

THE GUT MICROBIOTA–HISTIDINE–UROCANATE AXIS AND COGNITION: MECHANISTIC CONVERGENCE ACROSS PRECLINICAL AND CLINICAL EVIDENCE

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SUMMARY

Histidine and its non-histaminergic downstream metabolite trans-urocanic acid (trans-urocanate, UCA) have been implicated in a broad spectrum of neurological phenotypes, ranging from hippocampus-dependent learning and memory in rodents to fatigue, mood regulation, and neurodevelopmental outcomes in humans. The studies describe four distinct exposure categories: (i) dietary or supplemental histidine or UCA, (ii) histidinaemia resulting from histidine ammonia-lyase (HAL; histidase) deficiency, (iii) exogenous administration of UCA, and (iv) endogenous UCA derived from host or gut microbial histidine catabolism. Recent evidence demonstrates that infant gut microbiota composition, microbial histidine ammonia-lyase (HutH) activity, and host histidine-UCA metabolite profiles are associated with cognitive performance, thereby repositioning microbially derived UCA - rather than histidine or histamine - as a potential mechanistic contributor to the microbiota-gut-brain axis. In parallel, experimental studies indicate that systemic UCA crosses the blood-brain barrier (BBB), accumulates in brain regions involved in memory processing, and modulates synaptic plasticity through urocanase (UROC1)-dependent conversion to glutamate, as well as via non-glutamatergic mechanisms including GABA-A receptor modulation, oxidative stress pathways, and cGAS-STING-associated cellular senescence. This review synthesizes preclinical and clinical evidence along the histidine ammonia-lyase → UCA → BBB transport → hippocampus → memory axis and critically evaluates the strength of evidence supporting causal roles for histidine, UCA, or both in cognitive function. Histaminergic and histidine decarboxylase-dependent pathways are intentionally excluded, as they represent a distinct branch of histidine metabolism previously reviewed elsewhere.

INTRODUCTION

L-histidine is an essential amino acid whose neurobiology has traditionally been dominated by its role as the precursor of histamine via histidine decarboxylase (HDC) (*Holeček, 2020a*). However, histidine is also catabolized

through a quantitatively major alternative pathway initiated by HAL (EC 4.3.1.3), which deaminates histidine to UCA. UCA is subsequently metabolized by UROC1 to generate downstream intermediates including gluta-

mate and formiminoglutamate, linking histidine metabolism to central carbon and folate-dependent one-carbon pathways. Loss-of-function mutations in HAL cause histidinaemia, one of the most frequently identified inborn errors of amino acid metabolism in newborn screening programs (*Widhalm and Virmani, 1994; Rojas et al., 2013*). Whether histidinaemia is associated with clinically meaningful neurological impairment has remained unresolved for decades (*Widhalm and Virmani, 1994; Coulombe et al., 1983; Rosenmann et al., 1983*), and this uncertainty has shaped longstanding debate regarding the physiological relevance of the HAL-UCA pathway in human cognition.

Historically, interest in UCA as a biologically active metabolite was largely confined to dermatology and photoimmunology. This view changed following experimental evidence that moderate UV exposure increases systemic UCA levels, enabling its passage across BBB and its participation in a previously unrecognized neuronal metabolic route leading to glutamate synthesis. In rodents, UV-induced enhancement of rotarod performance and object recognition memory is reproduced by systemic administration of UCA and abolished by inhibition or knockdown of neuronal UROC1, indicating a mechanistic dependence on UCA metabolism within the brain (*Zhu et al., 2018*). Consistently, subsequent pharmacological studies demonstrated that systemic UCA enhances acquisition, consolidation, and reconsolidation of object recognition and object location memory, as well as spatial working memory in behavioural paradigms such as the Y-maze (*Yu et al., 2021; Yu et al., 2022; Wang et al., 2023*).

More recently, the mechanistic framework has been extended by micro-

biome-focused evidence. Cerdó and colleagues integrated infant cohort data, metaproteomics of gut microbiota, targeted metabolomics, and faecal microbiota transplantation (FMT) into germ-free mice to demonstrate that gut microbial histidine ammonia-lyase (HutH) activity and host histidine-UCA metabolite profiles are associated with cognitive performance, and that memory-related phenotypes are transferable via microbiota (*Cerdó et al., 2023*). This study provides the first *in vivo* human-linked evidence implicating bacterial histidine catabolism in cognitive outcomes and reframes earlier observations by positioning microbially derived UCA as a potential mechanistic intermediary linking gut microbial function to brain physiology.

Against this background, the present review has three objectives. First, it synthesizes evidence for neurological effects of histidine and UCA across human and animal studies, while explicitly distinguishing among physiological dietary intake, pharmacological supplementation, histidinaemia, exogenous UCA administration, and endogenous microbially derived UCA-exposures that are frequently conflated in the literature. Second, it evaluates a mechanistic model in which HAL-derived or microbiota-derived UCA crosses BBB, accumulates in brain regions involved in memory processing, and modulates synaptic plasticity via both UROC1-dependent conversion to glutamate and non-glutamatergic mechanisms, including GABA-A receptor modulation, oxidative stress regulation, and cGAS-STING-mediated cellular senescence pathways. Third, it critically assesses the current evidence for causal roles of histidine, UCA, or both in cognitive function and identifies key experimental gaps required to resolve remaining uncertainty.

MATERIALS AND METHODS

Review design and data collection

This narrative systematic review was conducted in accordance with PRISMA 2020 guidelines, adapted to a heterogeneous evidence base spanning inborn errors of metabolism, pharmacological rodent studies, human dietary intervention trials, and microbiome-omics investigations. Literature identification, screening, and data extraction were performed by a single reviewer. A second independent reviewer assessed a random subset of included records to verify eligibility decisions and extraction accuracy. Discrepancies were resolved through consensus. Given the integrative and interpretive nature of the synthesis, no quantitative meta-analysis was pre-specified. Where relevant prior meta-analyses existed (e.g., histidine-containing dipeptides and cognition), their pooled effect estimates were incorporated into the qualitative synthesis (Bell et al., 2024).

Literature search strategy and data sources

Systematic searches were conducted using a federated academic search platform indexing PubMed/MEDLINE, Semantic Scholar, and OpenAlex databases. These searches were supplemented by targeted retrieval of the key reference study by Cerdó and colleagues and its accompanying editorial (Cerdó et al., 2023; Rabot, 2023).

Search strategies were designed to capture six semantically distinct domains, each queried independently and in combination:

1. Mechanistic studies of UCA in brain function, memory, and hippocampal physiology.
2. HAL biology, including genetic knockouts and enzymatic deficiency.
3. Histidinaemia and related inborn

errors of histidine metabolism with neurological outcomes.

4. Dietary or supplemental histidine interventions assessing cognition, fatigue, or mood.
5. Microbiome-brain axis studies linking histidine metabolism or UCA to neural outcomes.
6. BBB transport and CNS accessibility of UCA.

Free-text search terms combined MeSH-equivalent descriptors and metabolite synonyms, including “urocanic acid,” “urocanate,” “histidine ammonia-lyase,” “histidase,” “histidinaemia,” “urocanase,” and “UROC1.” Grey literature and supplementary records were identified through manual screening of reference lists from the study by Cerdó and colleagues (Cerdó et al. (2023) and two comprehensive reviews of histidine biology (Holeček, 2020a; Thalacker-Mercer and Gheller, 2020). The search included all records available up to July 2026. Bibliographic metadata and abstracts were retrieved for screening. Full texts were obtained for all shortlisted studies and were used for data extraction when studies contributed mechanistic, quantitative, or clinically relevant findings.

Eligibility criteria

Inclusion criteria

Studies were included if they were peer-reviewed original research articles or systematic reviews/meta-analyses and reported at least one neurological, cognitive, behavioural, electrophysiological, or neurodevelopmental outcome. Eligible studies involved one or more of the following exposures: Histidine administration or dietary manipulation; histidinaemia (human cohorts or animal models); trans- or cis-urocanic acid administration; manipulation of HAL, HutH, or UROC1; or microbiota-

derived histidine catabolism. Human studies of any age and all rodent strains were eligible. Germ-free, gnotobiotic, and FMT studies were prioritised for causal inference.

Exclusion criteria

Studies were excluded if their primary focus was histaminergic signalling, including histamine receptors (H1-H4) or HDC, unless required to distinguish histaminergic from non-histaminergic histidine effects. Studies on histidine-containing dipeptides (e.g., carnosine, anserine) were excluded unless supported by formal meta-analytic synthesis of cognitive outcomes (Bell et al., 2024). Purely photochemical or photoimmunological studies of urocanic acid without neurological endpoints were excluded. Case reports lacking neuropsychological or neurological outcome measures were also excluded.

Data extraction and synthesis

For each included study, the following variables were extracted: study population or experimental model, exposure type (compound, dose, route, duration), comparator condition, primary neurological outcome, reported effect sizes

with precision metrics where available, and mechanistic readouts (biochemical, electrophysiological, or histological). Given the substantial heterogeneity in dosing regimens (spanning three orders of magnitude), administration routes (oral, intraperitoneal, intravenous, and intracerebroventricular), and exposure durations, all interventions were standardised into compound-dose-route-duration frameworks to enable structured comparison across studies. Neurological outcomes were categorised *a priori* into learning, memory acquisition, memory consolidation, reconsolidation, long-term memory, spatial and non-spatial memory, hippocampal plasticity, locomotor activity, anxiety-related behaviour, mood and fatigue measures, and neurodevelopmental outcomes. Findings were synthesised narratively along the HAL or HutH→UCA→BBB transport→hippocampus→memory axis. Where inconsistencies between studies were identified, these were evaluated in relation to differences in exposure classification (histidine versus UCA versus histidinaemia), dosing, route of administration, and outcome measurement paradigms.

RESULTS

Characteristics of included studies

The synthesis included studies grouped into six partially overlapping domains:

- (i) pharmacological studies administering UCA in rodents and assessing recognition and spatial memory outcomes (Zhu et al., 2018; Yu et al., 2021; Yu et al., 2022; Wang et al., 2023);
- (ii) a mechanistic study of UCA in D-galactose-induced cognitive impairment identifying ZCCHC3 as a molecular target and implicating the cGAS–STING pathway (Hu et al., 2026);
- (iii) electrophysiological studies demonstrating UCA activity at ionotropic receptors, particularly GABA-A receptors (Uusi-Oukari et al., 2000);
- (iv) histidinaemia case reports, retrospective analyses, prospective screening cohorts, and dietary intervention follow-ups spanning several decades (Rosenmann et al., 1983; Coulombe et al., 1983; Ishikawa, 1987; Widhalm and Virmani, 1994; Suárez et al., 2017);

- (v) rodent models of experimentally induced histidinaemia via HAL inhibition or dietary histidine loading (Dutra-Filho et al., 1989; Tansini et al., 2004; Rojas et al., 2012; 2013); and
- (vi) human interventional and observational studies of histidine supplementation assessing cognition, fatigue, mood, or safety outcomes (Sasahara et al., 2015; Loy et al., 2019; Holeček, 2020a; Thalacker-Mercer and Gheller, 2020; Bell et al., 2024; Shimomasuda et al., 2026).

These datasets are complemented by microbiome-brain axis studies, particularly the work of Cerdó and colleagues (Cerdó et al., 2023; Rabot, 2023). Additional supporting evidence comes from studies associating microbial histidine metabolism with systemic metabolic phenotypes such as non-alcoholic fatty liver disease and glycaemic regulation (Quesada-Vázquez et al., 2023; Warmbrunn et al., 2024).

Human studies were generally small and heterogeneous. Histidinaemia investigations ranged from isolated case reports (Suárez et al., 2017) to the Austrian newborn screening cohort reported by Widhalm and Virmani (1994). They detected 124 children with histidinaemia in the Austrian Neonates Screening Program, receiving long-term follow-up. Fifty nine patients were treated with a histidine-restricted diet (35 mg/kg). The follow-up included determining biochemical parameters, physical examination and psychological assessment of 58 treated and 43 untreated patients which were followed longitudinally to school age. Adult supplementation trials included a crossover study involving 20 participants assessing repeated histidine administration (Sasahara et al., 2015) and a single-dose randomized trial in a comparable sample (Shimomasuda et al., 2026). A meta-analysis of histidine-

containing dipeptides integrated ten randomized controlled trials from an initial screening of 2,653 records (Bell et al., 2024).

Rodent studies were predominantly single-laboratory pharmacological experiments with group sizes of 8-20 animals. Behavioural paradigms included novel object recognition (NOR), object location recognition (OLR), Y-maze, radial arm maze, Morris water maze, elevated plus maze, and open-field testing. Interventions ranged from acute intraperitoneal UCA administration (10-30 mg/kg) (Wang et al., 2023), to chronic dietary histidine manipulation, to genetic or pharmacological modulation of UROC1 activity (Zhu et al., 2018). Across studies, outcome measures converged primarily on hippocampus-dependent learning and memory processes.

Neurological outcomes in animal models

UCA enhances hippocampus-dependent memory

Across independent studies, UCA consistently enhances hippocampus-dependent learning and memory. The most robust and reproducible finding is that systemic administration of UCA facilitates both recognition and spatial memory.

Zhu and colleagues established the primary mechanistic framework by demonstrating that moderate UV exposure increases circulating UCA levels, that UCA crosses BBB, and that neuronal UROC1-dependent metabolism of UCA to glutamate in hippocampus and motor cortex contributes to improved rotarod performance and enhanced object recognition memory (Zhu et al., 2018). These effects were reproduced by intravenous UCA administration and abolished by UROC1 inhibition or neuronal knockdown, supporting a causal

role for UCA metabolism in cognitive enhancement.

Subsequent pharmacological studies confirmed and extended these findings. Intraperitoneal administration of UCA facilitated acquisition of NOR and OLR memory at 10 mg/kg, while a higher dose (30 mg/kg) selectively enhanced long-term memory in NOR, indicating a dose-dependent dissociation between short- and long-term memory processes (Wang et al., 2023). In addition, UCA modulated both memory consolidation and reconsolidation when administered within defined post-training or post-reactivation windows, but not when delivered outside the consolidation period, indicating temporal specificity of action (Yu et al., 2021). UCA also improved spatial working memory in the Y-maze and spatial recognition performance in OLR paradigms (Yu et al., 2022). Importantly, these cognitive effects occurred without significant alterations in locomotor activity or exploratory behaviour, indicating that they are not attributable to nonspecific changes in arousal or motor function (Wang et al., 2023; Yu et al., 2021). Network-based analyses further implicated MAPK, NF- κ B, insulin signalling, and serotonergic synapse pathways as potential downstream mediators of UCA-induced cognitive effects (Yu et al., 2022).

UCA acts through multiple molecular mechanisms

Beyond its role as a metabolic intermediate in the UCA-to-glutamate pathway, UCA engages additional molecular targets. Uusi-Oukari and colleagues demonstrated that UCA acts as a stereoselective modulator of GABA-A receptors in *Xenopus* oocytes expressing recombinant $\alpha 1\beta 1\gamma 2S$ subunits, with efficacy enhanced under acidic conditions, whereas cis-UCA lacked activity (Uusi-Oukari et al., 2000). Although the

physiological relevance of this mechanism under physiological brain pH remains uncertain, the findings indicate that UCA can directly modulate inhibitory neurotransmission. Hu and colleagues further showed that UCA ameliorates cognitive impairment in D-galactose-induced aging models by binding ZCCHC3 and suppressing cGAS–STING signalling, resulting in reduced astrocytic senescence, apoptosis, and inflammatory cytokine release. Genetic or pharmacological activation of the pathway abolished the cognitive benefits of UCA, supporting a causal mechanistic role (Hu et al., 2026). These findings suggest that UCA may influence cognition through both metabolic conversion to glutamate and direct regulation of inflammatory and senescence-associated pathways. Collectively, these mechanisms are not mutually exclusive and may represent parallel or context-dependent pathways downstream of systemic UCA availability.

Histidine effects in rodents: mixed and pathway-dependent

Systemic histidine administration produces heterogeneous behavioural outcomes that often reflect downstream histaminergic signalling rather than direct histidine action. Song and colleagues reported that histidine administration improved cognitive performance in a chronic cerebral hypoperfusion model, accompanied by increased neurogenesis, improved microvascular perfusion, and upregulation of the tight junction protein zonula occludens-1, suggesting partial restoration of BBB integrity (Song et al., 2018). In contrast, several studies show that histidine-induced improvements in pharmacologically impaired cognition (e.g., scopolamine-, 5-HT_{1A} agonist-, or N-methyl-D-aspartate (NMDA) antagonist-induced deficits) are abolished by HDC inhibition or H₁ receptor antagonism,

indicating that these effects are mediated primarily through histamine signalling rather than histidine per se (Miya-zaki et al., 1995a; 1995b; Isayama et al., 2001). Dietary histidine depletion in rodents reduces brain histamine levels and produces paradoxical behavioural effects, including enhanced performance in some spatial learning tasks alongside increased susceptibility to NMDA antagonist-induced deficits (Nishiga et al., 2002). These findings underscore the necessity of distinguishing histidine metabolism from histaminergic neurotransmission when interpreting behavioural outcomes. Although outside the primary scope of this review, these data are relevant for interpretation because behavioural effects attributed to histidine frequently depend on whether histidine is acting as a precursor for histamine, a substrate for alternative catabolic pathways, or a metabolic perturbation of amino acid homeostasis.

Rodent histidinemia models and systemic effects

Experimental histidinaemia, induced by combined histidine administration and histidine ammonia-lyase inhibition, reduces locomotor activity but does not consistently produce robust cognitive impairment in adult rodents (Dutra-Filho et al., 1989). Developmental exposure, however, yields more pronounced effects. Maternal histidine loading during gestation and lactation induces oxidative stress in offspring hippocampus and cortex, with partial normalization during postnatal maturation (Rojas et al., 2012). It also disrupts energy metabolism, including alterations in pyruvate kinase and creatine kinase activity and dysregulation of adenylate kinase systems (Rojas et al., 2013). *In vitro* studies indicate that histidine induces oxidative stress only at supraphysiological concentrations,

whereas imidazolelactic acid exhibits dose-dependent antioxidant properties (Tansini et al., 2004). Collectively, these findings suggest that the neurological consequences of histidinaemia are modest in adulthood but may depend on developmental timing, metabolic context, and redox balance.

Consensus and divergence across studies

Across multiple independent rodent studies, UCA emerges as a consistent positive modulator of hippocampus-dependent learning and memory across acquisition, consolidation, and reconsolidation phases (Zhu et al., 2018; Yu et al., 2021; Yu et al., 2022; Wang et al., 2023). However, two main sources of heterogeneity are evident. First, a dose-dependent effect. Lower doses of UCA (10 mg/kg) enhance both short- and long-term memory, whereas higher doses (30 mg/kg) preferentially affect long-term memory, suggesting non-linear dose-response dynamics (Wang et al., 2023). Second, cognitive effects vary depending on behavioural paradigm, timing of administration, and whether outcomes reflect acquisition, consolidation, or reconsolidation processes. Overall, the convergence of behavioural, pharmacological, and molecular evidence supports a robust cognitive effect of UCA in rodents, while also indicating complex dose- and context-dependent modulation.

Neurological outcomes in humans

Histidinaemia exhibits a substantially milder and more heterogeneous neurological phenotype than early case reports suggested

In a retrospective analysis of 43 probands and 26 siblings, Rosenmann and colleagues reported that 79% of probands and approximately 50% of siblings exhibited a “disadaptive” central nervous system phenotype, including

intellectual disability, speech impairment, seizures, behavioural abnormalities, and learning difficulties, with a modal IQ of ~70. Importantly, no correlation was observed between blood histidine concentration and severity of neurological presentation (Rosenmann et al., 1983). The same authors estimated that clinically reported cases with neurological involvement represent approximately 1% of all individuals with histidinaemia, indicating substantial ascertainment bias in the historical case literature. Prospective cohort data contrast sharply with these early reports. In the study by Coulombe and colleagues, 21 individuals identified through newborn screening (including probands and siblings) demonstrated normal cognitive development, including full-scale, verbal, and performance IQ, as well as intact visual-motor integration and school achievement. Outlier values were not associated with the degree of histidinaemia, leading the authors to conclude that histidinaemia identified through population screening is largely a non-disadaptive condition (Coulombe et al., 1983). Longitudinal data from the Austrian newborn screening cohort (Widhalm and Virmani, 1994; n = 124) further support this interpretation. Although dietary histidine restriction reduced plasma histidine concentrations, treated children (aged 4 and 6 years) exhibited significantly lower IQ scores than untreated peers ($p < 0.05$), and clinical symptoms - when present - were similarly distributed between groups. The authors concluded that dietary histidine restriction does not confer cognitive benefit in histidinaemia (Widhalm and Virmani, 1994). Additional reports from Japanese longitudinal cohorts describe a subset of individuals with histidinaemia exhibiting autistic traits, language impairment, reduced visual-motor performance, and abnormal electroencephalographic findings

(Ishikawa, 1987). Case reports of atypical histidinaemia continue to describe motor, cognitive, and academic impairments (Suárez et al., 2017). However, these studies are strongly influenced by selection bias and are not representative of population-level outcomes.

Collectively, the human literature supports four converging conclusions:

- (i) histidinaemia is biochemically common but clinically mild in most individuals
- (ii) a minority of individuals exhibit neurological symptoms
- (iii) symptom severity does not correlate with circulating histidine levels
- (iv) dietary histidine restriction does not improve and may worsen cognitive outcomes (Widhalm and Virmani, 1994; Rosenmann et al., 1983; Coulombe et al., 1983).

This pattern is difficult to reconcile with a model in which histidine itself is directly neurotoxic. It is more consistent with a model in which flux through HAL and downstream metabolites - particularly UCA - may be more relevant to neurological outcomes than absolute histidine concentration.

Dietary and supplemental histidine effects in humans

Controlled trials indicate that histidine supplementation at physiological to moderate pharmacological doses influences fatigue, mood, and select cognitive domains. In a placebo-controlled, double-blind crossover trial involving 20 adults with elevated fatigue and sleep disruption scores, daily histidine supplementation over two weeks significantly reduced Profile of Mood States fatigue T-scores, improved working memory reaction times, and increased subjective ratings of attentiveness and clear thinking (all $p < 0.05$) (Sasahara et al., 2015). A subsequent randomized controlled trial using a single-dose design reported

no significant effects in the overall cohort. However, prespecified subgroup analyses showed that individuals with high baseline fatigue experienced reductions in fatigue-inertia, confusion-bewilderment, and depression-dejection, alongside increased vigor-activity ($p = 0.022$ - 0.049) (Shimomasuda et al., 2026). A systematic review and meta-analysis of ten randomized controlled trials evaluating histidine-containing dipeptides (primarily carnosine) reported improvements in delayed recall on the Wechsler Memory Scale (weighted mean difference 1.5; 95% CI 0.6-2.5; $p < 0.01$), while showing no significant effects on global cognitive measures such as Alzheimer's Disease Assessment Scale-Cognitive Subscale, Mini-Mental State Examination, or immediate recall indices (Bell et al., 2024). Cross-sectional evidence further indicates that serum histidine levels are lower in women with multiple sclerosis who report higher fatigue compared with those reporting lower fatigue (64.57 vs. 70.48 nmol/mL; $p = 0.048$; Hedges' $g = 0.75$), independent of depressive symptoms (Loy et al., 2019).

Safety, dose dependence, and adverse effects

Histidine exhibits a narrow and non-linear dose-response profile. Dietary intakes of approximately 4.0-4.5 g/day have been associated with improvements in metabolic parameters, including reductions in body mass index, adiposity, glycaemic markers, inflammatory cytokines, and oxidative stress indicators (Thalacker-Mercer and Gheller, 2020). In contrast, intakes exceeding ~24 g/day have been associated with adverse outcomes, including reduced serum zinc levels and cognitive impairment, although a formal tolerable upper intake level has not been established due to limited data between 4.5 and 24 g/day (Thalacker-Mercer and

Gheller, 2020). High-dose intravenous histidine administration, such as that used in cardioplegic solutions (raising plasma concentrations from ~70 μ M to ~21,000 μ M), induces marked metabolic perturbations, including increased blood and urinary ammonia, elevated urea production, depletion of hepatic and muscular ATP, and reductions in circulating branched-chain amino acids, accompanied by increases in glutamine and alanine at 24 hours (Holeček and Vodeníčarovová, 2019). Consistent with these findings, Holeček and colleagues caution against histidine supplementation in hepatic dysfunction due to the combined burden of ammonia accumulation, glutamine elevation, and branched-chain amino acid depletion (Holeček, 2020a; 2020b).

Integrated interpretation across exposure classes

When considered as a unified dataset, the four principal human exposure classes—dietary intake, supplementation, histidinemia, and high-dose pharmacological exposure—exhibit a coherent but non-linear relationship with neurological outcomes. Physiological dietary histidine intake supports normal cognitive function and is associated with reduced fatigue in clinical populations such as multiple sclerosis. Moderate supplementation (approximately 2–4 g/day) improves fatigue, mood, and select working memory outcomes. In contrast, histidinemia - despite markedly elevated circulating histidine - is generally neurologically benign in unbiased populations. At very high intake levels (>24 g/day or acute pharmacological exposure), histidine is associated with metabolic dysregulation and cognitive impairment. This pattern is best described as an inverted-U shaped dose-response relationship. Importantly, the dissociation between circulating histidine levels and neurological phenotype suggests

that histidine itself is unlikely to be the proximal effector. Instead, neurological effects may be more closely related to flux through downstream metabolic pathways, particularly histidine ammonia-lyase-mediated production of UCA.

Biochemical and mechanistic pathways

The integrated mechanistic model supported by the reviewed evidence is: Histidine → histidine ammonia-lyase (host and microbial) → UCA → BBB transport → accumulation in hippocampus and perirhinal cortex → UROC1-dependent conversion to glutamate and receptor-mediated signalling → modulation of synaptic plasticity → effects on recognition and spatial memory.

Multiple convergent lines of evidence support this pathway. First, HAL is expressed in host tissues, including liver and skin, and in gut microbial taxa. Microbial HutH activity correlates with infant cognitive performance and systemic histidine metabolite profiles (Cerdó et al., 2023). Second, systemic UCA - derived from ultraviolet-induced skin metabolism, exogenous administration, or microbial histidine catabolism - crosses BBB and accumulates in memory-related brain regions, including hippocampus and prefrontal cortex (Zhu et al., 2018; Yu et al., 2022). Third, neuronal UCA serves as a substrate for UROC1-dependent conversion to glutamate, which is incorporated into synaptic vesicles and released at glutamatergic synapses within hippocampal and cortical circuits (Zhu et al., 2018). Fourth, UCA directly modulates GABA-A receptor function in a stereoselective and pH-dependent manner, indicating additional non-metabolic neuromodulatory activity (Uusi-Oukari et al., 2000). Fifth, UCA suppresses cGAS-STING-mediated astrocytic senescence via interaction with ZCCHC3, suggesting a role in neuroinflammatory regulation and brain aging

(Hu et al., 2026). Sixth, network pharmacology analyses converge on MAPK, NF-κB, insulin signalling, serotonergic synapses, and amino acid metabolic pathways as downstream mediators of UCA-associated cognitive effects (Yu et al., 2022).

Causal and adjacent mechanisms

Microbiome-brain axis studies further support a role for microbial histidine metabolism in host physiology. The study by Cerdó and colleagues demonstrated that microbial histidine ammonia-lyase (HutH) activity correlates with infant cognitive performance, and that behavioural phenotypes are transferable via faecal microbiota transplantation into germ-free mice (Cerdó et al., 2023). Cognitive performance was associated with lower faecal histidine and altered UCA-to-histidine and UCA-to-glutamate ratios in brain tissue, consistent with altered flux through the histidine-UCA pathway. Adjacent human studies show that oral histidine reshaped gut microbiota and mucosal-associated invariant T cell populations in type 2 diabetes (Warmbrunn et al., 2024), and that microbial histidine catabolism modified non-alcoholic fatty liver disease phenotypes (Quesada-Vázquez et al., 2023), indicating that microbe-mediated histidine turnover had systemic effects beyond the CNS. Besides, histidine is a physiologically important zinc chelator; supplementation above ~24 g/d lowered serum zinc and, plausibly through this route, impaired cognition, supporting the U-shaped safety curve (Thalacker-Mercer and Gheller, 2020). Histidine has also both antioxidant (physiological concentrations) and pro-oxidant (>2.5 mM *in vitro*) properties, and maternal histidine loading disrupted offspring cortical and hippocampal redox balance and phosphoryl-transfer capacity (Tansini et al., 2004; Rojas et al., 2012; 2013). Finally, UCA

increased glutamatergic tone via UROC1-dependent glutamate synthesis (Zhu et al., 2018) while also modulating GABA-A receptors (Uusi-Oukari et al., 2000), positioning it as a candidate regulator of excitation-inhibition balance in hippocampal circuits.

Overall, the current evidence sup-

ports UCA - not histidine - as the proximal effector of the histidine-brain axis, with host HAL and microbial HutH activity determining the size of the pool that reaches the brain, and neuronal UROC1 determining how much of that pool is channelled into glutamate.

DISCUSSION

Cross-species integration

Evidence across species supports a partially conserved histidine-UCA axis, although translational fidelity is asymmetric between rodent models and humans. In rodents, systemic UCA crosses BBB, is metabolized to glutamate via neuronal UROC1, and enhances hippocampus- and perirhinal cortex-dependent memory performance. In humans, key enzymatic components of this pathway, including HAL and UROC1, are expressed in liver and peripheral tissues, and loss-of-function mutations in UROC1 cause urocanic aciduria, confirming pathway conservation at the biochemical level (Cerdó et al., 2023). Moreover, the association between microbial HutH activity, systemic histidine metabolism, and infant cognitive outcomes reported by Cerdó and colleagues provides *in vivo* human evidence linking this metabolic axis to neurodevelopment (Cerdó et al., 2023).

However, translational extrapolation from rodents to humans remains limited at the level of behavioural outcomes. Rodent NOR and OLR tasks depend on hippocampal and perirhinal cortex circuits and are considered partial analogues of human declarative recognition memory, but they do not fully recapitulate its complexity. Consequently, extrapolating acute intraperitoneal UCA effects in mice (e.g., 10 mg/kg improving 24-hour memory performance) to human cognitive enhancement is not

currently justified. Furthermore, no controlled studies have evaluated systemic UCA administration in humans, precluding direct assessment of dose-response relationships, including the inverted-U pattern observed in rodents.

Species-specific differences further constrain quantitative translation. These include differences in HAL expression, microbial ecosystem composition, and UROC1 activity between rodents and humans. In particular, laboratory mouse microbiomes and histidine metabolic fluxes differ substantially from those of free-living humans, limiting direct scaling of microbial UCA production. Rodent histidine turnover is also generally more rapid, potentially amplifying metabolic signals that may be attenuated in humans.

Behavioural interpretation is additionally complicated by state-dependent effects. Although locomotor confounding has been largely excluded in UCA studies, state-dependent memory phenomena - well documented for histidine-mediated histaminergic signaling - remain a potential confounder. Histidine can induce H1 receptor-dependent state-dependent alterations in memory performance, yet no studies have systematically evaluated whether UCA exhibits similar state dependence (Gianlorenço et al., 2011).

Histidine versus urocanate

Although histidine and UCA produce

partially overlapping behavioural phenotypes, their mechanistic bases are distinct. Systemic administration of UCA consistently enhances hippocampus-dependent learning across acquisition, consolidation, and reconsolidation phases in rodents (*Zhu et al., 2018; Yu et al., 2021; Yu et al., 2022; Wang et al., 2023*). In contrast, histidine exerts cognitive and behavioural effects primarily through conversion to histamine rather than via histidine itself. Pharmacological dissection consistently supports a histaminergic mechanism for histidine-induced behavioural effects. The amelioration of scopolamine-, MK-801-, and 5-HT1A agonist-induced cognitive deficits by histidine is abolished by inhibition of HDC or blockade of H1 receptors, indicating dependence on histamine signalling (*Miyazaki et al., 1995a; 1995b; Isayama et al., 2001*). Similarly, histidine-induced enhancement of prefrontal cortex-dependent working memory is mediated by histaminergic activation of basal forebrain-prefrontal circuits rather than direct histidine action (*Nakamura et al., 2022*). In humans, improvements in fatigue and working memory following dietary histidine supplementation are consistent with a histaminergic contribution, although a potential contribution of downstream UCA has not been directly assessed.

Two observations specifically implicate UCA rather than histidine as the relevant cognitive intermediate. First, in histidinaemia, dietary histidine restriction reduces substrate availability for HAL and therefore decreases downstream UCA production. Despite this, dietary restriction does not improve - and in some cases worsens - cognitive outcomes (*Widhalm and Virmani, 1994*). This finding is inconsistent with histidine toxicity as the primary driver of neurological phenotype and is more compatible with a deficiency of a downstream metabolite within the HAL pathway. Second, microbiome-linked evidence from Cerdó and colleagues demonstrates that higher cognitive performance in infants is associated with reduced faecal histidine and altered UCA-related ratios in brain tissue, consistent with increased metabolic flux through microbial histidine catabolism and more efficient downstream processing of UCA (*Cerdó et al., 2023*). Together with rodent data showing that UCA is converted to glutamate at glutamatergic terminals to support memory enhancement (*Zhu et al., 2018*), these findings support a model in which UCA occupies a central intermediate position, with either its metabolic conversion to glutamate or its direct neuromodulatory actions mediating cognitive effects.

CONCLUSION

Collectively, the available evidence supports a moderate-strength causal role for UCA - rather than histidine itself - as a proximal effector within the histidine-brain axis, particularly in rodent models of hippocampus-dependent recognition and spatial memory.

This conclusion is supported by four convergent lines of evidence:

(i) multiple independent rodent studies demonstrating that systemic

UCA enhances acquisition, consolidation, and reconsolidation of memory (*Zhu et al., 2018; Wang et al., 2023; Yu et al., 2021; 2022*).

(ii) a validated neuronal mechanism in which UCA is metabolized to glutamate via UROC1, with genetic loss-of-function confirmation (*Zhu et al., 2018*).

(iii) mechanistically distinct anti-senescence effects mediated

- through ZCCHC3 and suppression of cGAS-STING signalling, supported by pharmacological and genetic validation (Hu et al., 2026).
- (iv) the first *in vivo* human evidence linking microbial histidine catabolism, systemic metabolite profiles, and cognitive outcomes, with microbiota-dependent transmissibility in germ-free mice (Cerdó et al., 2023).

In contrast, histidine itself appears to exert indirect and context-dependent effects. At physiological to moderate supplemental doses, histidine modulates fatigue, mood, and select cognitive measures in humans, but mechanistic studies consistently attribute behavioural effects in rodents to downstream histamine signalling rather than histidine *per se* (Miyazaki et al., 1995a; 1995b; Isayama et al., 2001; Sasahara et al., 2015; Bell et al., 2024; Shimomatsuda et al., 2026). In population-level analyses, histidinaemia is largely non-disadaptive when ascertained without bias (Coulombe et al., 1983; Widhalm

and Virmani, 1994), and dietary histidine restriction fails to improve - and may worsen - cognitive outcomes. This pattern is more consistent with reduced flux through the HAL–UCA pathway than with histidine toxicity.

Several key uncertainties remain. It is not known whether the cognitive effects of UCA observed in rodents translate quantitatively to humans. It also remains unclear whether orally administered UCA achieves sufficient brain concentrations to engage neuronal UROC1-dependent pathways. In addition, the causal contribution of microbial UCA to the cognitive phenotype observed by Cerdó and colleagues (Cerdó et al., 2023) remains to be experimentally isolated from broader microbial metabolic shifts. Finally, the biological basis of neurological impairment in the small subset of individuals with histidinaemia-associated CNS phenotypes remains unresolved and may reflect distinct downstream metabolic or developmental modifiers.

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