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EDITORIAL

Perspective

Astrocytes as Histaminergic Gatekeepers of Anxiety: A New Pathway for Emotional Control

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The mammalian brain harbors a remarkable variety of neuromodulatory systems that continuously adapt behavior to environmental demands. The histaminergic system—originating from the tuberomammillary nucleus (TMN) of the hypothalamus—has long been recognized for its roles in arousal, attention and cognition. However, the contribution of the histaminergic system to anxiety has remained puzzling. Conventional wisdom is that anxiety is predominantly regulated by serotonergic neuromodulatory input provided by the dorsal and median raphe nuclei (Marcinkiewcz et al. 2016; Chin and Augustine 2025). But pharmacological and genetic manipulations of histamine signaling can also produce both anxiogenic and anxiolytic outcomes (Alhusaini et al. 2022). In a paper recently published in *Neuron* (Li et al. 2026), Li and colleagues have clarified the role of histamine by discovering that histamine released in the ventral CA1 (vCA1) region of the hippocampus suppresses anxiety-like behavior. Further, they show that histamine suppresses anxiety-like behavior by triggering a calcium-dependent release of GABA from astrocytes, rather than neurons. This discovery advances our understanding of how a classic neuromodulator operates and places astrocytes at the center of a dedicated anxiolytic mechanism.

Astrocytes release numerous signaling molecules and modulate synaptic transmission (Araque et al. 1999; Verkhratsky et al. 2016). However, the physiological relevance of these astrocytic pathways in behaving animals has been difficult to establish. Li et al. now provide a compelling case for the physiological relevance of gliotransmitter signaling by demonstrating that histamine engages a specific astrocyte population to control a specific behavior.

Using a newly developed, genetically encoded histamine sensor (HA1m) and fiber photometry, the authors first show that anxiogenic contexts (the center of an open field, the open arms of an elevated plus maze) evoke a brisk and region-selective increase in histamine release in the vCA1 that is directly linked to the emotional valence of the environment. By combining anterograde tracing, optogenetics, and cytosolic Ca^{2+} imaging, they further demonstrated that histaminergic terminals from the TMN directly innervate the vCA1 and that activation of these terminals is sufficient to produce anxiolysis.

The key twist—and the conceptual advance—lies in the cellular target of histamine. Selective knockdown of the vCA1 astrocytic H_3 histamine receptor (H_3R), but not the neuronal H_3R or astrocytic H_1R/H_2R, induced anxiety-like behavior. Conversely, selective activation of astrocytic H3R mimicked the anxiolytic effect. These astrocyte-dependent effects required intracellular Ca^{2+} signaling, because buffering astrocytic Ca^{2+} abolished the behavioral responses. Moreover, activation of astrocytic H3R led to extracellular release of the inhibitory transmitter, GABA, whereas the blockade of $GABA_A$ receptors abolished the anxiolytic effect of astrocytic H_3R activation. Thus, the signaling pathway is elegant and simple: histamine → astrocytic H_3R → astrocyte Ca^{2+} → astrocyte-dependent GABA release → $GABA_A$ receptor activation → reduced anxiety (Figure 1). GABA-ergic astrocytes are present throughout the brain; they accumulate with aging and accompany pathologies (Garaschuk and Verkhratsky 2019). Astrocytes emerge as key elements of inhibitory circuits in the brain that can release GABA to mediate tonic inhibition (Lee et al. 2010; Kwak et al. 2020) and serve as a Cl^- source to maintain synaptic inhibition (Untiet et al. 2023).

Abbreviations: ALDH1L1, aldehyde dehydrogenase 1 family member a1; BLA, basolateral amygdala; DAO, diamine oxidase; GABA, γ-aminobutyric acid; H_3R, H_3 histamine receptor; HA1m, genetically encoded histamine sensor; MAO-B, monoaminoxidase-B; TMN, tuberomammillary nucleus; vCA1, ventral CA1 region of the hippocampus.

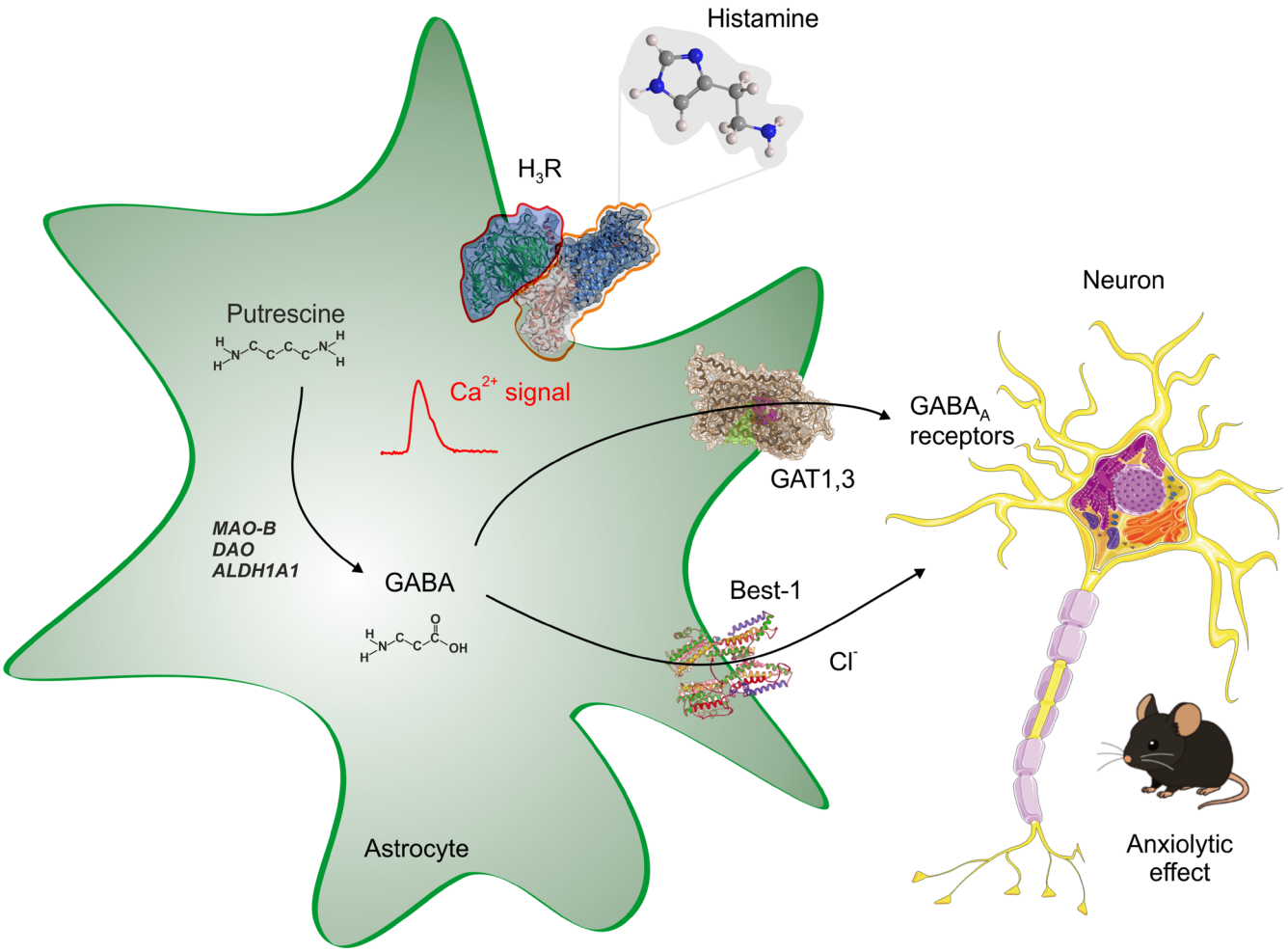

FIGURE 1 | Schematic of the TMN-vCA1-astrocytic H_3R anxiolytic pathway. Histaminergic neurons in the TMN project to the vCA1 region of the hippocampus. In response to anxiogenic conditions, histamine is released and acts on H_3Rs expressed on astrocytes. Activation of astrocytic H_3Rs elevates intracellular Ca^{2+}, triggering the release of GABA, which is produced in astrocytes from putrescine through monoacetylation of putrescine by monoaminoxidase-B (MAO-B) or by two-step putrescine conversion catalyzed by diamine oxidase (DAO) and the subsequent aldehyde dehydrogenase 1 family member a1 (ALDH1L1). Astrocyte-derived GABA activates $GABA_A$ receptors on local neurons, ultimately reducing anxiety-like behavior.

From a mechanistic perspective, several questions arise. How does histamine, acting on a G-protein–coupled receptor, evoke increases in Ca^{2+} in astrocytes? The canonical view is that Gi/o signaling acts via adenylyl cyclase, yet Li et al. clearly reported robust increases in Ca^{2+}. One possibility is that H_3Rs on astrocytes are coupled to other signaling pathways, perhaps through $\beta\gamma$ subunits or through transactivation of other receptors. Alternatively, Ca^{2+} signaling might be mediated by release from intracellular stores triggered by downstream messengers such as $InsP_3$. Resolving the precise molecular cascade is important for understanding how this pathway can be pharmacologically targeted. While astrocytic H_3R activation clearly triggers GABA release, the mechanism of GABA release is currently unclear. Potential mechanisms include reversal of GABA transporters, diffusion through Bestrophin-1 channels (Lee et al. 2010) or even vesicular exocytosis (Mederos and Perea 2019). Determining which of these pathways is engaged by histamine will provide important insight into the dynamics of gliotransmission in vivo.

One of the most striking findings of Li et al. (2026) is that chronic stress, a major risk factor for anxiety disorders, upregulates H_3R expression in vCA1 astrocytes. This upregulation is functionally relevant: enhancing astrocytic H_3R signaling—either by optogenetic activation or by astrocyte-specific H_3R overexpression—was sufficient to rescue the anxiety phenotype induced by chronic social defeat stress. These findings suggest that the astrocytic H_3R pathway is not merely a passive sensor but instead functions as an active homeostatic mechanism that is recruited to counter prolonged stress. In other words, the pathway appears to be part of an endogenous resilience mechanism.

The vCA1 is a well-established node in anxiety circuits, but histaminergic fibers innervate virtually the entire forebrain. Does the mechanism uncovered in vCA1 operate elsewhere? Are there other brain regions where astrocytic H_3Rs control emotional behavior, or is this a specialized function of the ventral hippocampus? Conversely, do other neuromodulators—serotonin, noradrenaline, and dopamine—engage analogous astrocyte-specific

pathways to regulate distinct behavioral states? Recent work has begun to reveal such astrocyte-mediated actions for serotonin and noradrenaline (Gonzalez-Arias et al. 2023; Reitman et al. 2023), suggesting that the principle may be general. If so, astrocytes could represent a common "final common pathway" through which diverse neuromodulators shape emotional behavior. The amygdala may provide a striking example of this principle, as we discuss below. Moreover, histamine may exert region-specific—perhaps even opposing—effects on emotional state, depending on which astrocyte population is recruited. After all, the vCA1 is but one node in a vast network of histamine-sensitive astrocytes. What happens when histamine meets astrocytes in the amygdala, the prefrontal cortex, the hypothalamus, or even the cerebellum? Could it be that, depending on the circuit context, the same neuromodulator can both calm and alarm?

Evidence for such region-specific astrocyte function is already emerging. In another recent study, Ghenissa and colleagues investigated the basolateral amygdala (BLA) and reported that astrocytes also encode anxiety but with the opposite valence (Ghenissa et al. 2026). In the BLA, noradrenaline acting on astrocytic α1 adrenergic receptors triggers cytosolic calcium signals that increase anxiety, and chemogenetic activation of BLA astrocytes recapitulates this anxiogenic effect (Ghenissa et al. 2026). Taken together, the Li et al. (2026) and Ghenissa et al. (2026) studies reveal a compelling convergence: In two distinct brain regions—the vCA1 and the BLA—astrocytes, not neurons, are the primary cellular substrate for anxiety encoding. However, the mechanisms differ, suggesting that astrocytes are not merely passive sensors but instead are highly specialized integrators that can bidirectionally shape emotional states depending on the neuromodulatory context. The hippocampus and amygdala may thus represent two poles of astrocyte-mediated valence control: one that calms and one that alarms.

Li and colleagues have discovered a new principle in neuromodulation: a histaminergic circuit that controls anxiety not by directly influencing neurons but by recruiting astrocytes to release GABA (Figure 1). This work adds to a growing body of evidence that astrocytes are integral components of brain circuits and are capable of sensing and responding to specific neuromodulators to shape behavior in a pathway-specific manner. The TMN-vCA1-astrocytic H_3R axis represents a clear entry point for the development of novel anxiolytics that work through mechanisms distinct from those of current serotonin-based therapies. As we move toward a more comprehensive understanding of astrocyte-neuron interactions, it is likely that other such dedicated "gliotransmitter" pathways will be uncovered, each tuned to a specific neuromodulator and a specific behavioral function.

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George J. Augustine: conceptualization, writing – original draft, writing – review and editing. **Alexei Verkhratsky:** conceptualization, writing – original draft, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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