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HISTAMINE H3 AND H4 RECEPTORS AS A NEUROIMMUNE CONTROL AXIS: INTEGRATING SYNAPTIC SIGNALING WITH IMMUNE INFLAMMATION

Aurangzeb Khan[*1], Tayyaba Yaseen[2], Muzzammil Siraj[3]

[*1]*SBB Dewan University, Karachi*
[2]*MPhil, Department of Pharmacology, Karachi University*
[3]*Lecturer, Department of Pharmacy ,SBB Dewan University*

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Aurangzeb Khan

Abstract

Histamine is classically associated with inflammation and gastric acid release in the histamine H1 and H2 receptors. Conversely, the new data indicate the pressing role of non-classical histamine H3 and H4 receptors in neuro-inflammation process and immune regulation. H3 receptor is found primarily in the central nervous system, where it regulates the secretion of neurotransmitters, synaptic activity, and microglial functionality, and H4 receptor is found on immune cells, and regulates the chemotaxis of immune cells, generation of cytokines, and inflammatory reactions of chronic inflammation. The clinical and preclinical data indicate that the neuroimmune bi-directional communication between the H3 and H4 receptors is achieved through the processes that entail neuronal signaling, peripheral immune stimulation, and blood-brain barrier interaction. The disruption in the functioning of these pathways has been identified with neuroinflammatory and neurodegenerative diseases. Although pharmacological targeting of H3 and H4 receptors has potential therapeutic utility, receptor specificity, penetration into the central nervous system, and biomarker discovery remain problematic. To achieve the full therapeutic capabilities of H3Rs and H4Rs modulation of neuroinflammatory and neurodegenerative disease, it may be necessary to integrate biomarker-guided strategies that deal with neuronal and immune components be integrated. This review summarizes the existing body of knowledge in the expression pattern, functional roles of H3R & H4R, and special attention is paid to their contribution to neuroimmune cross-talk. We also assess the advancement and constraints of therapeutic approaches to these receptors in clinical development, as well as treatment of neuroinflammatory and immune-mediated disease interventions.

1. Introduction

Histamine, a biogenic amine (Jutel & Akdis, 2011; Thurmond et al., 2008), is synthesized from histidine by histidine decarboxylase, which is either in the form of intracellular granules or synthesized de novo upon cellular activation, depending upon cell type (Haas et al., 2008; Parsons & Ganellin, 2006; Patel & Mohiuddin, 2025). Upon release, histamine mainly acts in an autocrine or paracrine mode, which results in spatially and temporally constrained signaling (Haas et al., 2008; Huang et al., 2018). By this mechanism, histamine shows inflammatory responses, neurotransmission, tissue homeostasis,

and immune regulation (Branco et al., 2018; Colonna & Butovsky, 2017; Panula & Nuutinen, 2013; Passani & Blandina, 2011). H1 receptors are localized in the smooth muscles, sensory neurons, endothelial cells, and immune cells. Studies show that the activation of Gq/11-coupled pathways is responsible for the activation of phospholipase C, mobilization of intracellular calcium, and protein kinase C signaling(Bruysters et al., 2005; Notcovich et al., 2010; Wellner-Kienitz et al., 2003). Together, these pathways amplified the vascular penetrability, smooth muscle contraction(Wang et al., 2018), and activation of sensory nerves, which underlie the acute allergic and inflammatory reactions (Brozovich et al., 2016). Studies indicate that the presence of Histamine H2 receptors in gastric parietal cells controls the secretion of gastric acids by Gs-mediated stimulation of cAMP production (Wellner-Kienitz et al., 2003). Signaling of H2 receptors also ensues in the CVS and immune cells, signifying the functions further than the GIT system (Alonso et al., 2015).

The discovery of histamine H3 and H4 receptors broadened the action of the histaminergic signaling (Panula & Nuutinen, 2013). H3 receptor is mostly concentrated in the CNS (Leurs et al., 2005), where it acts as a presynaptic auto and heteroreceptor in adaptable the production and release of histamine and other neurotransmitters, such as acetylcholine (Blasco-Fontecilla, 2023), dopamine, serotonin, and 7-aminobutyric acid (Hepsomali et al., 2020). Activation of H3 receptors is associated with Gi / o proteins, which inhibit adenylyl cyclase and affect the activity of ion channels, thus regulating neuron excitability and synaptic transmission(Dauvilliers et al., 2013; DiSabato et al., 2016). According to the experimental studies, the H3 receptor signaling is involved in neuroinflammatory processes(Skaper et al., 2015), which is regulated indirectly by modulating the microglial activity and cytokine signaling(Salter & Stevens, 2017; Skaper et al., 2015). Immune cells are the most common carriers of the histamine H4 receptor, namely, mast cells, eosinophils, dendritic cells, and T lymphocytes. H4 receptors are involved in the interaction of innate and adaptive immune responses through the regulation of immune cell migration, cytokine generation, and polarization of inflammation(Kondo et al., 2021). The chronic inflammatory and autoimmune diseases, which are marked by prolonged immune activation, have been linked to H4 receptor signaling(Schneider & Seifert, 2016).

Comprehensively, the characterization of histamine H3 and H4 receptors has changed how histamine signaling was viewed, as comprising isolated allergic and gastrointestinal responses to integrated neuroimmune responses(Deiteren et al., 2015; Thangam et al., 2018). The specific and overlapping roles of these receptors are of paramount importance in the relationship of histamine-dependent mechanisms in chronic inflammatory(Thurmond et al., 2008; Zampeli & Tiligada, 2009), neuroinflammatory(Zhou et al., 2024), and immune-mediated diseases.

Table 1: Histamine receptor subtypes: distribution, signaling, functional domains

Receptor	Dominant expression	G-protein	Canonical signaling	Core physiological roles	Typical pharmacology	References
H1R	endothelium, smooth muscle, CNS	Gq/11	PLC→IP3/DAG→Ca^{2+}	allergy, pruritus, bronchospasm, wakefulness	antagonists (2nd gen)	(Black et al., 2012; Bruysters et al., 2005; Fahy, 2015; Gebski et al., 2022)

H2R	gastric parietal cells, immune cells	Gs	↑cAMP/PKA	gastric acid secretion, immune modulation	antagonists (H2 blockers)	(Engevik et al., 2020)
H3R	CNS neurons (presynaptic)	Gi/o	↓cAMP; ↓Ca^{2+} influx; ↑K^+ conductance	neurotransmitter regulation, arousal/cognition	inverse agonists/antagonists	(Carthy & Ellender, 2021; Esbenshade et al., 2008a)
H4R	mast cells, eosinophils, DCs, T cells	Gi/o	↓cAMP; Ca^{2+} mobilization; chemotaxis pathways	leukocyte trafficking, cytokine polarization, chronic inflammation	antagonists (investigational)	(Felger & Lotrich, 2013; A. P. Kollmeier et al., 2018)

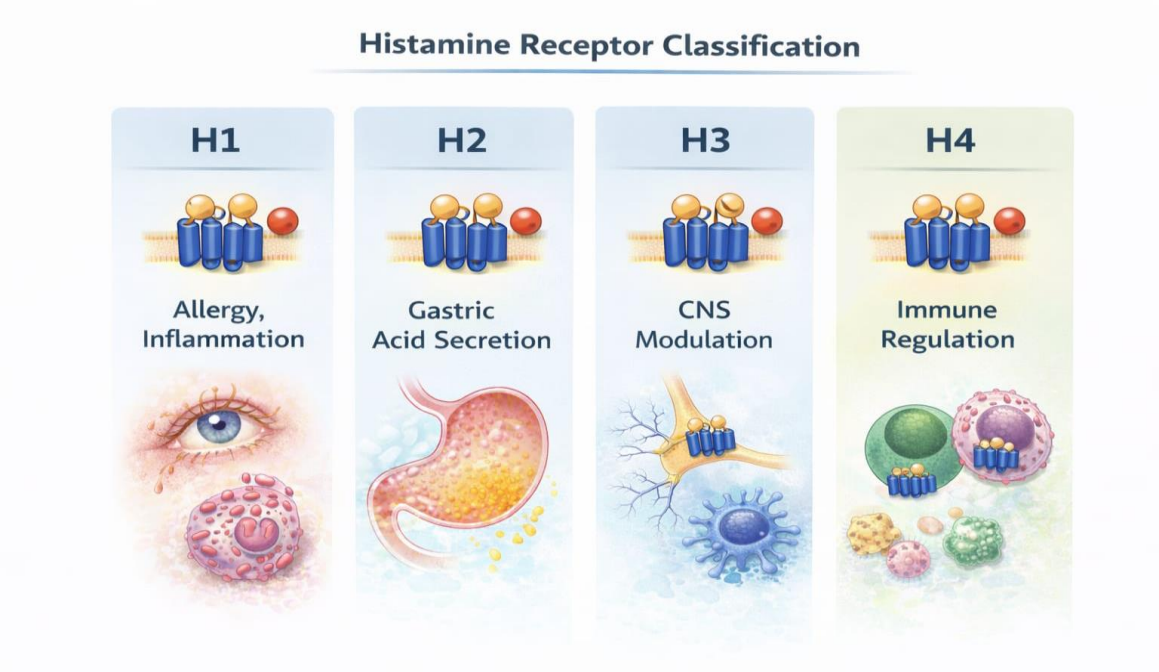


Figure 1. Histamine mediates its biological effects through four individual receptor subtypes, H1–H4. H1 and H2 receptors are traditionally associated with allergic inflammation and gastric acid secretion, respectively, the identification of H3 and H4 receptors has expanded the functional scope of histamine signaling to include central nervous system modulation and immune regulation. Together, these receptor subtypes account for the pleiotropic actions of histamine across physiological systems, and their classification along with their principal functional roles is summarized schematically.

2. Histamine H3 Receptors in Neuroinflammation

2.1 Expression and Signaling of Histamine H3 Receptors

Histamine H3 receptors (H3Rs) are a separate subclass of histamine receptors (Parsons & Ganellin, 2006), which are mainly expressed in the CNS as well as are identified as being presynaptic (Thakkar, 2011). The high level of expression of H3R has been consistently proven by autoradiographic, transcriptomic, and immunohistochemical studies in regions of the brain engaged in cognitive functions, arousal, motor control, and emotional regulation, such as the cerebral cortex, hippocampus, basal ganglia, thalamus, and hypothalamus(Leurs et al., 2005; Schlicker & Kathmann, 2016). Unlike H1 and H2 receptors, H3Rs are predominantly post-synaptic receptors and are distributed widely in both central and peripheral tissue, showing that H3Rs are highly specific neuromodulators. H3Rs are mainly localized to presynaptic nerve terminals, where they are both autoreceptors and heteroreceptors (Thomas et al., 2024). Being autoreceptors, H3Rs are found on histaminergic neurons and are derived from the tuberomammillary nucleus of the hypothalamus. When these receptors are activated, synthesis and release of histamine are inhibited, which forms a negative feedback mechanism that closely controls the histaminergic tone (Arumuham et al., 2024; Yan et al., 2014). This auto-regulatory process is essential in keeping the balance of wake and sleep, arousal, and alertness. The H3R-mediated feedback has been implicated in the sleep-wake disorders and cognitive dysfunction cases of dysregulation(Irwin, 2019; Lin et al., 2011). Besides having an autoreceptor action, H3Rs have heteroreceptors on non-histaminergic neurons, where they regulate the release of various neurotransmitters, such as dopamine, acetylcholine, norepinephrine, serotonin, glutamate, and γ-aminobutyric acid (GABA)(Arumuham et al., 2024; Hepsomali et al., 2020; Panula & Nuutinen, 2013). H3Rs mediate cross talk between significant neurotransmitter systems through this expansive regulatory ability and are associated with synaptic plasticity, network synchronisation, and cognitive processing(Ligneau et al., 2007; Skaper et al., 2015). Recent experiments have also associated the H3R activity with the regulation of microglial activity and neuroinflammatory signaling indirectly by changing neuronal functions and the availability of neurotransmitters, indicating that H3Rs might be involved in neuron glia communication(Butovsky & Weiner, 2018). On the molecular level, H3Rs are bound to Gi/o proteins. Activation of receptors causes adenylyl cyclase inhibition, which causes a drop in intracellular cyclic adenosine monophosphate (cAMP). H3R signaling also prevents the influx of calcium in the presynaptic cell through the voltage-gated calcium channels and stimulates the opening of potassium channels, resulting in membrane hyperpolarization(Block et al., 2007). Taken together, these signaling events reduce neuron transmitter release and allow for regulating neuron excitability and synaptic transmission (Figure 2).

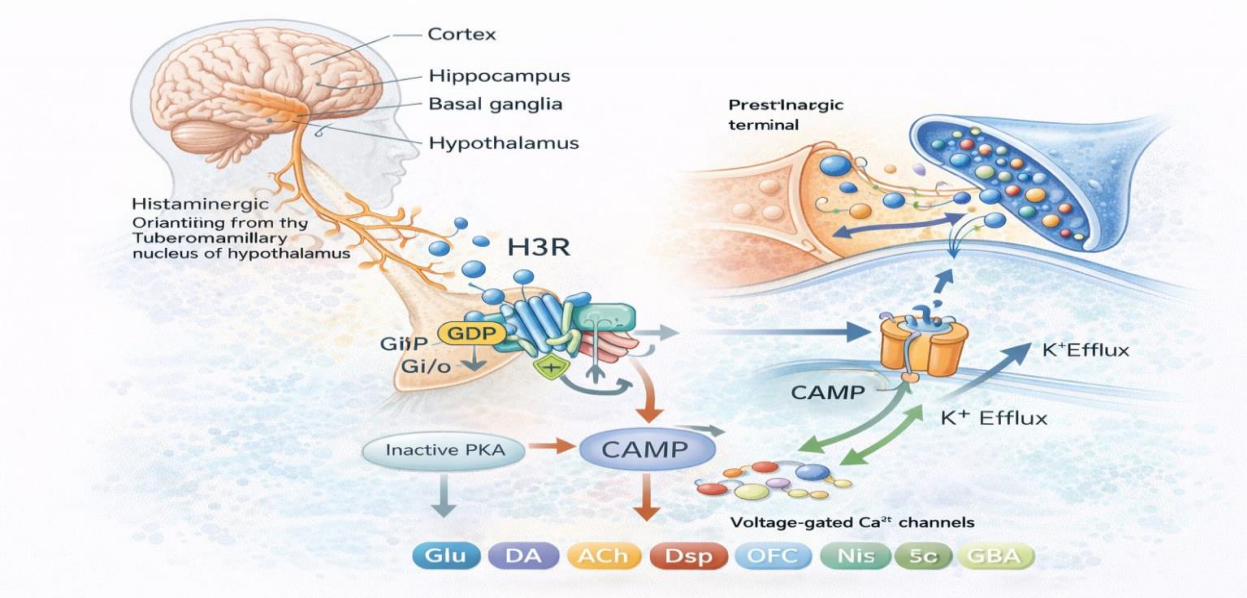


Figure 2: Histamine H3 receptors are presynaptically localized and coupled to Gi/o proteins. This signaling cascade suppresses voltage-gated calcium channel activity while enhancing potassium efflux, resulting in membrane hyperpolarization. Collectively, these mechanisms reduce neurotransmitter release and neuronal excitability, thereby modulating synaptic transmission and network activity.

2.2 Role of Histamine H3 Receptors in Neuroinflammation

Neuroinflammation is a highly self regulated process in the CNS comprising multifaceted interactions between neurons, microglia, astrocytes, and the neurovasculature (Colonna & Butovsky, 2017; Y. Zhao et al., 2024). Although histamine H3 receptors Gq/11(H3Rs) are more expressed on neurons than on glial cells(Wellner-Kienitz et al., 2003), mounting evidence suggests that they have an important indirect effect on neuroinflammatory events by regulating neurotransmitter release and neuronal activity (Bruysters et al., 2005; Calsolaro & Edison, 2016; Garmendia et al., 2024). H3Rs modulate the microenvironment perceived by glial cells by controlling synaptic signaling in inflammatory responses of the CNS. Microglia are the main innate immune cells of the CNS and constantly survey neuronal activity with receptors to various neurotransmitters. Alterations of neurotransmission that include over-stimulation of glutamatergic neurons or dysfunctional cholinergic tone have been known to enhance microglial proliferation and release of pro-inflammatory factors. The H3Rs, via their presynaptic inhibitory action, control the release of these neurotransmitters and, in turn, affect neuron glia communication pathways, which determine the state of microglial activation (Krabbe et al., 2013). The experimental research results have indicated that H3R signaling restrains excitotoxic neurotransmission and maintains cholinergic anti-inflammatory signaling, both of which are important determinants of microglial inflammatory polarization (Zuchero & Barres, 2015). Pharmacological and genetic preclinical research has been growing in pointing toward a role of H3Rs in the regulation of neuroinflammation (Y. Zhao et al., 2024). H3R antagonists and inverse agonists have been reported to suppress microglial activation and the expression of pro inflammatory cytokines (Felger & Lotrich, 2013) such as TNF-alpha, IL-1 beta, and IL-6 in neurodegenerative diseases, traumatic brain injury, and neurotoxic models (Ishijima & Nakajima, 2021). These anti-inflammatory outcomes are often followed by a decrease in oxidative stress, maintenance of synaptic proteins, and enhancement of neuronal survival and neuronal performance. Newer findings also indicate that H3R modulation has effects on

astrocytic reactivity and blood brain barrier integrity, indicating that it has effects outside of microglia(Banks, 2008; Shimizu & Nakamori, 2024; Y. Zhao et al., 2024). Direct clinical correlations of H3R modulation with neuroinflammatory outcomes are not known, but a variety of H3R antagonists with neurological applications have displayed positive central nervous system safety and biomarker responses, which are localized evidence of decreased neuroinflammatory tone(Prinz & Priller, 2017). These results demonstrate the relevance of H3Rs as neuroimmune modulators in translation. Integrated actions on neurotransmitter homeostasis, neuroglia communication, oxidative stress, and synaptic integrity are integrated effects of H3 receptor mediated regulation of neuroinflammation(Y. Zhao et al., 2024). By these interrelated mechanisms, H3Rs are an indirect functional node of neuroinflammatory signaling and a therapeutic target of inflammatory and neurodegenerative diseases.

Table 2: Representative preclinical links between H3R modulation and neuroinflammation (mechanism-level synthesis)

Mechanistic domain	H3R-related effect (conceptual)	Biomarkers/outputs commonly reported	Translational note	Reference
Microglial activation	altered activation state via neurotransmitter	Iba1 morphology, TNF-α/IL-1β changes	needs PET TSPO / CSF cytokines in humans	(Arumuham et al., 2024; Salter & Stevens, 2017)
Synaptic plasticity	enhanced cholinergic/histaminergic tone	LTP/LTD, BDNF, cognition tasks	may be symptomatic-only	(Toader et al., 2025)
Oxidative stress	reductions in ROS pathways in some models	MDA, SOD, catalase	heterogeneity across models	(Anwar et al., 2025; Meng et al., 2025)
Neurotransmitter balance	increased ACh/DA/NE release	microdialysis, receptor expression changes	Patient stratification is likely needed	(Darvesh et al., 2011)

2.3. H3 Receptors in Neurodegenerative and Neuropsychiatric Disorders

Since the presynaptic H3 receptors are mostly concentrated in the CNS (Prinz & Priller, 2017), H3 receptors regulate histaminergic, dopaminergic, cholinergic, and GABAergic signaling pathways commonly impaired in such disorders(Kaczmarski et al., 2023; Panula & Nuutinen, 2013). As a result, dysfunctional alteration of H3 receptor-mediated signaling has been associated with dysfunction of cognitive performance, arousal, and inflammation. Synaptic dysfunction and chronic neuroinflammation are key pathophysiological factors of neuroways in neurodegenerative diseases (Ferreira & Romero-Ramos, 2018; Glass et al., 2010; Heneka et al., 2015; Leng & Edison, 2021; Tansey & Goldberg, 2010). The preclinical trials have indicated that H3 receptor antagonism has the potential to raise cortical acetylcholine and dopamine release, increase cognitive functioning, and reduce neuroinflammatory indicators(Ligneau et al., 2007). Degeneration of dopaminergic neurons in the striatum in Parkinson's disease may be associated with intense microglial activation and an increase in production of pro inflammatory cytokines(Dantzer, 2001; Thomas et al., 2024). Since H3 receptors control the release of dopamine within striatal circuits, their regulation can have an indirect effect on inflammatory

signaling via dopaminergic circuits. These findings demonstrate that, despite the fact that there is still limited clinical evidence, the targeting of the H3 receptor can be a promising solution addressing the non-motor symptoms, such as cognitive impairment and fatigue, and the neuroinflammatory aspects of the disease(Esbenshade et al., 2008b; Heppner et al., 2015). Neuropsychiatric disorders (schizophrenia(Arumuham et al., 2024), depression, attention deficit hyperactivity disorder, etc.) are also typified by arousal, attention, and executive dysfunction that have been implicated in histaminergic and monoaminergic neurotransmission dysregulation. Experimental research has indicated that H3 receptor antagonists have the effect of bringing about wake-promoting and thinking enhancement(Saper & Fuller, 2017). Besides, in multifocal sclerosis and other forms of demyelination, neuroinflammation occurs as a result of complicated interactions between immune cell infiltration, activities of glial responses, and impaired neuronal functioning(Pavlov & Tracey, 2017). Although H3 receptors have no direct effect on the immune cell trafficking, their effect on the neuronal signaling and pathways involved in fatigue indicates an indirect effect on central inflammatory tone and symptoms of disease(Capuron & Miller, 2011). Taken together, these observations demonstrate that neurotransmitter dysregulation under H3 receptor dependence is involved in the pathogenesis of neuroinflammation and clinical presentation in the spectrum of neurodegenerative and neuropsychiatric conditions(Kempuraj et al., 2016; Miller & Raison, 2016), schematically depicted in Figure 3.

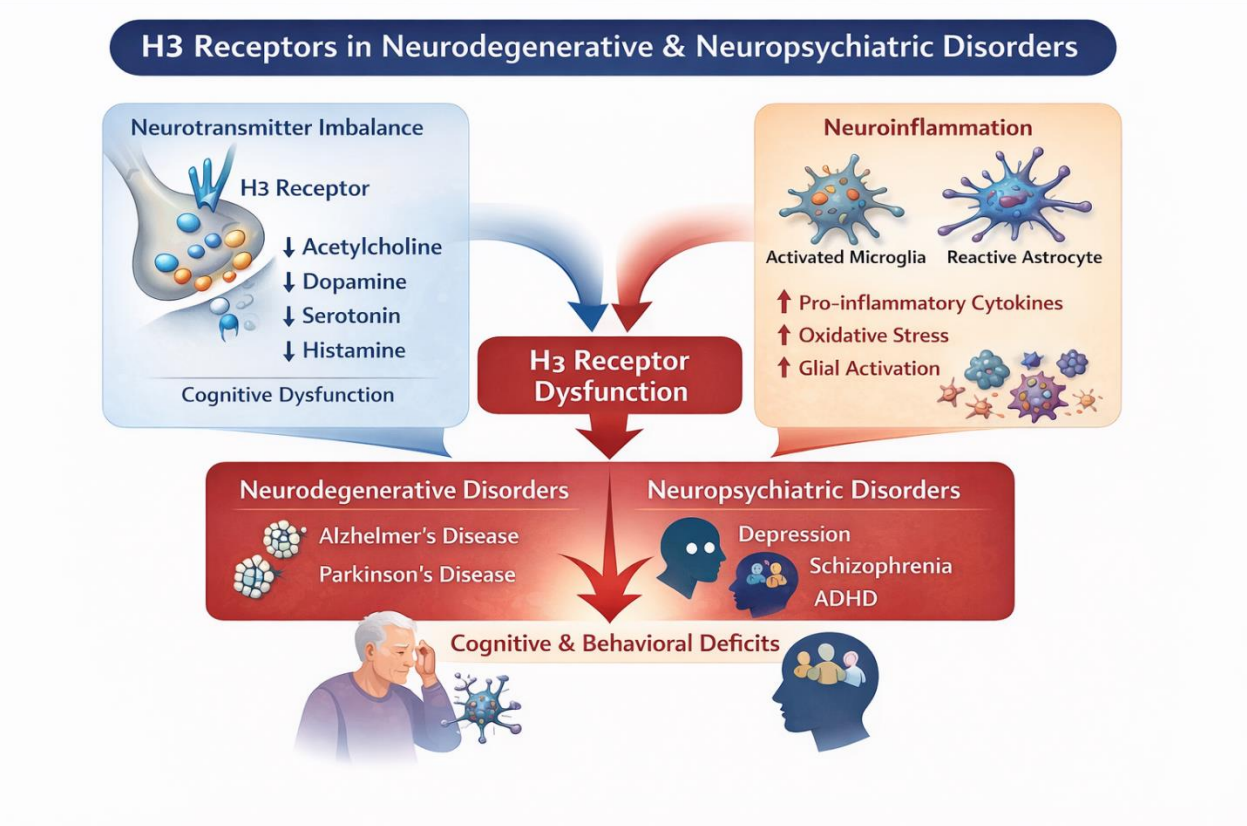


Figure 3: Histamine H3 receptors play a central role in regulating neurotransmitter release and neuroinflammatory signaling in the CNS. Dysregulation of H3 receptor signaling affects dopaminergic, cholinergic, and histaminergic pathways and promotes glial activation and cytokine production, ultimately leading to cognitive and behavioral deficits.

3. Histamine H4 Receptors in Immune Modulation

3.1 Expression and Signaling of Histamine H4 Receptors

Histamine H4 receptors (H4Rs) are mainly found on hematopoietic-origin cells and are now considered to be significant modulators of immune and inflammatory responses(Zampeli & Tiligada, 2009). Early cloning and expression studies with more recent single cell transcriptomic and flow cytometric studies have also shown high expression of H4R on mast cells, eosinophils, dendritic cells, basophils, monocytes, and T lymphocytes, with relatively low or no expression in the majority of non-immune tissues(Hartwig et al., 2015; Wu et al., 2022). This is an immune-restricted distribution, which makes H4Rs unique in comparison to histamine H1 and H2 receptors and the basis of their immunomodulatory signaling. H4Rs have a key role in immune cell chemotaxis and tissue recruitment, which is functional. H4R activity in eosinophils triggers directed migration, cytoskeletal rearrangement, and actin polymerization, which are successfully inhibited by selective H4R antagonists. The same chemotactic responses were found in mast cells, in which H4R signaling enhances cellular recruitment to inflammatory sites and regulates cellular degranulation and mediator release(Thangam et al., 2018). H4Rs have also been shown to play a role in leukocyte infiltration in the model of allergic inflammation, dermatitis(Brunner et al., 2017; Chovatiya & Silverberg, 2022), and asthma(Black et al., 2012; Holgate, 2008) by in vivo experiments involving H4R deficient mice or pharmacological antagonism(Gebski et al., 2022; Oda et al., 2000). H4R expression of dendritic cells has been demonstrated to affect the uptake, maturation, and production of cytokines, and subsequently affect T-cell priming and adaptive immune responses(Gebski et al., 2022). H4R dendritic cell signaling has the potential to modify tolerogenic versus pro-inflammatory dendritic cell phenotype with implications on the downstream T helper cell differentiation. H4Rs control the profile of secretion of cytokines, such as IL-4, IL-17, and IFN-gamma, and H4R signaling is implicated in both Th2 (Gutzmer et al., 2009) and Th17-mediated inflammatory responses in T lymphocytes (Ishijima & Nakajima, 2021). Most recent reports have also associated H4R activity with T-cell regulatory activity and immune polarization in chronic inflammatory and autoimmune diseases. On a molecular level, H4Rs are G protein-linked receptors that are mostly linked to Gi/o proteins. When stimulated, H4Rs suppress the adenylyl cyclase, resulting in decreased intracellular cyclic adenosine monophosphate (cAMP) concentration. Parallel to this, H4R signaling triggers intracellular calcium release and activates downstream signaling pathways, such as extracellular signal-regulated kinases (ERK1/2), p38 MAPK, and additional mitogen-activated protein kinases(Block et al., 2007). All of these pathways are involved in the regulation of the migration of immune cells, the production of cytokines, survival, and the increase of inflammation (Figure 4). The combination of the expression and signaling property of the H4Rs makes this receptor a key mediator of immune cell communication and inflammatory regulation, and thus warrants further exploration as an immune-mediating and inflammatory disease therapeutic target.

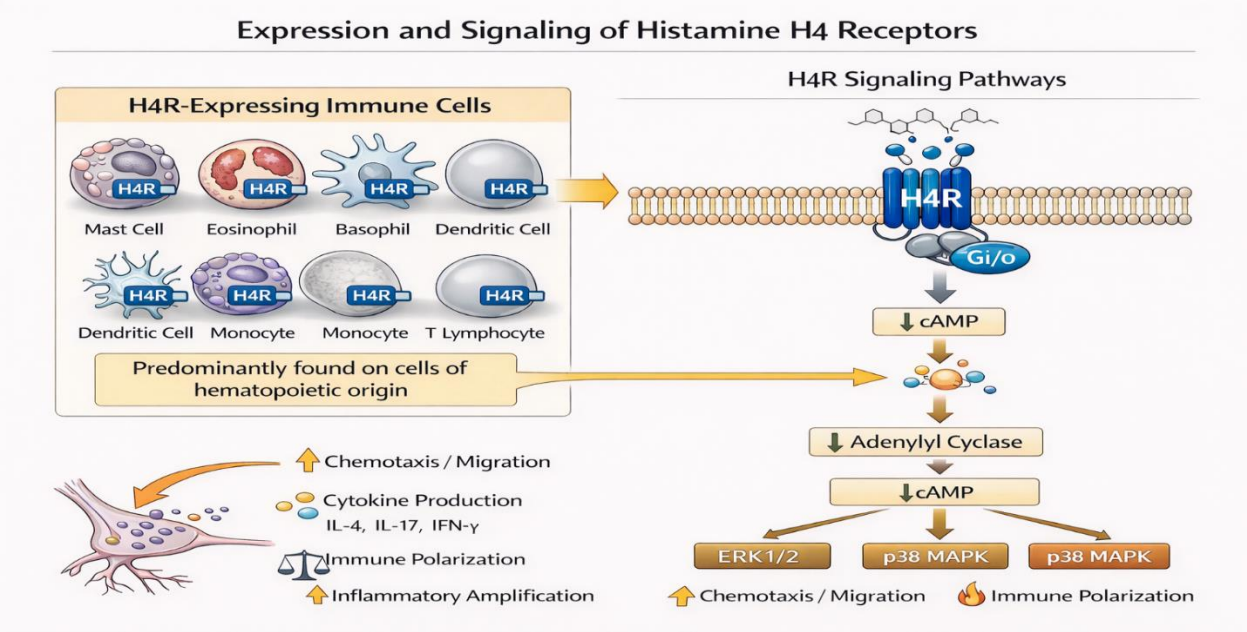


Figure 4: The schematic summarizes histamine H4 receptor–mediated immune signaling. Histamine binding activates Gi/o-coupled signaling, leading to inhibition of adenylyl cyclase, reduced cAMP levels, calcium mobilization, and activation of ERK1/2 and p38 MAPK pathways. These signaling events regulate immune cell chemotaxis, cytokine production, immune polarization, and inflammatory amplification.

3.2 Role of Histamine H4 Receptors in Immune Regulation

There is significant experimental data to indicate that histamine H4 receptors (H4Rs) play a major role in the control of immune cell trafficking and the inflammatory process. In vitro and in vivo experiments indicate that the histamine-induced chemotaxis of eosinophils, mast cells, dendritic cells, and T lymphocytes is regulated mainly by H4R signal (Dunford et al., 2006). Immune cell recruitment to allergen exposure sites and tissue injury is significantly decreased by pharmacological blockade or genetic deletion of H4Rs, indicating that H4Rs are an important histaminergic checkpoint to leukocyte infiltration and tissue amplification of inflammatory responses(Oda et al., 2000). In addition to chemotaxis, H4Rs have a strong regulatory action on cytokine production and polarization of immune cells. H4Rs activation regulates the levels of pro-inflammatory and regulatory cytokines, such as IL-4, IL-5, IL-13, IL-17, TNF-alpha, and IL-10. With these actions, H4R signaling regulates the dendritic cell maturation, antigen presentation, and T-cell differentiation and shapes adaptive immune responses. It is particularly worth noting that H4R-dependent pathways have been associated with hyperstimulation of the Th2 and Th17 skewed immune phenotypes typical of allergic inflammation and autoimmune pathology(Van Acker et al., 2023). Preclinical disease models have shown convincingly that H4Rs are involved in chronic inflammatory disease. H4Rs inhibition or genetic ablation suppresses airway hyperresponsiveness and eosinophilic inflammation in asthma models(Holgate, 2008), skin inflammation(Uluckan et al., 2023) and pruritus in atopic dermatitis, and disease severity in experimental models of rheumatoid arthritis(Kondo et al., 2021) and inflammatory bowel disease(Bertaccini & Coruzzi, 1983). These anti-inflammatories have been linked to a decrease in leukocyte infiltration, inhibition of pathogenic cytokine networks, and re-establishment of immune homeostasis(Oda et al., 2000). A number of selective H4R antagonists have progressed into early-phase clinical trials in inflammatory and

pruritic diseases(A. Kollmeier et al., 2014). These studies have verified H4Rs target engagement and immune biomarker modulation, even though there has been inconsistent clinical efficacy, which demonstrates the relevance of the H4Rs in human inflammatory disease. Together, these results put H4Rs as key control mechanisms of immune cell communication and chronic inflammation and emphasize their further consideration as a therapeutic option in allergic, autoimmune, and immune-mediated inflammatory diseases(Blasco-Fontecilla, 2023).

3.3 Neuroimmune Interaction

Recent discoveries suggest that histamine H4 receptors (H4Rs), which were described as peripheral immune receptors, are also involved in reciprocal neuroimmune responses that regulate central nervous system (CNS) inflammation. Though the greatest expression of H4R is found on hematopoietic lineage immune cells, recent transcriptomic profiling, single-cell RNA sequencing, and immunohistochemical studies show that H4R can be expressed in CNS-resident immune cells, especially microglia, in response to inflammatory and neuronal degenerative conditions(Aguzzi et al., 2013; Amor et al., 2014). This situation-specific upregulation indicates that H4Rs serve as adaptive immunomodulatory receptors in the inflamed CNS, where peripheral immune activation is coupled to neuroinflammatory signaling at the point. Microglia are core mediators of neuroimmune homeostasis as they detect peripheral cytokines, neurotransmitters, and DAMPs (Müller et al., 2025). The H4R stimulation in microglia activates Gi/o-dependent signaling pathway leading to inhibition of adenylyl cyclase, depletion of intracellular cAMP, and calcium release. These upstream signals cross on the MAPK cascade of ERK1/2 and p38 MAPK and downstream transcriptional factors, such as NF-kB and AP-1 (Ng et al., 2024; Shamsnia et al., 2023). These processes mediate the action of H4R signaling on microglial activation status, gene expression of cytokines, and phagocytic ability. The long-term effects of H4R activation on microglia have been shown to modify microglia to a pro-inflammatory state, reflected in enhanced production of TNF-α, IL-1β, and IL-6, and simultaneously modulate regulatory cytokine networks with IL-10 and TGF-β (Komai et al., 2018). This disequilibrium is a cause of persistent neuroinflammation, impaired synaptic activity, and vulnerability of neurons. In addition to direct action of microglia, H4Rs indirectly control neuroimmune crosstalk through regulating the peripheral immune cell trafficking at the BBB (Shimizu & Nakamori, 2024). Mast cells, eosinophils, monocytes, and T-lymphocytes (Theoharides et al., 2012). H4R-dependent chemotaxis promotes the infiltration of immune cells into the CNS in pathological conditions. Released by these infiltrating cells, further inflammatory mediators disrupt BBB integrity, stimulate oxidative stress, and amplify local cytokine gradients, forming a feed-forward loop that perpetuates neuroinflammation. These mechanisms have been involved in the pathophysiology of several diseases, including multiple sclerosis (Baecher-Allan et al., 2018). Translationalally, pharmacological H4R regulation has proved neuroprotective in preclinical models, such as the prevention of microglial overactivation, pro-inflammatory cytokine cascades, and synaptic and neuronal integrity. Even though clinical evidence is still scarce and diffuse, preclinical evidence using selective H4R antagonists has affirmed central immune biomarker modification, which justifies the significance of H4R-mediated neuroimmune responses to human disease. Taken together, these results make H4Rs powerful controllers of immune-CNS interactions and emphasize them as potential therapies in neuroinflammatory and neurodegenerative diseases, which are typified by chronic immune dysregulation.

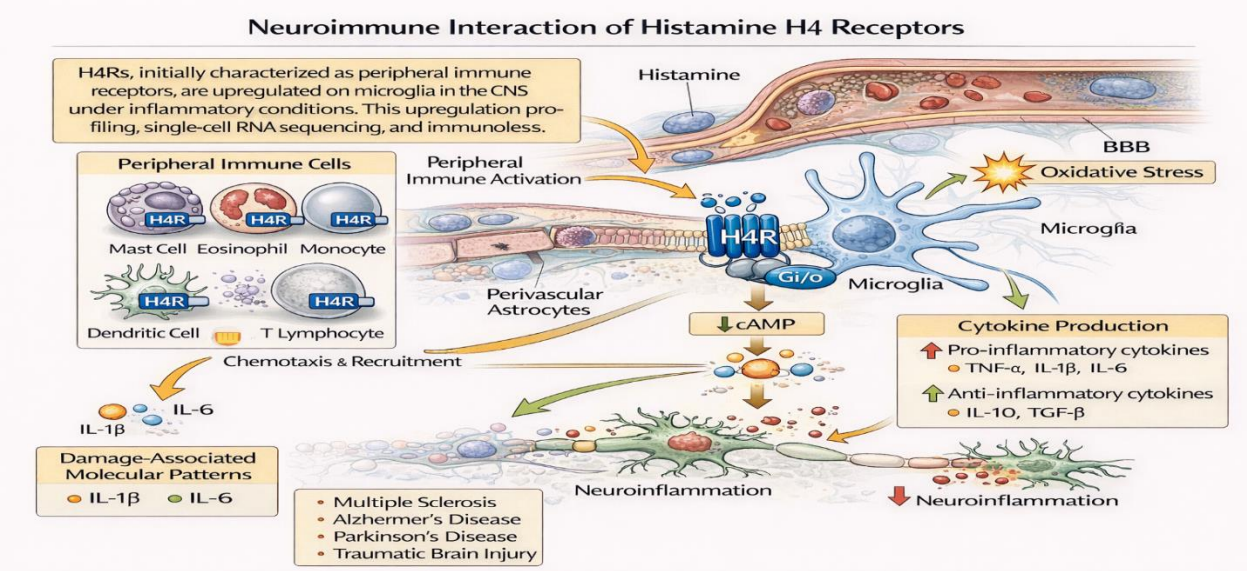


Figure 5: **Histamine H4 receptors, predominantly expressed on peripheral immune cells, are upregulated on microglia under inflammatory conditions. H4R-dependent chemotaxis promotes recruitment of mast cells, eosinophils, monocytes, and T lymphocytes across the blood–brain barrier, amplifying neuroimmune signaling. In microglia, H4R activation engages Gi/o-mediated pathways, leading to reduced intracellular cAMP levels, calcium mobilization, and activation of MAPK signaling cascades. These events regulate cytokine production, oxidative stress, and microglial activation states, contributing to neuroinflammation and synaptic dysfunction in neuroinflammatory and neurodegenerative disorders.**

4. H3–H4 Receptor Crosstalk in Neuroimmune Regulation

The histamine H3 and H4 receptors mediate different, but overlapping points in the neuroimmune expression system that allow coordination between neuronal output and immune responses in central and peripheral systems. H3 receptors (H3Rs) are expressed primarily in the presynaptic neurons of the CNS and perform the role of auto- and heteroreceptors in the release of neurotransmitters and the synaptic excitability. Histamine H4 receptors (H4Rs), in contrast, are expressed predominantly on hematopoietic-origin immune cells and induced on CNS-resident microglia during the conditions of inflammatory and neurodegenerative diseases. This reciprocal expression pattern makes the H3 4 receptor crosstalk the core of a neuroimmune axis. H3R-mediated activation regulates the release of histamine and various neurotransmitters, which have a direct effect on microglial surveillance and polarization. Specifically, the H3R-dependent cholinergic and glutamatergic tone changes control excitotoxic stress and overlap with the cholinergic anti-inflammatory pathway, thus limiting microglial cytokine production and oxidative stress (Su et al., 2022). These processes mediate H3Rs as upstream modulators in the communication of synaptic activity to immune-relevant CNS signals. Simultaneously, H4R signaling controls the chemotaxis of immune cells, cytokine synthesis, and inflammatory amplification of the peripheral tissues and the CNS. The H4R-mediated mast cell recruitment, eosinophils, monocytes, and T lymphocytes recruitment across the blood-brain barrier(Shimizu & Nakamori, 2024) increases the interaction between immune cells and microglia and maintains neuroinflammatory cascades(Boziki et al., 2024; Dileepan et al., 2023). H4R signaling by microglia activates Gi/o-coupled pathways that converge on MAPK, NF, KB as well as inflammasome signaling to sustain production of pro-inflammatory cytokines and reactive oxygen species(Meng et al., 2025). New demonstrations

suggest that H3R and H4R signaling overlap on common intracellular nodes, such as Gi/o-sensitive suppression of cyclic adenosine monophosphate (cAMP), cal-200 signaling, and immune and synaptic gene transcriptional regulation. This common architecture facilitates synergistic or context-specific effects on microglial activation, synaptic plasticity, and immune gene expression, and it can aid long-term inflammatory memory by reprogramming epigenetic and metabolic programs(Raos et al., 2020). H3H4 receptor crosstalk dysregulation has been associated with chronic neuroinflammatory and neuropsychiatric diseases (Arumuham et al., 2024; Baecher-Allan et al., 2018; Heppner et al., 2015; Tansey & Goldberg, 2010). It is preclinical evidence that a dual modulation of H3Rs and H4Rs has a higher therapeutic value than mono-receptor stimulation in restoring neurotransmitter homeostasis, inhibiting networks of pathogenic cytokines, and maintaining synaptic integrity(J. Zhao et al., 2022). Combined, these results find crosstalk of H3 H4 receptors as a key factor of neuroimmune homeostasis and a future target of next-generation therapies in immune-mediated CNS diseases.

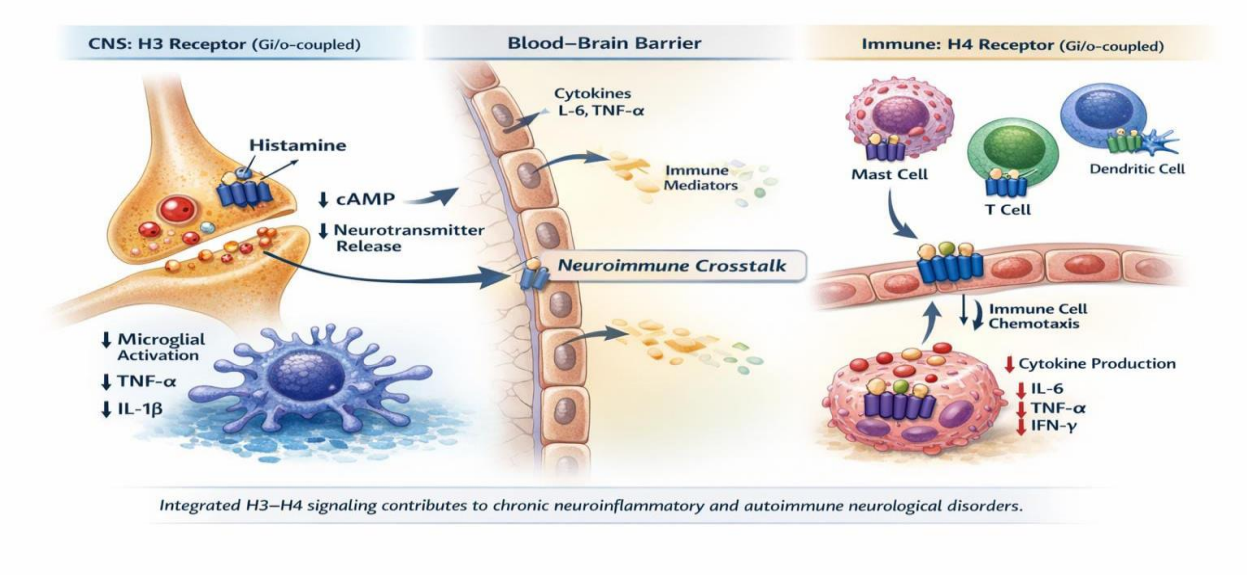


Figure 6: Histamine acting on presynaptic H3 receptors in the central nervous system regulates neurotransmitter release and attenuates neuroinflammatory signaling. In parallel, histamine interaction with H4 receptors expressed on immune cells such as mast cells and T lymphocytes modulates chemotaxis and cytokine production. The bidirectional neuroimmune crosstalk highlights the integrative role of H3 and H4 receptors in chronic neuroinflammatory conditions.

Table 3: Complementary and Distinct Roles of Histamine H3 and H4 Receptors in Neuroimmune Regulation

Dimension	Histamine H3 Receptor (Neuronal Axis)	Histamine H4 Receptor (Immune Axis)	References
Evolutionary specialization	Optimized for fine control of neurotransmission and synaptic efficiency	Optimized for rapid immune surveillance and inflammatory amplification	(Yan et al., 2014)
Primary signaling environment	Synaptic and extrasynaptic neuronal microdomains	Inflammatory and lymphoid tissue microenvironments	(Chao et al., 2025; Müller et al., 2025)

Key intracellular signaling bias	Ion channel modulation and synaptic vesicle regulation	Cytoskeletal remodeling and calcium-dependent migration pathways	(Burke & Bender, 2019; Song et al., 2019)
Impact on glial biology	Modulates neuron–microglia communication and glial reactivity thresholds	Alters microglial activation indirectly through cytokine gradients	(Zuchero & Barres, 2015)
Contribution to neuroinflammation	Shapes CNS vulnerability to inflammatory stimuli	Drives peripheral inflammatory signals impacting the CNS	(Thomas et al., 2024)
Disease stage relevance	Predominantly involved in symptom modulation and network dysfunction	Predominantly involved in disease initiation and immune escalation	(Garmendia et al., 2024)
Influence on CNS plasticity	Regulates synaptic plasticity and cognitive flexibility	Alters neuroplasticity indirectly through chronic inflammation	(Price & Duman, 2020)
Interaction with blood–blood-brain barrier	Modifies neurovascular signaling via neuronal activity	Promotes immune cell transmigration through cytokine release	(Abbott et al., 2010)
Role in neuroimmune crosstalk	Determines CNS responsiveness to immune signals	Determines immune to brain inflammatory signaling intensity	(Tian et al., 2012)

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5. Therapeutic Implications and Clinical Studies

The receptors of histamine H3 and H4 belong to separate but convergent locations of the neuroimmune signaling network, which helps to integrate neuron activity and immune response of central and peripheral compartments. H3 receptors (H3Rs) are almost exclusively located on the presynaptic neurons of the central nervous system (CNS), where they act as auto- and heteroreceptors in the control of the release of neurotransmitters and the excitability of the synapses. Histamine H4 receptors (H4Rs), conversely, are found exclusively on immune cells of hematopoietic origin and are inducibly expressed on CNS-resident microglia in the inflammatory and neurodegenerative states (Glass et al., 2010). Such an orthogonal expression system locates Neuroimmune regulation H3H4 receptor crosstalk as a key axis. The release of histamine and various neurotransmitters, such as glutamate, acetylcholine, dopamine, serotonin, and γ-aminobutyric acid (GABA)(Hepsomali et al., 2020; Kaczmarski et al., 2023), is controlled by H3R-mediated signaling, which has a direct effect on microglial surveillance and polarization. Specifically, the H3R-dependent changes in glutamatergic and cholinergic tone control excitotoxic stress and overlap with the cholinergic anti-inflammatory axis, thus limiting microglial cytokine synthesis and oxidative stress(Meng et al., 2025; Zuchero & Barres, 2015). H3Rs can engage in signals in the CNS via these mechanisms. H4R signals, in parallel, control the immune cell chemotaxis, cytokine production, and inflammatory amplification of peripheral tissues and the CNS. The presence of recruitment of mast cells, eosinophils, monocytes, and T lymphocytes across the blood-brain barrier by H4R promotes interactions between immune cells and microglia and neuroinflammatory cascades. H4Rs of microglia can activate Gi/o-coupled pathways that

converge on the MAPK, NF-κB, and inflammasome pathways, which sustain the continuous release of pro-inflammatory cytokines and reactive oxygen species(W. Liang et al., 2022). The new evidence suggests that the overlap between H3R and H4R signaling is at common nodes in the intracellular connection, such as Gi/o-dependent suppression of cyclic adenosine monophosphate (cAMP), calcium-dependent signaling, and transcriptional regulation of immune and synaptic genes(Robichaux & Cheng, 2018). The similar architecture allows the synergistic or context-dependent influence on microglial activation, synaptic plasticity, and immune gene expression, and could lead to the long-term inflammatory memory due to the epigenetic and metabolic reprogramming(Amor et al., 2014). Such crosstalk instability of H3 H4 receptors has been suggested in chronic neuroinflammatory and neuropsychiatric diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, major depressive disorder, and schizophrenia. It has been proposed based on preclinical findings that dual H3Rs/H4Rs modulation is more beneficial in therapy than single-receptor targeting of any single synaptic end, and that the modulation of these two receptors offers better neurotransmitter homeostasis, blockage of pathogenic cytokine cascades, as well as synaptic integrity(Müller et al., 2025). The combined results point to the H3-H4 receptor crosstalk as a key determinant of neuroimmune homeostasis and future generation therapy in immune-mediated CNS diseases.

Table 4. The table summarizes representative clinical studies, including therapeutic indications, trial phases, and key efficacy or limitation outcomes, highlighting both successful translation and challenges encountered during clinical development.

Target	Compound	Pharmacology	Indication / Study Type	Clinical Phase	Key Outcome / Limitation	Reference
H3R	Pitolisant	Antagonist / inverse agonist	Narcolepsy (EDS, cataplexy); regulatory programs	Phase 3; Approved (EMA, FDA)	Validates human CNS efficacy and feasibility of chronic H3R modulation	(Dauvilliers et al., 2013; Schwartz, 2011)
H3R	ABT-288	Antagonist	Alzheimer's disease cognitive trials	Phase 2	Target engagement achieved; no significant cognitive benefit	(Haig et al., 2014)
H3R	MK-0249	Antagonist	ADHD randomized clinical trial	Phase 2	Wakefulness effects observed; insufficient efficacy on core symptoms	(Herring et al., 2012)

H3R	GSK189254	Antagonist / inverse agonist	Cognitive impairment (AD, schizophrenia)	Phase 2	Strong preclinical rationale; limited clinical translation	(Medhurst et al., 2007)
H4R	JNJ-39758979	Antagonist	Randomized human pruritus model	Phase 1/2	Proof-of-mechanism for itch reduction in humans	(A. Kollmeier et al., 2014)
H4R	Toreforant	Antagonist	Rheumatoid arthritis synovial biopsy study	Phase 2	Clear mechanistic tissue effects; clinical endpoint challenges	(Boyle et al., 2019)
H4R	Toreforant	Antagonist	Eosinophilic asthma	Phase 2a	Signal supports biomarker-guided patient enrichment	(A. P. Kollmeier et al., 2018)
H4R	Adriforant (ZPL-3893787)	Functional antagonist	Atopic dermatitis	Phase 2b	Strong mechanistic rationale; primary efficacy endpoints not met	(Chovatiya & Silverberg, 2022; Uluckan et al., 2023)

Table 5: Rationale for Integrated, Biomarker-Guided Targeting of Histamine H3 and H4 Receptors

Domain	H3 receptor (neuronal component)	H4 receptor (immune component)	Representative biomarkers	Implication for therapy	Referencs
Neurotransmission	Regulates histamine, ACh, dopamine, glutamate, and GABA	Indirect effects via cytokine-mediated neural modulation	Neurotransmitter metabolites, EEG, sleep–wake metrics	Supports H3R modulation for synaptic stabilization	(Kaczmarski et al., 2023)

Microglial activation	Indirect regulation via neuron–glia signaling	Peripheral cytokines prime microglia	TSPO-PET, Iba1, CSF TNF-α, IL-1β, IL-6	Combined targeting may better suppress microglial reactivity	(Arumuham et al., 2024; Felger & Lotrich, 2013)
Peripheral immune activation	Minimal direct role	Direct control of chemotaxis and cytokine release	Plasma IL-6, IL-17, TNF-α, and immune cell phenotyping	Justifies H4R antagonism	(Ishijima & Nakajima, 2021)
Blood–brain barrier effects	Alters neurovascular signaling	Promotes immune-to-brain signaling	BBB permeability markers, cytokine gradients	Integrated approach limits immune-driven CNS damage	(Abbott et al., 2010; Banks, 2008; Kealy et al., 2020)
Disease heterogeneity	Variable neuronal dysfunction across patients	Variable immune activation across patients	Multimodal biomarker panels	Biomarkers needed for patient stratification	(J. Liang et al., 2025)
Clinical trial outcomes	Target engagement without consistent efficacy	Immune modulation with limited CNS benefit	PET occupancy, cytokine response profiles	Explains the failure of monotherapies	(Arumuham et al., 2024)

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6. Strengths & Limitations

One of the main advantages of the given field is a growing body of mechanistic evidence that shows that the modification of the H3 receptor alters neuroinflammatory pathways, which is mostly due to the control of neurotransmitter release and glia–neuron interactions. These results have enhanced the knowledge of the histaminergic regulation of central immune responses and promote H3 receptors as therapeutic agents in the case of inflammatory-related neurological disorders. Nevertheless, there are some significant shortcomings. Much of the evidence of the role of H3 receptor activity in neuroinflammation is based on preclinical models, in which microglial effects are frequently indirectly observed and inferred through the effects on neurotransmitter tone, but not directly observed by demonstration of receptor expression or signaling in immune cells. Also, the unavailability of strong and receptor-specific biomarkers in humans increases the challenge of measuring target engagement and mechanistic relevance in clinical trials. H4 receptor studies have also produced significant information on immune regulation, especially in peripheral inflammatory conditions, but suffer due to strong species-specific variations in receptor expression, ligand selectivity, and downstream signaling. These components decrease the relevance of animal models to the human body and lead to a lack of correlation with clinical performance despite a high level of preclinical effectiveness. Another emerging problem is the sparse nature of the characterization of H3 and H4 functional crosstalk in neuroimmune regulation. In spite of the conceptual strength of coordinated histaminergic signaling between neuronal and immune systems, little research has directly explored how these receptors interact in pathologically relevant processes. To close this gap,

there will be a need to use integrated translational systems, which involve the integration of sophisticated imaging, immune profiling, and biomarker-directed clinical trial designs to more profoundly integrate mechanistic understanding with therapeutic results.

7. Conclusions

The role of histamine H3 and H4 receptors as non-classical regulators of neuroimmune dysregulation has led to a more comprehensive understanding of the role of neuroimmune dysregulation. The action of these receptors and connections between neuronal signaling, microglial responses, peripheral immune responses, and the functioning of the blood-brain barrier. The H3 receptors mainly induce changes in neuroinflammation by acting on neurotransmitter release, synaptic functions, and sleep-wake processes, and the impact of H4 receptors is greater on the immune cells and cytokine amplification in chronic states of inflammation. Clinical translation of H3- and H4-targeted therapies has met with inconsistent results despite their strong preclinical evidence, illustrating the complexity of neuroimmune signaling and the shortcomings of single-target therapies. The way forward will be through a better mechanistic understanding, the development of biomarkers, and a patient stratification plan. A combination of therapies to treat central neuronal impairment and peripheral immune activation could be of increased therapeutic value in neurodegenerative(Glass et al., 2010), neuropsychiatric, and inflammatory diseases mediated by immune-mediated mechanisms.

8. REFERENCES

Abbott, N. J., Patabendige, A. A. K., Dolman, D. E. M., Yusof, S. R., & Begley, D. J. (2010). Structure and function of the blood–brain barrier. *Neurobiology of Disease*, *37*(1), 13–25. https://doi.org/10.1016/j.nbd.2009.07.030

Aguzzi, A., Barres, B. A., & Bennett, M. L. (2013). Microglia: Scapegoat, Saboteur, or Something Else? *Science*, *339*(6116), 156–161. https://doi.org/10.1126/science.1227901

Alonso, N., Zappia, C. D., Cabrera, M., Davio, C. A., Shayo, C., Monczor, F., & FernÃ¡ndez, N. C. (2015). Physiological implications of biased signaling at histamine H2 receptors. *Frontiers in Pharmacology*, *6*. https://doi.org/10.3389/fphar.2015.00045

Amor, S., Peferoen, L. A. N., Vogel, D. Y. S., Breur, M., Van Der Valk, P., Baker, D., & Van Noort, J. M. (2014). Inflammation in neurodegenerative diseases – an update. *Immunology*, *142*(2), 151–166. https://doi.org/10.1111/imm.12233

Anwar, S., Sarwar, T., Khan, A. A., & Rahmani, A. H. (2025). Therapeutic Applications and Mechanisms of Superoxide Dismutase (SOD) in Different Pathogenesis. *Biomolecules*, *15*(8), 1130. https://doi.org/10.3390/biom15081130

Arumuham, A., Nour, M. M., Veronese, M., Beck, K., Onwordi, E. C., Lythgoe, D. J., Jauhar, S., Rabiner, E. A., & Howes, O. D. (2024). Histamine-3 Receptor Availability and Glutamate Levels in the Brain: A PET-1H-MRS Study of Patients With Schizophrenia and Healthy Controls. *International Journal of Neuropsychopharmacology*, *27*(3), pyae011. https://doi.org/10.1093/ijnp/pyae011

Baecher-Allan, C., Kaskow, B. J., & Weiner, H. L. (2018). Multiple Sclerosis: Mechanisms and Immunotherapy. *Neuron*, *97*(4), 742–768. https://doi.org/10.1016/j.neuron.2018.01.021

Banks, W. A. (2008). Blood–Brain Barrier Transport of Cytokines. In *NeuroImmune Biology* (Vol. 6, pp. 93–107). Elsevier. https://doi.org/10.1016/S1567-7443(07)10006-5

Bertaccini, G., & Coruzzi, G. (1983). Extragastric H2-Receptors: *Journal of Clinical Gastroenterology*, *5*, 57–70. https://doi.org/10.1097/00004836-198312001-00006

Black, J. L., Panettieri, R. A., Banerjee, A., & Berger, P. (2012). Airway Smooth Muscle in Asthma. *Clinics in Chest Medicine*, *33*(3), 543–558. https://doi.org/10.1016/j.ccm.2012.05.002

Blasco-Fontecilla, H. (2023). Is Histamine and Not Acetylcholine the Missing Link between ADHD and Allergies? Speer Allergic Tension Fatigue Syndrome Re-Visited. *Journal of Clinical Medicine*, *12*(16), 5350. https://doi.org/10.3390/jcm12165350

Block, M. L., Zecca, L., & Hong, J.-S. (2007). Microglia-mediated neurotoxicity: Uncovering the molecular mechanisms. *Nature Reviews Neuroscience*, *8*(1), 57–69. https://doi.org/10.1038/nrn2038

Boyle, D. L., DePrimo, S. E., Calderon, C., Chen, D., Dunford, P. J., Barchuk, W., Firestein, G. S., & Thurmond, R. L. (2019). Toreforant, an orally active histamine H4-receptor antagonist, in patients with active rheumatoid arthritis despite methotrexate: Mechanism of action results from a phase 2, multicenter, randomized, double-blind, placebo-controlled synovial biopsy study. *Inflammation Research*, *68*(4), 261–274. https://doi.org/10.1007/s00011-019-01218-y

Boziki, M., Theotokis, P., Kesidou, E., Nella, M., Bakirtzis, C., Karafoulidou, E., Tzitiridou-Chatzopoulou, M., Doulberis, M., Kazakos, E., Deretzi, G., Grigoriadis, N., & Kountouras, J. (2024). Impact of Mast Cell Activation on Neurodegeneration: A Potential Role for Gut–Brain Axis and Helicobacter pylori Infection. *Neurology International*, *16*(6), 1750–1778. https://doi.org/10.3390/neurolint16060127

Branco, A. C. C. C., Yoshikawa, F. S. Y., Pietrobon, A. J., & Sato, M. N. (2018). Role of Histamine in Modulating the Immune Response and Inflammation. *Mediators of Inflammation*, *2018*, 1–10. https://doi.org/10.1155/2018/9524075

Brozovich, F. V., Nicholson, C. J., Degen, C. V., Gao, Y. Z., Aggarwal, M., & Morgan, K. G. (2016). Mechanisms of Vascular Smooth Muscle Contraction and the Basis for Pharmacologic Treatment of Smooth Muscle Disorders. *Pharmacological Reviews*, *68*(2), 476–532. https://doi.org/10.1124/pr.115.010652

Brunner, P. M., Guttman-Yassky, E., & Leung, D. Y. M. (2017). The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *Journal of Allergy and Clinical Immunology*, *139*(4), S65–S76. https://doi.org/10.1016/j.jaci.2017.01.011

Bruysters, M., Jongejan, A., Akdemir, A., Bakker, R. A., & Leurs, R. (2005). A Gq/11-coupled Mutant Histamine H1 Receptor F435A Activated Solely by Synthetic Ligands (RASSL). *Journal of Biological Chemistry*, *280*(41), 34741–34746. https://doi.org/10.1074/jbc.M504165200

Burke, K. J., & Bender, K. J. (2019). Modulation of Ion Channels in the Axon: Mechanisms and Function. *Frontiers in Cellular Neuroscience*, *13*, 221. https://doi.org/10.3389/fncel.2019.00221

Butovsky, O., & Weiner, H. L. (2018). Microglial signatures and their role in health and disease. *Nature Reviews Neuroscience*, *19*(10), 622–635. https://doi.org/10.1038/s41583-018-0057-5

Calsolaro, V., & Edison, P. (2016). Neuroinflammation in Alzheimer's disease: Current evidence and future directions. *Alzheimer's & Dementia*, *12*(6), 719–732. https://doi.org/10.1016/j.jalz.2016.02.010

Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling: Neuropsychopharmacological implications. *Pharmacology & Therapeutics*, *130*(2), 226–238. https://doi.org/10.1016/j.pharmthera.2011.01.014

Carthy, E., & Ellender, T. (2021). Histamine, Neuroinflammation and Neurodevelopment: A Review. *Frontiers in Neuroscience*, *15*, 680214. https://doi.org/10.3389/fnins.2021.680214

Chao, Z., Mei, Q., Yang, C., Luo, J., Liu, P., Peng, H., Guo, X., Yin, Z., Li, L., & Wang, Z. (2025). Immunological synapse: Structures, molecular mechanisms and therapeutic implications in disease. *Signal Transduction and Targeted Therapy*, *10*(1), 254. https://doi.org/10.1038/s41392-025-02332-6

Chovatiya, R., & Silverberg, J. I. (2022). The Heterogeneity of Atopic Dermatitis. *Journal of Drugs in Dermatology*, *21*(2), 172–176. https://doi.org/10.36849/JDD.6408

Colonna, M., & Butovsky, O. (2017). Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Annual Review of Immunology*, *35*(1), 441–468. https://doi.org/10.1146/annurev-immunol-051116-052358

Dantzer, R. (2001). Cytokine-Induced Sickness Behavior: Mechanisms and Implications. *Annals of the New York Academy of Sciences*, *933*(1), 222–234. https://doi.org/10.1111/j.1749-6632.2001.tb05827.x

Darvesh, A. S., Carroll, R. T., Geldenhuys, W. J., Gudelsky, G. A., Klein, J., Meshul, C. K., & Van Der Schyf, C. J. (2011). *In vivo* brain microdialysis: Advances in neuropsychopharmacology and drug discovery. *Expert Opinion on Drug Discovery*, *6*(2), 109–127. https://doi.org/10.1517/17460441.2011.547189

Dauvilliers, Y., Bassetti, C., Lammers, G. J., Arnulf, I., Mayer, G., Rodenbeck, A., Lehert, P., Ding, C.-L., Lecomte, J.-M., & Schwartz, J.-C. (2013). Pitolisant versus placebo or modafinil in patients with narcolepsy: A double-blind, randomised trial. *The Lancet Neurology*, *12*(11), 1068–1075. https://doi.org/10.1016/S1474-4422(13)70225-4

Deiteren, A., De Man, J. G., Pelckmans, P. A., & De Winter, B. Y. (2015). Histamine H_4 receptors in the gastrointestinal tract. *British Journal of Pharmacology*, *172*(5), 1165–1178. https://doi.org/10.1111/bph.12989

Dileepan, K. N., Raveendran, V. V., Sharma, R., Abraham, H., Barua, R., Singh, V., Sharma, R., & Sharma, M. (2023). Mast cell-mediated immune regulation in health and disease. *Frontiers in Medicine*, *10*, 1213320. https://doi.org/10.3389/fmed.2023.1213320

DiSabato, D. J., Quan, N., & Godbout, J. P. (2016). Neuroinflammation: The devil is in the details. *Journal of Neurochemistry*, *139*(S2), 136–153. https://doi.org/10.1111/jnc.13607

Dunford, P. J., O'Donnell, N., Riley, J. P., Williams, K. N., Karlsson, L., & Thurmond, R. L. (2006). The Histamine H4 Receptor Mediates Allergic Airway Inflammation by Regulating the Activation of CD4+ T Cells. *The Journal of Immunology*, *176*(11), 7062–7070. https://doi.org/10.4049/jimmunol.176.11.7062

Engevik, A. C., Kaji, I., & Goldenring, J. R. (2020). The Physiology of the Gastric Parietal Cell. *Physiological Reviews*, *100*(2), 573–602. https://doi.org/10.1152/physrev.00016.2019

Esbenshade, T. A., Browman, K. E., Bitner, R. S., Strakhova, M., Cowart, M. D., & Brioni, J. D. (2008a). The histamine H_3 receptor: An attractive target for the treatment of cognitive disorders. *British Journal of Pharmacology*, *154*(6), 1166–1181. https://doi.org/10.1038/bjp.2008.147

Esbenshade, T. A., Browman, K. E., Bitner, R. S., Strakhova, M., Cowart, M. D., & Brioni, J. D. (2008b). The histamine H_3 receptor: An attractive target for the treatment of cognitive disorders. *British Journal of Pharmacology*, *154*(6), 1166–1181. https://doi.org/10.1038/bjp.2008.147

Fahy, J. V. (2015). Type 2 inflammation in asthma—Present in most, absent in many. *Nature Reviews Immunology*, *15*(1), 57–65. https://doi.org/10.1038/nri3786

Felger, J. C., & Lotrich, F. E. (2013). Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications. *Neuroscience*, *246*, 199–229. https://doi.org/10.1016/j.neuroscience.2013.04.060

Ferreira, S. A., & Romero-Ramos, M. (2018). Microglia Response During Parkinson's Disease: Alpha-Synuclein Intervention. *Frontiers in Cellular Neuroscience*, *12*, 247. https://doi.org/10.3389/fncel.2018.00247

Garmendia, J. V., De Sanctis, C. V., Das, V., Annadurai, N., Hajduch, M., & De Sanctis, J. B. (2024). Inflammation, Autoimmunity and Neurodegenerative Diseases,Therapeutics and Beyond. *Current Neuropharmacology*, *22*(6), 1080–1109. https://doi.org/10.2174/1570159X22666231017141636

Gebski, E. B., Anaspure, O., Panettieri, R. A., & Koziol-White, C. J. (2022). Airway smooth muscle and airway hyperresponsiveness in asthma: Mechanisms of airway smooth muscle dysfunction. *Minerva Medica*, *113*(1). https://doi.org/10.23736/S0026-4806.21.07283-9

Glass, C. K., Saijo, K., Winner, B., Marchetto, M. C., & Gage, F. H. (2010). Mechanisms Underlying Inflammation in Neurodegeneration. *Cell*, *140*(6), 918–934. https://doi.org/10.1016/j.cell.2010.02.016

Gutzmer, R., Mommert, S., Gschwandtner, M., Zwingmann, K., Stark, H., & Werfel, T. (2009). The histamine H4 receptor is functionally expressed on TH2 cells. *Journal of Allergy and Clinical Immunology*, *123*(3), 619–625. https://doi.org/10.1016/j.jaci.2008.12.1110

Haas, H. L., Sergeeva, O. A., & Selbach, O. (2008). Histamine in the Nervous System. *Physiological Reviews*, *88*(3), 1183–1241. https://doi.org/10.1152/physrev.00043.2007

Haig, G. M., Pritchett, Y., Meier, A., Othman, A. A., Hall, C., Gault, L. M., & Lenz, R. A. (2014). A Randomized Study of H3 Antagonist ABT-288 in Mild-To-Moderate Alzheimer's Dementia1. *Journal of Alzheimer's Disease*, *42*(3), 959–971. https://doi.org/10.3233/JAD-140291

Hartwig, C., Munder, A., Glage, S., Wedekind, D., Schenk, H., Seifert, R., & Neumann, D. (2015). The histamine H_4 -receptor (H_4 R) regulates eosinophilic inflammation in ovalbumin-induced experimental allergic asthma in mice. *European Journal of Immunology*, *45*(4), 1129–1140. https://doi.org/10.1002/eji.201445179

Heneka, M. T., Carson, M. J., Khoury, J. E., Landreth, G. E., Brosseron, F., Feinstein, D. L., Jacobs, A. H., Wyss-Coray, T., Vitorica, J., Ransohoff, R. M., Herrup, K., Frautschy, S. A., Finsen, B., Brown, G. C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., … Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. *The Lancet Neurology*, *14*(4), 388–405. https://doi.org/10.1016/S1474-4422(15)70016-5

Heppner, F. L., Ransohoff, R. M., & Becher, B. (2015). Immune attack: The role of inflammation in Alzheimer disease. *Nature Reviews Neuroscience*, *16*(6), 358–372. https://doi.org/10.1038/nrn3880

Hepsomali, P., Groeger, J. A., Nishihira, J., & Scholey, A. (2020). Effects of Oral Gamma-Aminobutyric Acid (GABA) Administration on Stress and Sleep in Humans: A Systematic Review. *Frontiers in Neuroscience*, *14*, 923. https://doi.org/10.3389/fnins.2020.00923

Herring, W. J., Wilens, T. E., Adler, L. A., Baranak, C., Liu, K., Snavely, D. B., Lines, C. R., & Michelson, D. (2012). Randomized Controlled Study of the Histamine H3 Inverse Agonist MK-0249 in Adult Attention-Deficit/Hyperactivity Disorder. *The Journal of Clinical Psychiatry*, *73*(07), e891–e898. https://doi.org/10.4088/JCP.11m07178

Holgate, S. T. (2008). Pathogenesis of Asthma. *Clinical & Experimental Allergy*, *38*(6), 872–897. https://doi.org/10.1111/j.1365-2222.2008.02971.x

Huang, H., Li, Y., Liang, J., & Finkelman, F. D. (2018). Molecular Regulation of Histamine Synthesis. *Frontiers in Immunology*, *9*, 1392. https://doi.org/10.3389/fimmu.2018.01392

Irwin, M. R. (2019). Sleep and inflammation: Partners in sickness and in health. *Nature Reviews Immunology*, *19*(11), 702–715. https://doi.org/10.1038/s41577-019-0190-z

Ishijima, T., & Nakajima, K. (2021). Inflammatory cytokines TNFα, IL-1β, and IL-6 are induced in endotoxin- stimulated microglia through different signaling cascades. *Science Progress*, *104*(4), 00368504211054985. https://doi.org/10.1177/00368504211054985

Jutel, M., & Akdis, C. A. (2011). Immunological mechanisms of allergen-specific immunotherapy: Immunological mechanisms of allergen-specific immunotherapy. *Allergy*, *66*(6), 725–732. https://doi.org/10.1111/j.1398-9995.2011.02589.x

Kaczmarski, P., Sochal, M., Strzelecki, D., Białasiewicz, P., & Gabryelska, A. (2023). Influence of glutamatergic and GABAergic neurotransmission on obstructive sleep apnea. *Frontiers in Neuroscience*, *17*, 1213971. https://doi.org/10.3389/fnins.2023.1213971

Kealy, J., Greene, C., & Campbell, M. (2020). Blood-brain barrier regulation in psychiatric disorders. *Neuroscience Letters*, *726*, 133664. https://doi.org/10.1016/j.neulet.2018.06.033

Kempuraj, D., Thangavel, R., Natteru, P. A., Selvakumar, G. P., Saeed, D., Zahoor, H., Zaheer, S., Iyer, S. S., & Zaheer, A. (2016). Neuroinflammation Induces Neurodegeneration. *Journal of Neurology, Neurosurgery and Spine*, *1*(1), 1003.

Kollmeier, A., Francke, K., Chen, B., Dunford, P. J., Greenspan, A. J., Xia, Y., Xu, X. L., Zhou, B., & Thurmond, R. L. (2014). The Histamine H4 Receptor Antagonist, JNJ 39758979, Is Effective in Reducing Histamine-Induced Pruritus in a Randomized Clinical Study in Healthy Subjects. *The Journal of Pharmacology and Experimental Therapeutics*, *350*(1), 181–187. https://doi.org/10.1124/jpet.114.215749

Kollmeier, A. P., Greenspan, A., Xu, X. L., Silkoff, P. E., Barnathan, E. S., Loza, M. J., Jiang, J., Zhou, B., Chen, B., & Thurmond, R. L. (2018). Phase 2a, randomized, double-blind, placebo-controlled, multicentre, parallel-group study of an H_4 R-antagonist (JNJ -39758979) in adults with uncontrolled asthma. *Clinical & Experimental Allergy*, *48*(8), 957–969. https://doi.org/10.1111/cea.13154

Komai, T., Inoue, M., Okamura, T., Morita, K., Iwasaki, Y., Sumitomo, S., Shoda, H., Yamamoto, K., & Fujio, K. (2018). Transforming Growth Factor-β and Interleukin-10 Synergistically Regulate Humoral Immunity via Modulating Metabolic Signals. *Frontiers in Immunology*, *9*, 1364. https://doi.org/10.3389/fimmu.2018.01364

Kondo, N., Kuroda, T., & Kobayashi, D. (2021). Cytokine Networks in the Pathogenesis of Rheumatoid Arthritis. *International Journal of Molecular Sciences*, *22*(20), 10922. https://doi.org/10.3390/ijms222010922

Krabbe, G., Halle, A., Matyash, V., Rinnenthal, J. L., Eom, G. D., Bernhardt, U., Miller, K. R., Prokop, S., Kettenmann, H., & Heppner, F. L. (2013). Functional Impairment of Microglia Coincides with Beta-Amyloid Deposition in Mice with Alzheimer-Like Pathology. *PLoS ONE*, *8*(4), e60921. https://doi.org/10.1371/journal.pone.0060921

Leng, F., & Edison, P. (2021). Neuroinflammation and microglial activation in Alzheimer disease: Where do we go from here? *Nature Reviews Neurology*, *17*(3), 157–172. https://doi.org/10.1038/s41582-020-00435-y

Leurs, R., Bakker, R. A., Timmerman, H., & De Esch, I. J. P. (2005). The histamine H3 receptor: From gene cloning to H3 receptor drugs. *Nature Reviews Drug Discovery*, *4*(2), 107–120. https://doi.org/10.1038/nrd1631

Liang, J., Guo, Q., Xiang, S., Wang, Y., & Li, J. (2025). Heterogeneity-optimized method for predicting immune checkpoint blockade response. *Scientific Reports*, *15*(1), 32259. https://doi.org/10.1038/s41598-025-17718-3

Liang, W., Han, B., Hai, Y., Liu, Y., Liu, X., Yang, J., Sun, D., & Yin, P. (2022). The Role of Microglia/Macrophages Activation and TLR4/NF-κB/MAPK Pathway in Distraction Spinal Cord Injury-Induced Inflammation. *Frontiers in Cellular Neuroscience*, *16*, 926453. https://doi.org/10.3389/fncel.2022.926453

Ligneau, X., Perrin, D., Landais, L., Camelin, J.-C., Calmels, T. P. G., Berrebi-Bertrand, I., Lecomte, J.-M., Parmentier, R., Anaclet, C., Lin, J.-S., Bertaina-Anglade, V., La Rochelle, C. D., d'Aniello, F., Rouleau, A., Gbahou, F., Arrang, J.-M., Ganellin, C. R., Stark, H., Schunack, W., & Schwartz, J.-C. (2007). BF2.649 [1-{3-[3-(4-Chlorophenyl)propoxy]propyl}piperidine, Hydrochloride], a Nonimidazole Inverse Agonist/Antagonist at the Human Histamine H3 Receptor: Preclinical Pharmacology. *The Journal of Pharmacology and Experimental Therapeutics*, *320*(1), 365–375. https://doi.org/10.1124/jpet.106.111039

Lin, J.-S., Sergeeva, O. A., & Haas, H. L. (2011). Histamine H3 Receptors and Sleep-Wake Regulation. *The Journal of Pharmacology and Experimental Therapeutics*, *336*(1), 17–23. https://doi.org/10.1124/jpet.110.170134

Medhurst, A. D., Atkins, A. R., Beresford, I. J., Brackenborough, K., Briggs, M. A., Calver, A. R., Cilia, J., Cluderay, J. E., Crook, B., Davis, J. B., Davis, R. K., Davis, R. P., Dawson, L. A., Foley, A. G., Gartlon, J., Gonzalez, M. I., Heslop, T., Hirst, W. D., Jennings, C., … Wilson, D. M. (2007). GSK189254, a Novel H3 Receptor Antagonist That Binds to Histamine H3 Receptors in Alzheimer's Disease Brain and Improves Cognitive Performance in Preclinical Models. *The Journal of Pharmacology and Experimental Therapeutics*, *321*(3), 1032–1045. https://doi.org/10.1124/jpet.107.120311

Meng, L., Liu, S., Luo, J., Tu, Y., Li, T., Li, P., Yu, J., & Shi, L. (2025). Oxidative stress and reactive oxygen species in otorhinolaryngological diseases: Insights from pathophysiology to targeted antioxidant therapies. *Redox Report*, *30*(1), 2458942. https://doi.org/10.1080/13510002.2025.2458942

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, *16*(1), 22–34. https://doi.org/10.1038/nri.2015.5

Müller, L., Di Benedetto, S., & Müller, V. (2025). From Homeostasis to Neuroinflammation: Insights into Cellular and Molecular Interactions and Network Dynamics. *Cells*, *14*(1), 54. https://doi.org/10.3390/cells14010054

Ng, G. Y. Q., Loh, Z. W.-L., Fann, D. Y., Mallilankaraman, K., Arumugam, T. V., & Hande, M. P. (2024). Role of Mitogen-Activated Protein (MAP) Kinase Pathways in Metabolic Diseases. *Genome Integrity*, *15*. https://doi.org/10.14293/genint.14.1.004

Notcovich, C., Diez, F., Tubio, M. R., Baldi, A., Kazanietz, M. G., Davio, C., & Shayo, C. (2010). Histamine acting on H1 receptor promotes inhibition of proliferation via PLC, RAC, and JNK-dependent pathways. *Experimental Cell Research*, *316*(3), 401–411. https://doi.org/10.1016/j.yexcr.2009.11.002

Oda, T., Morikawa, N., Saito, Y., Masuho, Y., & Matsumoto, S. (2000). Molecular Cloning and Characterization of a Novel Type of Histamine Receptor Preferentially Expressed in Leukocytes. *Journal of Biological Chemistry*, *275*(47), 36781–36786. https://doi.org/10.1074/jbc.M006480200

Panula, P., & Nuutinen, S. (2013). The histaminergic network in the brain: Basic organization and role in disease. *Nature Reviews Neuroscience*, *14*(7), 472–487. https://doi.org/10.1038/nrn3526

Parsons, M. E., & Ganellin, C. R. (2006). Histamine and its receptors. *British Journal of Pharmacology*, *147*(S1). https://doi.org/10.1038/sj.bjp.0706440

Passani, M. B., & Blandina, P. (2011). Histamine receptors in the CNS as targets for therapeutic intervention. *Trends in Pharmacological Sciences*, *32*(4), 242–249. https://doi.org/10.1016/j.tips.2011.01.003

Patel, R. H., & Mohiuddin, S. S. (2025). Biochemistry, Histamine. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK557790/

Pavlov, V. A., & Tracey, K. J. (2017). Neural regulation of immunity: Molecular mechanisms and clinical translation. *Nature Neuroscience*, *20*(2), 156–166. https://doi.org/10.1038/nn.4477

Price, R. B., & Duman, R. (2020). Neuroplasticity in cognitive and psychological mechanisms of depression: An integrative model. *Molecular Psychiatry*, *25*(3), 530–543. https://doi.org/10.1038/s41380-019-0615-x

Prinz, M., & Priller, J. (2017). The role of peripheral immune cells in the CNS in steady state and disease. *Nature Neuroscience*, *20*(2), 136–144. https://doi.org/10.1038/nn.4475

Raos, D., Ulamec, M., Katusic Bojanac, A., Bulic-Jakus, F., Jezek, D., & Sincic, N. (2020). Epigenetically inactivated RASSF1A as a tumor biomarker. *Bosnian Journal of Basic Medical Sciences*. https://doi.org/10.17305/bjbms.2020.5219

Robichaux, W. G., & Cheng, X. (2018). Intracellular cAMP Sensor EPAC: Physiology, Pathophysiology, and Therapeutics Development. *Physiological Reviews*, *98*(2), 919–1053. https://doi.org/10.1152/physrev.00025.2017

Salter, M. W., & Stevens, B. (2017). Microglia emerge as central players in brain disease. *Nature Medicine*, *23*(9), 1018–1027. https://doi.org/10.1038/nm.4397

Saper, C. B., & Fuller, P. M. (2017). Wake–sleep circuitry: An overview. *Current Opinion in Neurobiology*, *44*, 186–192. https://doi.org/10.1016/j.conb.2017.03.021

Schlicker, E., & Kathmann, M. (2016). Role of the Histamine H3 Receptor in the Central Nervous System. In Y. Hattori & R. Seifert (Eds.), *Histamine and Histamine Receptors in Health and Disease* (Vol. 241, pp. 277–299). Springer International Publishing. https://doi.org/10.1007/164_2016_12

Schneider, E. H., & Seifert, R. (2016). The histamine H4-receptor and the central and peripheral nervous system: A critical analysis of the literature. *Neuropharmacology*, *106*, 116–128. https://doi.org/10.1016/j.neuropharm.2015.05.004

Schwartz, J. (2011). The histamine H3 receptor: From discovery to clinical trials with pitolisant. *British Journal of Pharmacology*, *163*(4), 713–721. https://doi.org/10.1111/j.1476-5381.2011.01286.x

Shamsnia, H. S., Roustaei, M., Ahmadvand, D., Butler, A. E., Amirlou, D., Soltani, S., Momtaz, S., Jamialahmadi, T., Abdolghaffari, A. H., & Sahebkar, A. (2023). Impact of curcumin on p38 MAPK: Therapeutic implications. *Inflammopharmacology*, *31*(5), 2201–2212. https://doi.org/10.1007/s10787-023-01265-2

Shimizu, F., & Nakamori, M. (2024). Blood–Brain Barrier Disruption in Neuroimmunological Disease. *International Journal of Molecular Sciences*, *25*(19), 10625. https://doi.org/10.3390/ijms251910625

Skaper, S., Facci, L., & Giusti, P. (2015). Neuroinflammation, Microglia and Mast Cells in the Pathophysiology of Neurocognitive Disorders: A Review. *CNS & Neurological Disorders - Drug Targets*, *13*(10), 1654–1666. https://doi.org/10.2174/1871527313666141130224206

Song, Z., Wang, Y., Zhang, F., Yao, F., & Sun, C. (2019). Calcium Signaling Pathways: Key Pathways in the Regulation of Obesity. *International Journal of Molecular Sciences*, *20*(11), 2768. https://doi.org/10.3390/ijms20112768

Su, Y., Zhang, W., Zhang, R., Yuan, Q., Wu, R., Liu, X., Wuri, J., Li, R., & Yan, T. (2022). Activation of Cholinergic Anti-Inflammatory Pathway Ameliorates Cerebral and Cardiac Dysfunction After Intracerebral Hemorrhage Through Autophagy. *Frontiers in Immunology*, *13*, 870174. https://doi.org/10.3389/fimmu.2022.870174

Tansey, M. G., & Goldberg, M. S. (2010). Neuroinflammation in Parkinson's disease: Its role in neuronal death and implications for therapeutic intervention. *Neurobiology of Disease*, *37*(3), 510–518. https://doi.org/10.1016/j.nbd.2009.11.004

Thakkar, M. M. (2011). Histamine in the regulation of wakefulness. *Sleep Medicine Reviews*, *15*(1), 65–74. https://doi.org/10.1016/j.smrv.2010.06.004

Thangam, E. B., Jemima, E. A., Singh, H., Baig, M. S., Khan, M., Mathias, C. B., Church, M. K., & Saluja, R. (2018). The Role of Histamine and Histamine Receptors in Mast Cell-Mediated Allergy and Inflammation: The Hunt for New Therapeutic Targets. *Frontiers in Immunology*, *9*, 1873. https://doi.org/10.3389/fimmu.2018.01873

Theoharides, T. C., Alysandratos, K.-D., Angelidou, A., Delivanis, D.-A., Sismanopoulos, N., Zhang, B., Asadi, S., Vasiadi, M., Weng, Z., Miniati, A., & Kalogeromitros, D. (2012). Mast cells and inflammation. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1822*(1), 21–33. https://doi.org/10.1016/j.bbadis.2010.12.014

Thomas, S. D., Abdalla, S., Eissa, N., Akour, A., Jha, N. K., Ojha, S., & Sadek, B. (2024). Targeting Microglia in Neuroinflammation: H3 Receptor Antagonists as a Novel Therapeutic Approach for Alzheimer's Disease, Parkinson's Disease, and Autism Spectrum Disorder. *Pharmaceuticals*, *17*(7), 831. https://doi.org/10.3390/ph17070831

Thurmond, R. L., Gelfand, E. W., & Dunford, P. J. (2008). The role of histamine H1 and H4 receptors in allergic inflammation: The search for new antihistamines. *Nature Reviews Drug Discovery*, *7*(1), 41–53. https://doi.org/10.1038/nrd2465

Tian, L., Ma, L., Kaarela, T., & Li, Z. (2012). Neuroimmune crosstalk in the central nervous system and its significance for neurological diseases. *Journal of Neuroinflammation*, *9*(1), 594. https://doi.org/10.1186/1742-2094-9-155

Toader, C., Serban, M., Munteanu, O., Covache-Busuioc, R.-A., Enyedi, M., Ciurea, A. V., & Tataru, C. P. (2025). From Synaptic Plasticity to Neurodegeneration: BDNF as a Transformative Target in Medicine. *International Journal of Molecular Sciences*, *26*(9), 4271. https://doi.org/10.3390/ijms26094271

Uluckan, Ö., Bruno, S., Wang, Y., Wack, N., Wilzopolski, J., Goetschy, J.-F., Delucis-Bronn, C., Urban, B., Fehlmann, D., Stark, H., Hauchard, A., Roussel, E., Kempf, D., Kaupmann, K., Raulf, F., Bäumer, W., Röhn, T. A., & Zerwes, H. G. (2023). Adriforant is a functional antagonist of histamine receptor 4 and attenuates itch and skin inflammation in mice. *European Journal of Pharmacology*, *945*, 175533. https://doi.org/10.1016/j.ejphar.2023.175533

Van Acker, M. M., Schwartz, R. R., Andrews, K., Seiffert-Sinha, K., & Sinha, A. A. (2023). Inheritance-Specific Dysregulation of Th1- and Th17-Associated Cytokines in Alopecia Areata. *Biomolecules*, *13*(9), 1285. https://doi.org/10.3390/biom13091285

Wang, P., Zhao, W., Sun, J., Tao, T., Chen, X., Zheng, Y.-Y., Zhang, C.-H., Chen, Z., Gao, Y.-Q., She, F., Li, Y.-Q., Wei, L.-S., Lu, P., Chen, C.-P., Zhou, J., Wang, D.-Q., Chen, L., Shi, X.-H., Deng, L., … Zhu, M.-S. (2018). Inflammatory mediators mediate airway smooth muscle contraction through a G protein-coupled receptor–transmembrane protein 16A–voltage-dependent Ca2+ channel axis and contribute to bronchial hyperresponsiveness in asthma. *Journal of Allergy and Clinical Immunology*, *141*(4), 1259-1268.e11. https://doi.org/10.1016/j.jaci.2017.05.053

Wellner-Kienitz, M.-C., Bender, K., Meyer, T., & Pott, L. (2003). Coupling to Gs and Gq/11 of histamine H2 receptors heterologously expressed in adult rat atrial myocytes. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, *1642*(1–2), 67–77. https://doi.org/10.1016/S0167-4889(03)00101-0

Wu, C., Boey, D., Bril, O., Grootens, J., Vijayabaskar, M. S., Sorini, C., Ekoff, M., Wilson, N. K., Ungerstedt, J. S., Nilsson, G., & Dahlin, J. S. (2022). Single-cell transcriptomics reveals the identity and regulators of human mast cell progenitors. *Blood Advances*, *6*(15), 4439–4449. https://doi.org/10.1182/bloodadvances.2022006969

Yan, H., Zhang, X., Hu, W., Ma, J., Hou, W., Zhang, X., Wang, X., Gao, J., Shen, Y., Lv, J., Ohtsu, H., Han, F., Wang, G., & Chen, Z. (2014). Histamine H3 receptors aggravate cerebral ischaemic injury by histamine-independent mechanisms. *Nature Communications*, *5*(1), 3334. https://doi.org/10.1038/ncomms4334

Zampeli, E., & Tiligada, E. (2009). The role of histamine H_4 receptor in immune and inflammatory disorders. *British Journal of Pharmacology*, *157*(1), 24–33. https://doi.org/10.1111/j.1476-5381.2009.00151.x

Zhao, J., Shi, W., Lu, Y., Gao, X., Wang, A., Zhang, S., Du, Y., Wang, Y., & Li, L. (2022). Alterations of monoamine neurotransmitters, HPA-axis hormones, and inflammation cytokines in reserpine-induced hyperalgesia and depression comorbidity rat model. *BMC Psychiatry*, *22*(1), 419. https://doi.org/10.1186/s12888-022-04065-0

Zhao, Y., Huang, Y., Cao, Y., & Yang, J. (2024). Astrocyte-Mediated Neuroinflammation in Neurological Conditions. *Biomolecules*, *14*(10), 1204. https://doi.org/10.3390/biom14101204

Zhou, Z., An, Q., Zhang, W., Li, Y., Zhang, Q., & Yan, H. (2024). Histamine and receptors in neuroinflammation: Their roles on neurodegenerative diseases. *Behavioural Brain Research*, *465*, 114964. https://doi.org/10.1016/j.bbr.2024.114964

Zuchero, J. B., & Barres, B. A. (2015). Glia in mammalian development and disease. *Development*, *142*(22), 3805–3809. https://doi.org/10.1242/dev.129304

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