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The Role of Activation of the Tryptophan-Kynurenine Axis in the Pathogenesis of Acute Cerebrovascular Diseases: A Literature Review

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Abstract

Introduction: Acute cerebrovascular disorders are a major contributor to adult disability. The underlying processes that contribute to their development include inflammation, excitotoxicity, oxidative stress, and dysregulation of the tryptophan–kynurenine pathway, which is essential for neuronal survival. However, the precise mechanisms and significance of these processes are not fully comprehended, and their influence on the efficacy of therapeutic approaches remains uncertain.

The aim of this study is to investigate the role of the tryptophan-kynurenine metabolic pathway in the development of stroke and its potential as a biomarker and therapeutic target.

Results and Conclusions: Tryptophan metabolism primarily occurs through the kynurenine pathway. Among its metabolites, kynurenine, kynurenic and choline acids are the most significant. Them have both neuroprotective and neurotoxic effects. Activation of the kynurenine pathway is linked to chronic inflammation, increasing the risk of cardiovascular and neurodegenerative conditions. Kynurenic and choline acids regulate N-methyl-D-aspartate receptor activity and oxidative stress. The increased production of choline and 3-hydroxyanthranilic acid due to oxidative stress is a major mechanism of neuronal damage under ischemic. The regulation of the balance between the neuroprotective and neurotoxic properties of metabolites produced by the kynurenine pathway is essential for normal brain function.

Keywords: Cerebrovascular Disorders, Kynurenine, Tryptophan, Inflammation, Oxidative Stress, NMDA Receptors.

Introduction

Acute cerebrovascular events, including ischemic strokes, are characterized by a sudden onset of neurological impairment due to reduced blood flow to the brain or bleeding in the brain. The underlying mechanisms involve a complex interplay of inflammatory responses, glutamate toxicity, oxidative stress, and metabolic imbalances, particularly in regard to the tryptophan-kynurenine pathway [1].

The data from the studies conducted demonstrate that levels of metabolites in the kynurenine pathway, including kynurenine (KYN) and kynurenic acid (KYNA), vary in patients with cerebrovascular disorders. Elevated levels of KYN and related metabolites have been associated with the severity of atherosclerosis and other cardiovascular conditions, which are risk factors for stroke [2, 3].

Furthermore, a metabolic analysis of blood samples has revealed a significant correlation between plasma levels of tryptophan (TRP) metabolites and indicators of inflammation and oxidative stress in patients with stroke [4]. These findings support the idea that alterations in the kynurenine pathway may serve as both biomarkers and potential treatment targets for acute cerebrovascular disorders.

The KYN pathway has received significant attention due to its potential for therapeutic applications in various neurological and mental health conditions, particularly in relation to acute cerebrovascular disorders. Preclinical research has demonstrated that manipulating the KYN pathway may provide an effective treatment option for patients with limited therapeutic alternatives, highlighting the importance of ongoing research in this field [5].

Therefore, the question remains unanswered: what is the role of the activation of the tryptophan-kynurenine pathway in the pathogenesis of acute cerebrovascular disorders.

The aim of this study was to investigate the effect

of alterations in the kynurenine metabolic pathway on the key pathogenic mechanisms underlying acute cerebrovascular disease, and to explore the potential use of pathway components as biomarkers and therapeutic targets for acute cerebrovascular therapy.

To conduct this literature review, two researchers independently carried out a comprehensive analysis of scientific publications published in peer-reviewed journals and scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Each publication was evaluated based on the following criteria: transparency and validity of research methodology, amount of experimental data, statistical significance of results, representativeness of study sample (in case of clinical trials), and correctness of data interpretation. A total of 21 review articles and 3 case-control studies were included in the analysis. Additionally, 1 Mendelian randomization trial, 3 experimental studies, and 1 cohort study were considered. A comparative analysis of literature sources is presented in Supplementary File, Table 1.

Table 1 Comparative analysis of the original research used in the literary review.

Acute ischemic stroke (AIS), significant carotid artery stenosis (SCAS), kynurenine (KYN) pathway (KP), tryptophan (TRP), 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), quinolinic acid (QA), picolinic acid (PA), kynurenic acid (KA), anthranilic acid (AA), serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), melatonin (MEL), tryptamine (TA), neopterin (NEO), KTR: 1000 × [KYN]/[TRP], oxidative stress (OS), malondialdehyde (MDA), riboflavin (RBF), liquid chromatography–tandem mass spectrometry (LC-MS/MS), high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), trauma brain injure (TBI), late-life depression (LLD), healthy controls (HC), Mental Disorders (MD), cardiovascular disease (CVD)

Source	Type of research	Methodology description	People/ animals	N	Mean age, years	Sex female/ male	What was measured	Method	limitations
Hajsl, 2020[1]	Case-control	+	people	25 SCAS, 18 AIS, 25 HC	70 (59.0–78.6) SCAS/ 71 (46.8–82.6) AIS / 59 (38.2–65.0) HC	8/17 SCAS / 11/7 AIS / 11/14 HC	KP and serotonin pathway metabolites (TRP, KYN, 3-HK, 3-HAA, KA, AA, QA, PA, 5-HT, 5-HIAA, MEL), TA, markers of inflammation (NEO, KTR), OS marker MDA, and RBF	LC-MS/MS	Small number of probands in studied groups; no information about dietary habits
Genestet, 2014[2]	Analysis of kynurenine production of cultured P. Aeruginosa strains.								
Yan, 2015[3]	Case-control	+	people	28 severe TBI/ 11 patients undergoing elective neurosurgery for implantation of ventriculo-peritoneal shunts following a diagnosis of hydrocephalus (controls) and 20 healthy controls	35 (21-69) TBI; 52 (30-74) controls; 38 (21-55) healthy controls	6/22 TBI; 5/6 controls; 12/8 healthy controls	TRP, KYN, KA, QA, AA, 3HAA	HPLC and GC-MS	no commercially available antibody for the dephosphorylated/ inactive form of IDO1 to allow for its detection in situ; the limited number of tissues stained and the variety of brain regions analysed.
Wu, 2018[4]	Case-control	+	people	156 LLD (85 with MD, 71 without MD)/ 129 HC	66.38±7.34 LLD with MD / 66.78±6.99 LLD without MD / 67.08±6.86 HC	65/20 LLD with MD / 49/22 LLD without MD / 91/38 HC	TRP,KYN, KYNA	LC-MS/MS	the neurotoxic KYN metabolites (QUIN) were not measured.
Ramírez-Ortega, 2017[5]	experimental	+	Animals (rats)	Assessed the impact of 3-hydroxykynurenine and 3-hydroxyanthranilic acid on copper toxicity in astrocyte cell cultures.					
Zuo, 2016[6]	Cohort study	+	people	7,010	Age group 46-49 – 52.8%; age group 70-74 – 47.2%	55.3%/44.7%	KYN, TRP, NEO, KA, 3-HK, 3-HAA, QA	LC-MS/MS	Information on CVD and diabetes at baseline may have been subject to misclassification due to the reliance on self-reporting. The study cohort was from a small geographical area representing 2 narrow age groups.
Wang, 2023[7]	experimental	evaluation of the effect of 3-hydroxykynurenine and 3-hydroxyanthranilic acid on copper toxicity in rat astrocyte cells using cell culture and cell viability analysis techniques.							
Li, 2020[8]	Mendelian Randomization study	+	people	6056 Twins UK cohort, 1768 KORA F4 study	53.4 Twins UK cohort, 60.8 KORA F4 study	92.9% female Twins UK cohort, 51.5% female KORA F4 study	TRP, 5-HT, KYN	genome-wide associations	findings, largely in Europeans, may not be applicable to other populations; No SNPs for serotonin were genome-wide significant, which may bias toward the null in two-sample MR; a Bonferroni correction to account formul tiple comparisons may increase type 2 error

Tryptophan Metabolism

TRP is an essential amino acid that performs many functions in the body, including acting as a precursor to key neurotransmitters such as serotonin and melatonin. About 95% of tryptophan is degraded, mainly through the kynurenine pathway, while the remaining 5% is converted to serotonin through tryptophan hydroxylase (TPH) [2, 6].

The kynurenine pathway (Figure 1) is an essential metabolic process that begins with the breakdown of TRP and leads to the formation of several neuroactive metabolites, such as KYN, KYNA and quinolic acid (QA) [7]. The initial stage of the KYN pathway is catalyzed by enzymes such as indolamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO). These enzymes lead to the formation of N-formyl-l-kynurene, which is then converted to KYN. [2]. KYN can be converted into KYNA through the action of kynurenine aminotransferases I (KAT I), II, and III, which are primarily expressed in astrocytes and are responsible for the majority of KYNA biosynthesis. KYNA exerts a neuroprotective effect by acting as an antagonist at N-methyl-D-aspartate (NMDA) receptors, α7n-nicotinic acetylcholine receptors (α7n-nAChRs), and, at higher concentrations, also acts as a weak antagonist at α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and kainate receptors [5], thereby mitigating excitotoxic effects and regulating neurotransmitter levels [8]. In turn, QA promotes the synthesis of nicotinamide adenine dinucleotide (NAD+), which is essential for energy metabolism and plays a significant role in inflammatory responses [2].

It is generally accepted that TRP is converted to QA in microglial and macrophage cells, or to KYNA in astrocytic cells. Depending on the activity of these metabolites, this process is considered neuroprotective in astrocytes, but neurotoxic in microglial and macrophage cell types, leading to a dualistic perspective on its role in disease [8]. QA is an important product of the kynurenine pathway that contributes significantly to neuronal cell death and chronic dysfunction via at least nine distinct mechanisms, including the generation of reactive oxygen species (ROS), compromised blood-brain barrier (BBB), glutamate-induced excitotoxicity, cytoskeletal instability, mitochondrial dysregulation, stimulation of tau phosphorylation, and impairment of autophagy [9].

3-Hydroxyanthranilic acid (3-HAA) is a metabolite of the kynurenine pathway that has been recognized as a neurotoxic substance capable of inducing neuronal apoptosis. Despite this, 3-HAA has also been shown to have anti-inflammatory properties, as it can reduce inflammation caused by Th17 cells. In blood vessels, 3-HAA inhibits the uptake of low-density lipoproteins (LDL) by macrophages, thereby decreasing local vascular inflammation and the risk of atherosclerosis. Additionally, 3-HAA lowers the levels of very low-density lipoproteins and exhibits beneficial lipid-lowering properties [2].

Kynurenine metabolism and inflammation

Neuroinflammation plays a significant role in the pathogenesis of cerebrovascular disorders, with the kynurenine pathway serving as a connection between inflammation and neuronal damage [8, 10]. Inflammation is a complex process that can lead to the activation of the kynurenine pathway, which is associated with the development of chronic, nonspecific inflammation. This inflammation can exacerbate a range of conditions, including those related to the cardiovascular and neurodegenerative systems [2]. KYN has the potential to cross the BBB and affect neuronal excitability, potentially leading to neuroinflammation and neuronal damage [7]. An increased level of KYN also results in a decrease in ROS production by activated neutrophils [11].

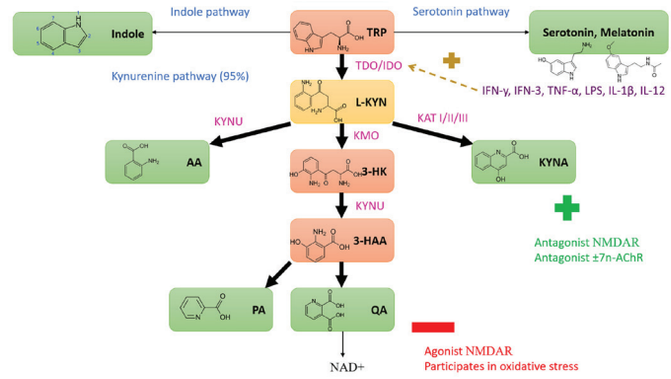

Figure 1 – TRP Metabolism and kynurenine pathway. TRP – tryptophan, KYN – kynurenine, TDO – tryptophan 2,3-dioxygenase, IDO – indoleamine 2,3-dioxygenase, IFN-y – interferon gamma, IFN-3 – interferon 3, TNF-α – tumor necrosis factor, LPS – lipopolysaccharide, IL-1β – interleukin-1 beta, IL-12 – interleukin-12, KYNA – kynurenic acid, KAT – kynurenine aminotransferase, 3-HK – 3-hydroxykynurenine, KMO – kynurenine 3-monooxygenase, AA – anthranilic acid, KYNU – kynureninase, 3-HAA – 3-hydroxyanthranilic acid, QA – quinolinic acid, PA – picolinic acid, NAD+ – nicotinamide adenine dinucleotide +, NMDAR – N-Methyl-d-Aspartate receptor, ±7n-AChR – ± α7 acetylcholine nicotinic receptor

During the acute phase of ischemic stroke, a series of inflammatory processes are initiated, leading to the activation of resident microglia and the infiltration of peripheral white blood cells into the injured brain tissue [4, 10]. This infiltration results in the release of pro-inflammatory cytokines, which enhances the internal inflammatory response of brain cells. The inflammatory mediators released by the infiltrating leukocytes can activate the kynurenine pathway, specifically its neurotoxic metabolites, leading to neuronal damage and affecting clinical outcomes [2, 4]. Pro-inflammatory cytokines may increase IDO activity, which enhances the conversion of TRP to KYN, thereby altering metabolism towards the generation of neurotoxic instead of neuroprotective substances [12, 13]. These downstream metabolites, including KYN, 3-HK, 3-HAA and QA, have been shown to induce apoptosis in various types of immune cells, including T cells, B cells, natural killer cells, and neutrophils [14]. Therefore, they help to reduce inflammatory responses. KYNA may reduce the formation of pro-inflammatory cells by regulating the immunosuppressive effects of AhR [2]. However, KYNA can also contribute to the development of vascular disease through chronic inflammation [15].

Assessment of the concentration of TRP metabolites in the blood of patients with acute cerebrovascular disorders and significant stenosis of the carotid arteries showed that patients with stenosis of the carotid artery and stroke had reduced levels of TRP and 3-HAA, as well as elevated levels of circulating AA and 3-NK [4]. Data from another study of stroke patients showed a positive correlation between the KYN/TRP ratio and the severity of the stroke [16]. As the subarachnoid hemorrhage progressed, the TRP level rose dramatically in conjunction with the development of vasospasm [6].

In the context of stroke, acute inflammation can lead to an increase in neurotoxic metabolite levels, which may affect the severity of neurological impairments and recovery outcomes [1, 8]. According to the study, patients with acute ischemic stroke showed decreased serum levels of TRP and KYNA, as well as increased levels of inflammatory biomarkers such as highly sensitive C-reactive protein (CRP) [10]. Activation of the KYN pathway has been associated with the severity of stroke, as measured by the National Institutes of Health Stroke Scale

(NIHSS). Furthermore, increased activity of IDO has been found to correlate positively with levels of CRP, suggesting a potential link between inflammation and TRP metabolism in stroke patients [10].

Kynurenine metabolism and excitotoxicity

In the context of excitotoxicity, metabolites of KYN exhibit both neuroprotective and neurotoxic effects, depending on their concentration and specific metabolic pathways activated. KYNA exhibits neuroprotective effects as it is an endogenous antagonist of NMDA receptors, which are involved in regulating neuronal excitability, synaptic plasticity, and neuroinflammation through activation by glutamate. QA, on the other hand, has the opposite effect by increasing excitotoxicity as it acts as a potent agonist for NMDA receptors, leading to their overactivation [2, 8, 17, 18] and uncontrolled release of glutamate into the synapse [19, 20]. This leads to an increase in Ca2+ influx into cells, which results in a cascade of damaging events, including the activation of pro-apoptotic pathways, mitochondrial dysfunction, and oxidative stress. This process is particularly significant in conditions of ischemia, such as stroke, where the concentration of ROS increases significantly in affected tissues, leading to cell death in the perifocal area.

The balance between these metabolites is essential for the proper functioning of neurons. Any imbalance can lead to damage to neurons and the progression of acute cerebrovascular disorders [13, 20].

Kynurenine metabolism and oxidative stress

Recent research has shown that activation of the kynurenine pathway during acute ischemia events leads to an accumulation of neurotoxic metabolites, such as QA and 3-HK, which contribute to neuronal damage and oxidative stress [2, 12]. Even relatively low levels of 3-HAA can cause neurotoxicity by inducing oxidative stress [21]. QA also contributes to oxidative stress development by participating in lipid peroxidation reactions and producing ROS [2]. KMO, located on the outer mitochondrial membrane, is the main synthetase in the QA pathway. It converts KYN to 3-HK, which then penetrates the BBB and increases the concentration of a substrate necessary for QA production. This leads to apoptosis of neurons, the generation of free radicals, and the initiation of oxidative stress in the brain, at nanomolar levels. These effects result in increased metal toxicity in astrocyte cultures, and a synergistic effect on neurotoxicity from QA [22]. PA is a non-specific metal ion chelator and neuroprotective agent that has the potential to inhibit QA-induced neurotoxicity. However, its inhibitory effect is less potent than that of KYNA [12]. When the QA level is high, microglial and neuronal NAD+ catabolic activity is limited, which in turn results in the cumulative neurotoxicity of QA in patients with recurrent major depressive disorder, as evidenced by higher levels of KYN metabolites [23]. Oxidative stress is a significant mechanism responsible for QA-induced neurotoxicity. Free radicals can activate various signaling pathways, resulting in pathological alterations in brain cells [5].

KYN has also been shown to reduce DNA and protein degradation caused by the hydroxyl radical and peroxynitrite, as well as weaken the production of ROS and lipid peroxidation induced by pro-oxidant compounds, such as iron(II) sulfate, peroxynitrite, and 3-nitropropionic acid, in rat brain homogenates [5].

Kynurenine metabolism and atherosclerosis

There is evidence suggesting increased levels of KYN, QA and KNA in the blood plasma of patients with atherosclerotic disease [24]. In addition, it has been demonstrated in an animal model of atherosclerosis that the level of IDO1 significantly increases in the blood serum during the development of atherosclerosis and correlates positively with its advanced stages [25]. This may be due to the activation of T cells and the production of IFN-γ, which results in an increase in IDO1 levels. This process leads to macrophage apoptosis and foam cell formation, thereby accelerating atherosclerosis progression. Subsequently, the process also activates AhR in macrophages, resulting in the production of ROS, which exacerbates inflammation of the vessel wall and contributes to lipid accumulation in blood vessels, ultimately leading to vascular atherosclerosis [2]. IDO1 also demonstrates a positive association with both stroke and other conditions such as coronary artery disease, diabetes mellitus, and prostate cancer [26].

The analysis of neuroprotective effects of kynurenine pathway metabolites

Therefore, the neuroprotective effects of the metabolic products of the kynurenic pathway are:

– KYNA, by antagonistically interacting with the NMDAR (reduction of excitotoxicity), a7n-nAChR (immunosuppressive effects [2]), and at higher concentrations with AMPA and kainate receptors [5], thereby reducing excitotoxicity [8], modulating cholinergic and dopaminergic transmission is important for cognitive function.

– 3-HAA, due to its anti-inflammatory and hypolipidemic properties [2].

– KYN causes neuroinflammation, damage to neurons [7], by reducing the degradation of DNA and proteins caused by hydroxyl radicals and peroxynitrites; reduces ROS and lipid peroxidation, [5]

– PA by reducing neurotoxicity of QA [12].

The analysis of neurotoxic effects of kynurenine pathway metabolites

In turn, the following metabolites of the kynurenine pathway have the potential to cause neurotoxic effects:

– KYN reduces ROS production [11].

– QA by synthesizing NAD+ for inflammatory processes [2]; QA by ROS formation, BBB disorders, glutamate-induced excitotoxicity [2, 8, 17, 18, 19, 20], cytoskeletal instability, mitochondrial dysregulation, tau protein stimulation. phosphorylation and autophagy disorders, increasing cell death in the perifocal area [9].

– 3-HAA, causing apoptosis of neurons and oxidative stress

– An increase in IDO activity changes kynurenine metabolism towards the production of neurotoxic rather than neuroprotective substances [12, 13].

– KMO, increasing the number of QA [22].

The role of the tryptophan-kynurenine axis in acute cerebrovascular diseases

The findings of the investigation indicate that TRP performs a significant function in the body by serving as a precursor for neurotransmitters like serotonin and melatonin. Approximately 95 percent of TRP undergoes degradation through the kynurenine metabolic pathway, which influences the formation of neuroactive substances such as KYNA and QA. These metabolites can potentially have either neuroprotective or neurotoxic consequences, depending on the specific cell type.

The action of metabolites produced by the kynurenine

pathway, including 3-HAA, can be neurotoxic, but they can also have anti-inflammatory and lipid-lowering effects. These findings suggest a complex relationship between TRP metabolites and the pathogenesis of various conditions, which warrants further research to elucidate the mechanisms of their actions in the body.

KYN metabolism also plays a significant role in the development of neuroinflammation, and is linked to acute and chronic inflammatory responses that affect the condition of brain tissue and neurons. Increased levels of KYN may activate neurotoxic metabolites, leading to neuronal damage and reduced production of ROS.

Research has highlighted the role of peripheral inflammation in regulating the metabolism of KYN and its systemic effects. It has been demonstrated that exercise can increase the removal of KYN from skeletal muscles, potentially decreasing its accumulation in the brain and alleviating related mood disorders [7]. This emphasizes the significance of inter-organ communication facilitated by KYN metabolites, which not only influence immune responses but also impact overall health.

In addition, the metabolism of KYN plays an important role in the regulation of the neuroprotective and neurotoxic potential of its metabolites, which affects the function of NMDA receptors and the level of excitotoxicity in neurons. Based on the specific effects that KYN metabolism has on excitotoxicity, it is possible to assume that the modulation of these metabolites could represent a potential treatment strategy for neurological diseases associated with an imbalance between neuroprotective and neurotoxic effects. Further research in this field could lead to the development of new drug therapies aimed at stabilizing the metabolism of KYN and preventing neuronal damage in conditions of increased excitotoxicity.

The data from the studies conducted indicate that activation of the kynurenine pathway may lead to neurotoxicity due to the action of certain metabolites, such as QA and 3-HK, and can cause oxidative stress within brain cells. Additionally, QA may contribute to the development of oxidative stress by activating lipid peroxidation reactions and generating ROS. At the same time, mechanisms of protection against QA-induced neurotoxicity may include non-selective metal ion chelation by reactive astrocytes and the ability of kynurenine to reduce oxidative stress within neurons.

The research findings suggest a significant elevation in the levels of KYN and its metabolites in the plasma of patients with atherosclerotic disease, which may be linked to the activation of IDO1, an increase in T cell count, and IFN-γ. Animal studies demonstrate that higher IDO1 levels in atherosclerosis induce macrophage apoptosis and formation of foam cells, thereby accelerating disease progression. Additionally, the activation of AhR in macrophages during atherosclerotic conditions leads to enhanced inflammation of the vascular wall, accumulation of lipids, and ultimately worsening of atherosclerosis and increased risk of cardiovascular events.

Recent research on the KYN catabolic pathway has suggested that targeting specific enzymes within this pathway could contribute to the development of therapeutic approaches based on a mechanistic understanding. These strategies seek to regulate the balance between neuroprotective and neurotoxic metabolites by increasing levels of KYNA while decreasing concentrations of excitotoxic substances such as QA [27]. By preventing the buildup of neurotoxic substances, pharmacological or genetic intervention can pave the way for novel preventive strategies against conditions characterized by inflammation and degeneration of nerve cells [28]. By understanding how metabolites in the kynurenine pathway influence inflammatory pathways, healthcare professionals will be better equipped to develop targeted therapies that take into consideration both the underlying mechanisms and the clinical manifestations of acute cerebrovascular conditions [29].

IDO1 and KYN may also be potential therapeutic targets for hypertension in patients with systemic inflammatory conditions. Additionally, IDO1 plays an important role in the formation of atherosclerotic plaque and inflammation. By modulating IDO1, it is possible to effectively slow down the progression of atherosclerosis and reduce overall inflammation in the body [2].

Therapeutic Approaches

1. Kynurenine Metabolism Modulators

KAT activators: These agents aim to enhance the activity of KAT, promoting the conversion of KYN into KYNA. This process has neuroprotective effects, potentially reducing neurotoxicity caused by elevated levels of quinolinate, a known neurotoxic metabolite. However, the specificity of these activators and potential off-target effects should be carefully considered. Additionally, it is important to maintain a balanced ratio between neuroprotective and neurotoxic metabolites.

2. Inhibition of IDO

IDO inhibitors: IDO is the first enzyme in the kynurenine pathway, and is often increased in inflammatory conditions. By inhibiting IDO, the production of KYN and its neurotoxic metabolites can be reduced. Although reducing KYN can alleviate some neurotoxic effects, it may also impair the production of neuroprotective substances. Additionally, systemic inhibition of IDO may cause immune dysfunction.

3. TRP Precursor Supplementation

TRP supplementation: Providing TRP or its precursor may enhance serotonin synthesis and support neuroprotective effects. The efficacy of this approach may be influenced by diet and individual metabolic factors. Additionally, excessive TRP intake could lead **to elevated KYN levels and potentially exacerbate neurotoxicity.**

4. Use of Neuroprotective Agents

The direct administration of KYNA has been investigated due to its potential neuroprotective properties. While the pharmacokinetics and optimal dosing regimens for KYNA have not been fully established, further research is needed to determine these factors. Additionally, the long-term safety profile of this treatment requires further investigation to ensure appropriate monitoring and management of potential side effects.

5. Lifestyle Modifications

Diets that are rich in omega-3 fatty acids and antioxidant-rich foods may help to modulate the tryptophan-kynurenine pathway by reducing inflammation and oxidative stress. However, the impact of dietary modifications on this pathway is complex and can vary among individuals. Further research is needed to determine specific dietary recommendations based on individual needs.

Conclusions

Therefore, the kynurenine pathway represents a crucial component in the pathogenesis of acute cerebrovascular disorders, serving as a link between various pathogenic mechanisms, including systemic inflammation, excitotoxicity induced by glutamate, neuroinflammation, and oxidative stress. Future investigations in this field may lead to the development of strategies for modulating the kynurenine pathway, potentially improving treatment outcomes for ischemic stroke and other neurodegenerative conditions.

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