-HT3A/3B, 5-HT4A/4B/4C/4D, 5-HT5A/5B, 5-HT6, and 5-HT7A/7B/7C/7D). (Meneses, 1999; Xu et al., 2012) In this way, the serotonergic system is one of the most diverse neurotransmitter systems anatomically and functionally in the central nervous system. (Lai et al., 2011) Moreover, changes in 5-HT receptors are associated with of cognitive impairments, some subtypes of these receptors have a part in learning and memory. (Lai et al., 2011; Xu et al., 2012) In this connection, Xu et al. summarized the role of 5-HT receptors in neurodegenerative disorders such as the AD. (Xu et al., 2012)

2.1.1. 5-HT1 receptors

The 5-HT1A receptors play their role as autoreceptors in the raphe nuclei and as postsynaptic receptors in other regions of forebrain; they are related to learning, suicidal behaviors, depression, and aggression. (Lai et al., 2003) Cognitive functions are affected by activation of 5-HT1A receptors that cause inhibition of memory acquisition and consolidation, in other words, ascending 5-HT1A receptor density is associated with cognitive impairment in AD patients. (Noristani et al., 2010; Xu et al., 2012) Therefore, using of 5-HT1A receptor antagonists is required in the treatment of AD. (Xu et al., 2012) Since 5-HT1A receptor antagonists overcome memory impairments that result from cholinergic and glutamatergic deficits, they increase the release of ACh in the hippocampus and the cerebral cortex. (Rodríguez et al., 2012) Loss of 5-HT1A receptors is related to depressive symptoms on the contrary blockade of 5-HT1A receptors provides an improvement in cognition. (Lai et al., 2011; Rodríguez et al., 2012) On this matter, Lai et al. reported that lack of 5-HT1A binding in AD might constitute the neurochemical basis of aggression but it requires a further study. (Lai et al., 2003) Kepe et al. observed a major decrease in 5-HT1A receptor densities in the living brains of patients with AD in their study with [F-18] MPPF, a selective serotonin 1A (5-HT1A) molecular imaging probe, by using positron emission tomography (PET). (Kepe et al., 2006; Vermeiren et al., 2014) Also, Truchot et al. demonstrated a considerable decline of 5-HT1A receptor density in the hippocampus, para-hippocampus, inferior occipital gyrus and inferior temporal gyrus of patients with AD in their study with [F-18] MPPF by using positron emission tomography (PET) in 3D mode. (Truchot et al., 2008)

2.1.2. 5-HT2 receptors

The 5-HT2 receptors are thoroughly spread in the brain. (Xu et al., 2012) Activation of 5-HT2A receptors improves learning and memory consolidation. Glutamate and GABA release from presynaptic terminals enhances when 5-HT2A receptors are active and so when voltage-gated K+ channels are inhibited. (Rodríguez et al., 2012) Also, previous studies demonstrated that there are considerable declines of 5-HT2 receptor binding in the cerebral cortex, reductions in 5-HT2A receptor density in frontal and temporal cortical neurons of AD patients. (Xu et al., 2012) These situations mean that 5-HT2A receptor deficiencies are related to cognitive decline in AD. (Lai et al., 2011; Rodríguez et al., 2012; Xu et al., 2012) Therefore, 5-HT2A receptor agonists can be used. However, 5-HT2A receptor antagonists should not be used because of their negative effect on learning in the treatment of AD. (Rodríguez et al., 2012; Xu et al., 2012)

2.1.3. 5-HT3 receptors

In the areas of cortex and limbic system that are included in learning and memory, 5-HT3 receptors have a high density in patients with neurodegenerative disorders,

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especially AD. (Fakhfouri et al., 2012) Some studies with rats have shown that inhibition 5-HT3 receptors increase memory retention and spatial memory in rats. (Rodríguez et al., 2012) Therefore, 5-HT3 receptor antagonists can be used as an adjuvant for cognitive functions in the treatment of memory deficits that are related to neurodegenerative disorders. (Fakhfouri et al., 2012)

2.1.4. 5-HT4 receptors

Previous studies proved that 5-HT4 receptor density decreases in AD and 5-HT4 receptors are not markedly involved in cognitive regulation. (Meneses, 1999; Xu et al., 2012; Meneses, 2015) However deficiencies in 5-HT4, 5-HT6 receptors are associated with Behavioral and Psychological Symptoms of Dementia (BPSDs), i.e., psychosis, hyperphagia, depression, overactivity... (Lai et al., 2011)

2.1.5. 5-HT5 receptors

The 5-HT5 receptor family that has two subtypes entitled as 5-HT5A and 5-HT5B receptors is located in several areas of the brain such as the cerebral cortex, raphe nuclei, and hippocampus which are related to learning and memory. (Wesołowska, 2002; Hoyer, 2011; Gonzalez et al., 2013; Meneses, 2015) The 5-HT5A receptor subtypes are widely distributed in the central nervous system, whereas the 5-HT5B receptor subtypes have a limited distribution. (Hoyer, 2011) Additionally, only the 5-HT5B receptor subtypes have not been identified in humans, although both receptor subtypes have been identified in the mouse and rat; the reason is that the coding sequence of the human 5-HT5B gene is interrupted by stop codons. (Grailhe et al., 2001; Hoyer, 2011) For this reason, the first sample of a brain-specific protein which is not found in humans is the 5-HT5B receptor. (Grailhe et al., 2001)

2.1.6. 5-HT6 receptors

The 5-HT6 receptors, which have a specific range in the central nervous system, are distributed in the hippocampal, cortical, and striatal areas of the brain. (Xu et al., 2012) In connection with their possession of multiple modulating processes, modulation by 5-HT6 receptors makes learning and memory processes easier by releasing other neurotransmitters, such as acetylcholine and glutamate. (Xu et al., 2012) 5-HT6 receptors and cascades of signaling are altered depending on aging and AD. (Meneses, 2015) Both long and short-term memory is affected by activation of 5-HT6 receptors. (Rodríguez et al., 2012) In this context, blockade of 5-HT6 receptors provides recovery of learning deficits and enhances consolidation, acquirement, and storage of memory. (Rodríguez et al., 2012; Xu et al., 2012) Accordingly, 5-HT6 receptor antagonists have an important mission in AD for the treatment of cognitive impairments. (Xu et al., 2012; Meneses, 2015)

2.1.7. 5-HT7 receptors

The 5-HT7 receptors, which are widely distributed in the hippocampus are one of the newly identified types of the 5-HT receptor family. (Nikiforuk, 2015; Hashemi-Firouzi et al., 2017) Also, the 5-HT7 receptors are located in the dorsal raphe nucleus, thalamus, hypothalamus and frontal cortex. (Kusek et al., 2015) As stated by Hashemi-Firouzi et al., the 5-HT7 receptors are associated with behavioral disorders such as depression, memory, anxiety, learning, and other hippocampal functions. (Hashemi-Firouzi et al., 2017) Additionally, Nikiforuk et al. mentioned that the 5-HT7 receptors both have a physiological role in the regulation of the central nervous (CNS) system and a potential therapeutic role in treating CNS disorders. (Nikiforuk, 2015) In this context, Hashemi-Firouzi et al. have summarized ligands of the 5-HT7 receptors in CNS disorders and the present data about the effects of the ligands in animal models as models of central nervous system (CNS) disorders. (Hashemi-Firouzi et al., 2017) However, they suggest further studies to widen information about the 5-HT7 receptors and therapeutic potential of their ligands. (Hashemi-Firouzi et al., 2017)

Kusek et al. have determined that the inhibition of the 5-HT7 receptors increases both release and metabolism of 5-HT in the prefrontal cortex. (Kusek et al., 2015) Additionally, blockade of the 5-HT7 receptors is thought to be beneficial against schizophrenia-like cognitive disorders; the 5-HT7 receptors might have role in the treatment of depression. (Nikiforuk, 2015)

2.2. Serotonin Transporter (SERT) And Serotonin Re-uptake Sites (5-HTT)

The serotonin transporter (SERT) is one of the serotonergic markers. (Meneses, 2015) The SERT, which is a protein structure, is present in many peripheral tissues and the brain. (Rudnick, 2007; de la Torre et al., 2013) The SERT transports serotonin to several structures such as platelets, enterochromaffin cells or neurons. (de la Torre et al., 2013) In addition to this, it has another mission which is the regulation of serotonin function by causing the ending of the serotonin action by re-uptake in synapses. (Rudnick, 2011)

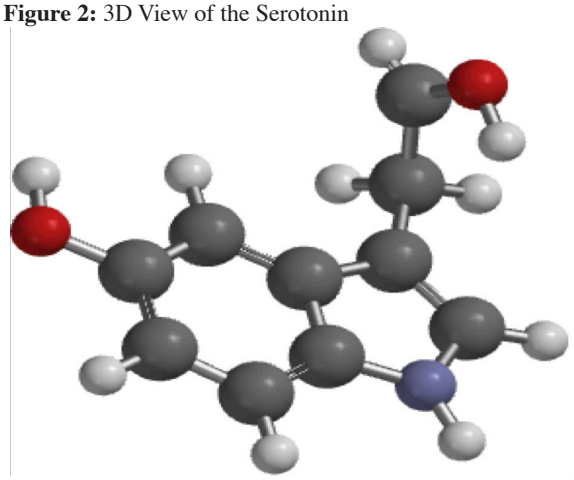
It is evident that considerable reductions in SERTs are seen in the frontal cortex, temporal cortex and the hippocampus of AD patients. (Lai et al., 2011; Rodríguez et al., 2012; Meneses, 2015) These deficits are correlated with unusual 5-HT homeostasis/transmission in the hippocampus, some BPSDs (i.e., overactivity, depression, hyperphagia, psychosis, etc.), neuropsychiatric behaviors and the cognitive impairment associated with AD. (Lai et al., 2011; Rodríguez et al., 2012)

Blockade of SERT enhances the serotonin concentration in the brain synaptic cleft that results in an increased serotonergic neurotransmission and so potentiation of 5-HT activity. (Toda et al., 2010; Haney et al., 2013) Therefore, serotonergic drugs that are serotonin transporter inhibitors, also known as selective serotonin reuptake inhibitors (SSRIs), are used in the treatment of AD, especially for the depressive symptoms and aggression. (Toda et al., 2010; Lai et al., 2011; Haney et al., 2013)

2.3. Serotonin Metabolite (5-HIAA)

Several studies have demonstrated that the cortical 5-HT and 5-hydroxyindoleacetic acid (serotonin metabolite, 5-HIAA) (Figure 2) levels have extremely important connections in people with schizophrenia and AD patients with cognitive deficits. (Meneses, 1999) Additionally, there is the adequate knowledge that explains the presence of changes in serotonergic neuronal function in the CNS of patients with major depression. (Owens & Nemeroff, 1994) Some of the indicators of these changes are reduction in cerebrospinal fluid (CSF) concentrations of 5-HIAA and reduction in concentrations of 5-HT and 5-HIAA in postmortem brain tissue in depressed patients. (Owens & Nemeroff, 1994)

Figure 2: 3D View of the Serotonin



3. Conclusion

The serotonergic system has an important role in learning, memory and cognitive process. All of the serotonergic markers, especially 5-HT receptors, are found in the brain areas that are affected by AD-associated neurodegeneration, and they have various and significant roles in cognitive functions. Since the inhibition/activation or excess/deficiency of the 5-HT receptors changes the 5-HT neurotransmission level, they are also related with AD. Reduced 5-HT and 5-hydroxyindoleacetic acid (metabolite of 5-HT, 5HIAA) concentrations, decreased 5-HT neurotransmission cause cognitive and behavioral changes in AD patients. In accordance with this review; it is evident that all markers and related signaling pathways of the serotonergic system should be completely examined to discover novel as well as effective treatment methods for AD. Additionally, dual inhibitors for various 5-HT receptors that need to be blocked or dual activators for several 5-HT receptors that need to be activated for treating of AD can be designed by several ways, including computational drug design. Furthermore, a new type of inhibitors which will block both 5-HT receptors and SERTs can also be designed. New therapies for depressive symptoms and behavioral changes of AD patients that are caused by reduced 5-HT neurotransmission can be generated. Moreover, current alternative medicine methods can be revised for AD, as well as developing new methods. Personalized medicine for the serotonergic system of each AD patient can also be a new treatment method but it requires plenty of time.

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