Mini Review

Microbiota-derived indole-3-propionic acid in autism spectrum disorder: From metabolic associations to neural functional responses

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Abstract

Abnormalities in neural circuit organization and synaptic function are implicated in autism spectrum disorder (ASD), but the relevance of gut microbial metabolites to these alterations remains unclear. Indole-3-propionic acid (IPA), a microbial tryptophan metabolite capable of reaching the central nervous system, provides a potential link between intestinal metabolism and ASD-related neural function. Human studies report heterogeneous IPA profiles, including associations with selected neurobehavioral phenotypes and inconsistent differences between diagnostic groups. In ASD-related experimental models, IPA supplementation modifies glial activity, synaptic organization, GABAergic neurotransmission, and behavioral outcomes, whereas a broader microbiota intervention improved ASD-like behavior despite reduced IPA levels. This Mini-Review

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integrates these findings with evidence concerning IPA production, neural exposure, host sensing, and synaptic regulation. By distinguishing metabolic association, functional responsiveness, and causal pathway dependence, this review clarifies the biological relevance of IPA to ASD and identifies the mechanistic relationships requiring further investigation.

Keywords: Autism spectrum disorder, indole-3-propionic acid, gut-brain axis, neuroimmune regulation, microglia, synaptic plasticity, GABAergic neurotransmission

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by persistent differences in social communication and interaction, alongside restricted and repetitive patterns of behavior[1,2]. Despite diverse genetic, environmental, and developmental influences, ASD risk converges in part on processes governing neuronal development, synaptic organization, and circuit function[3-5]. These processes also respond to metabolic and immune signals beyond the nervous system[6,7]. The microbiota-gut-brain axis provides a framework for understanding how intestinal microbial activity may interact with these neural processes[8,9]. Although associations between gut microbial profiles and ASD may be influenced by dietary preferences and host characteristics[10], integrated analyses across multiple datasets have identified ASD-associated patterns involving microbial metabolic functions, inflammatory profiles, and brain gene expression[11]. These findings suggest that gut microorganisms may contribute to gut-brain communication through metabolic and immune signaling pathways, with potential implications for neurodevelopment and neural function.

Among microbiota-derived metabolites, tryptophan-derived indoles represent a group of microbial products capable of engaging host signaling pathways involved in epithelial homeostasis and immune regulation[12]. Indole-3-propionic acid (IPA), produced through microbial reductive metabolism of tryptophan, has been detected in human plasma and

cerebrospinal fluid, providing evidence of its availability beyond the intestinal environment[13,14]. Experimental studies have demonstrated that IPA contributes to intestinal barrier regulation and exhibits antioxidant activity[15,16]. Its biological relevance also extends to neural regulation, as IPA attenuates inflammatory responses in activated microglia, while conditioned medium from IPA-treated microglia enhances neuronal brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) production[17]. Together with broader evidence of IPA-associated neuroimmune and neuronal responses[18], these findings provide a biological rationale for examining how this microbial metabolite may influence neural processes implicated in ASD, particularly those involving glial regulation and synaptic function.

Nevertheless, the biological significance of IPA in ASD cannot be determined from metabolic alterations alone. Human metabolomic studies, direct IPA supplementation, and microbiota-based interventions provide different perspectives on its relationship with neural function, encompassing metabolic associations, experimental responses, and broader microbial effects. A central question is whether IPA-associated changes in glial activity, synaptic architecture, and inhibitory neurotransmission reflect interconnected molecular mechanisms or distinct responses arising under different neurodevelopmental conditions. This Mini-Review therefore integrates evidence on microbial IPA production and neural exposure with findings from ASD-related experimental models, focusing on host sensing and neuroimmune regulation, glial-synaptic interactions and structural remodeling, and GABAergic inhibitory transmission [Figure 1]. By distinguishing metabolic association, functional responsiveness, and causal pathway dependence, this review aims to clarify the biological mechanisms underlying IPA-associated neural responses and their relevance to ASD-related functional abnormalities.

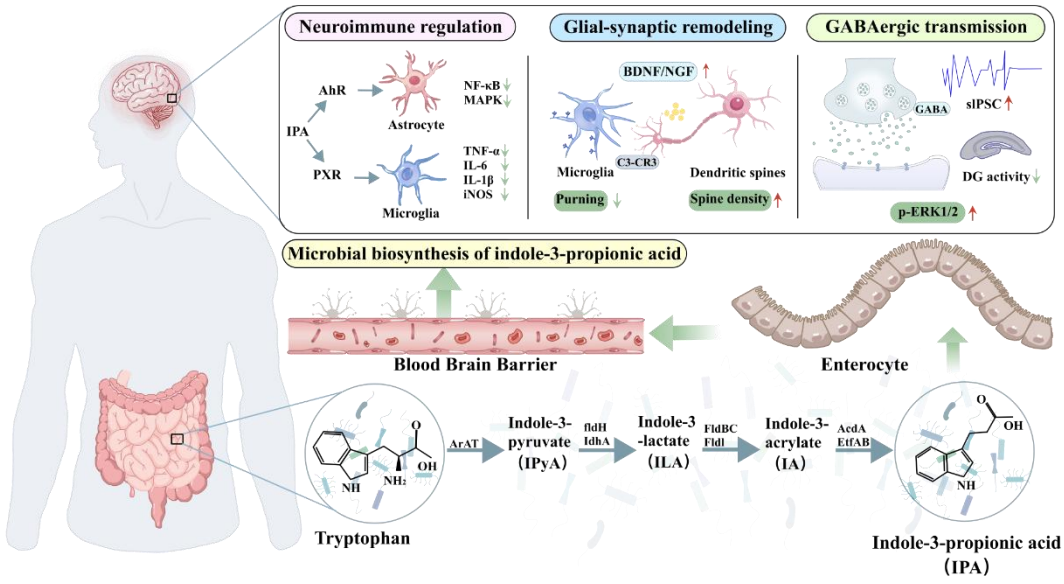


Figure 1. Microbial biosynthesis of indole-3-propionic acid and its potential neuroimmune and synaptic regulatory mechanisms. IPA is synthesized by intestinal microorganisms through the reductive metabolism of Trp. Trp is initially converted to IPyA through ArAT-mediated transamination, followed by the reduction of IPyA to ILA through FldH/LdhA. ILA is subsequently converted to IA through the FldBC/FldI enzyme system, and IA is further reduced to IPA by AcdA/EtfAB. Following intestinal absorption, IPA enters the systemic circulation and can reach the CNS across the BBB, where it is associated with three aspects of neural regulation: (1) Neuroimmune regulation: IPA-associated PXR and AhR signaling is involved in the modulation of inflammatory responses, including reduced NF-κB/MAPK activity and decreased expression of TNF-α, IL-6, IL-1β, and iNOS. (2) Glial-synaptic remodeling: IPA-associated glial responses involve BDNF/NGF signaling, C3-CR3-related synaptic regulation, reduced excessive microglial pruning, and increased dendritic spine density. (3) GABAergic transmission: IPA supplementation is associated with increased GABAergic inhibitory transmission and sIPSCs, enhanced p-ERK1/2, and reduced excessive neuronal activity in the DG. Abbreviations: IPA, indole-3-propionic acid; Trp, tryptophan; IPyA, indole-3-pyruvate; ILA, indole-3-lactate; IA, indole-3-acrylate; ArAT, aromatic amino acid aminotransferase; FldH, phenyllactate dehydrogenase; LdhA, D-2-hydroxyacid dehydrogenase; FldBC, phenyllactate dehydratase subunits B and C; FldI, phenyllactate dehydratase activating

enzyme; AcdA, acyl-CoA dehydrogenase; EtfAB, electron transfer flavoprotein subunits A and B; CNS, central nervous system; BBB, blood-brain barrier; PXR, pregnane X receptor; AhR, aryl hydrocarbon receptor; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-1β, interleukin-1 beta; iNOS, inducible nitric oxide synthase; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; C3, complement component 3; CR3, complement receptor 3; GABA, gamma-aminobutyric acid; sIPSCs, spontaneous inhibitory postsynaptic currents; p-ERK1/2, phosphorylated extracellular signal-regulated kinases 1/2; DG, dentate gyrus.

MICROBIAL ORIGIN AND NEURAL EXPOSURE OF INDOLE-3-PROPIONIC ACID

Indole-3-propionic acid (IPA) is generated through the reductive metabolism of tryptophan by intestinal microorganisms, with its production determined by both bacterial enzymatic capacity and metabolic interactions within the gut community[19]. Genetic disruption of the fldC component of phenyllactate dehydratase in *Clostridium sporogenes* markedly reduced circulating IPA levels in colonized mice, establishing a direct link between bacterial biosynthetic activity and host IPA exposure[20]. However, the presence of IPA-producing bacteria alone does not determine the metabolic output of the intestinal community[21]. Competition for tryptophan between indole-producing and IPA-producing bacteria can be altered by fiber-derived carbohydrates, which suppress indole formation and increase substrate availability for IPA synthesis[22, 23]. Beyond substrate competition, interspecies metabolic cooperation provides an additional route for IPA production, as indole-3-lactate generated by *Lachnospira eligens* can be further converted into IPA by *Enterocloster aldenensis*, a bacterium unable to produce IPA directly from tryptophan[24,25]. These findings indicate that intestinal IPA production is regulated not only by the biosynthetic capacity of individual microorganisms but also by substrate allocation and metabolic exchange across microbial species, collectively determining the potential microbial contribution to host IPA exposure.

Evidence that microbial IPA production contributes to host circulation raises the question of whether this peripheral metabolite can further reach the central nervous system. IPA has been quantified in human plasma and cerebrospinal fluid, while experimental investigations in rats have traced cerebrospinal fluid IPA to intestinal bacterial metabolism[13,14]. Further evidence comes from studies examining the distribution of IPA following peripheral administration. In rats, a single oral dose of IPA (200 mg/kg) increased its concentration in the frontal cortex approximately 56-fold at 90 min, with levels remaining about sevenfold higher at 6 h[26]. *In vivo* microdialysis further demonstrated increased extracellular IPA concentrations in the medial prefrontal cortex, while repeated dietary administration also increased brain IPA levels. Consistent with these observations, independent biodistribution experiments in mice detected IPA in brain tissue within one hour following intraperitoneal administration[27]. Together, these findings demonstrate that IPA can reach central nervous system compartments and that its neural exposure can be altered through peripheral administration.

The biological significance of neural IPA exposure extends beyond its detection in brain tissue. In addition to increasing brain IPA concentrations, oral administration in rats elevated cortical kynurenic acid (KYNA), a neuroactive metabolite involved in the regulation of neurotransmission[28,29], indicating that changes in peripheral IPA availability can be accompanied by alterations in the brain's neuroactive metabolic environment[26]. These observations extend the biological connection between intestinal microbial metabolism and the nervous system from metabolite production and systemic distribution to potential modulation of the central metabolic environment. Microbial synthesis determines the supply of IPA, while its absorption and distribution influence the extent to which this metabolite becomes available to neural tissues. This relationship provides a basis for understanding how changes in IPA availability may influence neural processes associated with ASD, particularly those involving glial regulation, synaptic organization, and neuronal activity. The functional relevance of this connection is further

supported by experimental studies examining IPA-associated neural and behavioral responses in ASD-related models.

IPA ALTERATIONS AND BIOLOGICAL RELEVANCE IN ASD

Following evidence that IPA can reach the central nervous system, studies in ASD populations have begun to link alterations in IPA metabolism with intestinal microbial changes and clinically relevant neurobehavioral phenotypes. An integrative multi-omics analysis of children with severe ASD identified reduced fecal IPA levels alongside alterations in intestinal microbial composition, with IPA abundance showing negative correlations with *Anaerostipes* and *Romboutsia*[30]. Extending these observations to neurobehavioral outcomes, a 12-week open-label synbiotic study in children with ASD found that increases in fecal IPA were associated with reductions in anxiety and sensory hyperresponsiveness[31]. However, a separate cohort of 160 children with ASD and 69 typically developing controls found no significant between-group difference in fecal IPA concentrations[32]. These findings suggest that IPA-associated metabolic variation may be related to specific clinical phenotypes or metabolic contexts rather than a uniform difference between diagnostic groups.

Differences in IPA measurements across studies reflect variations in age, diet, gastrointestinal characteristics, medication exposure, and host metabolism, as well as differences in sampling and analytical methods[33-35]. Although these factors may contribute to the observed heterogeneity, their relative influences remain unclear. Beyond these variable clinical profiles, evidence from neurodevelopmental models has linked changes in IPA availability to alterations in neural structure, synaptic function, and ASD-like behaviors.

In experimental models representing distinct neurodevelopmental disturbances, reduced IPA levels have been accompanied by abnormalities in neural function and social behavior. In intrauterine growth restriction (IUGR) rats, postnatal IPA supplementation attenuated

hippocampal microglial hyperactivation, excessive synaptic pruning, and ASD-like behavioral abnormalities[36]. Complementary findings in 16p11.2 microdeletion mice demonstrated that IPA administration improved social interaction and recognition memory while restoring impaired hippocampal inhibitory synaptic transmission and reducing abnormal neuronal activation[37]. Although these models differ in their developmental origins and neural alterations, both demonstrate that increased IPA exposure can modify ASD-relevant behavioral outcomes alongside measurable changes in glial or neuronal function.

A different pattern has emerged from interventions targeting the intestinal microbial community[38,39]. In BTBR mice, administration of *Faecalibacterium hominis* 4P-15 improved ASD-like behavioral outcomes while reducing fecal and cerebellar IPA concentrations, together with changes in other indole metabolites. These metabolic alterations were accompanied by increased expression of selected glutamate transporter and GABA receptor genes[40]. Previous studies have implicated AhR in the regulation of glutamate transporters[41] and GABA_A receptor expression during cerebellar development[42], providing a potential mechanistic context for these transcriptional changes. In contrast to direct IPA supplementation, this intervention altered a broader network of microbial metabolites and host responses. Nevertheless, findings across these experimental systems converge on the involvement of synaptic organization, glial regulation, and inhibitory neurotransmission in IPA-associated neural responses, providing a biological connection between microbial indole metabolism and neural processes relevant to ASD.

IPA IN NEUROIMMUNE AND SYNAPTIC REGULATION

Host sensing and neuroimmune regulation

IPA-associated neuroimmune regulation involves host signaling pathways that translate microbial metabolic exposure into cellular inflammatory responses. Pregnane X receptor (PXR) represents one such pathway[15]. Fibroblast-specific PXR deletion exacerbated

intestinal inflammation and fibrosis, whereas IPA administration attenuated these responses[43]. Evidence from neural tissue further supports the involvement of PXR in IPA-responsive inflammatory regulation. Neuronal PXR knockdown diminished IPA-associated reductions in hippocampal NF-κB phosphorylation and inflammatory mediators, including TNF-α[27]. These intervention findings establish a connection between IPA-responsive PXR signaling and inflammatory regulation across peripheral and neural cellular environments.

Aryl hydrocarbon receptor (AhR) provides another mechanism linking microbial indole metabolism to glial regulation. In primary astrocytes, IPA attenuated TNF-α-induced expression of IL-6, IL-1β, iNOS, and inflammatory chemokines through AhR-associated suppression of NF-κB and MAPK signaling[44]. AhR-dependent regulation also extends to communication between glial populations. Other microbiota-derived tryptophan metabolites influence microglial production of TGF-α and VEGF-B, which exert opposing effects on astrocyte inflammatory activity through ErbB1 and FLT-1 signaling, respectively[45]. This intercellular mechanism illustrates how microbial metabolic signals can influence the neuroimmune environment through coordinated glial responses. In an ASD-related microbiota intervention, changes in brain indole metabolites, including IPA, were accompanied by altered expression of genes associated with AhR-regulated neurotransmitter signaling[40]. Although this intervention affected multiple microbial metabolites, it connects indole-sensitive host signaling with neural regulatory processes implicated in ASD.

Additional IPA-responsive intracellular pathways have been identified in experimental studies of neuroinflammation. IPA suppressed microglial inflammatory responses through inhibition of RAGE-JAK2-STAT3 signaling, while pharmacological activation of JAK2-STAT3 partially reversed these effects[46]. Reduced inflammatory mediator expression, Wnt1 expression, and STAT3 phosphorylation were also observed in irradiated microglia following IPA treatment[47]. Across these experimental settings, IPA-associated changes

in intracellular signaling converge on the regulation of glial inflammatory activity. Such responses provide a biological basis for considering how microbial metabolic signals may influence the cellular environment involved in neuronal development and synaptic maintenance, processes relevant to ASD-associated neural dysfunction.

Glial-synaptic interactions and structural remodeling

IPA-associated changes in microglial activity may influence synaptic organization through interactions between glial cells and neurons. IPA treatment reduced TNF-α production in activated microglia, while conditioned medium from IPA-treated microglia increased neuronal BDNF and NGF production[17]. This response suggests that IPA can modify microglia-derived signals involved in the regulation of neuronal function. Microglial BDNF has been shown to promote neuronal TrkB phosphorylation and activity-dependent synapse formation[48], while direct microglial contact facilitates dendritic filopodia formation through localized calcium signaling and actin remodeling[49]. Additional evidence indicates that microglial IL-10 can promote neuronal synapse formation[50], while microglial contact with existing synapses can enhance synaptic activity and local network synchronization[51]. These complementary mechanisms illustrate how changes in microglial signaling and cellular interactions may influence the formation and maintenance of neuronal connections, providing a biological basis for considering IPA-associated glial responses in relation to synaptic development.

The maintenance of synaptic architecture also depends on the regulated elimination of neuronal connections. During neural circuit development, complement C3-CR3 signaling contributes to activity-dependent microglial engulfment of synaptic elements[52]. The relevance of this process to ASD is supported by evidence of excessive complement-associated postsynaptic elimination in SCN2A-deficient mice, accompanied by reduced dendritic spine density and impaired synaptic transmission. Microglial depletion partially restored these abnormalities, while human cerebral organoids carrying an ASD-associated SCN2A mutation exhibited increased microglial elimination of postsynaptic structures[53].

Altered neuron-microglia communication has also been linked to ASD-related neural dysfunction, as CX3CR1 deficiency disrupted developmental synaptic pruning, functional connectivity, and social behavior[54]. Additional developmental studies have demonstrated that microglial synaptic pruning is required for normal brain maturation and that the classical complement cascade contributes to CNS synapse elimination[55,56]. These observations establish microglial regulation of synaptic elimination as an important component of neural circuit development, connecting altered glial activity with structural and functional abnormalities relevant to ASD.

Evidence from IPA supplementation experiments provides a more direct connection between microbial metabolite exposure and synaptic structural regulation. In an ASD-like developmental-risk setting, IPA administration attenuated hippocampal microglial hyperactivation and abnormal synaptic pruning, accompanied by improvements in dendritic organization, spine density, and synaptic ultrastructure. The structural responses extended beyond changes in spine abundance to include synaptic vesicle number, postsynaptic density thickness, and synaptic active-zone organization. Experimental manipulation of AhR signaling and microglia-neuron co-culture further demonstrated that alterations in glial signaling were accompanied by changes in neuronal dendritic organization and synapse-associated markers[36]. Complementary evidence from a non-ASD experimental setting associated IPA treatment with reduced microglial inflammation and changes in postsynaptic density morphology[47]. This evidence connects IPA-responsive microglial activity with measurable aspects of synaptic architecture in an ASD-relevant neurodevelopmental context, supporting a potential role for microbiota-derived metabolic signals in the regulation of neuronal connectivity.

Synaptic transmission and neuronal activity

The functional relevance of IPA to ASD can also be examined at the level of synaptic transmission and neuronal excitability. GABAergic signaling regulates neuronal firing, synaptic integration, and the temporal coordination of neural circuit activity[57].

Reduced brain GABA concentrations have been reported in ASD, particularly among children and in limbic regions[58]. Regional studies have further identified associations between cerebellar GABA+/glutamate ratios and social impairment[59], alongside altered GABA and glutamate concentrations in the temporal cortex[60]. Pharmacological modulation of GABA receptors and targeted manipulation of inhibitory circuits have improved selected social and repetitive behavioral outcomes[61-63]. More specifically, restoration of hippocampal parvalbumin interneuron-mediated feedforward inhibition improved social recognition[64], whereas stimulation of prefrontal inhibitory interneurons modified gamma oscillatory activity and improved social novelty processing[65]. Excessive activity in prefrontal-amygdala pathways disrupted the temporal coordination of socially responsive neurons, with circuit-specific inhibition partially restoring social behavior[66]. These neurophysiological observations provide a basis for examining IPA-associated changes in inhibitory neurotransmission and their relevance to ASD-related neural function.

IPA supplementation has been shown to modulate multiple components of hippocampal inhibitory neurotransmission. In 16p11.2 microdeletion mice, dentate gyrus granule cells exhibited reduced spontaneous inhibitory postsynaptic current (sIPSC) amplitude, accompanied by lower hippocampal GABA concentrations and reduced GAD65/67-related measures. IPA administration increased both sIPSC amplitude and frequency, elevated hippocampal GABA concentrations and GAD65/67-positive puncta and reduced excessive neuronal activation in the dentate gyrus. These physiological changes were accompanied by improvements in social interaction and recognition memory, alongside enhanced hippocampal ERK1/2 phosphorylation[37]. The combination of neurochemical, electrophysiological, and neuronal activity measurements provides direct evidence that IPA-associated functional responses extend from inhibitory neurotransmitter regulation to changes in synaptic signaling and hippocampal neuronal excitability.

The relationship among these physiological responses is particularly relevant to

understanding IPA-associated neural regulation. Changes in sIPSC amplitude reflect the magnitude of individual inhibitory synaptic events, whereas changes in frequency indicate how often such events occur[67]. Their accompanying association with increased GABA concentrations and GAD65/67-positive puncta is consistent with the involvement of GABA synthesis and availability in inhibitory synaptic signaling[68]. Independent evidence of region-specific GABAergic abnormalities and disrupted functional connectivity in 16p11.2 deletion mice further supports the relevance of inhibitory regulation to ASD-associated neural dysfunction[69]. Reduced dentate gyrus neuronal activation indicates an associated change in neuronal activity, while independent circuit studies have established the involvement of dentate gyrus pathways in social memory processing[70]. Enhanced ERK1/2 phosphorylation identifies a potential intracellular signaling component, consistent with evidence implicating ERK signaling in GABAergic synaptic plasticity[71]. By linking neurotransmitter-related measures with synaptic physiology and neuronal excitability, these findings provide a functional basis for understanding how IPA may influence neural processes implicated in ASD-related social and cognitive abnormalities.

CONCLUSIONS AND FUTURE PERSPECTIVES

A central question in understanding the biological relevance of IPA to ASD is whether changes in its microbial metabolism are associated with, or functionally contribute to, ASD-related neural abnormalities. Current evidence indicates that intestinal microbial interactions regulate IPA production and that this metabolite can reach the central nervous system, providing a biological basis for its potential neural actions. However, human studies have reported variable IPA profiles across ASD populations, with associations involving selected neurobehavioral characteristics rather than consistent differences between diagnostic groups. The significance of IPA in ASD may therefore lie less in its direction of metabolic alteration than in the neural processes and functional phenotypes associated with its availability.

Experimental findings extend this relationship beyond metabolic association. IPA supplementation has been shown to modify hippocampal microglial responses, synaptic organization, inhibitory neurotransmission, and neuronal activity, accompanied by improvements in selected ASD-related behavioral outcomes. These responses suggest that IPA may influence neural function at multiple biological levels, involving both the cellular environment supporting synaptic organization and the physiological regulation of neuronal activity. AhR-associated glial signaling and ERK-related neuronal responses provide potential molecular connections, while PXR and other inflammatory signaling pathways identified in complementary experimental systems broaden the understanding of IPA-responsive cellular regulation. The available findings do not establish these processes as components of a single sequential mechanism, but they indicate that IPA can influence neural functions relevant to ASD through distinct cellular and physiological responses. Importantly, improvements in ASD-like behaviors have also been observed following broader microbiota interventions accompanied by reductions in IPA and alterations in other indole metabolites. Such findings distinguish the effects of direct IPA exposure from those arising through changes in the microbial metabolic environment, emphasizing the importance of interpreting IPA-associated neural responses in relation to their biological context.

The distinction between metabolic association, functional responsiveness, and causal pathway dependence provides a framework for advancing this field. Human metabolomic observations and experimental supplementation establish different levels of evidence, whereas determining the contribution of endogenous microbial IPA requires direct investigation of the relationships among microbial production, host exposure, neural availability, and functional outcomes. Future studies integrating longitudinal human metabolomics with targeted manipulation of microbial IPA biosynthesis, controlled supplementation, and cell-specific perturbation of candidate signaling pathways could help resolve these relationships. Combining such approaches with human-derived neural models, electrophysiological measurements, and standardized ASD-related functional

assessments would further clarify how IPA-associated neuroimmune and synaptic responses contribute to behavioral phenotypes. Establishing these mechanistic connections is essential for determining the biological significance of IPA in ASD and evaluating whether its metabolic production or downstream signaling pathways represent meaningful targets for future intervention.

DECLARATIONS

Authors' contributions

Contributed to conceptualization: Shi WH, Yu YX;

Contributed to writing-original draft and visualization: Shi WH, Zhou SC, Xu YX;

Contributed to writing-original draft: Song HN, Yang YZ;

Contributed to supervision and writing-review and editing: Yu YX;

All authors have read and approved the final manuscript.

Availability of data and materials

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The authors declare no competing interests.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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