



Kynurenine Pathway and Its Metabolites in Autism Spectrum Disorder: a Close Link*

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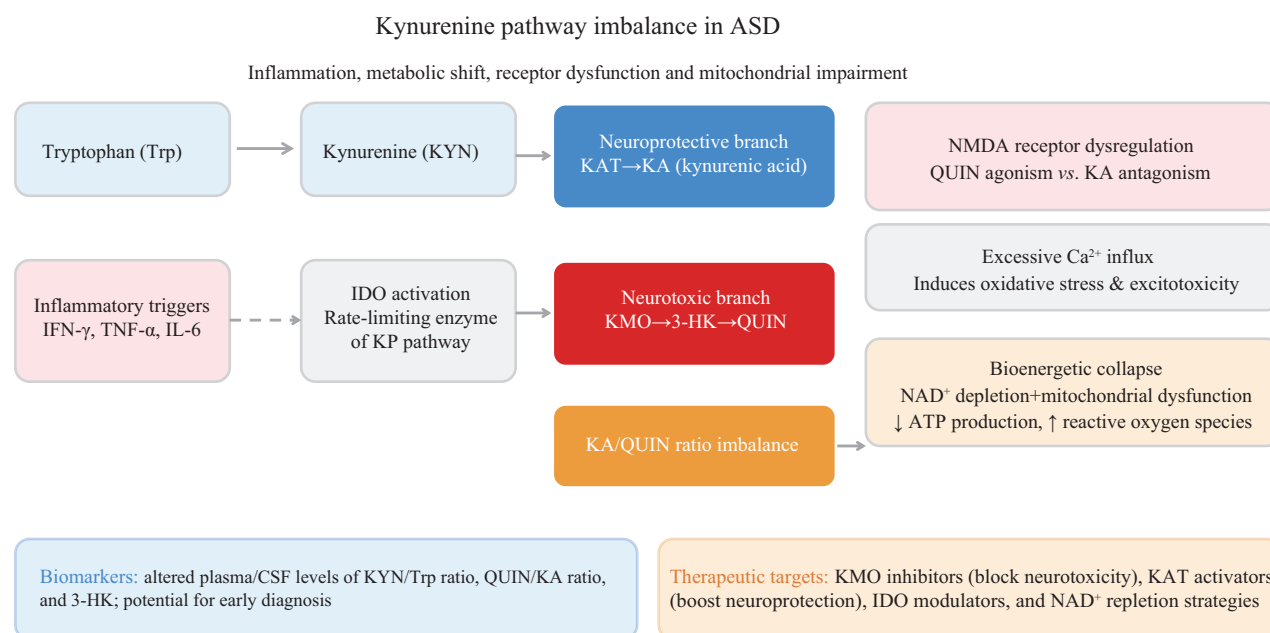
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Graphical abstract



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Abstract Kynurenine pathway (KP) is a major catabolic route of tryptophan, generating a series of bioactive metabolites including kynurenine, kynurenic acid (KA), quinolinic acid, and 3-hydroxykynurenine. Beyond its fundamental role in amino acid metabolism, KP exerts critical regulatory functions in neurodevelopment, synaptic plasticity, and immune modulation. Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition with onset in early childhood, characterized by persistent deficits in social communication and restricted, repetitive behaviors. Despite extensive research, the etiological mechanisms underlying ASD remain highly complex and incompletely understood, involving genetic, environmental, and immunological factors. Emerging clinical evidence has consistently revealed a significant imbalance in KP metabolites in individuals with ASD, often accompanied by altered ratios of neuroprotective versus neurotoxic byproducts. However, the primary drivers of this metabolic dysregulation and its causative contribution to ASD pathogenesis are not yet fully elucidated. In this review, we systematically review the enzymatic steps of KP and the principal physiological functions of its major metabolites, with particular emphasis on their dual roles in neuroprotection and neurotoxicity. We then analyze the potential pathogenic mechanisms through which KP dysfunction may contribute to ASD, focusing on two interconnected etiological dimensions. First, KP imbalance can promote oxidative stress, which in turn triggers chronic inflammatory responses *via* microglial activation and release of pro-inflammatory cytokines, thereby disrupting neuronal homeostasis. Second, aberrant KP metabolism affects neurotransmitter systems, particularly glutamatergic and dopaminergic signaling, leading to impaired neural circuit development and synaptic pruning. By integrating current findings on the KP-ASD association, this review offers a comprehensive etiological framework and a clinically relevant paradigm. Furthermore, we highlight that specific KP metabolites, such as the KA/quinolinic acid ratio, hold promise as peripheral biomarkers for early diagnosis and disease stratification. Finally, we discuss the therapeutic potential of targeting KP enzymes or receptors for personalized intervention strategies, while acknowledging the challenges in translating these findings into clinical practice.

Key words autism spectrum disorder (ASD), redox imbalance, abnormal ncRNA expression, disruption of the “gut-brain axis”, pathogenic mechanisms of ASD, ASD diagnosis and treatment

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Autism spectrum disorder (ASD) is a group of hereditary neurobehavioral disorders characterized by core behavioral deficits in communication, social interaction, and repetitive, stereotyped behaviors^[1]. The prevalence of ASD has been rising steadily in recent decades. Although the exact cause remains unclear, it is generally believed to result from the combined effects of genetic and environmental factors^[2]. At the metabolic level, tryptophan is primarily degraded *via* the kynurenine pathway (KP), which accounts for more than 95% of its metabolic flux and produces various neuroactive metabolites that exert complex regulatory functions by acting on glutamatergic and cholinergic receptors^[3].

Within the complex systemic metabolic dysregulation observed in ASD, KP dysfunction occupies a central hub: it not only passively reflects systemic metabolic abnormalities but also actively links peripheral immune activation, oxidative stress, and central neurotransmitter imbalances. Neurotoxic metabolites generated by KP activation can cause long-term impairment of nutritional support, disrupt the glutamatergic system and synaptic plasticity, and induce persistent neuroinflammation, directly exacerbating the well-recognized excitation/inhibition

(E/I) imbalance in ASD, thereby translating genetic and environmental risks into brain dysfunction. Therefore, focusing on the role of KP in neurodevelopment provides a key integrative perspective for a deeper understanding of the pathogenesis of ASD^[4].

Previous studies have confirmed significant and specific alterations in KP downstream metabolites in individuals with ASD^[5]. At the molecular level, kynurenic acid (KA) and quinolinic acid (QUIN) exhibit diametrically opposed biological activities: in addition to acting as N-methyl-D-aspartate receptor (NMDAR) antagonists and agonists, respectively, they also differentially regulate the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR)^[6]. KA inhibits α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) and fucoidic acid receptors, stimulates potassium channels and aromatic hydrocarbon receptors, and possesses antioxidant properties; in contrast, QUIN drives oxidative stress-induced damage associated with lipid peroxidation by promoting reactive oxygen species (ROS) production, enhancing nitric oxide synthase (NOS) activity, and reducing superoxide dismutase (SOD) activity and glutathione levels^[7-9]. The metabolic imbalance

between KA and QUIN constitutes the core mechanism by which KP drives neuropathological changes in ASD.

Previous reviews have explored the association between KP and ASD. Santana-Coelho^[10] systematically summarized the evidence for tryptophan metabolic abnormalities in ASD but explicitly noted that this relationship remains in its preliminary stages; Giuliano and Tognini^[4], on the other hand, provided a broader overview of the role of tryptophan metabolism in various neurodevelopmental disorders, including ASD, attention-deficit hyperactivity disorder, and Rett syndrome. The aforementioned studies laid the foundation for understanding the relationship between KP and ASD. Most studies have focused on a single dimension, failing to systematically elucidate KP's bridging role between immunity and neuroregulation. They have also not thoroughly examined the bidirectional regulatory mechanisms of KA/QUIN at the NMDAR and $\alpha 7$ nACh receptor levels and their impact on the E/I balance, nor have they directly linked NAD^+ deficiency caused by QUIN accumulation to mitochondrial energy metabolism disorders in ASD. To address these gaps, this study adopts a dual-dimensional approach—"oxidative stress-inflammation" and "neurotransmission-development"—to systematically analyze the regulatory role of KP metabolic imbalance in ASD, clarifying that the imbalance in the KA/QUIN ratio constitutes the molecular basis of E/I dysregulation, proposing a pathogenic cascade of "inflammation $\rightarrow$ QUIN $\uparrow \rightarrow \text{NAD}^+ \downarrow \rightarrow$ energy metabolism dysfunction $\rightarrow$ impaired synaptic function", and exploring the translational potential of KP metabolites as early screening biomarkers and targets for therapeutic strategies. This paper will review the latest advances in the association between KP and ASD, aiming to provide an integrated metabolic-immune-neuroregulatory model for understanding the complex etiology of ASD.

1 Kynurenine pathway

Tryptophan is an essential amino acid that cannot be synthesized by the human body and must be obtained from food. Tryptophan metabolism primarily involves the kynurenine, 5-hydroxytryptamine (5-HT), and indole pathways. The various bioactive

compounds produced through tryptophan metabolism can regulate a range of physiological functions, including inflammation, metabolism, immune responses, and neural function^[11]. In the human body, approximately 5% of tryptophan is converted into serotonin *via* the methoxyindole pathway, while approximately 95% of tryptophan is metabolized into kynurenine.

1.1 The basic metabolic pathway of kynurenine

KP is primarily localized in the liver, which contains all the enzymes required for the synthesis of NAD^+ from tryptophan and is responsible for approximately 90% of tryptophan degradation under normal physiological conditions^[12]. In addition, KP also occurs extrahepatically, where its contribution to tryptophan degradation is typically small (5%–10%), but becomes more significant under conditions of immune activation^[13].

The first step in KP is the rate-limiting step of the pathway, in which indoleamine 2,3-dioxygenase (IDO) or tryptophan dioxygenase (TDO) converts tryptophan to kynurenine. The former is distributed throughout various tissue cells and is primarily induced by pro-inflammatory cytokines, while the latter is mainly found in hepatocytes and is induced by cortisol^[14]. There are two main pathways for kynurenine metabolism: first, kynurenine is directly converted to para-aminobenzoic acid (AA) by kynureninase A; second, kynurenine is catalyzed by kynurenine monooxygenase (KMO) to form 3-hydroxycanine kynurenine (3-HK), which is then hydrolyzed by kynureninase B to produce 3-hydroxy-o-aminobenzoic acid (3-HAA), 3-HAA is subsequently converted to quinolinic acid, ultimately yielding NAD^+ to participate in redox reactions and a series of energy metabolism processes^[15-16]. In addition, kynurenine aminotransferase (KAT) can convert the remaining canine uric acid and 3-HK into KA and xanthogenic acid (XA).

1.2 Kynurenine and neurotransmission

A portion of kynurenine is metabolized by KAT to produce KA, while another portion is metabolized by KMO to form QUIN. Both KA and QUIN are neuroactive metabolites, acting as antagonists and agonists of the NMDAR, respectively^[17].

As an NMDAR inhibitor, KA is generally regarded as an "endogenous anti-excitotoxic" agent^[18]. On the one hand, KA acts as a

neurotransmitter at physiological concentrations; when its concentration increases, it can inhibit the excessive activation of NMDARs and mitigate glutamate excitotoxicity under pathological conditions. On the other hand, KA can also allosterically modulate $\alpha 7$ nAChR, and is therefore generally considered to possess neuroprotective and anticonvulsant effects.

As an NMDAR agonist, QUIN is a neurotoxic KP metabolite that increases neuronal activity and elevates intracellular calcium concentrations^[19]. This leads to impaired cytoskeletal homeostasis, reduced mitochondrial function, and ultimately induces cell death^[20]. QUIN selectively acts on NMDAR subtypes containing the NMDAR2A and NMDAR2B subunits^[21], leading to neurochemical, behavioral, and pathological changes that result in selective neuronal damage in the hippocampus and striatum. Furthermore, QUIN can directly stimulate synaptic terminals to release glutamate and inhibit the reuptake of glutamate from the synaptic cleft by astrocytes, and is therefore considered neurotoxic^[22].

In summary, kynurenine crosses the blood-brain barrier to enter the central nervous system (CNS), where it is metabolized into kynurenine or QUIN, which act as an NMDAR antagonist and agonist, respectively, exhibiting both neuroprotective and neurotoxic effects. Numerous studies have now demonstrated elevated CNS levels of QUIN in various neurological disorders, including Alzheimer's disease (AD), depression, epilepsy, autism, and schizophrenia, and patients are at increased risk of suicide^[23]. Therefore, within KP, elevated CNS levels of QUIN play a crucial role in the pathogenesis of these diseases through its action on NMDARs^[24], and changes in QUIN-to-KA ratio are important for maintaining nervous system homeostasis.

1.3 Kynurenine pathway and inflammation

1.3.1 Inflammatory factors regulate key metabolic enzymes involved in kynurenine pathway

The inflammatory process significantly alters the balance of neurotoxicity by converting tryptophan metabolism into kynurenine production. As the rate-limiting enzyme in the first step of tryptophan metabolism to kynurenine, IDO is considered a key enzyme involved in inflammatory diseases arising in various cell types, including macrophages, microglia, neurons, and astrocytes. Previous studies have shown

that the *IDO* gene is upregulated by inflammatory factors such as IFN- γ , TNF- α , IL-1 β , and IL-6. Other secondary rate-limiting enzymes, such as KAT, can also be downregulated by IL-1 β ^[25].

IDO is widely expressed in the colon, small intestine, brain, spleen, lungs, and epididymis, as well as in bone marrow cells, including macrophages and dendritic cells. A reduction in IDO's immunosuppressive function may exacerbate inflammatory responses in these tissues^[26]. For example, in IDO1 deficiency, the number of inflammatory cells in the colon and peripheral blood is reduced^[27], while in various experimental models, LPS administration in rodents upregulates IDO^[28], and poly IC can also upregulate IDO in placental trophoblast cells, primary astrocyte cultures, and rodent brains^[29]. Since the KP is regulated by inflammation, it is also a potential therapeutic target for various inflammatory diseases.

1.3.2 Inflammatory factors regulate kynurenine metabolites

Inflammation not only regulates the activity of the KP rate-limiting enzyme but also directly alters the profile of downstream metabolic products. The cytokine-mediated inflammatory processes activates IDO and induces the conversion of kynurenine to QUIN^[30], thereby shifting the metabolic balance from the neuroprotective metabolite KA to the neurotoxic metabolite QUIN (Figure 1). It is worth noting that different cell types respond differently to the same inflammatory factor: for example, IL-6 reduces kynurenine levels in astrocytes but increases them in neurons^[31]. This cell-type-specific metabolic response suggests that the regulatory role of inflammation on the KP is highly complex within the nervous system. Furthermore, bacterial or viral-induced inflammatory stimuli can also modulate the production of KP metabolites. Regarding bacterial infections, during infection by *Edwardsiella piscicida*, its antitoxin protein HigA is transported *via* the type VI secretion system into the nuclei of host intestinal chromaffin cells, where it directly binds to the promoter region of IDO1—the rate-limiting enzyme in the tryptophan metabolism KP—and upregulates its expression, thereby promoting the flow of tryptophan into the KP; the research team further discovered that HigA homologs can similarly regulate intestinal serotonin levels and influence intestinal tissue damage in a

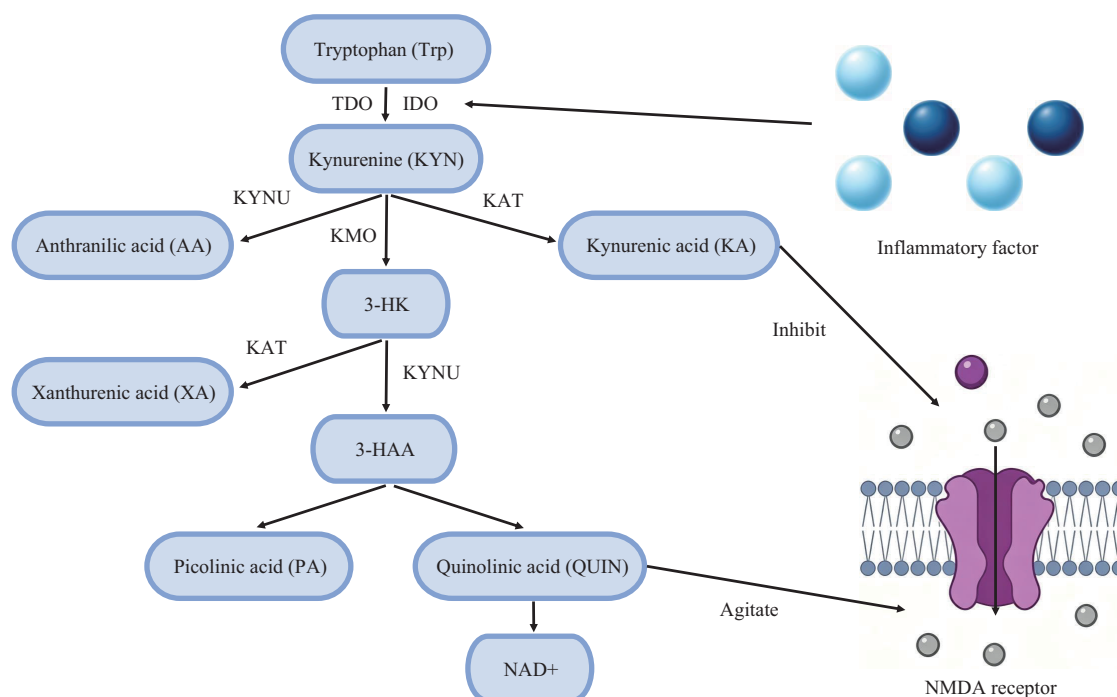


Fig. 1 Diagram of the main mechanisms of kynurenine metabolism

mouse model of *Salmonella* infection, indicating that the T6SS-HigA-serotonin axis is widely present in interactions between intestinal pathogens and hosts. In the context of viral infection, infection with bovine viral diarrhea virus can sustainably upregulate IDO1 expression in host cells, leading to reduced extracellular tryptophan levels and elevated kynurenine levels. These examples further expand the pathological significance of the inflammation-KP axis in infection- and immune-related diseases.

Inflammatory factors can stimulate the rate-limiting enzyme IDO to shift tryptophan metabolism toward kynurenine synthesis, which undergoes a series of reactions to produce kynurenine and QUIN, which are antagonists and agonists, respectively, of NMDAR.

2 The potential role of kynurenine metabolism in autism

2.1 Clinical evidence

2.1.1 Kynurenine metabolism abnormalities in individuals with ASD

Numerous clinical studies have established that KP metabolism is significantly altered in individuals with ASD, with these alterations spanning pediatric

and adult populations.

In children with ASD, a cross-sectional family-based study comparing newly diagnosed ASD children to their age-matched healthy siblings revealed elevated levels of kynurenine and QUIN, an increased kynurenine/tryptophan ratio and QA concentration, alongside reduced pyridole carboxylic acid (PA). Notably, these metabolic changes were accompanied by elevated pro-inflammatory cytokines, including IL-6 and IL-17 α , suggesting a link between peripheral inflammation and KP dysregulation in pediatric ASD^[32]. Similarly, a Norwegian study demonstrated that serum KA levels were lower in the ASD group compared to typically developing children^[33]. Urinary metabolomic analysis further revealed decreased levels of KA, kynurenine, and 5-HT, with elevated XA and QUIN levels in children with ASD^[34]. A comparative study across various developmental disorders indicated that children with childhood autism and intellectual disabilities had lower serum KA levels, whereas those with Asperger's syndrome exhibited lower 5-HT but higher tryptophan levels, highlighting the heterogeneity of KP alterations across ASD subtypes^[35].

In contrast, literature on KP alterations in adults

with ASD remains sparse. The majority of adult studies have focused on tryptophan and serotonin metabolism. An early study by Li demonstrated that short-term tryptophan depletion could precipitate autistic symptoms in adults^[36]. A more recent study directly assessing KP metabolism in adults with ASD found that patients had lower levels of tryptophan and KA compared to both healthy controls and relatives with a broad autism phenotype (BAP)^[37].

Collectively, these clinical studies indicate that KP imbalance is a common feature across the lifespan of ASD, primarily characterized by reduced KA (neuroprotective) and elevated QUIN (neurotoxic). However, kynurenine levels show variable trends across studies, potentially reflecting differences in sample types (serum vs. urine), disease subtypes, or inflammatory states. These findings not only establish the presence of KP metabolic abnormalities but also suggest that the degree of KA/QUIN imbalance may correlate with disease severity, serving as potential peripheral biomarkers for ASD diagnosis and stratification. However, establishing causality and identifying the precise mechanisms by which these peripheral metabolic changes influence central nervous system function remains a critical challenge.

2.1.2 Alterations in kynurenine in ASD animal models

Alterations in KP have also been observed in animal model studies of ASD. BTBR mice are an inbred strain exhibiting an autism-like phenotype; one study found that, compared to C57 mice, BTBR mice had lower levels of extracellular acetylcholine and higher levels of KA in the medial prefrontal cortex^[38]. In another study using *Ptchd1* KO mice as an animal model of ASD, levels of KP-related metabolites were measured in the serum and prefrontal cortex of 11-week-old mice following the observation of abnormal behavioral phenotypes. The results showed that levels of kynurenine, KA, 3-HK, and AA in the serum, as well as levels of AA, 3-HAA, and 3-HK in the prefrontal cortex, were significantly higher in *Ptchd1* KO mice than in WT mice^[39].

2.2 Kynurenine metabolism contributes to ASD through inflammatory responses

2.2.1 ASD and inflammatory response

Inflammation is increasingly recognized as a key contributor to ASD pathophysiology, with oxidative stress and immune dysregulation forming

interconnected pathological loops.

Numerous studies have documented oxidative stress imbalances in children with ASD, characterized by mitochondrial dysfunction and elevated oxidative stress markers, including reduced antioxidant enzyme activities, increased lipid peroxidation, and accumulation of advanced glycation end products in peripheral blood^[40]. These oxidative stress and mitochondrial abnormalities trigger a vicious feedback loop, exacerbating cellular damage and impairing brain development, thereby contributing to neurodevelopmental dysfunction.

Concurrently, immune system abnormalities have been consistently observed in both peripheral tissues of ASD patients and in experimental animal models. Chronic neuroinflammation in ASD is evidenced by increased numbers of activated microglia and astrocytes, alongside elevated production of cytokines and chemokines within the brain^[41-42]. Elevated IL-6 levels represent a particularly robust finding in ASD brains^[43]. Notably, inflammation-induced KP activation creates a bridge connecting peripheral immune dysfunction to central neuropathology. The pro-inflammatory cytokine milieu stimulates IDO, shifting tryptophan metabolism toward KP and away from serotonin synthesis, while simultaneously promoting the production of neurotoxic QUIN. This dual effect—reducing neuroprotective serotonin while increasing neurotoxic metabolites—positions the inflammation-KP axis as a critical pathway linking immunological disturbances to the core behavioral features of ASD.

2.2.2 Inflammation-induced NAD⁺ dysregulation and ASD

QUIN, produced during inflammatory responses, is a glutamatergic excitotoxin with dual metabolic and neurotoxic functions. In human neurons, QPRT catalyzes QUIN conversion to NAD⁺; however, high-level QUIN accumulation paradoxically leads to downstream NAD⁺ depletion due to feedback inhibition or substrate overload^[44]. Reduced NAD⁺ levels have been observed in children with ASD^[45], strongly suggesting QUIN accumulation as a contributing factor.

NAD⁺ deficiency has far-reaching consequences for neuronal health and function. As a critical coenzyme in mitochondrial energy metabolism, NAD⁺ depletion directly impairs ATP production,

compromising neuronal energy supply essential for maintaining synaptic transmission and plasticity. Furthermore, NAD^+ is a necessary substrate for SIRT1, a NAD^+ -dependent deacetylase that regulates oxidative stress responses, neuroinflammation, and neuronal survival. NAD^+ depletion thus impairs SIRT1 activity, weakening antioxidant defenses, exacerbating oxidative stress, and promoting a pro-inflammatory state. The resulting mitochondrial dysfunction and impaired synaptic plasticity collectively contribute to neurodevelopmental abnormalities and cognitive deficits characteristic of ASD.

Therefore, inflammation-induced QUIN accumulation serves as a critical mechanistic link between immune activation and neurometabolic disturbances in ASD. By triggering NAD^+ depletion, QUIN disrupts cellular energy homeostasis and redox balance, impairing neurodevelopment and synaptic function. This pathway may explain, at least in part, the mitochondrial dysfunction and energy metabolic abnormalities commonly observed in ASD. The QUIN- NAD^+ -SIRT1 axis represents a potentially targetable pathway for therapeutic intervention: strategies aimed at reducing QUIN production, enhancing NAD^+ levels, or activating SIRT1 could mitigate ASD-associated neuropathology.

2.2.3 Inflammation-induced imbalance in KP metabolites and ASD

The KP metabolites KA and QUIN represent a delicate balance between neuroprotection and neurotoxicity. Inflammation critically disrupts this balance by altering IDO activity and KP metabolic flux.

As previously described, varying degrees of neuroinflammation in ASD result in significant secondary changes in central nervous system KP metabolite levels. IDO activation, driven by pro-inflammatory cytokines, increases tryptophan conversion to kynurenine, shifting the metabolic balance away from serotonin synthesis and toward QUIN production. This inflammatory shift promotes the accumulation of neurotoxic QUIN while potentially reducing neuroprotective KA levels, disrupting the KA/QUIN ratio that is essential for maintaining normal neurotransmission and synaptic function.

The functional consequences of this KA/QUIN

imbalance are profound. KA, by acting as an NMDAR antagonist, limits excessive glutamatergic excitation, providing neuroprotection. Conversely, QUIN as an NMDAR agonist promotes excitatory neurotransmission. Under inflammatory conditions, an elevated QUIN/KA ratio shifts the balance toward excitotoxicity, resulting in elevated intracellular calcium influx, mitochondrial dysfunction, oxidative stress, and ultimately, neuronal damage. Furthermore, the competition between the pro-inflammatory QUIN and immunosuppressive KA may determine the overall inflammatory state and clinical manifestations associated with neuroinflammation^[46].

Thus, inflammation-induced imbalance in KP metabolites—particularly the KA/QUIN ratio—constitutes a central mechanism linking neuroinflammation to ASD pathophysiology. This imbalance not only modulates glutamatergic and cholinergic neurotransmission but also influences neuronal survival, synaptic plasticity, and neural circuit development. Importantly, this pathway suggests that pharmacological strategies to restore the KA/QUIN balance, such as KMO inhibitors to reduce QUIN production or KAT activators to enhance KA synthesis, may offer novel therapeutic approaches for ASD.

2.3 Kynurenine metabolic factors affect key receptors involved in neurodevelopment in ASD

The cerebral cortex contains a wealth of KP metabolite targets from early childhood, including two key receptor targets: $\alpha 7\text{nACh}$ and NMDARs^[47]. A series of studies in this area have shown that, beginning in early neurodevelopment, neurotransmission dysfunction involving these receptors may have a causal relationship with central nervous system abnormalities in various disorders, including ASD.

2.3.1 NMDARs and ASD

NMDARs are pivotal in brain development, regulating neuronal migration, synapse formation, neurite outgrowth, and dendritic spine development^[48]. KP metabolites exert opposing effects on NMDAR activity: QUIN functions as an agonist, whereas KA acts as an antagonist, creating a yin-yang regulatory mechanism.

The opposing actions of KA and QUIN on NMDARs have critical functional consequences for ASD pathophysiology. Under normal physiological

conditions, KA limits excessive NMDAR activation, preventing excitotoxicity and maintaining appropriate synaptic pruning and neural circuit refinement. However, excessive KA accumulation—as observed in BTBR mice—may paradoxically impair cognitive function through excessive NMDAR blockade, disrupting synaptic plasticity and learning processes essential for social cognition. Conversely, elevated QUIN promotes excessive NMDAR activation, increasing intracellular Ca^{2+} influx^[49] and activating downstream signaling cascades that can lead to excitotoxicity and neuronal cell death. Such structural and functional changes in NMDAR-mediated neurotransmission are associated with behavioral abnormalities and various neuropsychiatric disorders^[50].

The vulnerability of the developing brain to KP-mediated NMDAR modulation is particularly relevant for ASD. During critical developmental periods, appropriate NMDAR signaling is essential for experience-dependent synaptic plasticity and refinement of neural circuits underlying social behavior, communication, and cognitive flexibility. Disruption of this delicate KA/QUIN balance—whether toward excessive blockade (KA-driven) or excessive activation (QUIN-driven)—could result in the characteristic neurodevelopmental abnormalities observed in ASD. Furthermore, the NMDAR system represents a key point for therapeutic intervention: balancing KA/QUIN levels or modulating NMDAR function could potentially ameliorate ASD-associated behavioral abnormalities.

2.3.2 $\alpha 7$ nACh receptor and ASD

$\alpha 7$ nACh plays crucial roles in neuronal growth, differentiation, and development, alongside their well-established function in synaptic plasticity^[51]. During brain development, $\alpha 7$ nACh expression is tightly regulated during critical periods for synaptic plasticity establishment^[10], and IDO-mediated tryptophan metabolism *via* KA creates competition with melatonin from the serotonin pathway in regulating $\alpha 7$ nACh receptor function^[52].

$\alpha 7$ nACh receptors are abundantly expressed throughout the central nervous system and peripheral tissues, playing key roles in synaptic plasticity and the pathogenesis of numerous diseases^[53]. Notably, *$\alpha 7$ nACh* mRNA is widely distributed throughout the

embryonic mouse nervous system, with ubiquitous expression in the central, peripheral, and enteric nervous systems^[54]. Its developmental expression pattern suggests a fundamental role in neural circuit formation and refinement.

The relevance of $\alpha 7$ nACh to ASD is supported by multiple lines of evidence. The basal forebrain, which provides the primary cholinergic innervation to the cortex and hippocampus, shows abnormalities in ASD: children with ASD exhibit an increased number of neurons in the basal forebrain, whereas adult ASD patients display smaller and fewer neurons compared to controls, suggesting a progressive disruption in cholinergic transmission. This developmental trajectory—from early overgrowth to subsequent atrophy—is consistent with the broader neurodevelopmental abnormalities observed in ASD^[55].

Furthermore, the interplay between KP metabolism and $\alpha 7$ nACh receptor function offers a mechanistic link to ASD pathophysiology. IDO activation shifts tryptophan metabolism toward KP production, potentially reducing serotonin pathway availability for melatonin synthesis. Melatonin, in turn, has been shown to modulate $\alpha 7$ nACh receptor function. Therefore, inflammation-induced IDO activation and subsequent KP metabolite alterations may indirectly influence cholinergic neurotransmission *via* $\alpha 7$ nACh receptors, contributing to the neural circuit dysfunction underlying ASD.

In summary, the influence of KP metabolites on both NMDARs and $\alpha 7$ nACh receptors constitutes a dual-receptor mechanism through which KP dysregulation contributes to ASD pathophysiology. The opposing actions of KA and QUIN on NMDARs, coupled with the complex interactions between KP metabolites and cholinergic signaling, underscore the multifaceted role of KP in neurodevelopment. Therapeutic strategies targeting these receptor systems—whether through modulating KA/QUIN balance, administering NMDAR modulators, or enhancing $\alpha 7$ nACh receptor function—hold promise for ASD intervention. However, the spatiotemporal complexity of receptor expression during development necessitates careful consideration of developmental stage, brain region, and receptor subtype specificity in designing therapeutic interventions.

3 Questions and reflections

The aforementioned studies suggest that KP may play an important role in the pathogenesis of ASD, primarily through two pathways: inflammation and neurotransmitter transmission. However, research in this field is still in its early stages, and further study is needed to elucidate the specific mechanisms and clinical applications.

3.1 Uncertainties regarding mechanisms

First, the specific mechanisms by which KP metabolites act in ASD remain unclear. Although bidirectional regulation of NMDARs and $\alpha 7$ nACh receptors by KA and QUIN has been demonstrated, there is still a lack of direct causal evidence regarding how these receptor-level changes specifically influence the core symptoms of ASD. Existing studies are primarily observational and largely rely on inferences based on indirect correlations; it remains unclear whether KP metabolic abnormalities are a cause of ASD or merely a concomitant phenomenon in the disease process. Second, differences in KP metabolites across different ASD subtypes have not yet been elucidated. ASD is highly heterogeneous; recent studies suggest that QUIN contributes most significantly to ASD pathogenesis in the subgroup with high inflammation levels (accounting for approximately 70%), indicating that KP metabolic abnormalities may be associated only with specific subtypes. However, research on the metabolic characteristics of KP across different subtypes remains extremely limited. Furthermore, the mechanisms linking KP metabolites to mitochondrial energy metabolism have not been fully elucidated: the specific molecular pathways by which QUIN accumulation leads to NAD^+ deficiency and subsequently affects mitochondrial function remain to be validated, and there is a lack of systematic research on how KP metabolites differentially influence neurodevelopment across different brain regions and cell types.

3.2 Bottlenecks in clinical translation

Regarding biomarker development, reported changes in KP metabolites vary across studies. Some studies have found reduced serum KA and elevated QUIN levels in individuals with ASD, while meta-analyses suggest no significant abnormalities in peripheral blood tryptophan metabolism; trends in

kynurenine levels in cerebrospinal fluid and urine are also inconsistent. These discrepancies in results between peripheral and central systems, as well as across different biological samples, severely limit the translational application of KP metabolites as clinical biomarkers for ASD. Regarding therapeutic interventions, no ASD treatments targeting KP have yet entered the clinical trial phase, and the efficacy and safety of strategies such as IDO inhibitors, KMO inhibitors, or NAD^+ precursor supplementation have not been clinically validated. Furthermore, existing research suffers from methodological limitations: most studies have small sample sizes and do not adequately account for confounding factors such as gender, age, ASD subtypes, and comorbidities, which may lead to biased results.

3.3 Emerging research frontiers

As research deepens, several new questions are emerging. First, the role of KP in the “gut-brain axis” is attracting significant attention: ASD patients exhibit gut microbiota dysbiosis, and alterations in tryptophan-related gut metabolites are closely associated with the severity of ASD symptoms; however, the specific pathways by which KP metabolites derived from the gut microbiota cross the intestinal barrier to influence the central nervous system remain unclear. Second, the developmental stage specificity of KP metabolism urgently needs to be elucidated: the role of KP may vary across different stages of neurodevelopment, but the vast majority of studies have focused on children with ASD, while research on adolescents and adults with ASD is extremely scarce; mechanisms by which maternal inflammation during pregnancy increases the risk of ASD by affecting fetal KP metabolism are also only just beginning to be explored. Third, the interactions between KP and other metabolic pathways remain unclear: excessive KP activation may lead to reduced synthesis of serotonin and melatonin, and KP metabolites may also interact with other neurotransmitter systems; however, very little research has been conducted on how these cross-pathway effects influence the pathophysiological processes of ASD.

4 Prospect

ASD is a neurodevelopmental disorder that begins in early childhood. Although the exact cause

remains unclear, genetic and environmental factors are considered key contributors to its onset. In recent years, the roles of inflammation, oxidative stress, and neurotransmitter dysregulation in ASD have garnered significant attention.

KP, as a key hub linking these pathological processes, has received increasing attention. Inflammatory pathways are the core upstream events driving KP activation. Pro-inflammatory cytokines (such as IFN- γ , TNF- α , and IL-6) promote the metabolism of tryptophan along the KP by activating IDO and TDO, leading to significant changes in downstream metabolites. With regard to oxidative stress, KP metabolites are bidirectionally linked to redox status: 3-HK drives superoxide anion production; its downstream product, 3-HAA, promotes hydroxyl radical generation; and QUIN exacerbates lipid peroxidation damage. At the same time, KP metabolites are extensively involved in neurotransmitter regulation: KA can inhibit the release of dopamine and glutamate, while QUIN exerts excitotoxic effects as an NMDAR agonist, thereby regulating the glutamatergic, GABAergic, dopaminergic, and noradrenergic systems.

Although the association between inflammation, oxidative stress, neurotransmitter dysregulation, and neurological disorders has been repeatedly confirmed, the specific mechanisms and pathways linking these factors to the psychiatric symptoms of ASD remain unclear. Future research should focus on the signaling pathways through which KP directly influences behavioral abnormalities. Currently, inflammation and neurotransmission are considered potential mechanisms by which KP influences ASD; however, identifying specific pathways still requires large-scale samples, omics analyses, and validation of molecular mechanisms. Overall, KP presents both challenges and promise in ASD-related applications, with a broad range of prospects.

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犬尿氨酸代谢及其代谢产物与孤独症谱系障碍的内在关联*

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摘要 犬尿氨酸代谢是生物氨基酸代谢中的关键通路, 在神经发育中起着重要的作用。孤独症谱系障碍是一种始于儿童早期的神经发育障碍疾病, 致病机制十分复杂且尚无定论。目前许多临床数据表明, 在孤独症患者中犬尿氨酸代谢途径出现显著失衡, 且代谢产物发生改变, 这种代谢路径为何失衡, 又如何对孤独症发病进行调控, 这些问题尚不清楚。本文重点介绍了犬尿氨酸代谢过程和其代谢产物的主要生理功能, 并从氧化应激失衡引起的炎症反应、神经传递失调阻碍神经发育这两个与孤独症病因相关角度出发, 分析了犬尿氨酸代谢参与孤独症的可能致病机制。本文综述了犬尿氨酸代谢与孤独症的关联, 为孤独症的病因学提供了新的理论解释, 并为临床诊断与治疗构建了创新性范式。针对犬尿氨酸代谢及其代谢物的研究有望为孤独症的生物标志物筛选、靶向药物开发及个体化干预策略的制定提供关键依据与潜在靶点。

关键词 孤独症谱系障碍, 氧化还原失衡, 非编码核糖核酸表达异常, “肠-脑轴”紊乱, 孤独症致病机制, 孤独症诊断与治疗

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