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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-amyloidplaques (Aβ) and intracellular neurofibrillary tautangles (NFTs). Although cognitive decline is a disease-defining symptom of AD, sleep dysfunction, a common symptom often preceding cognitive decline, hasrecently gained more attention as a core AD symptom. Polysomnography and othersleep measures show sleep fragmentation with shortening of N_3 sleep togetherwith 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 thetuberomammillary nucleus (TMN) of the posterior hypothalamus, which projectunmyelinated axons to various parts of the brain. Histamine's role in cognitionand arousal is broadly recognized. Selective targeting of histaminergic subtype-3 and 4 receptors show therapeutic potential in rodent models of AD andaging.

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 highlight areas where moreresearch 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 brainand 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 therapeuticpotential of histamine in AD-related dysfunction.

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

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 (Aβ) 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 Aβ 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 Aβ and tau accumulation by severalfold in elderly individuals.[8–10] EDS has been linked to Aβ 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 (HA^N),[15–18] which suggests a primary role of WPNs in AD-related sleep dysfunction. Despite the known role of HA^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.

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.

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 a critical role in the clearance of toxic Aβ, 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 Aβ levels. Additionally, SWS may have an impact on synaptic strength.[28] Reduced synaptic activity has been linked to a decrease in interstitial fluid Aβ levels, while the exocytosis of synaptic vesicles has been linked to an increase in extracellular Aβ.[29] This suggests that SWS may protect against Aβ 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), serotoninergic 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 extensivel 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 NERM 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 ≈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 μm 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 rats [49] (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.

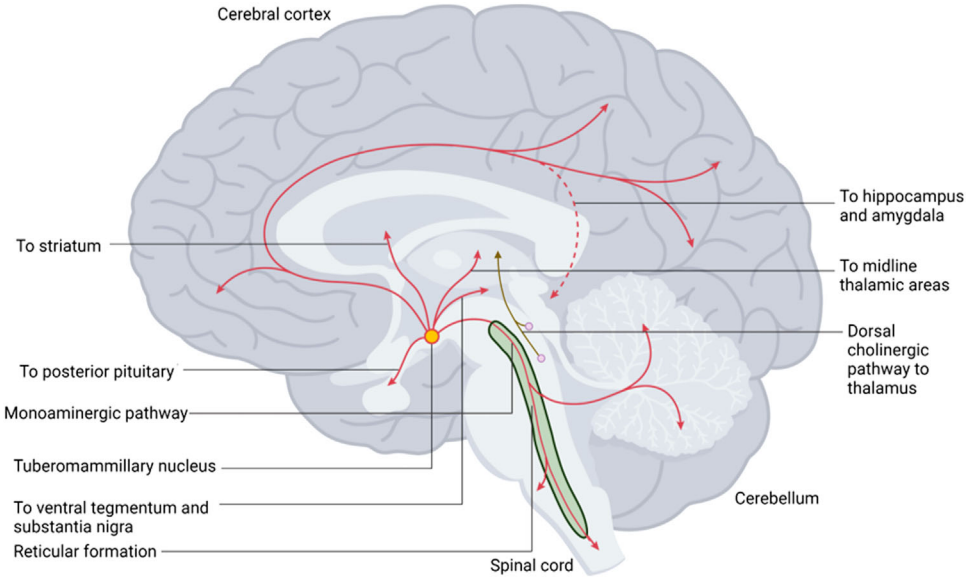

FIGURE 1 Histaminergic projections in the human brain; histaminergic cells are localized in the tuberomammillary nucleus in the posterior hypothalamus. Unmyelinated axons innervate the cerebral cortex, striatum, temporal cortex, thalamus, cerebellum, brainstem, and spinal cord

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-Novoa 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		$P < 0.001$	Marurkiewicz-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-methylhistamir (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]
		Human	2.76 ± 0.13 pmol/ml	—	2.14 ± 0.10 pmol/ml	$P < 0.01$	Motawaj et al., 2010[54]
	tele-methylimidazo acetic acid (t-MIAA)	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 CSFa 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.

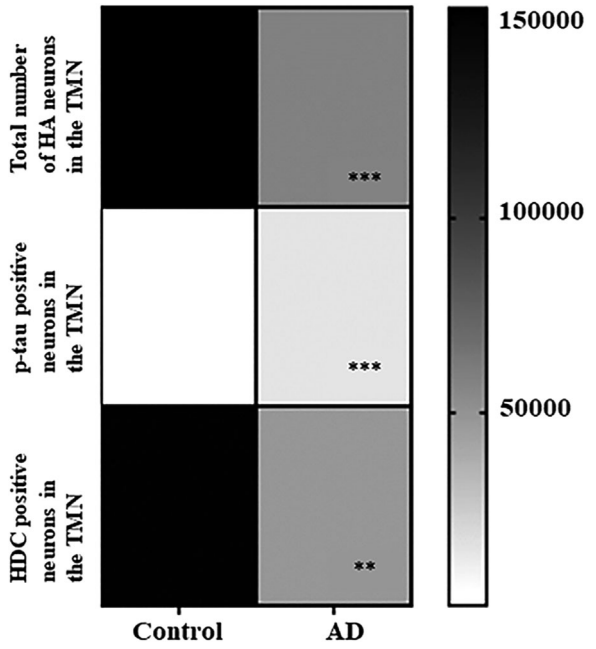

FIGURE 2 Loss of histaminergic neurons in later stages of AD. The scale bar on the right represents the cell population (mean) in the TMN. *Denotes statistical significance over control. AD, Alzheimer's disease; HDC, histidine decarboxylase; HA^N, histaminergic neurons; TMN, tuberomammillary nucleus

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 release[60] (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 (AβPPswe/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 (^{3}H 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 (GSK3β) pathways, apoptosis/autophagy, H2R modulation, and inflammatory responses.[68] Radioligand [^{11}C] 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/GSK3β 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/GSK3β 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 Aβ 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 (NFKβ) 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 amnestic 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 Aβ 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-1β, 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 NFkβ 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 Aβ, 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.

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SUPPORTING INFORMATION

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