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Review

The Histaminergic System: A Key Regulator of Pathogenesis and an Emerging Therapeutic Target in Autism Spectrum Disorder

Guojin Liu[1,2,†], Chenyue Shi[1,2,†], Wen Yan[1,2], Wenjie Yan[1,2], Siyuan Tian[1,2], Ying Zi[1,2], Ruoxi Shao[1,2], Qian-Xing Zhuang[1,2,*]

[1]Department of Physiology, School of Medicine, Nantong University, 226001 Nantong, Jiangsu, China
[2]Jiangsu Province Key Laboratory in University for Inflammation and Molecular Drug Target, School of Medicine, Nantong University, 226001 Nantong, Jiangsu, China
*Correspondence: qxzhuang@ntu.edu.cn (Qian-Xing Zhuang)
[†]These authors contributed equally.
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Abstract

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition defined by core deficits in social communication and restricted, repetitive behaviors. However, its pathogenesis remains incompletely understood and no therapy targeting the core symptoms has been approved for clinical use. Converging evidence now links ASD to dysregulation of the histaminergic system. Histamine H3 receptor (H3R) antagonism attenuates ASD-related neuroinflammation both by enhancing histaminergic transmission and acting directly on microglia. Histamine H1 receptor (H1R) and Histamine H2 receptor (H2R) signaling jointly supports synaptic plasticity and cognition, whereas the balance between H1R and H3R shapes the sleep-wake cycle. Molecular remodeling of the histaminergic system in the dorsolateral prefrontal cortex of individuals with ASD has been reported as a coordinated transcriptional signature linked to neuroinflammation and core behavioral abnormalities. Moreover, in preclinical ASD models, H3R antagonists/inverse agonists (e.g., DL77 and A-366) have produced encouraging effects on social and repetitive behaviors. Collectively, these results suggest that the histaminergic system integrates genetic risk, environmental triggers, immune impairment, and neuronal-circuit defects associated with ASD.

Keywords: autism spectrum disorder; histamine; histamine receptors; neuroinflammatory diseases; microglia; neuronal plasticity; neurogenesis; molecular targeted therapy

1. Introduction

Autism spectrum disorder (ASD) comprises a group of neurodevelopmental conditions whose core features are deficits in social communication and interaction together with restricted, repetitive, and stereotyped patterns of behavior [1,2,3]. Successive revisions to the diagnostic criteria and greater public awareness have driven a marked rise in reported global ASD prevalence over recent decades [4,5]. A recent systematic review of 71 studies (2012–2021) identified a median global autism prevalence of 1% (100/10,000), with markedly higher rates observed in several high-income countries [4]. These figures underscore the substantial burden that ASD places on public health systems worldwide, and the urgent need for mechanistic research and for more targeted interventions.

No curative regimen for ASD has yet been established, and clinical management remains largely symptomatic, aimed at alleviating associated comorbidities [6]. Atypical antipsychotics can control aggression and irritability; serotonin and norepinephrine reuptake inhibitors mitigate anxiety, depression, and obsessive-compulsive symptoms; and methylphenidate relieves comorbid attention-deficit/hyperactivity disorder (ADHD) [6]. However, these agents address comorbid features rather than the core deficits of ASD (social impairment, stereotyped behavior, and sensory abnormalities), against which none has established efficacy. Long-term use also carries a risk of metabolic disturbance, somnolence, and extrapyramidal reactions. Identifying novel targets that engage the neural circuits underlying the core symptoms is therefore a priority for the field.

The pathogenesis of ASD is complex and incompletely understood, although current evidence indicates that it is driven jointly by genetic and environmental factors [7]. Converging hypotheses now implicate neuroinflammation, which arises from the interplay between the immune and nervous systems, as a key pathogenic mechanism in a subset of cases [7]. Consistent with this, immunological studies report marked immune dysregulation in individuals with ASD: structural or functional abnormalities across immune cell lineages (T cells, B cells, monocytes, natural killer cells, and dendritic cells); imbalanced immunoglobulin levels with elevated autoantibody titers; and raised peripheral cytokine and chemokine levels accompanied by prominent neuroinflammatory responses [8]. Together, these findings establish immune dysregulation and neuroinflammation as

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tractable entry points for dissecting ASD pathogenesis, and as candidate targets for precision diagnosis and treatment.

Histamine is a nitrogen-containing bioactive amine composed of an imidazole ring and an ethylamine side chain. Synthesized from L-histidine by histidine decarboxylase (HDC), it is stored principally in neurons of the tuberomammillary nucleus (TMN) of the central nervous system (CNS) and in peripheral mast cells, where it contributes to local immune regulation and to the modulation of systemic physiological function [9,10,11,12,13]. Its biological effects are mediated by four G protein-coupled receptor subtypes (H1R, H2R, H3R, and H4R). The distinct anatomical distribution and signal transduction profile of each receptor provide the molecular basis for the functional diversity of the histaminergic system [14].

As an evolutionarily conserved "immuno-neural bifunctional neurotransmitter", histamine is increasingly regarded as a critical target in ASD research, reflecting its dual roles in regulating immune responses and in integrating neural circuit function [9,15]. The four receptors differ in distribution and in physiological function. H1R is broadly expressed throughout the CNS and is particularly enriched in regions governing arousal and the sleep-wake cycle, including the thalamus, cortex, cholinergic nuclei, locus coeruleus, and raphe nuclei [16,17]. Acting through these regions, H1R signaling modulates the sleep-wake cycle, arousal, and cognitive function [18]. H2R is expressed predominantly in the basal ganglia, hippocampus, amygdala, and cerebral cortex [16,19,20,21]. Coupling to Gs activates adenylyl cyclase and raises intracellular cyclic adenosine monophosphate (cAMP), which in turn activates protein kinase A (PKA) and the transcription factor cAMP-response element-binding protein (CREB). H2R activation also blocks Ca^{2+}-activated potassium conductance and inhibits both phospholipase A2 and arachidonic acid release [12]. H3R is largely confined to the CNS and is only weakly expressed peripherally. *In situ* hybridization shows abundant mRNA in the cortex, hippocampus, and caudate nucleus; moderate levels in the olfactory bulb, amygdala, bed nucleus of the stria terminalis, cerebellum, and thalamus; and low levels in the habenula, zona incerta, globus pallidus, substantia nigra, and substantia innominata [22]. As a presynaptic autoreceptor on histaminergic neurons, H3R exerts negative feedback on histamine synthesis and release. It is also expressed presynaptically on non-histaminergic neurons, where it acts as a heteroreceptor controlling the release of dopamine, glutamate, γ-aminobutyric acid (GABA), and acetylcholine [16,23,24,25]. H4R, the most recently identified subtype, is expressed mainly on immune cells, including mast cells, eosinophils, and dendritic cells [12]. Its neuronal expression remains poorly defined, although H4R is an established candidate target in inflammatory disease [26,27,28].

Histamine was long regarded as a peripheral mediator, acting through peripheral receptors in processes such as allergic responses and gastric acid secretion [14]. This view has since been substantially revised. The central histaminergic system is now recognized as a pivotal regulator of higher neural functions, including the sleep-wake cycle, cognitive processing, and feeding behavior. Disordered histaminergic transmission has been linked to the progression of narcolepsy, Alzheimer's disease, Parkinson's disease, schizophrenia, and Tourette syndrome (TS) [16,21,29]. Notably, the histaminergic system's capacity to regulate neural plasticity synergistically through multiple receptors offers a new framework for interrogating the neurobiology of core ASD symptoms such as social interaction deficits and repetitive stereotyped behavior. Preclinical work further suggests that selective histamine receptor modulators could restore synaptic homeostasis in ASD [30].

This narrative review was prepared in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidance for biomedical narrative reviews [31]; a systematic review or meta-analysis was not attempted. Three considerations preclude quantitative synthesis of the current evidence. First, controlled clinical trials of histamine receptor-targeted therapies in ASD remain few. Second, the preclinical literature is substantially heterogeneous, spanning different ASD models (BTBR, valproic acid, MK-801, and lipopolysaccharide-induced), inconsistent behavioral readouts, and widely varying doses and treatment durations. Third, most eligible studies do not report standardized effect sizes, which further precludes meta-analytic integration.

We conducted searches of PubMed, Scopus, and Web of Science on 7 May 2026. The search strategy employed Medical Subject Headings (MeSH) terms in combination with the following key keywords: "(Histamine OR Histamine receptors) AND (Autism spectrum disorder) AND (Neuroinflammatory diseases OR Microglia OR Neuronal plasticity OR Neurogenesis OR Molecular targeted therapy)". Eligible records were peer-reviewed, English-language original articles and reviews published up to 2026. Drawing on this literature, the present review examines the regulatory functions of the histaminergic system in ASD pathogenesis and evaluates the translational potential of histamine-targeted strategies, with the aim of informing both mechanistic research and clinical intervention.

2. The Histaminergic System in ASD: Pathological Associations and Intervention Potential

Diagnostically, ASD is defined by DSM-5 and ICD-11 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition/International Classification of Diseases, Eleventh Revision) criteria in terms of two core domains: persistent deficits in social communication and interaction, together with restricted, repetitive patterns of behavior, interests, or activities [32]. Cognitive impairment, sleep dis-

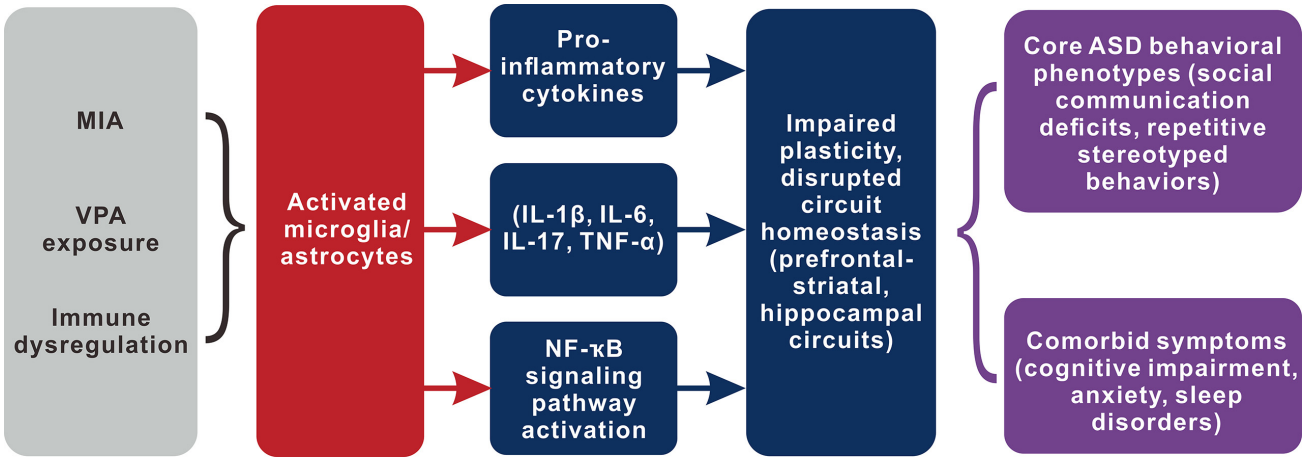


Fig. 1. The pro-inflammatory cytokine storm mediating ASD-related behavioral phenotypes. Persistent central-peripheral neuroinflammation is a core pathological feature of ASD, induced by genetic/environmental triggers (MIA, VPA exposure, immune dysregulation). Activated microglia and astrocytes secrete a cascade of pro-inflammatory cytokines (IL-1β, IL-6, IL-17, TNF-α) and activate the NF-κB signaling pathway. This pro-inflammatory cytokine storm impairs synaptic plasticity, disrupts neural circuit homeostasis (e.g., prefrontal-striatal, hippocampal circuits), and ultimately mediates the development of core ASD behavioral phenotypes (social communication deficits, repetitive stereotyped behaviors) and comorbid symptoms (cognitive impairment, anxiety, sleep disorders). ASD, Autism spectrum disorder; MIA, maternal immune activation; VPA, valproic acid.

turbance, epilepsy, ADHD-like symptoms, anxiety, irritability, and hyperactivity are all highly prevalent in this population, but they constitute comorbid features rather than core diagnostic criteria [33,34]. Despite this distinction, histaminergic dysfunction may act on both symptom dimensions through convergent but mechanistically separable pathways, and the system has been increasingly implicated in ASD pathophysiology through its regulation of neuroinflammation, synaptic plasticity, emotional homeostasis, and the sleep-wake cycle [35].

2.1 Neuroinflammation: One Critical Node Within ASD Pathological Processes

Persistent, low-grade neuroinflammation spanning central and peripheral compartments is now widely regarded as a core feature of ASD pathophysiology. In postmortem ASD brain tissue, markers of glial activation are elevated in the cortex, white matter, and cerebellum [36]. Astrocytes and microglia adopt pro-inflammatory phenotypes, with marked upregulation of interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-17 (IL-17), and tumor necrosis factor-α (TNF-α) [37]. The same pattern is reproduced in animal models: maternal immune activation and valproic acid (VPA) exposure both produce concurrent increases in peripheral cytokines (IL-1β, IL-6, IL-17, IL-18, IL-33, and TNF-α) and morphological activation of microglia and astrocytes [38]. Collectively, these findings suggest that cytokine-driven neuroinflammation may represent a common pathway to the core behavioral phenotypes of ASD (Fig. 1).

Within this inflammatory network, the histaminergic system, and H3R in particular, has attracted considerable attention. Multiple studies report that H3R antagonists reduce autism-like stereotyped behavior and repetitive movements in various ASD model animals [39,40,41], an effect closely tied to suppression of neuroinflammation. For example, the H3R antagonist ST713 lowers nuclear factor-κB (NF-κB) expression and blunts the rise in pro-inflammatory cytokines in BTBR autism model mice [42]; the dual-activity H3R antagonist E100 downregulates TNF-α, IL-1, and IL-6 and limits excessive microglial activation in VPA-induced ASD mice [43]; and the H3R antagonist DL77 suppresses pro-inflammatory cytokines in VPA-exposed mice [44]. Co-administration of H3R agonists abolishes both the anti-inflammatory and the behavioral benefits of these compounds, indicating that the effects are mediated by the central histaminergic system [43,44].

Mechanistic studies indicate that H3R antagonists act through two complementary neuroprotective pathways (Fig. 2). First, in ASD model animals, H3R antagonists enhance histamine release by relieving presynaptic autoinhibition, and the resulting histamine surge activates postsynaptic H2R-dependent signaling—likely via the Gs-cAMP/PKA/CREB cascade. Behavioral and electrophysiological studies confirm that H2R pharmacological blockade abrogates the beneficial effects of H3R antagonists on social interaction, spatial memory, and hippocampal long-term potentiation (LTP), positioning H2R as the principal downstream effector in this therapeutic pathway [45,46]. Second, in the ASD mouse model, H3R antagonists suppress microglial activation and the associated neuroinflammatory response by targeting H3R heteroreceptors on microglia, likely mediated through the PI3K/AKT/GSK-3β signaling pathway, which subsequently downregulates the

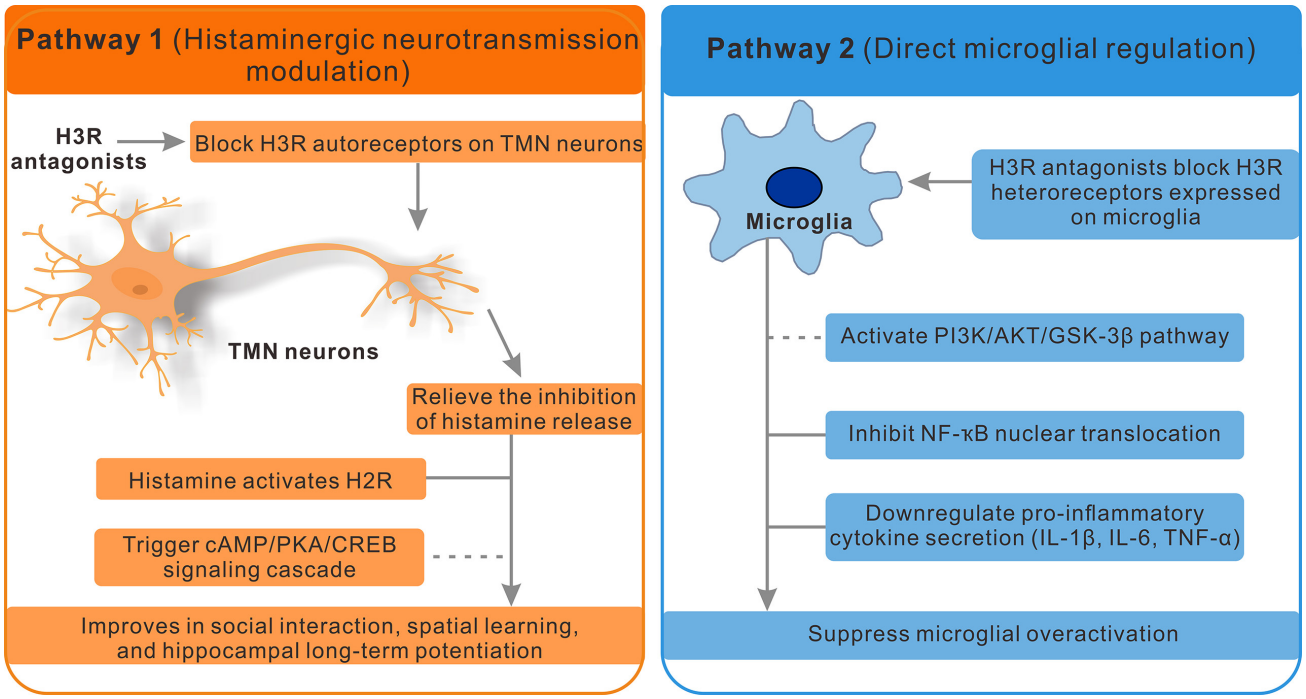


Fig. 2. The dual mechanisms of H3R antagonists ameliorating ASD-associated neuroinflammation and synaptic dysfunction. H3R antagonists exert neuroprotective effects in ASD through two synergistic pathways. (i) Histaminergic neurotransmission modulation: Block H3 autoreceptors on TMN neurons → relieve the inhibition of histamine release → histamine activates H2R → trigger cAMP/PKA/CREB signaling cascade → improves social interaction, spatial learning, and hippocampal long-term potentiation. (ii) Direct microglial regulation: Block H3R heteroreceptors expressed on microglia → activate PI3K/AKT/GSK-3β pathway → inhibit pro-inflammatory markers NF-κB, iNOS, COX-2 → downregulate pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) → suppress microglial overactivation. Dashed lines denote hypothetical pathways, with supporting evidence derived from non-ASD model mechanisms. ASD, Autism spectrum disorder; TMN, tuberomammillary nucleus; iNOS, inducible nitric oxide synthase; COX-2, Cyclooxygenase-2.

expression of pro-inflammatory markers such as NF-κB, iNOS, COX-2, and reduces the levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in the affected brain regions [43,46,47]. Together, these findings support the potential of H3R antagonists to alleviate ASD-related neuroinflammation and its behavioral consequences.

2.2 Integrated Mechanisms of Histaminergic Receptors in ASD

The histaminergic system regulates diverse CNS functions through four receptor subtypes (H1R, H2R, H3R, and H4R). Their region-specific expression and distinct downstream signaling underlie specialized contributions to ASD-relevant domains, including sleep disturbance, cognitive impairment, and emotional dysregulation (Table 1).

2.2.1 Synergistic Regulation of the Arousal-Sleep Cycle by H1R/H3R

Histaminergic neurons of the TMN are the sole source of histamine synthesis and release in the brain [48]. Their axons project widely to arousal-regulating networks, including the cortex and thalamus, where H1R activation raises neuronal excitability and sustains cortical arousal [49]. Preclinical work links the sleep problems common in ASD, such as delayed sleep onset and nocturnal awakening, to attenuated H1R signaling [50]: H1R knockout mice show an approximately 20-min reduction in waking time during the early dark period and a 25–30% shortening of sleep latency after behavioral challenge (bedding change, simulated injection), consistent with impaired maintenance of arousal. Their electroencephalogram (EEG) shows a reduced slow-wave sleep (SWS)-to-wakefulness power ratio and weakened theta (3–9 Hz) power, indicating insufficient cortical activation. Consistent with this, the brain-penetrant H1R antagonist triprolidine reproduces these sleep-wake abnormalities in wild-type mice (prolonged SWS, reduced waking time, and increased EEG slow-wave activity), whereas $H1R^{-/-}$ mice show no response, confirming the necessity of H1R-mediated histamine signaling for the maintenance of arousal [50].

Conversely, H3R on TMN neurons functions as an autoreceptor whose activation inhibits histamine synthesis and release, thereby forming a negative feedback loop on histaminergic neurotransmission [48]. The H3R inverse agonist pitolisant blocks this feedback, disinhibiting TMN neurons and promoting the coordinated release of histamine and of downstream arousal-promoting transmitters such as dopamine and norepinephrine, thereby enhancing arousal

Table 1. Possible roles of histamine receptors in ASD-related pathophysiology.

Receptor	Key brain regions/ Cellular targets	Relevant ASD pathology	Possible signaling mechanisms	Functional outcome
H1R	Thalamus, cortex, locus coeruleus, hippocampus (CA1)	Sleep–wake disruption; cognitive & emotional deficits	H1R-mediated arousal signaling; D-serine-NMDAR axis regulation of LTP	Maintains cortical arousal; amplifies NMDAR-EPSC; consolidates synaptic plasticity
H2R	Hippocampus, basal ganglia, cerebral cortex	Cognitive impairment, synaptic dysfunction	H2R-cAMP-PKA-CREB; BDNF upregulation	Restores hippocampal LTP; enhances synaptic plasticity and spatial learning/ memory
H3R	TMN, CeL, prefrontal-striatal circuit	Sleep fragmentation; anxiety; social/ cognitive deficits	Autorepression of histamine release; inhibition of glutamatergic transmission in CeL; modulation of monoamine/ACh release	Enhances arousal; reshapes CeL E/I balance; increases dopamine/ACh in PFC/striatum
H4R	Spleen $CD8^+$ T cells, brain tissue (mRNA/ protein expression)	Social deficits; immune abnormalities	Modulates RORγt/T-bet and STAT3 signaling; regulates IL-17A, IL-22, IL-10, Foxp3 expression	In irradiated BTBR mice: increases social interaction; reduces pro-inflammatory and increases regulatory $CD8^+$ T cell populations; modulates brain cytokine/transcription factor expression

NMDAR, N-methyl-D-aspartate receptor; LTP, Long-term potentiation; EPSC, Excitatory postsynaptic current; TMN, Tuberomammillary nucleus; CeL, Central lateral amygdala; E/I, Excitation-inhibition; BDNF, Brain-derived neurotrophic factor; ACh, acetylcholine; PFC, prefrontal cortex; NF-κB, nuclear factor-κB; RORγt, Retinoic acid-related orphan receptor gamma t; T-bet, T-box expressed in T cells; STAT3, Signal Transducer and Activator of Transcription 3; Foxp3, Forkhead box P3.

and reducing sleep fragmentation. In narcolepsy, pitolisant at 10–40 mg/day reduced cataplexy attacks by 75% and significantly alleviated daytime sleepiness [51]. This bidirectional modulation offers a mechanistic rationale for correcting sleep-wake disturbances in ASD; however, whereas pitolisant is clinically validated in narcolepsy, its relevance to ASD remains to be established through targeted clinical studies.

2.2.2 Synergistic Regulation of Synaptic Plasticity and Cognitive Function by H1R/H2R/H3R

Cognitive impairment is a prominent feature of ASD and is closely tied to disrupted synaptic plasticity. VPA-exposed model mice show marked spatial learning and memory deficits together with impaired LTP in hippocampal area CA1 [45]. VPA exposure reduces early-phase LTP amplitude by 35% and impairs late-phase LTP maintenance, manifesting behaviorally as prolonged escape latency and reduced target-quadrant dwell time in the Morris water maze. The histaminergic system regulates synaptic plasticity through synergy between H1R and H2R [40,45]. The H3R antagonist ciproxifan (CPX, 3 mg/kg) relieves autoreceptor-mediated inhibition of TMN neurons and raises hippocampal histamine. The resulting H2R signaling restores CA1 LTP in VPA model mice and reverses their spatial learning deficits.

In parallel, tonic H1R activation in hippocampal area CA1 regulates D-serine release through the astrocyte-neuron network, amplifying N-methyl-D-aspartate receptor (NMDAR)-mediated excitatory postsynaptic currents (EPSCs). The H1R antagonist pyrilamine (0.1 μM) reduces NMDAR-EPSC amplitude by 29% and weakens LTP induced by high-frequency stimulation; exogenous D-serine fully offsets this inhibition, indicating that H1R supports the consolidation of synaptic plasticity through the D-serine-NMDAR axis [52]. The two pathways are complementary. H3R antagonism raises global histamine release and thereby creates the conditions for improved plasticity, whereas H1R tunes synaptic efficacy locally by modulating NMDAR function. This "H1R-H3R complementary intervention" framework offers a multi-target, plasticity-centered strategy for the cognitive symptoms of ASD.

2.2.3 Regulation of Emotional Circuits and Anxiety Homeostasis by H3R

Individuals with ASD frequently present with anxiety and other affective disturbances, which have been linked to disrupted excitation-inhibition (E/I) balance within amygdala circuitry [53,54]. The histaminergic system exerts H3R-dependent "gating" over this circuit. Histamine activates H3 heteroreceptors on glutamatergic presynaptic terminals, particularly VGLUT1/VGLUT2-positive terminals, and selectively suppresses excitatory input from the basolateral amygdala to the central lateral amygdala (CeL) [55]. The effect is input-specific: it reduces glutamatergic transmission onto both pro-anxiety somatostatin $(SOM)^+$

and anti-anxiety PKC-δ^+ neurons of the CeL, seen as decreased miniature excitatory postsynaptic current (mEPSC) frequency and increased paired-pulse facilitation, without affecting inhibitory (GABAergic) transmission or intrinsic neuronal excitability [55].

The CeL is a core hub for fear and anxiety processing, and the balance of activity between its PKC-δ^+ and SOM$^+$ populations is critical for emotional homeostasis [56,57]. By gating excitatory input, H3R shifts the E/I ratio of the CeL microcircuit, such that activation of the histaminergic-H3R pathway favors attenuation of anxiety and fear responses. Optogenetic activation of the TMN-CeL projection reproduces the inhibitory effect of exogenous histamine, and this effect is blocked by H3R antagonists [55]. Given the frequency of affective disturbance and E/I imbalance in ASD [53,54], the actions of H3R within the CeL, namely selective inhibition of excitatory input, modulation of defined neuronal subpopulations, and restoration of E/I balance, identify selective H3R modulators as a plausible route to targeted anxiolytic treatment with a limited side-effect burden.

2.2.4 Modulation of Neuroimmune Interactions and Microglial Homeostasis by H4R

The histamine H4R has emerged as a mediator of neuroimmune interaction, extending the histaminergic role beyond neurotransmission into immune regulation. In addition to its well-established expression on peripheral immune cells, including mast cells, eosinophils, and dendritic cells, recent studies have demonstrated H4R expression on activated microglia within the CNS [27,58]. In non-ASD neuroinflammatory models, H4R activation has been reported to promote a pro-inflammatory microglial phenotype by engaging downstream NF-κB and MAPK signaling and enhancing the release of cytokines such as IL-1β, IL-6, and TNF-α [28,59]. Conversely, pharmacological blockade of H4R limits microglial overactivation and attenuates these responses [60]. However, evidence from other experimental settings, such as ALS, cerebral ischemia, and LPS-induced inflammation, indicates that H4R activation can negatively regulate NF-κB and MAPK (p38/ERK1/2) signaling and suppress the release of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-12 [58,61]. Collectively, these findings support a context-dependent functional role of H4R in regulating microglial activation and cytokine production in non-ASD neuroinflammatory models. It should be noted that these studies do not establish a dual pro- and anti-inflammatory role of H4R in ASD.

Because chronic neuroinflammation with sustained microglial activation is documented in a subset of individuals with ASD, the H4R pathway represents a promising but underexplored therapeutic target. Direct clinical evidence in ASD is lacking, and conclusions from PD and other neuroinflammatory models should be extrapolated cautiously. In the gamma-irradiated BTBR mouse model of autism, the selective H4R antagonist JNJ7777120 reduced immune abnormalities by modulating RORγt and T-bet signaling and altered the balance of pro- and anti-inflammatory cytokines, providing ASD-relevant preclinical support for H4R antagonism [62]. Although these findings suggest that H4R blockade may ameliorate neuroimmune dysfunction in ASD, they do not directly demonstrate restoration of microglial homeostasis. Whether H4R manipulation can modify ASD-associated behaviors or core disease mechanisms remains to be established in ASD-specific preclinical models and clinical studies.

The apparent pharmacological dichotomy between the neuroprotective and pro-cognitive effects of H1R/H2R activation and the clinical evaluation of H1R/H2R antagonists (e.g., famotidine, pyrilamine) probably reflects non-linear signaling dynamics and circuit-level modulation rather than a genuine mechanistic contradiction. Three factors are relevant. (i) Dose-dependent bidirectionality: histaminergic signaling frequently follows inverted U-shaped dose-response relationships [63]. Receptor activation and receptor blockade may therefore restore homeostasis under different conditions, depending on baseline histamine tone and arousal state within a given ASD subpopulation. (ii) Cross-transmitter modulation: the efficacy of certain antagonists may extend beyond direct receptor blockade to engage network-level feedback. Presynaptic H3 heteroreceptors tonically inhibit the release of dopamine and acetylcholine [21,25]; modulating these receptors, or activating histaminergic circuits more broadly, facilitates transmitter release and may compensate for downstream deficits. (iii) Developmental specificity: histamine serves distinct functions across ontogeny. During neurodevelopment it acts through H1R and H2R to drive neural stem cell proliferation and circuit maturation [64]. In mature circuits the physiological priority shifts toward preventing excitotoxicity and stabilizing network activity, so that dampening receptor sensitivity or reducing excessive histamine tone becomes advantageous. Resolving the apparent paradox of receptor activation versus blockade will require these receptor-specific mechanisms to be delineated within defined ASD endophenotypes and developmental stages.

3. Molecular Changes of the Histamine Signaling System in ASD

3.1 Transcriptional Remodeling in the Dorsolateral Prefrontal Cortex

The dorsolateral prefrontal cortex (dlPFC) is a key node in the neural circuits supporting executive function and working memory, and its functional integrity is associated with cognitive performance [65,66]. Recent studies indicate that histamine signaling in the dlPFC of individuals with ASD undergoes systematic, multi-level molecular remodeling, an important molecular feature that may correlate with disease pathogenesis.

Transcriptome analysis of postmortem brain tissue reveals significant dysregulation of histamine signaling gene expression in the dlPFC of individuals with ASD [15]. Although individual histaminergic genes did not reach statistical significance following multiple testing correction, gene set enrichment analysis demonstrated that the collective expression of core histamine signaling genes—*HNMT* (histamine N-methyltransferase), *HRH1*, *HRH2*, and *HRH3*—is significantly altered as a functional network. This system-level perturbation was successfully replicated in an independent postmortem cohort, pointing toward detectable alterations to the histaminergic pathway in the prefrontal cortex of individuals with ASD. Comparable perturbations of histaminergic pathway genes have been reported in patients with TS [67], suggesting that disturbed histamine metabolism may be a shared molecular feature of neurodevelopmental disorders. Transcript levels of the presynaptic autoreceptor H3R (*HRH3*) differ significantly between groups, but the direction of change fluctuates across datasets, suggesting that its regulatory network may be subtype-specific or environmentally dependent [15]. This bidirectionality may reflect functional heterogeneity among *HRH3* splice variants: the short variant acts as an autoreceptor regulating histamine release, whereas the long variant is thought to act through cross-transmitter regulation. An imbalance between the two could further aggravate circuit dysfunction in ASD.

To characterize change across the system as a whole, these investigators combined *HNMT*, *HRH1*, *HRH2*, and *HRH3* into a functional gene set for gene set enrichment analysis. In the ASD group this set deviated from the typical expression pattern, showing both coordinated upregulation and opposing changes between individual genes [15]. This "directionally discordant yet systemically coherent" transcriptomic signature was replicated in an independent cohort of 47 subjects, comprising 28 healthy controls and 19 individuals with ASD, indicating coordinated remodeling of the histaminergic network rather than isolated single-gene dysregulation. This molecular heterogeneity parallels the pronounced clinical diversity of ASD. These transcriptional perturbations have also been linked to markers of neuroinflammation, pointing to possible pathophysiological crosstalk, although the causal direction remains to be established. Consistent with this framework, individuals carrying the same histaminergic gene variant may show symptoms ranging from social withdrawal to stereotyped behavior [67], offering clues to the molecular basis of phenotypic heterogeneity in ASD.

Two mechanisms may link these molecular perturbations to the neuroinflammation and behavioral abnormalities described above. First, H3R imbalance may disturb the equilibrium between histamine and other transmitters, including glutamate, dopamine, and GABA. H3R antagonists would normally promote histamine and glutamate release, but disordered Hrh3 expression may instead drive excessive NMDAR activation, aggravating circuit E/I imbalance and promoting ASD-related symptoms such as stereotyped behavior [39,68]. Second, aberrant expression of the histamine-related gene set in the ASD dlPFC also correlates with neuroinflammatory markers such as microglial activation [15,69,70], suggesting that the histaminergic system contributes to immune dysregulation in ASD through its control of microglial function, and refining the "immune-neural" interaction framework.

Cross-species work supports the functional importance of histamine signaling in ASD. In VPA-induced models, histamine receptor antagonists reverse both synaptic plasticity deficits and social impairment [40]; and the overlap in histaminergic gene copy number variation between TS and ASD suggests that targeting this system could provide a shared therapeutic strategy across neurodevelopmental disorders [67]. In summary, molecular remodeling of histamine signaling in the dlPFC links immune dysregulation, synaptic dysfunction, and clinical phenotype, and may therefore be involved in the pathological processes underlying ASD.

3.2 Histaminergic Regulation of Neurogenesis and Neurodevelopment

Beyond its established roles in synaptic plasticity and neuroimmune modulation, histaminergic signaling regulates adult neurogenesis, the disruption of which is increasingly implicated in ASD [35,71]. Histamine acts at multiple stages of nervous system development across the lifespan, including neurogenesis, gliogenesis, neuronal maturation, and circuit integration [64]. Because histaminergic signaling shapes the neural stem cell (NSC) niche as well as mature networks, dysregulation during critical developmental windows could alter neurodevelopmental trajectories and contribute to ASD pathogenesis.

At the molecular level, H3R antagonism promotes neurogenesis through several convergent pathways. H3R blockade upregulates brain-derived neurotrophic factor (BDNF) through the cAMP/PKA/CREB cascade, which is essential for neuronal survival and hippocampal neurogenesis [46]. In aged mice, the H3R antagonist S 38093 enhances hippocampal neurogenesis and raises transcript levels of *Bdnf-IX*, *Bdnf-IV*, and *Bdnf-I*, together with improved contextual discrimination [72]. H3R antagonism also modulates the Akt/GSK-3β/β-catenin axis, a cascade that governs NSC proliferation and neuronal differentiation [73]. Histamine also promotes neuronal differentiation of NSCs through H1R-dependent signaling: its concentration peaks during periods of active neurogenesis, and selective H1R activation *in vitro* increases neuronal lineage commitment [74].

These molecular findings are supported *in vivo*. In the rodent subventricular zone, one of the two principal adult neurogenic niches, histamine drives NSC proliferation and neuronal differentiation through coordinated H1R and H2R

activation [74,75]. Consistent with this, H3R antagonists rescue hippocampal neurogenesis in lipopolysaccharide-induced models of neuroinflammation: H3R blockade suppresses microglial overactivation and pro-inflammatory cytokine secretion, restores hippocampal BDNF, and promotes the generation of newborn neurons, thereby reversing inflammation-associated cognitive impairment [46]. These findings are relevant to ASD, because chronic low-grade neuroinflammation, documented in a subset of patients, impairs both developmental and adult neurogenesis [35]. Given the links between aberrant neurodevelopment, impaired adult neurogenesis, and ASD, the combined anti-inflammatory and pro-neurogenic actions of histaminergic interventions provide a coherent mechanistic framework for ASD pathophysiology [64,71].

3.3 Glial Cell Activation and Histamine Receptor Modulation

Independently of glial activation by pro-inflammatory stimuli, histamine receptors are constitutively expressed on glial cells and shape their functional phenotype. Microglia, the resident immune cells of the CNS, express all four histamine receptor subtypes (H1R–H4R), with particularly high membrane enrichment of H4R [76,77]. The high enrichment of H4R on microglia serves as a critical driver of pro-inflammatory polarization, as detailed in Section 2.2.4.

In astrocytes, H1R and H2R mediate intracellular calcium signaling, glycogen metabolism, and gliotransmitter release, which together modulate synaptic transmission and network excitability [78,79]. H3R also acts as a heteroreceptor on both microglia and astrocytes, and its pharmacological modulation suppresses excessive neuroinflammation while promoting a homeostatic glial phenotype [46]. Beyond receptor-mediated signaling, astrocytes set cerebral histamine tone through a dedicated clearance system that depends on organic cation transporters (OCTs), predominantly organic cation transporter 3 (OCT3), which mediates extracellular histamine uptake and subsequent intracellular degradation [80,81]. Because glial overactivation and neuroimmune dysfunction are implicated in ASD, these findings indicate that histamine receptor-targeted agents could regulate glial reactivity directly and mitigate neuroinflammation. This glia-dependent mechanism provides a further rationale for the therapeutic use of histaminergic modulators in ASD.

4. Association Between Histamine Receptors and Symptoms of ASD

4.1 Social Behavior Disorders

ASD is diagnosed primarily from developmental history and behavioral observation across social domains (nonverbal communication, social reciprocity, peer relationships) and non-social domains (restricted repetitive behavior, atypical sensory responses) [82]. Although the pathogenesis of ASD remains incompletely understood, a growing literature links neurotransmitter dysfunction to social deficits, and the regulatory role of histamine receptors has become a particular focus.

Recent experimental work increasingly supports a role for histamine signaling in the regulation of social behavior. In preclinical ASD models, antagonism of H2, and H3 receptors produces significant effects on behavioral phenotypes that map onto core ASD symptoms such as social communication deficits. How far these findings translate into therapeutic efficacy in humans remains unclear, because controlled clinical trials targeting core symptoms are still few [15,83]. At the receptor-specific level, H2R antagonist famotidine is neuroprotective in MK-801-induced neurotoxicity models and may improve behavioral indices [84]. The evidence for famotidine is confined to preclinical neuroprotection and a small pilot single-subject study in selected pediatric populations; controlled clinical evidence against core ASD symptoms has not been established [85]. Accumulating evidence points to a capacity of H3R antagonists to ameliorate social deficits across distinct ASD models. In BTBR mice, ST713, an H3R antagonist that additionally targets dopamine D2/D3 receptors, reverses impaired sociability and repetitive self-grooming by suppressing the NF-κB pathway [42]. In the valproic acid-induced model, E100 restores social novelty preference in a dose-dependent manner, as shown by both the three-chamber test and the marble-burying assay [43]. DL77 attenuates MK-801-induced social withdrawal and stereotypic behavior [44,86], whereas ST-2223 enhances social approach behavior by modulating prefrontal cortical dopaminergic signaling [87].

The mechanism by which ST-2223 regulates social behavior may involve coordinated modulation of histamine and related transmitter systems. ST-2223 significantly increases cerebellar and striatal histamine in BTBR mice, which have lower baseline histamine than normal (B6 strain) controls, suggesting that restoration of endogenous histamine underlies the improvement in social behavior [87]. ST-2223 not only raises histamine but also promotes dopamine release in the prefrontal cortex and striatum by blocking H3R heteroreceptors, and increases acetylcholine in the prefrontal cortex and hippocampus [88]. Dopamine and acetylcholine are central to social cognitive processing and to the motivation for social interaction. By acting at heteroreceptors, H3R antagonism may therefore coordinate the release of several transmitters and so tune the network that governs social behavior.

Pharmacological reversal experiments confirm the central role of the histaminergic system in social regulation. Co-administration to BTBR mice of the brain-penetrant H3R agonist RAMH (R-α-methylhistamine) together with ST-2223 abolishes both the social improvement and the enhanced social novelty recognition produced by ST-2223 alone [87]. H3R therefore acts as a key regulatory node through which the histaminergic system influences social

behavior. H3R antagonists may improve social deficits in ASD by rebalancing histaminergic and other transmitter systems. In summary, histamine receptors contribute substantially to the regulation of social behavior, and H3R antagonists offer a plausible direction for treating social dysfunction in ASD through coordinated modulation of histamine and related transmitter release.

4.2 Repetitive Behaviors

Repetitive behaviors, including stereotyped motor patterns, tics, over-grooming, and obsessive thoughts and actions, are core symptoms of ASD, TS, and obsessive-compulsive disorder [89]. Recent evidence links histaminergic dysfunction to the pathophysiology of repetitive behavior, with central roles for H3R-mediated signaling and for histamine-dopamine interaction [16,68,90].

In TS research, *HDC* mutations are established as high-penetrance pathogenic variants [91,92]. *HDC* encodes histidine decarboxylase, the rate-limiting enzyme of histamine biosynthesis, and such mutations reduce or abolish histamine synthesis [10]. *Hdc* knockout (*Hdc*-KO) mice show TS-like repetitive behavior, including enhanced amphetamine-induced stereotypy and increased over-grooming after stress [93]. Striatal dopamine levels are markedly dysregulated in *Hdc*-KO mice, together with abnormally elevated phosphorylation of the activity marker ribosomal protein S6 [94], suggesting that histaminergic dysfunction promotes repetitive behavior by disrupting dopaminergic homeostasis and abnormally activating striatal circuits.

H3R has a distinct role in the regulation of repetitive behavior. It shows high constitutive activity, signaling continuously in the absence of an exogenous agonist [95]. In *Hdc*-KO mice, striatal H3R expression is upregulated, whereas H2R binding is reduced [96,97]. H3R agonists such as RAMH and immepip markedly enhance stereotyped behavior in *Hdc*-KO mice but not in wild-type mice, indicating that H3R activation promotes repetitive behavior specifically in a histamine-deficient context [97]. H3R agonist treatment also increases striatal DA in *Hdc*-KO but not wild-type mice, supporting the hypothesis that H3R regulates repetitive behavior through modulation of the dopaminergic system [96].

Chemogenetic experiments provide direct circuit-level evidence: selective activation of the cells targeted by RAMH (an H3R agonist) in the *Hdc*-KO mouse dorsal striatum is sufficient to induce stereotyped behavior, whereas inhibiting the same cells blocks RAMH-induced repetition [96]. Abnormal activation of H3R-positive cells in the dorsal striatum, acting through local circuits and regulation of DA levels, is therefore necessary for the expression of repetitive behavior.

Other work extends the role of the histaminergic system in repetitive behavior. Acute depletion of brain histamine with the irreversible HDC inhibitor α-fluoromethylhistidine increases the sequence complexity of exploratory behavior in the open field but does not affect grooming complexity [98], suggesting that histamine selectively regulates exploratory repetitive behavior. The D2/D3 receptor antagonist sulpiride partially reverses this abnormal complexity, further supporting a central role for histamine-dopamine interaction in the control of repetitive behavior [98].

The effects of H3R modulators on repetitive behavior are model-specific and dose-dependent. High-dose immethridine, an H3R agonist, increases stereotyped behavior in C57BL/6J mice, although this has been attributed to sedation. In BTBR T+ *Itpr3tf*/J autism model mice, H3R antagonism suppresses excessive motor activity in a novel environment but has no clear effect on repetitive behavior [41]. Taken together, these results indicate that histaminergic regulation of repetitive behavior depends on the pathology of the model, the dose used, and target specificity.

4.3 Neurodevelopmental Abnormalities

As a key CNS neuromodulator, histamine regulates nervous system development throughout the lifespan, with indispensable roles in neurogenesis, gliogenesis, neuronal and synaptic maturation, and circuit integration [35]. This regulation is spatiotemporally specific. Histamine is among the earliest neuromodulators to appear in the rodent brain, peaking prenatally on embryonic days 14–16 (E14–E16) [99]. This window coincides with the critical period of human substantia nigra synaptic development at 12–16 weeks of gestation [100], suggesting a role in the construction of embryonic neural circuits. The embryonic brain contains a transient histaminergic system of its own: histamine-immunopositive neurons are distributed widely across the rhombencephalon, mesencephalon, and diencephalon, and colocalize with serotonergic raphe neurons, thalamic projection neurons, and ependymal wall cells [101]. This broad distribution provides a structural basis for the regulation of early neurodevelopment. *In vitro*, NSCs functionally express three histamine receptor subtypes (H1R, H2R, and H3R) [102], suggesting that histamine may regulate early NSC fate directly through autocrine or paracrine signaling.

Histaminergic regulation of neurodevelopment extends from the embryonic period into adulthood and is stage-specific. During neurogenesis, H1R activation promotes differentiation of NSCs into neurons, whereas in the presence of basic fibroblast growth factor, H2R activation mainly enhances proliferation of cortical neuroepithelial cells [102,103]. This receptor-specific pattern raises the possibility of stage-selective intervention. During late differentiation, histamine contributes to morphological maturation, influencing dendritic and axonal growth, arborization, and synapse formation by regulating neurite number and length [75]. Recent work highlights an essential role of histamine in the formation of basal ganglia and cortical circuits [104]. The striatum, the principal input nucleus of

the basal ganglia and a core region for motor and cognitive control, expresses H1R, H2R, and H3R at high levels from the early postnatal period into adulthood [105,106], suggesting that receptor-mediated histamine signaling may regulate corticostriatal synaptic plasticity and thereby shape functional circuit maturation.

Neurodevelopmental disorders (NDDs), including ASD, intellectual disability, ADHD, and specific learning disorders, begin in early childhood and persist into adulthood, with a core pathology of abnormal formation of key neuronal circuits [107,108]. Neuroinflammation, a pathogenic factor common to NDDs, affects neurodevelopment directly and frequently co-occurs with neurodegenerative disease [109]. Within this network, histamine acts in two principal ways: (i) it modulates neuronal differentiation, synaptic plasticity, and circuit development directly through H1R, H2R, and H3R [110,111]; and (ii) its own homeostasis in the CNS is maintained by uptake into astrocytes and neurons through OCT3 and the plasma membrane monoamine transporter [112,113]. Astrocytes in turn support neurogenesis by maintaining neuronal survival, promoting migration, guiding axonal growth, and regulating synaptogenesis and circuit maturation [114]. The spatiotemporal distribution of histamine may therefore influence neurodevelopment through two complementary routes: direct regulation of neuronal function, and indirect modulation of developmental trajectories through astrocytes. Both may contribute to the onset and progression of NDDs.

The etiology of ASD, a prototypical NDD, is not fully understood, but synergy between neurotransmitter system dysfunction and neuroinflammation is widely considered central to its pathogenesis. Given the dual roles of histamine in neurodevelopment and in the regulation of neuroinflammation, its relationship to ASD pathology merits closer examination. Molecular evidence indicates increased expression of the *HNMT*, *HRH1*, *HRH2*, *HRH3* gene set in postmortem ASD brain tissue [15], and abnormal H3R expression has been linked to repetitive behavior in ASD [96]. Developmentally, histamine may shape circuit formation in ASD by directing the differentiation of embryonic NSCs into glutamatergic FOXP2-positive neurons [115]. FOXP2, a transcription factor governing development of the deep cortical layers [116], is linked to speech and language disorders, which are common comorbidities of ASD; histaminergic regulation of FOXP2 could therefore affect the maturation of language-related circuits. In summary, histamine may influence the onset and progression of ASD by modulating critical neurodevelopmental processes and by mediating interactions between neuroinflammatory pathways and neurotransmitter systems, and is therefore an attractive molecular target for further work on ASD pathophysiology (Fig. 3).

5. Therapeutic Agents Targeting the Histaminergic System in ASD

No targeted pharmacological therapy is currently approved for ASD. As key CNS signaling modulators, H1R, H2R, and H3R regulate neurodevelopment, synaptic plasticity, and neuroinflammation, which makes them promising candidates for therapeutic intervention (Table 2). In this section, each major claim is explicitly classified as supported by clinical evidence from human ASD studies or preclinical evidence from animal models.

5.1 H1R Antagonists: Clinical Evaluation of Sedative and Anxiolytic Agents

The clinical application of H1R antagonists in ASD has focused on the management of behavioral comorbidities rather than core symptoms. Niaprazine, a sedative H1R antagonist, was evaluated in an open-label study of patients with ASD (n = 25) with comorbid behavioral and sleep disorders (open-label study) [117]. Participants received 1 mg/kg daily for 60 days. On clinical efficacy assessment, 52% achieved a positive outcome, with improvement in hyperactivity, attentional instability, resistance to environmental change, and sleep disturbance. Efficacy was consistent across age subgroups (≥12 versus <12 years) and independent of comorbid epilepsy or neurological signs, although it was more pronounced in patients with mild-to-moderate intellectual disability. No serious adverse events were reported, supporting niaprazine as a candidate for the management of sleep and anxiety comorbidities in ASD.

In contrast to the sedative profile of niaprazine, cyproheptadine (an H1R antagonist with additional 5-HT2R antagonist activity) has shown efficacy against core ASD symptoms when given as an adjunct. In an 8-week, double-blind, placebo-controlled trial in children aged 3–11 years, the investigators compared cyproheptadine plus haloperidol with haloperidol monotherapy (double-blind RCT) [118]. The combination group received cyproheptadine (0.2 mg/kg/day) with haloperidol (0.05 mg/kg/day). On the Aberrant Behavior Checklist-Community and the Childhood Autism Rating Scale, combination therapy significantly outperformed monotherapy on total scores, particularly for interpersonal interaction and verbal communication, and also reduced stereotyped behavior. Extrapyramidal symptoms and overall adverse effects did not increase significantly compared with haloperidol alone, suggesting that adjunctive cyproheptadine improves core social deficits without adding to the safety burden of typical antipsychotics.

5.2 H2R Antagonists: From Clinical Repurposing to Cellular Mechanisms

5.2.1 Clinical Observations and Repurposing Hypotheses

The H2R antagonist famotidine has emerged as a candidate for repurposing in neuropsychiatric disorders. Open-label trials and case reports have documented ben-

Table 2. Summary of clinical and preclinical studies on histamine receptor antagonists in ASD and related models.

Agent	Target	Study type/model	Population/species & sample size	Intervention (dose & route)	Endpoints & symptoms targeted	Safety status
Cyproheptadine	H1R/5-HT2	RCT, Double-blind	40 children (3–11 y) with ASD, with 20 participants in each group	0.2 mg/kg/day (Oral) + Haloperidol	Core: Social interaction, verbal communication, stereotyped behaviors (ABC-C, CARS).	Comparable safety to monotherapy; no excess side effects
Niaprazine	H1R	Open-label study	25 ASD patients with behavioral/sleep disorders	1 mg/kg/day (Oral) for 60 days	Comorbidities: Sleep, hyperactivity, anxiety, aggression (52% efficacy).	Well-tolerated; no obvious side effects
Famotidine	H2R	Pilot single-subject research design, randomized, double-blind, placebo-controlled crossover study	9 ASD children	2 mg/kg/day orally in two divided doses, with a maximum total daily dose of 100 mg (Oral)	Core: Eye contact, repetitive behaviors, social communication. Behavioral improvement observed in only 4 of 9 children (44%); children with marked stereotyped behaviors did not respond.	Established pediatric safety profile
A-366	G9a and H3R	Animal study	BTBR mice (n = 5–7 male mice)	0.5, 1, and 2 mg/kg (i.p.)	Core: Social deficits, stereotyped behaviors, spatial working memory and social recognition. Comorbidities: reduced neuroinflammation.	Not reported
E100	H3R & AChE	Animal study	VPA mice (n = 5/group)	5, 10, and 15 mg/kg (i.p.)	Core: Social deficits, stereotyped behaviors. Comorbidities: reduced neuroinflammation.	Not reported
DL77	H3R	Animal study	VPA, LPS/VPA mice (n = 5/group)	10 or 15 mg/kg (i.p.)	Core: Social interaction, memory, Comorbidities: anticonvulsant & hyperactivity reduction.	Favorable safety window & PK profile
Pitolisant	H3R	Case report	A child with PWS comorbid with ASD	Oral, 4.5–36 mg/day	ABC-C (irritability, lethargy, hyperactivity)	Does not establish efficacy against core ASD symptoms
Pitolisant	H3R	Phase 3 trial (NCT06366464, ongoing)	PWS patients (not ASD-specific), n = 134, age ≥6 y	Oral QD; 1:1 Pitolisant/placebo; 77 d double-blind + 364 d open-label extension	Primary—EDS (PROMIS-SRI); Secondary—ABC-C irritability, CGI-S/ ESS-CHAD for EDS, hyperphagia (HQ-CT), ABC-C subdomains	Results pending; safety and efficacy not established
Ciproxifan	H3R	Animal study (multiple models)	BTBR/VPA/MK-801 models (n = 9–11/group)	3.0 mg/kg (i.p.)	Core: Social behavior (three-chamber test), repetitive behaviors (self-grooming); Comorbidities: anticonvulsant effects	Well-characterized PK

ASD, Autism spectrum disorder; RCT, Randomized controlled trial; ABC-C, Aberrant behavior checklist-community; CARS, Childhood autism rating scale; VPA, Valproic Acid; BTBR, BTBR T+ Itpr3tf/J; PK, Pharmacokinetics; PWS, Prader-willi syndrome; OCD, Obsessive-Compulsive Disorder; AChE, Acetylcholinesterase; QD, Quaque die; EDS, Excessive daytime sleepiness; PROMIS-SRI, Patient-Reported Outcomes Measurement Information System–Sleep-Related Impairment; CGI-S, Clinical Global Impression–Severity; ESS-CHAD, Epworth Sleepiness Scale for Children and Adolescents–Caregiver-reported version; HQ-CT, Hyperphagia Questionnaire for Clinical Trials. Clinical: Human studies (RCT, open-label, case reports); Preclinical: Animal models (BTBR, VPA, etc.) or *in vitro* studies.

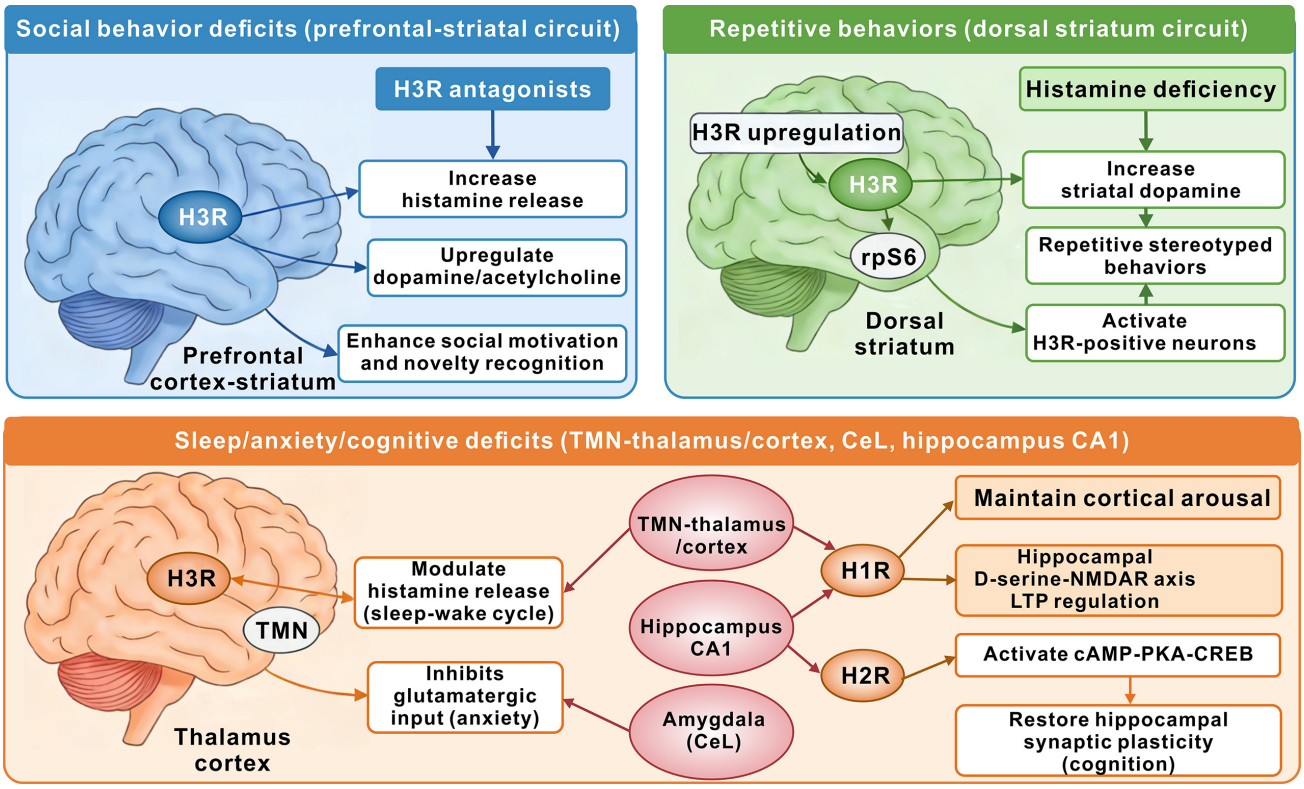


Fig. 3. Neural circuit mechanisms of the histaminergic system regulating ASD symptoms. The histaminergic system modulates ASD symptoms through distinct brain circuits and receptor-mediated mechanisms. (1) Social behavior deficits (prefrontal-striatal circuit): H3R antagonists increase histamine release, upregulate dopamine/acetylcholine levels in the prefrontal cortex and striatum, and enhance social motivation and social novelty recognition. (2) Repetitive behaviors (dorsal striatum circuit): Histamine deficiency leads to H3R upregulation in the dorsal striatum; H3R activation increases striatal dopamine levels and activates H3R-positive neurons, inducing stereotyped/repetitive behaviors. Inhibition of these neurons blocks repetitive behaviors. (3) Sleep/anxiety/cognitive deficits (TMN-thalamus/cortex, CeL, hippocampus CA1): H1R maintains cortical arousal and regulates hippocampal D-serine-NMDAR axis for LTP; H3R modulates TMN histamine release (sleep-wake cycle) and inhibits CeL glutamatergic input (anxiety); H2R activates cAMP-PKA-CREB to restore hippocampal synaptic plasticity (cognition). ASD, Autism spectrum disorder; rpS6, ribosomal protein S6; CeL, Central lateral amygdala; TMN, Tuberomammillary nucleus.

efit against the negative symptoms of schizophrenia, such as social withdrawal and emotional blunting (schizophrenia studies, not ASD-specific) [119,120]. On the basis of the phenotypic overlap between the negative symptoms of schizophrenia and the social deficits of ASD, famotidine was first proposed for use in ASD in 1997 [121]. Subsequent preliminary observations reported improved eye contact, reduced repetitive behavior, and enhanced social communication in children with ASD, including those without gastrointestinal comorbidity (a small pilot single-subject study involving nine children with ASD) [85]. These early observations motivated further clinical and mechanistic investigation.

5.2.2 Preclinical Mechanistic Insights

Recent *in vitro* work indicates that the neuroprotective effects of famotidine may extend beyond classical H2R antagonism. In human neuroblastoma SH-SY5Y cells, which lack histamine receptors, famotidine pretreatment blocked cell death induced by the NMDA receptor antagonist MK-801, a model of the excitotoxicity implicated in ASD and schizophrenia (human cell line, not ASD-specific) [84]. Famotidine inhibited MK-801-induced upregulation of GSK-3β activity and reversed the downregulation of β-catenin, acting through the Akt/GSK-3β/β-catenin pathway. Because this mechanism is independent of histamine receptor blockade, famotidine may promote synaptic plasticity and neuronal survival through direct molecular interactions, supporting its potential as a multi-target agent in ASD.

5.3 H3R Antagonists: Clinical Translation and Preclinical Validation

5.3.1 Clinical Translation: Pitolisant

Among H3R modulators, pitolisant is the most advanced lead compound and is already approved for narcolepsy. Owing to its optimal pharmacokinetic properties marked by high oral bioavailability and robust CNS per-

meability, it has been described in a single-case report in an adolescent with Prader-Willi syndrome (PWS) comorbid with ASD. Current evidence consists of case reports and compassionate release programs evaluating pitolisant for excessive daytime sleepiness and behavioral symptoms in pediatric patients with Prader-Willi syndrome, including those with comorbid ASD (PWS population, not ASD-specific) [122]. A Phase 3 randomized, double-blind, placebo-controlled trial (NCT06366464, planned n = 134, age ≥6 years) is currently ongoing, using a 1:1 randomization to pitolisant or matching placebo over a 77-day double-blind treatment period followed by an optional 364-day open-label extension, with excessive daytime sleepiness (PROMIS-SRI T-score) as the primary endpoint and behavioral symptoms (ABC-C, CGI-S, ESS-CHAD), hyperphagia (HQ-CT), and ABC-C subdomains as secondary endpoints. These data remain preliminary, however, and results have not yet been reported; therefore, its safety and efficacy in this population should not be presented as established, nor should they be read as evidence of clinical efficacy against core ASD symptoms.

5.3.2 Preclinical Evidence for Novel H3R Antagonists/Inverse Agonists

Unlike pitolisant and the H1/H2R agents discussed above, the evidence for emerging H3R candidates such as E100, DL77, and A-366, is confined to preclinical animal models. These compounds act primarily by blocking presynaptic H3 autoreceptors, thereby enhancing central histaminergic tone and reducing neuroinflammation. In the BTBR T+ *Itpr3tf*/J (BTBR) model of idiopathic autism and in the valproic acid (VPA)-induced model, H3R antagonists (DL77 and A-366) are robustly effective: a single systemic dose rapidly reverses social interaction deficits and reduces repetitive stereotyped behavior (ASD animal models (BTBR, VPA)) [39,43,123]. DL77 and A-366 additionally improved spatial working memory and social recognition [39,123]. The dual-activity molecule E100, which combines H3R antagonism with acetylcholinesterase inhibition, reduced the density of activated microglia and downregulated NF-κB, TNF-α, IL-1β, and IL-6 expression in VPA mice [43]. These benefits were abolished by co-administration of H3R agonists, confirming target engagement. The same compounds may also address comorbidity: DL77 and ciproxifan show anticonvulsant and antihyperactive effects of potential relevance to the epilepsy and ADHD-like symptoms that accompany ASD (seizure threshold and locomotion assays in rodents) [124,125].

6. Conclusion

The histaminergic system, through its combined neuroimmune functions and multi-receptor signaling, has become a focal point both for understanding the pathology of ASD and for developing new therapies. Abnormalities in its signaling pathways have been statistically associated with the chronic neuroinflammation, synaptic dysfunction, and circuit abnormalities seen in ASD. Preclinical studies in ASD models indicate that targeting histamine receptors, and H3R in particular, can attenuate neuroinflammation and improve behavioral phenotypes in animal models. H1R and H2R signaling have been shown to support synaptic plasticity and cognitive function in ASD models and general neurophysiology studies; H3R antagonists exert dual anti-inflammatory and neuroprotective effects by relieving autoreceptor-mediated inhibition of TMN histaminergic neurons and by acting on microglial heteroreceptor pathways; and H4R represents an emerging target for neuroimmune modulation based on non-ASD neuroinflammation models. Transcriptomic analyses have identified trend-level alterations in histaminergic gene expression (e.g., *HNMT* upregulation that did not survive multiple-testing correction, *HRH3* splice-variant associations) statistically associated with neuroinflammatory markers; however, causal relationships and downstream mechanistic links remain to be established. While challenges remain in translating these findings into approved therapies, the histaminergic system offers a promising avenue for the development of targeted interventions that address both the core symptoms and comorbidities of ASD. Future research should prioritize: (1) validation of transcriptomic findings in independent cohorts; (2) clarification of direct vs. indirect mechanisms of H3R antagonist effects; (3) characterization of H4R expression and function in the CNS; and (4) completion of ongoing clinical trials to determine therapeutic efficacy in human ASD populations.

Abbreviations

ASD, Autism spectrum disorder; CNS, Central nervous system; ADHD, Attention deficit hyperactivity disorder; HDC, Histidine decarboxylase; cAMP, Cyclic adenosine monophosphate; PKA, Protein kinase A; CREB, cAMP-responsive element-binding protein; GABA, γ-aminobutyric acid; TS, Tourette syndrome; IL-1β, Interleukin-1β; IL-6, Interleukin-6; IL-17, Interleukin-17; TNF-α, Tumor necrosis factor-α; NSC, neural stem cell; OCTs, Organic cation transporters; NDDs, Neurodevelopmental disorders; VPA, Valproic acid; NF-κB, Nuclear factor-κB; PI3K, Phosphoinositide 3-kinase; AKT, AKT serine/threonine kinase; GSK-3β, Glycogen synthase kinase-3β; EEG, Electroencephalogram; SWS, Slow-wave sleep; LTP, Long-term potentiation; NMDAR, N-methyl-D-aspartate receptor; CeL, central lateral amygdala; TMN, Tuberomammillary nucleus; EPSC, Excitatory postsynaptic current; E/I, Excitation/inhibition; BDNF, Brain-derived neurotrophic factor; dlPFC, dorsolateral prefrontal cortex; HNMT, Histamine N-methyltransferase; AChE, Acetylcholinesterase; RCT, Randomized controlled trial; ABC-C, Aberrant behavior checklist-community; CARS, Childhood autism rating scale; VPA, Valproic Acid; BTBR, BTBR T+ Itpr3tf/J; PK, Pharmacokinetics; PWS, Prader-

willi syndrome; OCD, Obsessive-Compulsive Disorder; QD, Quaque die; EDS, Excessive daytime sleepiness; PROMIS-SRI, Patient-Reported Outcomes Measurement Information System–Sleep-Related Impairment; CGI-S, Clinical Global Impression–Severity; ESS-CHAD, Epworth Sleepiness Scale for Children and Adolescents–Caregiver-reported version; HQ-CT, Hyperphagia Questionnaire for Clinical Trials.

Author Contributions

Conceptualization: QXZ; investigation: GJL and CYS; Writing-original draft and visualization: GJL CYS, WY, WJY, SYT, YZ and RXS; Funding acquisition: QXZ and SYT; Writing-review and editing: QXZ. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

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