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REVIEW ARTICLE

Histaminergic neurotransmission in aging and Alzheimer's disease: A review of therapeutic opportunities and gaps

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Abstract

Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder featuring a brain accumulation of extracellular β -amyloid plaques (A β) and intracellular neurofibrillary tangles (NFTs). Although cognitive decline is a disease-defining symptom of AD, sleep dysfunction, a common symptom often preceding cognitive decline, has recently gained more attention as a core AD symptom. Polysomnography and other sleep measures show sleep fragmentation with shortening of N₃ sleep together with excessive daytime sleepiness (EDS) and sundowning as the main findings in AD patients. The latter reflects dysfunction of the wake-promoting neurons (WPNs), including histaminergic neurons (HA^N) located in the tuberomammillary nucleus (TMN) of the posterior hypothalamus, which project unmyelinated axons to various parts of the brain. Histamine's role in cognition and arousal is broadly recognized. Selective targeting of histaminergic subtype-3 and 4 receptors show therapeutic potential in rodent models of AD and aging.

Method: Based on PubMed, Scopus, and Google Scholar databases search, this review summarizes the current knowledge on the histaminergic system in AD and aging, its therapeutic potential in AD, and highlights areas where more research is needed.

Results: Animal studies have demonstrated that pharmacological manipulation of histaminergic receptors or histamine supplementation improves cognition in AD models. However, measurements of HA or HA metabolite levels in the human brain and CSF present contradictory reports due to either lack of power or controls for known confounders.

Discussion: Systemic studies including broad age, sex, neuropathological diagnosis, and disease stage are warranted to fill the gap in our current understanding of the histaminergic neurotransmitter/neuromodulator system in humans, especially age-related changes, and therapeutic potential of histamine in AD-related dysfunction.

KEYWORDS

Alzheimer's disease, histamine, histamine receptors, sleep-wake dysfunction, tuberomammillary nucleus, wake-promoting neurons

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1 | INTRODUCTION

Alzheimer's disease (AD) is an age-associated, irreversible, progressive neurodegenerative disorder. It is the most common cause of cognitive impairment and dementia among the elderly. About 6.5 million Americans > 65 years are living with AD, which is already the fifth leading cause of death among individuals > 65 years.¹ AD is a mixed proteinopathy having extracellular amyloid beta ($A\beta$) plaques and intracellular neurofibrillary tau tangles (NFTs) as its cardinal neuropathological hallmarks. Glial activation, region-specific neuronal loss, synaptic remodeling, and synaptic dysfunction are associated pathological characteristics of AD.²

Sleep cycle disturbances are a common symptom in the early stages of AD,³ and epidemiological studies have shown a link between sleep problems and dementia.^{4,5} Dysfunction of the sleep cycle in AD features sleep fragmentation with shorter slow-wave sleep (SWS-N3), excessive daytime sleepiness (EDS), and sundowning.⁶ EDS is also associated with impaired cognitive functions in elderly individuals and patients with mild cognitive impairment.⁷ Measurement of non-rapid eye movement (NREM), slow wave activity (SWA), and sleep quality may predict the rate of $A\beta$ and tau accumulation in the cortex.^{8,9} Poor sleep quality with diminished low frequency (1 or 0.6 –1 Hz) SWA during NREM sleep and EDS exacerbates $A\beta$ and tau accumulation by severalfold in elderly individuals.^{8–10} EDS has been linked to $A\beta$ accumulation in the precuneus and cingulate gyrus.¹¹

The histaminergic system is critical for modulating wakefulness, cognition, neuroinflammation, and neurogenesis.^{12–14} Our previous studies have demonstrated a profound loss of subcortical wake-promoting neurons (WPNs) in AD, including histaminergic neurons (HAN^N),^{15–18} which suggests a primary role of WPNs in AD-related sleep dysfunction. Despite the known role of HAN^N in sleep regulation and the early involvement of these neurons in AD, there is a lack of understanding about their function during aging and AD progression. Further research could lead to the development of targeted treatments for managing sleep dysfunction, improving quality of life, and potentially slowing AD progression.

2 | SLEEP AND WAKE CYCLE

In mammals, sleep is defined as reduced body movement and electromyographic activity; responsiveness to external stimuli and breathing rates, closed eyes, altered body position, and a specific cyclical electrical brain wave architecture.¹⁹ Confluent evidence supports the role of sleep in memory function and consolidation, homeostasis, immune response, and metabolism.^{20–22} Sleep-wake dysfunction is a feature of many neurodegenerative disorders.²³ Evidence shows a bidirectional feed-forward mechanism involving poor sleep and exacerbation of abnormal protein deposits, as illustrated in recent work focusing on the glymphatic system and synaptic homeostasis hypothesis. The glymphatic system is a network of perivascular systems that promote the cerebrospinal fluid (CSF) movement into the brain. It plays

RESEARCH IN CONTEXT

- 1. Systemic review:** We searched for papers with keywords “Alzheimer's disease,” “aging,” “cognitive decline,” “sleep-wake cycle,” “hypothalamus,” “tuberomammillary nucleus,” “wakefulness/arousal system,” “histamine,” “histamine metabolites,” “CSF” in databases PubMed, Scopus, and Google Scholar. A total of 217 full articles in English were screened, and after applying our inclusion criteria, 69 articles were included in the final article.
- 2. Interpretation:** Previous studies have established histamine's role in maintaining wakefulness, cognitive processing, and inhibition of post-translational modification of proteins. Animal studies have demonstrated the cognitive benefits of pharmacological modulation of histaminergic receptors. However, the role of cerebral histamine in the initiation and progression of Alzheimer's disease (AD) in humans is not well understood. We identified several areas that require further research. For example, the cerebrospinal fluid levels of histamine metabolites may differ in aging with AD, and sex, age, and the disease state as factors influencing these changes.
- 3. Future directions:** This review provides an overview and consolidates the current understanding of the relationships among age, AD, and the histaminergic system. Thus, it sets the foundation for future studies to explore the potential of histamine as a therapeutic target in AD and leveraging existing drugs that modulate the histaminergic system as a treatment for AD.

a critical role in the clearance of toxic $A\beta$, tau, and α -synuclein.^{24–26} The CSF-mediated drainage of metabolic waste to the lymph nodes is under circadian control and depends on the polarization of aquaporin-4 channels.²⁷ SWS has been shown to play a role in modulating CSF $A\beta$ levels. Additionally, SWS may have an impact on synaptic strength.²⁸ Reduced synaptic activity has been linked to a decrease in interstitial fluid $A\beta$ levels, while the exocytosis of synaptic vesicles has been linked to an increase in extracellular $A\beta$.²⁹ This suggests that SWS may protect against $A\beta$ accumulation in the cortex.

A system of wake-promoting, sleep-promoting, and circadian neurons regulate sleep.^{30,31} Wakefulness is primarily sustained by the ascending arousal system, which consists of two components of substantial heterogeneous cell populations. The first branch, or dorsal cholinergic pathway to the thalamus, originates from the two cholinergic structures in the brainstem (pedunculopontine tegmental nucleus [PPT] and the laterodorsal tegmental nucleus [LDT]).^{30,31} PPT/LDT neurons activate the relay and reticular nuclei of the thalamus to maintain wakefulness and modulate consciousness.¹² They are most active during wakefulness and rapid eye movement (REM) sleep and discharge slow waves during NREM sleep. The second branch, or

monoaminergic or extra-thalamic pathway, originates from the rostral pons and innervates the hypothalamus and the cortex to modulate arousal and the behavioral state of wakefulness.¹² The extra-thalamic pathway includes the norepinephrine/noradrenergic (NE) neurons of the locus coeruleus (LC), serotonergic neurons (5-HT) from the dorsal and median raphe nuclei, dopaminergic (DA) neurons of the ventral periaqueductal gray matter and the HA^N from the tuberomammillary nucleus (TMN). The extra-thalamic pathway also contains GABAergic, cholinergic projections from the basal forebrain (BF) and the melanin-concentrating hormone (MCH) or hypocretin/orexin (ORX) neurons from the lateral hypothalamus.³⁰ The cholinergic projections of the BF are also associated with attentional focus and vigilance. Together, these interconnected pathways maintain and promote wakefulness and arousal.³²

Wake promotion involves several fast-acting and slow-acting neurotransmitters, such as glutamate (Glu), NE, 5-HT, DA, ORX, MCH, HA, and γ -aminobutyric acid (GABA). ORX, GABA, and Glu have been studied more extensively in sleep-wake cycle regulation.³³ Although the HA^N of the TMN exhibit the most selective wake discharge pattern in the brain,³⁴ their role in sleep-wake dysfunction in aging and age-related diseases has been neglected, probably due to its late molecular characterization compared to other WPN populations.³⁵

ORX and HA neurons are critical to maintaining the arousal state, work in synergy, complement each other, and control different aspects of wakefulness. ORX neurons are involved in motor coordination and electroencephalogram (EEG) activation. In contrast, the HA^N promotes cortical activation and cognitive activities during wakefulness.³⁶ Further, a decline in HA reduces cortical EEG power in theta rhythm during wakefulness and amplitude of slow activity during SWS. Simultaneously, the lack of ORX doesn't influence the quantitative aspect of the cortical EEG.³⁶ Wake-promoting TMN pathways and sleep-promoting ventrolateral preoptic nucleus (VLPO) pathways act as a flip-flop switch for rapid and complete transitions between wakefulness and sleep.³⁷ In a study, microinjection of L-Glu and H1R inhibitor triprolidine to VLPO resulted in the activation of the VLPO and increased NREM sleep. The blocking of the GABA receptors in the TMN with microinjection of bicuculline or L-Glu resulted in an increase in wakefulness with a concomitant decline in REM and NREM sleep in Sprague Dawley rats.³⁷ Pitolisant is a Food and Drug Administration-approved drug to treat EDS and cataplexy in people with narcolepsy. It is a competitive antagonist and inverse agonist of the histamine receptor 3 (H3R).³⁸ Pitolisant is also being studied as a potential treatment for central nervous system (CNS) disorders such as epilepsy, obstructive sleep apnea, and Parkinson's disease. Several other H3R antagonists are being tested to treat schizophrenia; AD (GSK239512, ABT-288); attention-deficit/hyperactivity disorder; EDS in patients with Parkinson's disease (JNJ-31001074), AD (SAR110894), and neuropathic pain (GSK189254); and to improve cognition and wake-promotion (CEP-26401).³⁹ In addition, doxepin, a selective blocker of H1R, is also used at low concentrations (1–6 mg) to treat insomnia.⁴⁰

3 | STRUCTURAL ORGANIZATION OF THE CEREBRAL HISTAMINERGIC SYSTEM

3.1 | Localization and anatomy of the mammillary body and tuberomammillary complex

The human hypothalamus is part of the diencephalon and comprises \approx 0.3% of the total brain volume. The hypothalamus is arranged in four rostrocaudal regions (preoptic, anterior, tuberal, and mammillary) or three mediolateral zones or areas (periventricular, medial, and lateral).⁴¹ The TMN seats on the mammillary region of the posterior hypothalamus between the arcuate nucleus rostrally and the caudal part of the medial mammillary nucleus, and the rostral part of the substantia nigra.⁴² TMN neurons are the only source of HA in rodents and humans.⁴³ HA^Ns are large (25–40 μ m in diameter), darkly stained, lipofuscin-laden neurons that extend into the zone basally between the medial and lateral mammillary nuclei. Humans have between 64,000 to 154,000 HA^N.⁴² The HA^N joins the NE and 5-HT fibers of the ventral branch of the ascending arousal system to innervate the neocortex (Figure 1). In addition to HA^N, the TMN also contains GABA, galanin, substance P, and MCH neurons.⁴¹ A detailed account of histamine structure, synthesis, metabolism, and mechanism of action, can be found in the supporting information (Figures S1, S2).

4 | HISTAMINERGIC SYSTEM IN AGING AND AD

Neuronal vulnerability to age-related diseases depends on multiple aspects, including the length of axonal projects and myelination. Unmyelinated or poorly myelinated neurons are prone to develop NFTs and are vulnerable to oxidative stress (OS).^{44,45} HA^Ns are predominantly unmyelinated and send long axonal projections to various brain parts. In AD, tau NFTs accumulate in the brainstem before they appear in the entorhinal cortex, the first cortical region to accumulate NFTs. This pattern aligns with the early accumulation of NFTs in other WPNs, such as the dorsal raphe nucleus and LC.^{15,46}

Age-dependent neurotransmitter synthesis and activity alterations cause functional decline. The two rate-limiting steps in HA synthesis are histidine (His) availability and histidine decarboxylase (HDC) expression and activity. L-His, the HA precursor, declines in the serum of AD patients.⁴⁷ However, the cortex, hypothalamus, and midbrain show an age-dependent, region-specific increase in HA in Sprague Dawley old rats.⁴⁸ Exposure to acute stress elevates hypothalamic HA in aged rats, indicating intact stress response of HA^N in 12-month-old Sprague Dawley rats⁴⁹ (Table 1). Given that our current knowledge of age-specific changes is based on rodent models or cell culture studies with very few contributions of studies in humans in a context of early vulnerability of the HA system to AD changes, there is a pressing need to expand the understanding of the role of the HA system in AD.

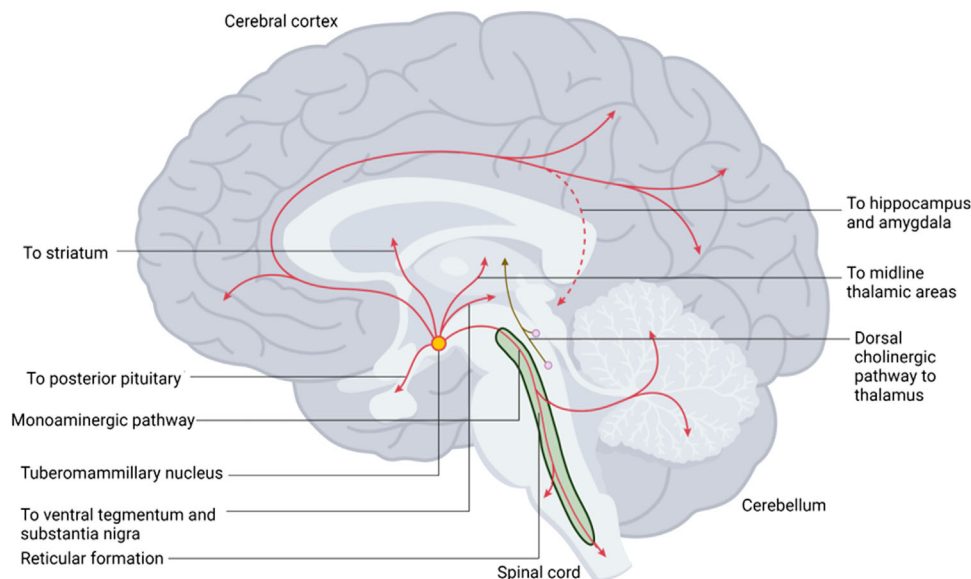


FIGURE 1 Histaminergic projections in the human brain; histaminergic cells are localized in the tuberomammillary nucleus in the posterior hypothalamus. Unmyelinated axons innervate the cerebral cortex, striatum, temporal cortex, thalamus, cerebellum, brainstem, and spinal cord

TABLE 1 Histamine and its metabolites in human and rat brain on aging and Alzheimer's disease

Compound	Model	Control	Aged/stressed	AD	Level of significance	Reference
Histamine	Sprague Dawley rat		-	29% increase	$P < 0.02$	Mazurkiewicz-Kwilecki et al., 1984 ⁴⁸
	Sprague Dawley rat	596±25 ng/g wet tissue	720±30 ng/g wet tissue		$P < 0.01$	Mazurkiewicz-Kwilecki et al., 1986 ⁴⁹
Histamine	Human		—	20%–45% decline	$P < 0.05$ to $P < 0.001$	Mazurkiewicz-Kwilecki et al., 1988 ⁵⁶
Histamine	Human		—	20%–55% increase	$P < 0.05$ to $P < 0.005$	Fernández-Nova and Cacabelos 2001 ⁵²
	Human		—	Increase in medial TMN in AD patients	$P = 0.047$	Shan et al., 2012 ⁵⁸
Histidine	Human		—	15%–30% decline	$P < 0.05$	Panula et al., 1998 ⁵⁷
HNMT	Sprague Dawley rat		39% decline		$P < 0.001$	Mazurkiewicz-Kwilecki et al., 1986 ⁴⁹
HRF	Human	2.91 ± 1.04	—	1.93 ± 0.83	$P < 0.05$	Kim et al., 2001 ⁵⁹
Baseline histamine release		≈230 c.p.m./mg protein (male) and ~130 c.p.m./mg protein (female) in 6-month-old Wistar-Kyoto strain rat	≈145 c.p.m./mg protein (male) and ≈130 c.p.m./mg protein (female) in 24-month-old Wistar-Kyoto strain rat	—	$P < 0.01$ (male) $P > 0.05$ (female)	Ferretti et al., 1998 ⁶⁰

Abbreviations: AD, Alzheimer's disease; HNMT, histamine N-methyltransferase; HRF, histaminergic releasing factor.

TABLE 2 Histamine and its metabolites in CSF during aging and in AD

Compound	Metabolite	Model	Control	Aged	AD	Level of significance	Reference
Histamine		Human	3.4 ± 1.4 pmol/ml 141.00 pM (50.00–430.00)	–	8.3 ± 2.9 pmol/ml 164.50 pM (50.00–642.00)	$P < 0.05$ $P = 0.51$	Fernández- Novoa and Cacabelos, 2001 ⁵² Gabelle et al., 2017 ⁵⁵
Histamine metabolite	tele- methylhistami (t-MeOH)	Human	1.52 ± 0.23 pmol/ml	2.86 ± 0.24 pmol/ml	–	$P < 0.005$	Prell et al., 1991 ⁵³
		Human	1.93 ± 0.33 pmol/ml	3.14 ± 0.24 pmol/ml	–	$P < 0.001$	Motawaj et al., 2010 ⁵⁴
		Human	1126.00 pM (600.00– 4087.00)	–	1803.00 (317.00–3904)	$P = 0.70$	Gabelle et al., 2017 ⁵⁵
tele- methylimidazo acetic acid (t-MIAA)	Human	Human	2.76 ± 0.13 pmol/ml	–	2.14 ± 0.10 pmol/ml	$P < 0.01$	Motawaj et al., 2010 ⁵⁴
		Human	5.60 ± 0.48 pmol/n	7.29 ± 0.39 pmol/ml	–	$P < 0.05$	Prell et al., 1991 ⁵³
		Human	1232.00 pM (984.00– 4146.00)	–	1967.50 pM (367.00– 4144.00)	$P = 0.16$	Gabelle et al., 2017 ⁵⁵

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid.

4.1 | Histamine and its metabolites in the CSF

CSF levels of HA metabolites reflect HA activity and thus represent a window into the changes in the HA system during aging and AD. Changes in CSF HA levels have been predominantly studied in sleep disorders, such as narcolepsy, obstructive sleep apnea syndrome, hypersomnia, and idiopathic hypersomnia. These studies, including people of ages 4 to 86 years, have aimed to understand the relationship between CSF levels of hypocretin-1, HA, and tele-methylhistamine (t-MeHA) in different sleep disorders and to investigate the effects of age, severity of the disorder, and medication on CSF metabolites.^{50,51} Little is known about changes in CSF HA or HA metabolites in aging or AD, and the few studies available show contradictory results. Fernández-Novoa and Cacabelos reported significantly increased CSF-HA levels in AD patients.⁵² Prell et al. demonstrated that an age-associated increase in CSF t-MeHA and tele-methylimidazole acetic acid (t-MIAA) levels were also sex-dependent (Table 2). CSF t-MeHA and t-MIAA were higher in females at the base level compared to males. CSF HA metabolite concentration in males exhibited an age-associated increase, while females had no such changes. However, it is worth noting that the study contains only two younger female participants.⁵³ The primary focus of the study was the effect of age and sex on levels of HA metabolites in the lumbar CSF, and the authors did not consider neuropathological diagnosis as an influencing factor.

Motawaj et al. made a similar observation showing an age-dependent increase in CSF t-MeHA levels, in which t-MeHA levels in 80-year-old females were 3.39 ± 0.29 pmol/mL compared to 2.50 ± 0.28 and 1.97 ± 0.36 pmol/mL in 60- and 40-year-old females, respectively. Similarly, among the males, the t-MeHA levels in 80-year-old participants were 2.90 ± 0.22 pmol/mL compared to 2.09 ± 0.18 and 1.89 ± 0.31 pmol/mL of their 60- and 40-year-old counterparts.⁵⁴ Further, they compared CSF t-MeHA levels in patients with AD-type dementia to controls and demonstrated a significant decline in AD (2.14 ± 0.10 vs. 2.76 ± 0.13 pmol/mL [$P < 0.01$]). The decline of CSF t-MeHA was higher among the female AD participants (2.06 ± 0.14 vs. 2.95 ± 0.21 pmol/mL, $P < 0.001$) than in males (2.26 ± 0.16 vs. 2.58 ± 0.16 pmol/mL). The CSF t-MeHA levels declined in AD patients over controls by 24%.⁵⁴ This contrasting CSF t-MeHA profile in aging and AD individuals is intriguing and needs further study to establish whether CSF t-MeHA is a possible AD marker. Gabelle et al. published an opposite report, which showed an insignificant increment in CSF t-MeHA levels in AD-type dementia and mild cognitive impairment compared to controls.⁵⁵ Although the authors used a precise technique for quantifying CSF t-MeHA level, the presence of outliers in the data is evident (Table 2). The outliers and the small sample size confound the interpretation of the results. Overall, it is clear that more studies are needed to understand the relationship between CSF HA or HA metabolites and AD; fewer studies with contradictory reports complicate the picture.

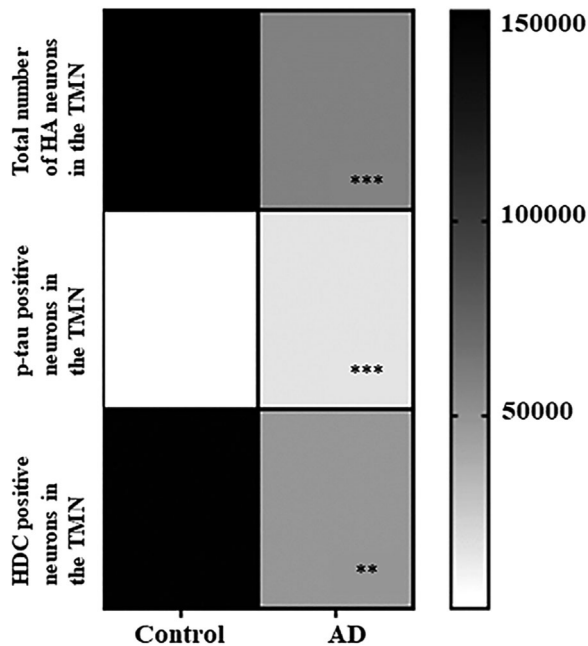


FIGURE 2 Loss of histaminergic neurons in later stages of AD. The scale bar on the right represents the cell population (mean) in the TMN. *Denotes statistical significance over control. AD, Alzheimer's disease; HDC, histidine decarboxylase; HA^N, histaminergic neurons; TMN, tuberomammillary nucleus

4.2 | Histamine in the aging brain and AD

Histamine levels increase in the brain of aging rodents, and it is unclear if the same is true in humans. Human *post mortem* studies with control and AD patients present contrasting findings. While one study found a maximum HA decline in the frontal cortex in AD brains,⁵⁶ another found a more severe decline in the temporal cortex and hippocampus.⁵⁷ In contrast, Fernández-Novoa and Cacabelos reported a substantial increase in cerebral HA concentration in the AD brain in discrete regions of the cerebral cortex, with the maximum concentrations found in the posterior hypothalamus.⁵² None of these studies estimated HA concentration in TMN. A third study found a decline in HA^N in the TMN in AD patients and downregulation of HDC mRNA only in the medial TMN.⁵⁸ In our current study on human *post mortem* TMN using the nCounter platform of Nanostring, we found a significant -1.61 -fold ($P = 0.038$) decline in HDC RNA expression in AD patients (Braak 6, $n = 6$) over controls (Braak 0, $n = 3$; unpublished). Finally, another study found a decline of hippocampal histaminergic releasing factor (HRF) in the temporal cortex of AD patients,⁵⁹ with age- and sex-dependent decline in HA release⁶⁰ (Table 1). Although contrasting reports exist regarding brain and CSF HA levels in AD, with a possible topographical and sex-related variation, a profound loss of HA^N is well established, varying between 57% to 62% in late-stage AD compared to healthy controls.^{17,58}

Pathological changes in the TMN include loss of HA^N and the presence of NFTs (Figure 2).¹⁷ The loss of HA^Ns with preserved HDC mRNA expression indicates the presence of a compensatory mechanism in

the TMN. The age-dependent increase in HA levels can protect against OS and neuroinflammation. Studies with cell cultures and a mouse model of AD (A β PP^{swe}/PSEN1dE9), demonstrate that supplementing HA or His-dipeptides such as anserine or carnosine can modulate neuroinflammation, OS, and caspase-dependent cell death, and can rescue the animals from cognitive deficits.^{61,62} HA protects against lipopolysaccharide (LPS)-mediated reactive astrogliosis and microgliosis in the hippocampus by inhibiting Toll-like receptor 4-associated pro-inflammatory mediators (interleukin-1 beta and HMGB1) while simultaneously increasing HRF levels,¹³ critical for strengthening the synaptic plasticity in the hippocampus.¹³ Additionally, research has suggested that HA may inhibit carbonyl stress and post-translational protein modification by reacting with and stabilizing lipid peroxidation products.⁶³ Based on the current research and literature, it is clear that there is a significant lack of understanding about the role of the histaminergic system in the development and progression of AD.

5 | THERAPEUTIC POTENTIAL OF HISTAMINE RECEPTORS TO AMELIORATE AGE- OR AD-ASSOCIATED COGNITIVE DECLINE

Arrang et al.⁶⁴ characterized H3Rs as presynaptic auto-receptors that regulate HA release by a negative feedback mechanism. H3Rs are predominantly expressed in the CNS with a relatively lower expression in the sympathetic and peripheral nervous systems.^{64–66} These G-protein coupled H3Rs regulate the release of acetylcholine (ACh), NE, DA, and 5-HT either directly as a presynaptic heteroreceptor or indirectly by altering the HA levels.^{43,66} Cognitive impairment in AD is generally treated with acetylcholinesterase inhibitors (AChEi) to counterbalance the effects of lower ACh neurotransmission; however, the moderate efficacy of AChEi is a concern,⁶⁷ and thus, it becomes imperative to look for targets capable of enhancing ACh neurotransmission.

The H3R mRNA expression in the human prefrontal cortex demonstrates a sex-dependent significant increase in severe AD dementia over cognitively intact subjects.⁵⁸ However, autoradiographic studies with H3R antagonists (³H GSK189254) in mice and human brains demonstrated preserved H3R density in the medial frontal cortex across AD progression; the study was inconclusive regarding the H3R downstream processes, such as cyclic adenosine monophosphate (cAMP)/cAMP-response element binding protein (CREB) and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/glycogen synthase kinase 3 beta (GSK3 β) pathways, apoptosis/autophagy, H2R modulation, and inflammatory responses.⁶⁸ Radioligand [¹¹C] GSK189254 has been used to quantify H3R receptors in humans by positron emission tomography.^{69,70} Activation of H3Rs is associated with a decline in ACh, Glu, and GABA, the neurotransmitters critical for maintaining cognition.⁴³ Selective blockage of H3Rs demonstrated increased HA, ACh, NE, and DA release from the hippocampus and anterior cingulate cortex and reinstated cognitive integrity in aged Wistar rats.^{71–73} Selective inactivation of H3Rs also enhances neurogenesis in the subgranular zone of the hippocampus, a region considered critical for cognition and highly vulnerable to AD.⁷⁴ Chronic administration of

S38093 (an inverse agonist/antagonist of H3R) enhanced hippocampal neurogenesis in adult 129/SvEvTac, aged C57Bl/6Jrj, and in APPSWE model of AD via upregulation of brain-derived neurotrophic factor (BDNF) BDNF-IX, BDNF-IV, and BDNF-I transcripts and increased vascular endothelial growth factor expression in aged mice.⁷⁵

Pharmacological inactivation of H3R mediates neuroprotection via cAMP/CREB and PI3K/AKT/GSK3 β pathway.⁷⁶ Inactivation of H3Rs leads to an increase in the intracellular levels of cAMP, upregulates CREB protein, and mediates protection via downregulation of AKT/GSK3 β in mice (APP/PS1) model of AD.⁷⁶ The loss of lysosomal function and accumulation of autophagic vesicles are associated with tau cleavage and spreading.⁷⁷ Downregulation of the extracellular signal-related kinase (ERK)/CREB pathway impairs autophagy in human neural stem cells.⁷⁸ Wang et al. demonstrated that H3R inhibition rescued the lysosomal impairment by activating CREB. The pCREB protein upregulated Atg7 and transcription factor EB (TFEB) expression, enhanced ablation of A β and beta-secretase 1, and reinstated cognitive integrity in the mouse model (APP/PS1) of AD.⁷⁹

Further, manipulation of the histaminergic system with an H3R antagonist resulted in a decline in inflammation in the hippocampus and cerebral cortex with a simultaneous reduction in astroglial and microglial reactivity in 9-month-old APP/PS1 mice. Inhibition of H3R altered astrocytic phenotype from reactive A1 to protective A2 astrocytes by increasing the cAMP/CREB phosphorylation and by suppressing phosphorylated nuclear factor kappa-light-chain-enhancer of beta (NF κ B) cells expression. Treatment of H89 (inhibitor of CREB signals) impedes H3R activation and provides neuroprotection by inhibiting astroglial and microglial activation.⁸⁰ Alachkar et al. demonstrated that the inactivation of H3Rs by E177 (non-imidazole H3R antagonist) significantly improved cognition in adult amnesic Wistar rats. However, this inhibition of H3Rs didn't affect anxiety-like or locomotor behavior.⁸¹

Manipulation of histaminergic receptors with a pharmacological agent capable of selectively inhibiting H3Rs and stimulating H4Rs emulated neuroprotective effects on the mouse AD model. In the A β infusion-induced AD model, clobenpropit (CLO), an inverse antagonist of H3Rs with partial H4R agonist, had a profound neuroprotective effect over BF2694, an inverse antagonist of H3R.⁸² Stimulating H4Rs and blocking H3R improves blood-brain barrier integrity in a rat AD model. Shan et al.⁸³ confirmed the anti-inflammatory potential of H4Rs in the LPS-mediated neuroinflammation model. The overexpression of H4R inhibited pro-inflammatory cytokines tumor necrosis factor α , IL-1 β , IL-6, and IL-12 in LPS-stimulated highly aggressively proliferating immortalized microglial cells. The anti-inflammatory effect of the H4R agonist 4-MeH was reversed when the LPS+4-MeH cells were pre-treated with an H4R antagonist. The H4R agonist exerts anti-inflammatory function by inhibiting the release of pro-inflammatory cytokines and phosphorylation of NF κ B p65, p38 mitogen-activated protein kinase, and ERK1/2.⁸³ Although the exact role of H4R is unclear, the results from various studies have provided a substantial backup for the candidature of the H4R agonist as an effective agent to mitigate the inflammation of the AD brain.

6 | CONCLUSION AND PERSPECTIVE

Evidence indicates that AD-specific vulnerability of WPNs is associated with sleep dysfunction in patients suffering from AD. Further, pathological changes in the HA^N correlate with cognitive deficits. The evolutionarily conserved signaling molecule HA acts as a neurotransmitter and is critical for the sleep-wake cycle, maintenance of biological rhythm, temperature regulation, and possibly cognition. As a neuromodulator, HA influences the activity of various neurotransmitters, including the cholinergic, glutamatergic, and nor-adrenergic systems through multiple HA receptors. Rodent studies with pharmacological manipulation of HA receptors corroborate the pro-cognitive potential of HA. Inhibition of H3R lowers lipid peroxidation and neuroinflammation by reducing reactive gliosis and upregulation of protective astrocytes. It also modulates autophagy by upregulating Atg7 and TFEB expression via pCREB. The H3R antagonists/inverse agonists have been shown to improve sleep-wake dysfunction and facilitate clearance of A β , tau, and other toxic metabolites and institute a homeostatic milieu that inhibits neuronal loss. In addition, the relatively preserved H3R density in AD makes it a vital candidate for therapeutic strategies. Less research is available on the histamine receptor H4R, but H4R agonists have anti-inflammatory properties that may enhance the effects of H3R agonists. Therefore, targeting the histaminergic neurotransmission system with an H3R antagonist/inverse agonist or H4R agonist, either alone or in combination, could be a promising new approach for treating AD.

Studies measuring HA or HA metabolite levels in the human brain and CSF present conflicting reports and often lack power or control for known confounders. Intriguingly, CSF HA metabolite levels demonstrate an age-dependent and sex-independent increase, whereas they decline in AD significantly. Therefore, systemic studies examining factors that may affect HA or HA metabolites in the brain and CSF, including age, sex, neuropathological diagnosis, and disease stage, are warranted and may inform on the utility of HA as a biomarker for AD. Also, mechanisms associated with HA-mediated post-translational modification of protein require elucidation.

Our review of the histaminergic system demonstrates critical gaps in knowledge and gross neglect of the histaminergic system and its role in AD progression. The role of cerebral HA in the progression of AD deserves further investigation.

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CONFLICT OF INTEREST STATEMENT

The authors do not have any conflicts of interest to disclose. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

There were no human subjects involved in this manuscript, thus consent was not necessary.

REFERENCES

- Alzheimer's Association. 2022 Alzheimer's Disease Facts and Figures. *Alzheimer's Dement.* 2022;18:700-789. <https://doi.org/10.1002/alz.12638>
- Ziegler-Waldkirch S, Meyer-Luehmann M. The role of glial cells and synapse loss in mouse models of Alzheimer's disease. *Front Cell Neurosci.* 2018;12:473. <https://doi.org/10.3389/fncel.2018.00473>
- Brzecka A, Leszek J, Ashraf GM, et al. Sleep disorders associated with Alzheimer's disease: a perspective. *Front Neurosci.* 2018;12:330. <https://doi.org/10.3389/fnins.2018.00330>
- Spira AP, Chen-Edinboro LP, Wu MN, Yaffe K. Impact of sleep on the risk of cognitive decline and dementia. *Curr Opin Psychiatry.* 2014;27(6):478-483. <https://doi.org/10.1097/YCO.000000000000106>
- Sabia S, Fayosse A, Dumurgier J, et al. Association of sleep duration in middle and old age with incidence of dementia. *Nat Commun.* 2021;12(1):2289. <https://doi.org/10.1038/s41467-021-22354-2>
- Zhang Y, Ren R, Yang L, et al. Sleep in Alzheimer's disease: a systematic review and meta-analysis of polysomnographic findings. *Transl Psychiatry.* 2022;12(1):136. <https://doi.org/10.1038/s41398-022-01897-y>
- Leng Y, Redline S, Stone KL, Ancoli-Israel S, Yaffe K. Objective napping, cognitive decline, and risk of cognitive impairment in older men. *Alzheimer's Dement.* 2019;15(8):1039-1047. <https://doi.org/10.1016/j.jalz.2019.04.009>
- Lucey BP, Mccullough A, Landsness EC, et al. Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Sci Transl Med.* 2019;11(474):eaau6550.
- Winer JR, Mander BA, Kumar S, et al. Sleep disturbance forecasts β -Amyloid accumulation across subsequent years. *Curr Biol.* 2020;30(21):4291-4298.e3. <https://doi.org/10.1016/j.cub.2020.08.017>
- Spira AP, An Y, Wu MN, et al. Excessive daytime sleepiness and napping in cognitively normal adults: associations with subsequent amyloid deposition measured by PiB PET. *Sleep.* 2018;41(10):zsy152. <https://doi.org/10.1093/sleep/zsy152>
- Carvalho DZ, St Louis EK, Knopman DS, et al. Association of excessive daytime sleepiness with longitudinal β -Amyloid accumulation in elderly persons without dementia. *JAMA Neurol.* 2018;75(6):672-680. <https://doi.org/10.1001/jamaneurol.2018.0049>
- Scammell TE, Arrigoni E, Lipton JO. Neural circuitry of wakefulness and sleep. *Neuron.* 2017;93(4):747-765. <https://doi.org/10.1016/j.neuron.2017.01.014>
- Saraiva C, Barata-Antunes S, Santos T, et al. Histamine modulates hippocampal inflammation and neurogenesis in adult mice. *Sci Rep.* 2019;9(1):8384. <https://doi.org/10.1038/s41598-019-44816-w>
- 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. Published online. 2018. <https://doi.org/10.1111/bph.v177.3/issuetoc>
- Theofilas P, Ehrenberg AJ, Dunlop S, et al. Locus coeruleus volume and cell population changes during Alzheimer's disease progression: a stereological study in human postmortem brains with potential implication for early-stage biomarker discovery. *Alzheimer's Dement.* 2017;13(3):236-246. <https://doi.org/10.1016/j.jalz.2016.06.2362>
- Eser RA, Ehrenberg AJ, Petersen C, et al. Selective vulnerability of brainstem nuclei in distinct tauopathies: a postmortem study. *J Neuropathol Exp Neurol.* 2018;77(2):149-161. <https://doi.org/10.1093/jnen/nlx113>
- Oh J, Eser RA, Ehrenberg AJ, et al. Profound degeneration of wake-promoting neurons in Alzheimer's disease. *Alzheimer's Dement.* 2019;15(10):1253-1263. <https://doi.org/10.1016/j.jalz.2019.06.3916>
- Oh JY, Walsh CM, Ransinghe K, et al. Subcortical neuronal correlates of sleep in neurodegenerative diseases. *JAMA Neurol.* 2022;79(5):498. <https://doi.org/10.1001/jamaneurol.2022.0429>
- Zielinski MR, McKenna JT, McCarley RW. Functions and mechanisms of sleep. *AIMS Neurosci.* 2016;3(1):67-104. <https://doi.org/10.3934/Neuroscience.2016.1.67>
- Potkin KT, Bunney WE. Sleep improves memory: the effect of sleep on long term memory in early adolescence. *PLoS One.* 2012;7(8):e42191. <https://doi.org/10.1371/journal.pone.0042191>
- Irwin MR. Sleep and inflammation: partners in sickness and in health. *Nat Rev Immunol.* 2019;19(11):702-715. <https://doi.org/10.1038/s41577-019-0190-z>
- Knutson KL, Spiegel K, Penev P, van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev.* 2007;11(3):163-178. <https://doi.org/10.1016/j.smrv.2007.01.002>
- Musiek ES, Holtzman DM. Mechanisms linking circadian clocks, sleep, and neurodegeneration. *Science.* 2016;354(6315):1004-1008. <https://doi.org/10.1126/science.aah4968>
- Holth JK, Fritsch SK, Wang C, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science.* 2019;363(6429):880-884. <https://doi.org/10.1126/science.aav2546>
- Shokri-Kojori E, Wang GJ, Wiers CE, et al. β -Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A.* 2018;115(17):4483-4488. <https://doi.org/10.1073/pnas.1721694115>
- Kylkilahti TM, Berends E, Ramos M, et al. Achieving brain clearance and preventing neurodegenerative diseases—a glymphatic perspective. *J Cereb Blood Flow Metab.* 2021;41(9):2137-2149. <https://doi.org/10.1177/0271678X20982388>
- Hablitz LM, Plá V, Giannetto M, et al. Circadian control of brain glymphatic and lymphatic fluid flow. *Nat Commun.* 2020;11(1):4411. <https://doi.org/10.1038/s41467-020-18115-2>
- Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron.* 2014;81(1):12-34. <https://doi.org/10.1016/j.neuron.2013.12.025>
- Cirrito JR, Yamada KA, Finn MB, et al. Synaptic activity regulates interstitial fluid amyloid- β levels in vivo. *Neuron.* 2005;48(6):913-922. <https://doi.org/10.1016/j.neuron.2005.10.028>
- Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature.* 2005;437(7063):1257-1263. <https://doi.org/10.1038/nature04284>
- Edlow BL, Takahashi E, Wu O, et al. Neuroanatomic connectivity of the human ascending arousal system critical to consciousness and its disorders. *J Neuropathol Exp Neurol.* 2012;71(6):531-546.
- Munn BR, Müller EJ, Wainstein G, Shine JM. The ascending arousal system shapes neural dynamics to mediate awareness of cognitive states. *Nat Commun.* 2021;12(1):6016. <https://doi.org/10.1038/s41467-021-26268-x>
- Siegel JM. The neurotransmitters of sleep. *J Clin Psychiatry.* 2004;65(16):4-7.
- Sakai K, Takahashi K, Anaclet C, Lin JS. Sleep-waking discharge of ventral tuberomammillary neurons in wild-type and histidine decarboxylase knock-out mice. *Front Behav Neurosci.* 2010;4:53. <https://doi.org/10.3389/fnbeh.2010.00053>
- Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. *Physiol Rev.* 2008;88(3):1183-1241. <https://doi.org/10.1152/physrev.00043.2007>
- Anaclet C, Parmentier R, Ouk K, et al. Orexin/hypocretin and histamine: distinct roles in the control of wakefulness demonstrated using knock-out mouse models. *J Neurosci.* 2009;29(46):14423-14438. <https://doi.org/10.1523/JNEUROSCI.2604-09.2009>

37. Cheng J, Wu F, Zhang M, et al. The interaction between the ventrolateral preoptic nucleus and the tuberomammillary nucleus in regulating the sleep-wakefulness cycle. *Front Neurosci.* 2020;14:615854. <https://doi.org/10.3389/fnins.2020.615854>
38. Guevarra JT, Hiensch R, Varga AW, Rapoport DM. Pitolisant to treat excessive daytime sleepiness and cataplexy in adults with narcolepsy: rationale and clinical utility. *Nat Sci Sleep.* 2020;12:709-719. <https://doi.org/10.2147/NSS.S264140>
39. Harwell V, Fasinu P. Pitolisant and other histamine-3 receptor antagonists—an update on therapeutic potentials and clinical prospects. *Medicines.* 2020;7(9):55. <https://doi.org/10.3390/medicines7090055>
40. Katwala J, Kumar AK, Sejjal JJ, Terrence M, Mishra M. Therapeutic rationale for low dose doxepin in insomnia patients. *Asian Pac J Trop Dis.* 2013;3(4):331-336. [https://doi.org/10.1016/S2222-1808\(13\)60080-8](https://doi.org/10.1016/S2222-1808(13)60080-8)
41. Nieuwenhuys R, Voogd J, Huijzen C. Diencephalon: hypothalamus. In: Nieuwenhuys R, Voogd J, Huijzen C, eds. *The Human Central Nervous System.* 4th ed. Springer; 2008:289-336.
42. Airaksinen MS, Paetau A, Paljärvi L, et al. Histamine neurons in human hypothalamus: anatomy in normal and Alzheimer diseases brains. *Neuroscience.* 1991;44(2):465-481.
43. Blandina P, Munari L, Provensi G, Passani MB. Histamine neurons in the tuberomammillary nucleus: a whole center or distinct subpopulations? *Front Syst Neurosci.* 2012;6:33. <https://doi.org/10.3389/fnsys.2012.00033>
44. Braak H, Tredici KK, Schultz C, Braak E. Vulnerability of select neuronal types to Alzheimer's disease. *Ann N Y Acad Sci.* 2006;924(1):53-61. <https://doi.org/10.1111/j.1749-6632.2000.tb05560.x>
45. Rubinski A, Franzmeier N, Dewenter A, et al. Higher levels of myelin are associated with higher resistance against tau pathology in Alzheimer's disease. *Alzheimers Res Ther.* 2022;14(1):139. Published online 2022. <https://doi.org/10.1101/2022.03.02.22271746>
46. Grinberg LT, Rüb U, Ferretti REL, et al. The dorsal raphe nucleus shows phospho-tau neurofibrillary changes before the transentorhinal region in Alzheimer's disease. A precocious onset? *Neuropathol Appl Neurobiol.* 2009;35(4):406-416. <https://doi.org/10.1111/j.1365-2990.2008.00997.x>
47. González-Domínguez R, García-Barrera T, Gómez-Ariza JL. Metabolite profiling for the identification of altered metabolic pathways in Alzheimer's disease. *J Pharm Biomed Anal.* 2015;107:75-81. <https://doi.org/10.1016/j.jpba.2014.10.010>
48. Mazurkiewicz-Kwilecki IM, Prell GD. Age-related changes in brain histamine. *Agents Actions.* 1984;14(3-4):554-557.
49. Mazurkiewicz-Kwilecki IM, Perll GD. Brain histamine response to stress in 12 month old rats. *Life Sci.* 1986;38:2339-2345.
50. Kanbayashi T, Kodama T, Kondo H, et al. CSF histamine contents in narcolepsy, idiopathic hypersomnia and obstructive sleep apnea syndrome. *Sleep.* 2009;32(2):181-187. <https://academic.oup.com/sleep/article/32/2/181/2454318>
51. Dauvilliers Y, Delalleé N, Jaussent I, et al. Normal cerebrospinal fluid histamine and tele-methylhistamine levels in hypersomnia conditions. *Sleep.* 2012;35(10):1359-1366. <https://doi.org/10.5665/sleep.2114>
52. Fernández-Novoa L, Cacabelos RN. Histamine function in brain disorders. *Behav Brain Res.* 2001;124:213-233.
53. Prell GD, Khandelwal JK, Stanley Burns R, Lewitt PA, Green JP. Influence of age and gender on the levels of histamine metabolites and pros-methylimidazoleacetic acid in human cerebrospinal fluid. *Arch Gerontol Geriatr.* 1991;12(1):1-12.
54. Motawaj M, Peoc'H K, Callebert J, Arrang JM. CSF levels of the histamine metabolite tele-methylhistamine are only slightly decreased in Alzheimer's disease. *J Alzheimers Dis.* 2010;22(3):861-871. <https://doi.org/10.3233/JAD-2010-100381>
55. Gabelle A, Jaussent I, Hirtz C, et al. Cerebrospinal fluid levels of orexin-A and histamine, and sleep profile within the Alzheimer process. *Neurobiol Aging.* 2017;53:59-66. <https://doi.org/10.1016/j.neurobiolaging.2017.01.011>
56. Mazurkiewicz-Kwilecki IM, Nsonwah S. Changes in the regional brain histamine and histidine levels in postmortem brains of Alzheimer patients. *Can J Physiol Pharmacol.* 1988;67:75-78.
57. Panula P, Rinne J, Kuokkanen K, et al. Neuronal histamine deficits in Alzheimer's disease. *Neuroscience.* 1998;82(4):993-997.
58. Shan L, Bossers K, Unmehopa U, Bao AM, Swaab DF. Alterations in the histaminergic system in Alzheimer's disease: a postmortem study. *Neurobiol Aging.* 2012;33(11):2585-2598. <https://doi.org/10.1016/j.neurobiolaging.2011.12.026>
59. 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;300:41-44.
60. Ferretti C, Blengio M, Ghi P, Adage T, Portaleone P, Ricci Gamalero S. Hypothalamic histamine release in normal and stressed rats is affected by sex and aging. *Pharmacol Biochem Behav.* 1998;59(1):255-260.
61. Kaneko J, Enya A, Enomoto K, Ding Q, Hisatsune T. Anserine (beta-alanyl-3-methyl-L-histidine) improves neurovascular-unit dysfunction and spatial memory in aged AβPPsw/PSEN1dE9 Alzheimer's-model mice. *Sci Rep.* 2017;7(1):12571. <https://doi.org/10.1038/s41598-017-12785-7>
62. Kim Y, Kim Y. L-histidine and l-carnosine exert anti-brain aging effects in d-galactose-induced aged neuronal cells. *Nutr Res Pract.* 2020;14(3):188-202. <https://doi.org/10.4162/nrp.2020.14.3.188>
63. Li L, Li G, Sheng S, Yin D. Substantial reaction between histamine and malondialdehyde: a new observation of carbonyl stress. *Neuro Endocrinol Lett.* 2005;26(6):799-805.
64. Arrang JM, Garbarg M, Schwartz JC. Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. *Nature.* 1983;302:832-837.
65. Chotard C, Ouimet T, Morisset S, Sahn U, Schwartz JC, Trottier S. Effects of histamine H3 receptor agonist and antagonist on histamine co-transmitter expression in rat brain. *J Neural Transm (Vienna).* 2002;109(3):293-306.
66. Berlin M, Boyce CW, de Lera Ruiz M. Histamine H3 receptor as a drug discovery target. *J Med Chem.* 2011;54(1):26-53. <https://doi.org/10.1021/jm100064d>
67. Marucci G, Buccioni M, Ben DD, Lambertucci C, Volpini R, Amenta F. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. *Neuropharmacology.* 2021;190:108352. <https://doi.org/10.1016/j.neuropharm.2020.108352>
68. Medhurst AD, Roberts JC, Lee J, et al. Characterization of histamine H3 receptors in Alzheimer's Disease brain and amyloid over-expressing TASTPM mice. *Br J Pharmacol.* 2009;157(1):130-138. <https://doi.org/10.1111/j.1476-5381.2008.00075.x>
69. Ashworth S, Rabiner EA, Gunn RN, et al. Evaluation of 11C-GSK189254 as a novel radioligand for the H3 receptor in humans using PET. *J Nucl Med.* 2010;51(7):1021-1029. <https://doi.org/10.2967/jnumed.109.071753>
70. Plisson C, Gunn RN, Cunningham VJ, et al. 11C-GSK189254: a selective radioligand for in vivo central nervous system imaging of histamine H3 receptors by PET. *J Nucl Med.* 2009;50(12):2064-2072. <https://doi.org/10.2967/jnumed.109.062919>
71. Medhurst AD, Atkins AR, Beresford IJ, et al. GSK189254, a novel H3 receptor antagonist that binds to histamine H3 receptors in Alzheimer's disease brain and improves cognitive performance in pre-clinical models. *J Pharmacol Exp Ther.* 2007;321(3):1032-1045. <https://doi.org/10.1124/jpet.107.120311>
72. Galici R, Boggs JD, Aluisio L, et al. JNJ-10181457, a selective non-imidazole histamine H3 receptor antagonist, normalizes acetylcholine neurotransmission and has efficacy in translational rat models of cognition. *Neuropharmacology.* 2009;56(8):1131-1137. <https://doi.org/10.1016/j.neuropharm.2009.03.011>

73. Sergeeva OA, Chepkova AN, Görg B, et al. Histamine-induced plasticity and gene expression in corticostriatal pathway under hyperammonemia. *CNS Neurosci Ther*. 2020;26(3):355-366. <https://doi.org/10.1111/cns.13223>
74. 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. <https://doi.org/10.1016/j.pharmthera.2017.02.039>
75. Guilloux JP, Samuels BA, Mendez-David I, et al. S 38093, a histamine H3 antagonist/inverse agonist, promotes hippocampal neurogenesis and improves context discrimination task in aged mice. *Sci Rep*. 2017;7:42946. <https://doi.org/10.1038/srep42946>
76. Wang L, Fang J, Jiang H, et al. 7-pyrrolidinethoxy-4'-methoxyisoflavone prevents amyloid β -induced injury by regulating histamine H3 receptor-mediated cAMP/CREB and AKT/GSK3 β pathways. *Front Neurosci*. 2019;13:334. <https://doi.org/10.3389/fnins.2019.00334>
77. Xu Y, Du S, Marsh JA, et al. TFEB regulates lysosomal exocytosis of tau and its loss of function exacerbates tau pathology and spreading. *Mol Psychiatry*. 2021;26(10):5925-5939. <https://doi.org/10.1038/s41380-020-0738-0>
78. Chong CM, Ke M, Tan Y, et al. Presenilin 1 deficiency suppresses autophagy in human neural stem cells through reducing γ -secretase-independent ERK/CREB signaling. *Cell Death Dis*. 2018;9(9):879. <https://doi.org/10.1038/s41419-018-0945-7>
79. Wang J, Xu Y, Zhao D, et al. Thioperamide Alleviates Lipopolysaccharide-Induced Neuroinflammation and Promotes Neurogenesis by Histamine Dependent Activation of H2R/PKA/CREB Pathway. *Res Sq*. Published online 2021:38. <https://doi.org/10.21203/rs.3.rs-1003030/v1>
80. Wang J, Liu B, Xu Y, et al. Thioperamide attenuates neuroinflammation and cognitive impairments in Alzheimer's disease via inhibiting gliosis. *Exp Neurol*. 2022;347:113870. <https://doi.org/10.1016/j.expneurol.2021.113870>
81. 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. <https://doi.org/10.2147/NDT.S193125>
82. 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. <https://doi.org/10.1007/s12035-017-0743-8>
83. Shan Y, Gao Y, Zhang L, Ma L, Shi Y, Liu X. H4 receptor inhibits Lipopolysaccharide-induced NF- κ B activation by interacting with tumor necrosis factor receptor-associated factor 6. *Neuroscience*. 2019;398:113-125. <https://doi.org/10.1016/j.neuroscience.2018.11.050>

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