

Cognitive Impairment in Alzheimer's Disease: Targeting the Histaminergic System

Alzheimer Hastalığında Kognitif Disfonksiyon: Histaminerjik Sistemin Hedeflenmesi

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Cite this article as: Çiçek B, Akpınar E, Hacımüftüoğlu A. Cognitive impairment in Alzheimer's disease: Targeting the histaminergic system. *Arch Basic Clin Res* 2022;4(1):35-41.

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ABSTRACT

Alzheimer's disease is a neurodegenerative disease characterized by a progressive decline in cognitive functions and in the ability to continue activities of daily living. The exact causes of Alzheimer's disease are yet unknown, but researchers suggest that the formation and aggregation of β -amyloid and phosphorylated tau plaques are among the well-known factors that explain the pathophysiology of the disease. The mechanisms by which β -amyloid leads to cognitive decline in Alzheimer's disease are associated with degeneration in both cholinergic and glutamatergic neurotransmission. However, it is proposed that different neurotransmitter systems with neuronal histamine also participate in the progress and continuance of cognitive deficits associated with Alzheimer's disease. Histamine serves as a neurotransmitter in brain. Histamine-containing neurons in the brain are concentrated mainly in tuberomammillary nucleus located posterior to the hypothalamus and project widely to the regions such as the cerebellum and hippocampus that are related to memory and cognitive functions. The cognitive function modulated by histamine is thanks to the effect of 4 metabotropic receptors: H1, H2, H3, and H4. Pathological changes in histamine level and histamine receptor expression in patients with Alzheimer's disease are largely predictive of ensuing cognitive deficits. The review gives a synopsis of the functions of histaminergic neurotransmission in Alzheimer's disease-related cognitive decline, as well as the effects of H1, H2, H3, and H4 on animal and clinical researches.

Keywords: Alzheimer's disease, cognition, histamine, H1, H2, H3, H4

ÖZ

Alzheimer hastalığı (AH), progresif olarak bilişsel işlevlerde ve günlük yaşam etkinliklerini sürdürme becerilerinde azalma ile karakterize nörodejeneratif bir hastalıktır. AH'na neden olan faktörler henüz tam olarak bilinmemesine rağmen yapılan araştırmalarda beta-amiloid ($A\beta$) plaklarının oluşumu ve agregasyonu ve fosforile Tau proteinlerin varlığı hastalığın en önemli patofizyolojik bulguları olduğu düşünülmektedir. AH'da $A\beta$ plaklarının neden olduğu bilişsel gerilemenin esas olarak kolinerjik ve glutamaterjik nörotransmisyon disfonksiyonu ile direkt ilişkili olduğu düşünülmektedir. Bununla birlikte son zamanlarda yapılan araştırmalarda nöronal histamin dahil diğer nörotransmitter sistemlerinin de AH ile ilişkili bilişsel eksikliklerin progresyonu ve sürdürülmesine katkıda bulunduğu öne sürülmüştür. Biyojenik amin olan histamin, beyinde nörotransmitter görevi görür. Beyinde histamin içeren nöronlar, arka hipotalamusun tüberomamiller çekirdeğinde bulunur ve bellek ve kognitif işlevlerle ilişkili olan serebellum ve hipokampus gibi beyin bölgelerine projekte olur. Histamin bilişsel işlevlerin modülasyonunu, beyinin farklı bölgelerinde farklı yoğunlukta eksprese olan dört metabotropik reseptörü H1, H2, H3 ve H4 üzerinden gerçekleştirir. AH'da histamin seviyesindeki ve histamin reseptör ekspresyonundaki patolojik değişikliklerin, büyük ölçüde bilişsel eksikliklerin ortaya çıkması ile ilişkili olduğu düşünülmektedir. Bu derlemede, histaminerjik nörotransmisyon ve H1, H2, H3 ve H4 reseptörlerin AH ilişkili kognitif azalmadaki rolü deneysel ve klinik araştırmalardan elde edilen veriler ile özetlenmektedir.

Anahtar Kelimeler: Alzheimer hastalığı, kognisyon, histamin, H1, H2, H3, H4

INTRODUCTION

Alzheimer's Disease

Neurodegenerative diseases are hereditary or sporadic conditions that lead to progressive degeneration and/or death of nerve cells. Alzheimer's disease (AD) is largely a reflection of a progressive neurodegenerative disorder, affecting a large population globally.^{1,2} Alzheimer's disease is regarded as the most widespread cause of dementia in 2018 by the World Health Organization, with nearly 47 million patients around the world. It is estimated that about 75 million people will suffer from AD; this number is projected to reach 140 million by 2050 worldwide, and AD will be a major public health concern because of no permanent cure.³ The main feature of this disorder is the impairment of learning, memory, language together with other cognitive symptoms. Impairments of cognitive function lead to the individual being unable to do daily life activities over time and needing the care and support of another individual.²

The exact causes of AD are yet not completely explained. Major pathophysiological characteristics of AD include β -amyloid ($A\beta$) plaques, neurofibrillary tangles formed by tau protein hyperphosphorylation, followed by alterations in synaptic signaling, synaptic loss, and neuronal degeneration.⁴ Also, $A\beta$ that accumulates along the blood vessels in the brain impairs blood flow in the brain structure and accelerates neuronal damage. The soluble form of $A\beta$ affects some biological events including the generation of new proteins and the formation of dendritic spines, which are involved in memory and cognitive functions.^{5,6} Another pathological alteration in AD patients is the deficiency or disruption of central neurotransmitter systems that cause clinical symptoms.⁷ The most prominent alterations are related to the acetylcholinergic and glutamatergic systems. Acetylcholine is the neurotransmitter used by all cholinergic neurons and is given the most attention in the pathogenesis of AD. Acetylcholine serves as a neuromodulator in the hippocampus, thus increasing the encoding and retrieval of memories.⁸ Glutamate, a major excitatory neurotransmitter in the brain, is another neurotransmitter that is given the most attention in AD. Glutamate binds to *N*-methyl-D-aspartate receptors (NMDARs) and maintains the synaptic plasticity that is involved in the regulation of memory and learning.⁹ β -amyloid induces basal forebrain acetylcholine-synthesizing neuron cell loss, a depletion in brain acetylcholine levels. Also, $A\beta$ plaques can induce excessive NMDARs activity by way of prevention of glutamate reuptake from the extracellular space. These changes are thought to be liable for AD-related cognitive impairment.⁷⁻⁹ Even though the dysfunction of

acetylcholine and glutamate has been well documented in cognitive impairment with AD pathogenesis, alterations in other central neurotransmitter systems can contribute to this pathology.¹⁰

Nowadays, it is increasingly noticed that the brain's histaminergic system, which has been largely neglected, also can become a potential target to struggle with cognitive impairments of AD. There are increasing evidences recommending that changes in histamine neurotransmission participate in the neurofibrillary tangles and tau aggregation.¹¹ The damage of tuberomammillary nucleus (TMN) that is the origin of histamine neurons and an altered expression of histamine receptors, which regulate histamine function, were determined in patients with AD. The histamine-related neuron action improves cognitive functions and memory. Therefore, dysfunction of histaminergic neurons and changes of histamine receptor binding may have taken part in the cognitive decline of AD patients.^{10,12} In this regard, it is very important to understand the histaminergic system, which is involved in the pathogenesis of AD, in order to struggle with cognitive symptoms in AD.

Histaminergic System in the Brain

Histamine functions as a signaling molecule in the stomach, the skin, and the immune system in the periphery. The histamine released from its granules performs many actions in the body such as gastric acid secretion, local immune responses, and increasing the working rate of the heart.¹³ Apart from these functions, histamine also functions as a neurotransmitter that transports chemical messages between nerve cells thereby maintaining the brain homeostasis and higher brain functions in the central nervous system.¹⁴ Histamine-synthesizing neurons in the brain are located mainly in the TMN and extend their axons to particularly large brain regions, including the hippocampus, arcuate nucleus, basal ganglia, and amygdala (Figure 1). In connection with these regions, histamine regulates many basic physiological functions such as endocrine homeostasis, synaptic flexibility, cognition, attention, learning, and memory.¹⁵

Histamine is synthesized from histidine by oxidative decarboxylation with the enzyme L-histidine decarboxylase in the mammalian brain (Figure 2). Upon synthesis, histamine is packaged in vesicles in both the soma and varicosities through vesicular monoamine transporter 2, and then calcium-dependent release of histamine happens as a result of depolarization of the histaminergic neuron. The released histamine is then metabolized in the postsynapses or glia by histamine *N*-methyltransferase to the inactive tele-methylhistamine.¹⁶

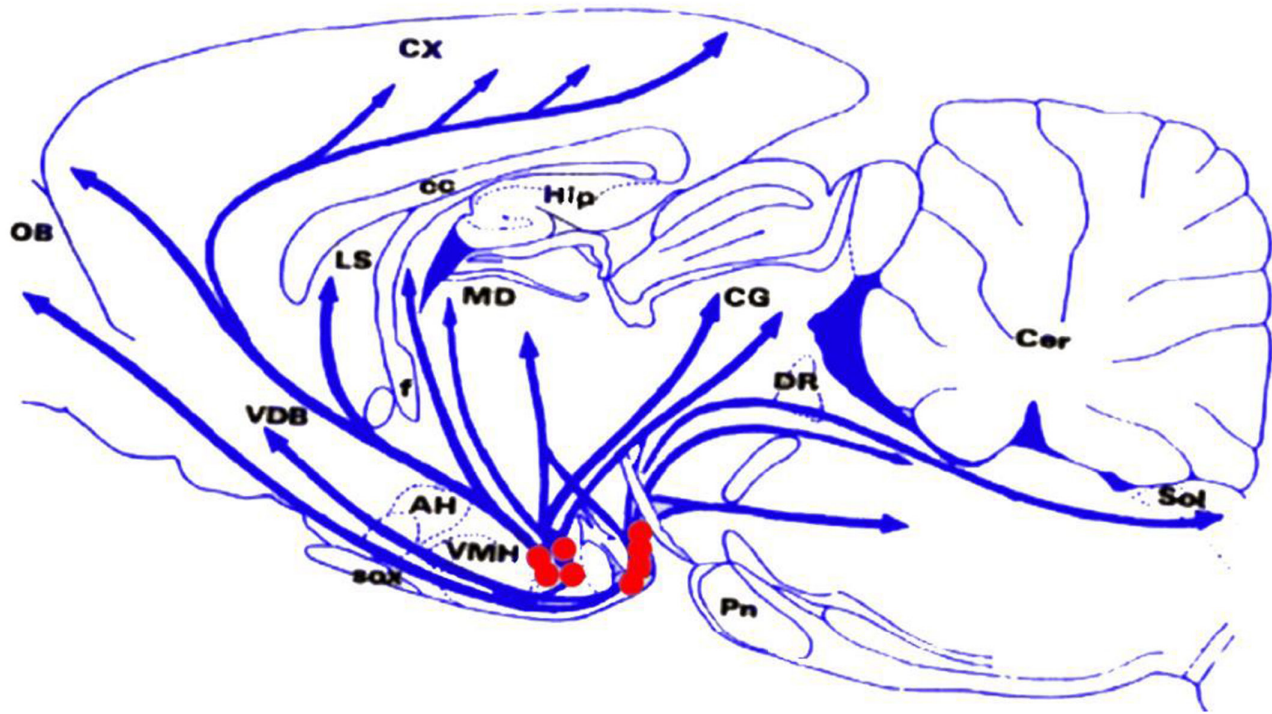


Figure 1. Schematic presentation of the neuronal histaminergic projections to memory and cognitive-relevant structures. Histaminergic neurons (red circles) are restricted to the TMN. AH, anterior hypothalamic area; Arc, arcuate nucleus; Cc, corpus callosum; Cer, cerebellum; CG, central gray; CX, cerebral cortex; DR, dorsal raphe nucleus; F, fornix; Hip, hippocampus; VMH, ventromedial hypothalamus; TMN, tuberomammillary nucleus (Modified from Köhler, 2011).

Histamine performs its physiological functions in the brain through stimulation of 4 distinct receptor types, as H1R, H2R, H3R, and H4R. These receptors belong to the 7-transmembrane domain, rhodopsin-like family of G-protein-coupled receptors.^{15,16} Inside the brain, H1, H2, and H3 receptors have unique regional distributions and are differently expressed by neurons, astrocytes, and endothelial cells. On the other hand, limited information is realized about the expression and neuronal role of H4R, the most recently discovered histamine receptor, on its brain localization.¹⁷ The H4R is generally found on immune cells and its expression is stimulated or changed in regard to inflammatory stimuli. Recent data demonstrate that H4R

can also be expressed in the inner granule layer of cerebral cortex, hippocampus, striatum, and thalamus.¹³ Molecular activation of these membrane receptors leads to a variety of biological responses because the receptors are coupled to different G-proteins including Gq/11, Gs, and Gi/o which are connected to phospholipase C, phospholipase A, and adenylyl cyclase. Intermediate complex effectors stimulate intracellular pathways, which lead to activation or inhibition of the neuron's functions. Perhaps, this is one of the reasons why different results have been reported for the histamine in some brain functions.^{14,18} The different effects of histamine receptors with respect to pharmacology and molecular properties have been reviewed in detail by other authors. Table 1 demonstrates the key points on histamine receptors in the brain.¹⁰

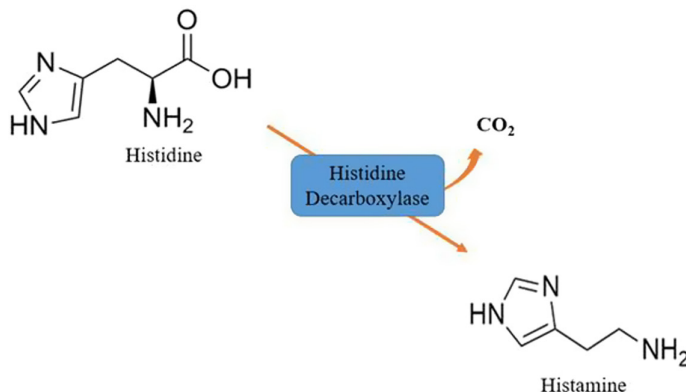


Figure 2. Neuronal histamine biosynthesis.

The Role of Histamine in Cognition

The behavioral functions are provided by neurons within the brain communicating with each other. This network is especially noticeable with respect to cognitive function from attentional decision-making and problem-solving to learning and memory processes.¹⁹ Cognitive function is related to some brain regions including components of the limbic system, such as the hippocampus and the amygdala, as well as the neocortex, and the basal forebrain cholinergic and midbrain monoaminergic nuclei, which send to projections dorsal and rostral

Table 1. Properties of Histamine Receptors in the Brain (Modified from Naddafi and Mirshafiey, 2013)

Characteristic	H1R	H2R	H3R	H4R
Localization	Thalamus, cortex, hippocampus, hypothalamus, amygdala, basal forebrain, molecular layer of the cerebellum, and nucleus tractus solitaries	Hippocampus, basal ganglia, pyramidal cells, amygdala, thalamic neurons, substantia nigra, and cerebral cortex	Cerebral cortex, hippocampus, hypothalamus, amygdala, nucleus accumbens, ventral and dorsal striatum, and olfactory tubercles	Cerebellum, hippocampus, and immune system cells
Homology	–	40% homology with H1	22% with H1 and 20% with H2	38–58% with H3
G-protein coupling	Gq/11	Gs	Gi/o	Gi/o
Signaling pathway	Activation of PLC, PLA2	Activation of cAMP synthesis, PKC, PLC	Inhibition of AC and PKA; activation of PLA2, MAPK	Inhibition of AC and PKA; activation of PLC, MAPK
General function	Behavioral state and reinforcement, cognition	Learning and memory (consolidation)	Regulation of histamine release and generation Behavior, learning and memory, cognition	Chemotaxis Blood–brain barrier

H1R, histamine H1 receptor; H2R, histamine H2 receptor; H3R, histamine H3 receptor; H4R, histamine H4 receptor; PLC, phospholipase C; PKA, protein kinase A; PLA2, phospholipase A2; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; MAP kinase, mitogen-activated protein kinase.

brain regions.²⁰ The interaction between these systems is provided by several neurotransmitters which are in communication with various brain regions and neuronal type. Neurotransmitters, on the principle, of cognitive function, are important in the principal understanding of how the nervous systems generate activities involving cognition.²¹ Conventionally, acetylcholine and glutamate are known as the most important neurotransmitters involved in cognitive functions. However, the literature confirms that cholinergic and glutamatergic systems are not alone in cognition, but the central histaminergic system can also be associated with cognitive process.^{21,22} The brain regions related to cognition such as the striatum, hippocampus, and frontal cortex express the high intensity of histamine receptors. Thus, the released histamine interacts with its receptors and affects cognitive function.^{10–12} The H1R and H2R are post- and extra-synaptic receptors that act a key role in attention.^{12,23} On the other hand, H3R serves as an autoreceptor on histaminergic axon terminals, where it controls the release of neuronal histamine. Inhibition of presynaptic H3 autoreceptors would therefore indirectly improves histamine-mediated attention in cognitive disorders such as AD. Furthermore, blockage of H3R can induce synthesis and release of various other neurotransmitters including acetylcholine and glutamate involved in cognitive processes (Figure 3).^{10,12,17,24} However, much less is known about the role of H4R, another histamine receptor, in brain functions such as cognition.^{25,26} The H1R, H2R, and H3R can bind to NMDARs and play an important role in numerous activities in the brain, such as excitability and plasticity. Glutamatergic neurons modulate the release of

histamine. Also, cholinergic transmission is managed by neighboring histaminergic neurons through its receptors.^{10,27,28} Current studies provide evidence that a failure in function of the histaminergic system is related to cognitive disorders seen in diseases such as AD (24). Although findings of the participation of the histaminergic system in cognition have been obtained mainly from *in vivo* studies, findings have accumulated over the decade indicating that histamine may also have a significant function in clinical studies. Therefore, the histaminergic system has been recognized as a possible target for improving the cognitive deficits in clinical disorders.^{12,18,29}

Alzheimer's Disease and Neuronal Histamine

Cognitive dysfunctions in AD have been associated with extracellular A β plaque deposition, which leads to degeneration of cholinergic and glutamatergic systems and neurofibrillary tangles in brain regions that are important for learning and memory formation.^{2,4,6,30} However, it has been increasingly accepted in recent studies that other pathologies such as dysfunctions in the brain histaminergic system take part in the cognitive disorders seen in these patients. In order to assess cognitive activities, various tests have been developed to analyze the particular domains of cognition in animals as well as in clinical trials. Considering the intricacy of the human brain, some preclinical animal studies show more or fewer similarities to behavioral testing in clinical trials.³¹ Preclinical studies demonstrate that histamine levels and histidine decarboxylase activity decrease in AD.³² A postmortem investigation from the brain of patients with AD demonstrated a considerable decrease in histamine levels in regions of

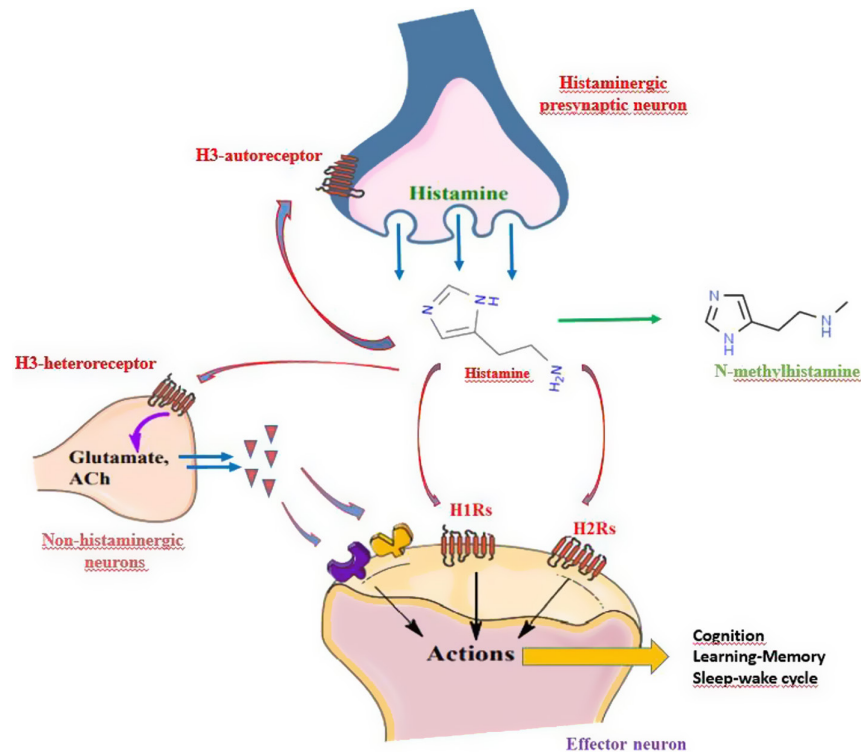


Figure 3. Schematic representation of the possible mechanisms of histamine and histamine receptors on cognitive functions in the central nervous system (Modified from Sadek, 2016).

the hypothalamus (42%), hippocampus (43%), and temporal cortex (53%).³³ Also having an AD caused decrease in histamine-releasing factor levels, progressive decline in H1R binding in the frontal cortex, and degeneration of histamine neurons in the TMN compared to their age-matched normal counterparts.^{34,35} The quantity of H1R binding in patients with AD is remarkably associated with the severity of their cognitive symptoms.³⁶ Similarly, H1R knockout mice were found to have impairments in learning and memory and thus affect both spatial and working memory.^{37,38} Moreover, deficits in severe episodic-like and procedural memory were determined in H1R knockout mice. It should be mentioned that some changes in acetylcholine esterase activity in the hippocampus in AD have been observed.³⁹ The histaminergic neuron system modulates cholinergic functions that affect learning and memory. When histaminergic agonists or antagonists are administered systemically and intracerebrally, acetylcholine is released into the brain and modulates learning and memory.^{27,28,40} By using an *in vitro* human astrocytic culture, histamine was shown to produce matrix metalloproteinase-9, possibly through the action of H1R. Matrix metalloproteinase-9 is capable of degrading A β protein, which is a neuropathological hallmark of AD.⁴¹ New research in H1R or H2R knockout mice indicates that H1R and H2R have a major role in cognition, and the frontal cortex, amygdala, and hippocampus are related to these processes.⁴² It is known that

both H1R and H2R are excitatory, while H3R is inhibitory and is an auto- and heteroreceptor. The H3R controls the release of histamine as well as noradrenaline, serotonin, and acetylcholine. The interactions of histamine and other neurotransmitter systems can modulate synaptic plasticity, learning, and memory.¹⁸ A previous preclinical study demonstrated that H3R knockout mice displayed enhanced spatial learning and memory in the Barnes maze.⁴³ Many findings have shown that central histamine remarkably changes cognitive deficits and that antagonists/inverse agonists selectively targeting central histamine H3Rs may possibly cause treatment option with potential clinical use in cognitive symptoms.⁴⁴ Imidazole-based H3R antagonist was determined to be mainly beneficial to many of behavioral *in vivo* models, including Barnes maze, elevated plus-maze learning, and Morris water maze.⁴⁵ In addition, H3R antagonist has been shown to improve memory in passive avoidance and new object recognition behavior tests in rats with memory impairment.⁴⁶ Working memory, the ability to hold new information for a short time, is considered to be as a core cognitive function. In a recent study, H3R density in the prefrontal cortex was determined using functional magnetic resonance imaging and positron emission tomography techniques. It was determined the higher neural activity of working memory was associated with lower H3 receptor density in the prefrontal cortex, the key region of cognitive

functions.²⁹ Histamine plays a role in stress-induced cell signals through its various receptors. It is likely that A β accumulation in AD leads to cellular stress and causes abnormal intracellular signaling. And this situation may be exacerbated as a result of distribution of the blood-brain barrier in the hippocampus, which is a region related to learning and memory.⁶ Histamine is a mediator of BBB function, and H4R is expressed in the hippocampus. A more recent study suggested that stimulation of H4 receptors inducing hyperpolarization of neurons has an added value in enhancing neuroprotection in AD pathology.²⁵ Furthermore, it has been reported that partial H4R agonist leads to a notable reduction in A β deposits in a rat model of Alzheimer-like brain pathology.⁴⁷ In contrast, a previous study with H4R-deficient mice found that H4R does not play an outstanding role in histaminergic modulation in the memory process. Although histaminergic neurons project to regions important for cognitive function, H4R-deficient mice did not demonstrate any alterations in both working and recognition memory.²⁶

CONCLUSION

The reviewed evidence suggests that the neuronal histaminergic system in general, and H1, H2, and H3 receptors in particular, has a major role in the pathogenesis of AD. Abnormalities of the histamine neurotransmitter signaling pathway and its receptors seem to be associated with cognitive impairment in AD. The data debated in this review are extensively consistent with the hypothesis that cognitive functional roles are performed by diverse histamine receptors, which implies that projections of histaminergic neurons to the different brain areas are required for certain cognitive functions. Due to its actions as an auto/heteroreceptor, modulating not only histamine synthesis but also the release of other important neurotransmitters including glutamate and acetylcholine that require cognition, the H3 receptor has received great attention from many academic groups to combat cognitive decline. In conclusion, the evaluation of the role of neuronal histamine in cognitive dysfunctions in AD has a very short history. For this reason, more in-depth preclinical as well as clinical studies are still required.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.H., B.C.; Design - B.C.; Supervision - A.H. E.A.; Resources - A.H.; B.C.; E.A.; Literature Search - B.C.; Writing Manuscript - A.H.; B.C.; Critical Review - A.H.; E.A.

Declaration of Interests: The authors have no other conflicts of interest to disclose.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir- A.H., B.Ç.; Tasarım- A.H., E.A., B.Ç.; Denetleme- A.H.; Kaynaklar- A.H., E.A., B.Ç.; Malzemeler- A.H., E.A., B.Ç.; Veri Toplanması ve/veya İşlenmesi- A.H.; Analiz ve/veya İşlenmesi- A.H.; Literatür taraması- A.H., E.A., B.Ç.; Yazıyı Yazan- A.H.; Eleştirel İnceleme- A.H., E.A., B.Ç.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu makalenin araştırılması, yazarlığı ve/veya yayınlanması için herhangi bir finansal destek almadıklarını bildirilmişlerdir.

REFERENCES

1. Wray S. Modelling neurodegenerative disease using brain organoids. *Semin Cell Dev Biol.* 2021;111:60-66. [\[CrossRef\]](#)
2. Guo T, Zhang D, Zeng Y, et al. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. *Mol Neurodegener.* 2020;15(1):40. [\[CrossRef\]](#)
3. Zhang P, Xu S, Zhu Z, Xu J. Multi-target design strategies for the improved treatment of Alzheimer's disease. *Eur J Med Chem.* 2019;176:228-247. [\[CrossRef\]](#)
4. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegener.* 2019;14(1):32. [\[CrossRef\]](#)
5. Korte N, Nortley R, Attwell D. Cerebral blood flow decrease as an early pathological mechanism in Alzheimer's disease. *Acta Neuropathol.* 2020;140(6):793-810. [\[CrossRef\]](#)
6. Sadigh-Eteghad S, Sabermarouf B, Majidi A, et al. Amyloid-beta: a crucial factor in Alzheimer's disease. *Med Princ Pract.* 2015;24(1):1-10. [\[CrossRef\]](#)
7. Choudhury A, Sahu T, Ramanujam PL, et al. Neurochemicals, behaviours and psychiatric perspectives of neurological diseases. *Neuropsychiatry.* 2018;8(1):395-424.
8. Haam J, Yakel JL. Cholinergic modulation of the hippocampal region and memory function. *J Neurochem.* 2017;142(suppl 2):111-121. [\[CrossRef\]](#)
9. Conway ME. Alzheimer's disease: targeting the glutamatergic system. *Biogerontology.* 2020;21(3):257-274. [\[CrossRef\]](#)
10. Naddafi F, Mirshafiey A. The neglected role of histamine in Alzheimer's disease. *Am J Alzheimers Dis Other Dement.* 2013;28(4):327-336. [\[CrossRef\]](#)
11. Dere E, Zlomuzica A, De Souza Silva MA, et al. Neuronal histamine and the interplay of memory, reinforcement and emotions. *Behav Brain Res.* 2010;215(2):209-220. [\[CrossRef\]](#)
12. Provensi G, Costa A, Izquierdo I, Blandina P, Passani MB. Brain histamine modulates recognition memory: possible implications in major cognitive disorders. *Br J Pharmacol.* 2020;177(3):539-556. [\[CrossRef\]](#)
13. Thangam EB, Jemima EA, Singh H, et al. The role of histamine and histamine receptors in mast cell-mediated allergy and inflammation: the hunt for new therapeutic targets. *Front Immunol.* 2018;9:873.
14. Yoshikawa T, Nakamura T, Yanai K. Histaminergic neurons in the tuberomammillary nucleus as a control centre for wakefulness. *Br J Pharmacol.* 2021;178(4):750-769. [\[CrossRef\]](#)

15. Köhler CA, Da Silva WC, Benetti F, Bonini JS. Histaminergic mechanisms for modulation of memory systems. *Neural Plast.* 2011;2011:328602. [\[CrossRef\]](#)
16. Parsons ME, Ganellin CR. Histamine and its receptors. *Br J Pharmacol.* 2006;147(1)(suppl 1):S127–S135. [\[CrossRef\]](#)
17. Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. *Prog Neurobiol.* 2001;63(6):637–672. [\[CrossRef\]](#)
18. Provensi G, Passani MB, Costa A, Izquierdo I, Blandina P. Neuronal histamine and the memory of emotionally salient events. *Br J Pharmacol.* 2020;177(3):557–569. [\[CrossRef\]](#)
19. Raffone A, Srinivasan N. Mindfulness and cognitive functions: toward a unifying neurocognitive framework. *Mindfulness.* 2017;8(1):1–9. [\[CrossRef\]](#)
20. <https://www.mayoclinic.org/brain-lobes/img>. Date of access 10/05/2021.
21. Handra C, Coman OA, Coman L, Enache T, Stoleru S. The connection between different neurotransmitters involved in cognitive processes. *FARMACIA.* 2019;67(2):193–201. [\[CrossRef\]](#)
22. Kandimalla R, Reddy PH. Therapeutics of neurotransmitters in Alzheimer's disease. *J Alzheimers Dis.* 2017;57(4):1049–1069. [\[CrossRef\]](#)
23. Lindskog M. Histamine receptors in the cross-talk between periphery and brain. *Int J Neuropsychopharmacol.* 2017;20(5):400–402. [\[CrossRef\]](#)
24. Sadek B, Saad A, Sadeq A, Jalal F, Stark H. Histamine H3 receptor as a potential target for cognitive symptoms in neuropsychiatric diseases. *Behav Brain Res.* 2016;312:415–430. [\[CrossRef\]](#)
25. Patnaik R, Sharma A, Skaper SD, et al. Histamine H3 inverse agonist BF 2649 or antagonist with partial H4 agonist activity clobenpropit reduces amyloid beta peptide-induced brain pathology in Alzheimer's disease. *Mol Neurobiol.* 2018;55(1):312–321. [\[CrossRef\]](#)
26. Sanna MD, Galeotti N. Central neuronal functions of histamine H4 receptors. *Oncotarget.* 2017;8(8):12556–12557. [\[CrossRef\]](#)
27. Zlomuzica A, Dere D, Binder S, et al. Neuronal histamine and cognitive symptoms in Alzheimer's disease. *Neuropharmacology.* 2016;106:135–145. [\[CrossRef\]](#)
28. Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. *Physiol Rev.* 2008;88(3):1183–1241. [\[CrossRef\]](#)
29. Mongula JE, Bakers FCH, Vöö S, et al. Positron emission tomography-magnetic resonance imaging (PET-MRI) for response assessment after radiation therapy of cervical carcinoma: a pilot study. *EJNMMI Res.* 2018;8(1):1. [\[CrossRef\]](#)
30. Findley CA, Bartke A, Hascup KN, Hascup ER. Amyloid beta-related alterations to glutamate signaling dynamics during Alzheimer's disease progression. *ASN Neuro.* 2019;11:1759091419855541. [\[CrossRef\]](#)
31. Masuoka N, Lei C, Li H, Hisatsune T. Influence of imidazole-dipeptides on cognitive status and preservation in elders: a narrative review. *Nutrients.* 2021;13(2):397–415. [\[CrossRef\]](#)
32. Haas H, Panula P. The role of histamine and the tuberomammillary nucleus in the nervous system. *Nat Rev Neurosci.* 2003;4(2):121–130. [\[CrossRef\]](#)
33. Panula P, Rinne J, Kuokkanen K, et al. Neuronal histamine deficit in Alzheimer's disease. *Neuroscience.* 1998;82(4):993–997. [\[CrossRef\]](#)
34. Kim SH, Cairns N, Fountoulakis M, Lubec G. Decreased brain histamine-releasing factor protein in patients with Down syndrome and Alzheimer's disease. *Neurosci Lett.* 2001;300(1):41–44. [\[CrossRef\]](#)
35. Ishunina TA, van Heerikhuijze JJ, Ravid R, Swaab DF. Estrogen receptors and metabolic activity in the human tuberomammillary nucleus: changes in relation to sex, aging and Alzheimer's disease. *Brain Res.* 2003;988(1–2):84–96. [\[CrossRef\]](#)
36. Zlomuzica A, Ruocco LA, Sadile AG, Huston JP, Dere E. Histamine H1 receptor knockout mice exhibit impaired spatial memory in the eight-arm radial maze. *Br J Pharmacol.* 2009;157(1):86–91. [\[CrossRef\]](#)
37. Kárpáti A, Yoshikawa T, Naganuma F, et al. Histamine H1 receptor on astrocytes and neurons controls distinct aspects of mouse behaviour. *Sci Rep.* 2019;9(1):1–13. [\[CrossRef\]](#)
38. Dere E, Zlomuzica A, Viggiano D, et al. Episodic-like and procedural memory impairments in histamine H1 receptor knockout mice coincide with changes in acetylcholine esterase activity in the hippocampus and dopamine turnover in the cerebellum. *Neuroscience.* 2008;157(3):532–541. [\[CrossRef\]](#)
39. Panula P, Nuutinen S. The histaminergic network in the brain: basic organization and role in disease. *Nat Rev Neurosci.* 2013;14(7):472–487. [\[CrossRef\]](#)
40. Patel A, Vasanathan V, Fu W, et al. Histamine induces the production of matrix metalloproteinase-9 in human astrocytic cultures via H1-receptor subtype. *Brain Struct Funct.* 2016;221(4):1845–1860. [\[CrossRef\]](#)
41. Dai H, Kaneko K, Kato H, et al. Selective cognitive dysfunction in mice lacking histamine H1 and H2 receptors. *Neurosci Res.* 2007;57(2):306–313. [\[CrossRef\]](#)
42. Rizk A, Curley J, Robertson J, Raber J. Anxiety and cognition in histamine H3 receptor-/- mice. *Eur J Neurosci.* 2004;19(7):1992–1996. [\[CrossRef\]](#)
43. Alachkar A, Khan N, Łażewska D, Kieć-Kononowicz K, Sadek B. Histamine H3 receptor antagonist E177 attenuates amnesia induced by dizocilpine without modulation of anxiety-like behaviors in rats. *Neuropsychiatr Dis Treat.* 2019;15:531–542. [\[CrossRef\]](#)
44. Hu W, Chen Z. The roles of histamine and its receptor ligands in central nervous system disorders: an update. *Pharmacol Ther.* 2017;175:116–132. [\[CrossRef\]](#)
45. Alachkar A, Łażewska D, Kieć-Kononowicz K, Sadek B. The histamine H3 receptor antagonist E159 reverses memory deficits induced by dizocilpine in passive avoidance and novel object recognition paradigm in rats. *Front Pharmacol.* 2017;8:709. [\[CrossRef\]](#)
46. Mehta P, Miszta P, Rządziejewicz P, et al. Enigmatic histamine receptor H4 for potential treatment of multiple inflammatory, autoimmune, and related diseases. *Life.* 2020;10(4):50. [\[CrossRef\]](#)