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The kynurenine pathway: Role in neurodegeneration and effects on neuronal damage

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ABSTRACT

Recent studies have identified the kynurenine pathway, a main route of tryptophan metabolism, as an important role in both neurotoxic and neuroprotective pathways. Quinolinic acid, a neurotoxic metabolite, and kynurenic acid, a neuroprotective metabolite, have opposite effects on neurons and are critical for understanding how the kynurenine pathway affects neuronal health. Imbalances in these metabolites are linked to cognitive impairment and neurodegeneration. Modulation of the kynurenine pathway provides prospective treatment methods by boosting kynurenic acid or decreasing quinolinic acid levels in order to reduce neuronal damage and decrease disease development. This review examines the significance of the kynurenine pathway in neuronal degeneration, the disorders linked with it, and existing therapy treatments, as well as prospective treatment directions.

Keywords: Kynurenic acid, neurotoxic metabolite, pathway, treatments.

The number of neurons, the cells of the nervous system, reaches up to trillions. The communication, physiology, and biochemical interactions between such a large number of nervous system cells are very complex. Thousands of studies have been and will be conducted to understand their interactions and to elucidate diseases derived from neuronal network systems because this network and system of neurons is very complex. Neuronal damage is a complex process that causes neurological problems and degenerative diseases. This process is initiated by various physiological processes such as oxidative stress, inflammation, apoptosis, and mitochondrial malfunction. In recent years, the kynurenine pathway has aroused widespread interest in understanding the underlying causes of neuronal damage. Quinurenine, a result of tryptophan metabolism, produces metabolites with both neurotoxic and beneficial properties. In particular, kynurenic acid and quinolinic acid play important roles in the pathogenesis of neurodegenerative diseases by acting on neurons in different ways. Neuronal damage is the destruction or death of neurons, which are the basic units of the nervous system that send messages throughout the body. Trauma, ischemia, neurodegenerative illnesses, infections, and toxic exposure can all cause this type of damage. The effects of neuronal injury are severe, frequently resulting in reduced cognitive function, motor impairments, and a variety of neurological illnesses.

GENERAL DEFINITION AND IMPORTANCE OF NEURON DAMAGE

Neurodegenerative diseases include a wide range of diseases. Alzheimer's disease, Parkinson's disease, multiple sclerosis (MS), and traumatic brain injuries, which are among the most well-known, popular diseases with the highest incidence, fall under the definition of neurodegenerative diseases. These diseases are caused by the loss of function, insufficiency, destruction, and morphological or structural integrity of neurons. Neuronal structure disorder is characterized by a decrease or loss of motor functions.[1,2] In Alzheimer's disease, for example, the accumulation of amyloid-beta plaques leads to synaptic damage and neuronal

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death, which is associated with the clinical symptoms observed in patients.[3]

Understanding all the cellular, molecular, biochemical, physiological or structural causes underlying neurodegenerative diseases caused by neuronal structure and dysfunction is of utmost importance for developing effective therapeutic strategies. Indeed, when all these mechanisms are elucidated, the cause of these degenerative diseases will be understood, effective treatments will be developed and future research will be shed light. In conditions such as ischemic stroke, the functioning of blood flow is disrupted and neuronal damage occurs as a result.[4,5] As a result of this damage, cells are exposed to oxidative stress and energy deficiency. Identifying oxidative stress pathways could be a therapeutic strategy for neuronal recovery, but this is a small example.[6]

The neurological system's regeneration capacity is limited, but knowing neuronal injury can help guide healing strategies. The goal of research into stem cell treatment and neuroprotective drugs is to enhance neuronal survival and regeneration after injury.[7] Fibroblast growth factor 10 has been found to enhance functional recovery following spinal cord injury by reducing neuronal damage and increasing healing mechanisms.[4]

Neurological damage can be used as a biomarker to diagnose and track the evolution of neurological disorders. Elevated levels of certain proteins linked with neuronal injury can be detected in the cerebrospinal fluid or blood, providing information on the extent of damage and potential treatment targets. This information can be used to guide treatment decisions and predict patient outcomes.[8]

Understanding the etiology of neurological illnesses requires a thorough investigation into the molecular causes of neuronal injury. Studies have indicated that reactive oxygen species and inflammation play important roles in brain damage, emphasizing the necessity for research into these pathways. By identifying the underlying mechanisms, researchers can create targeted medicines to prevent or reverse neuronal damage.[9]

THE KYNURENINE PATHWAY: METABOLIC AND NEUROLOGICAL IMPLICATIONS

The enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), which catalyze the conversion of tryptophan to kynurenine, commence the kynurenine pathway. This process is regulated by a variety of circumstances, including inflammation and stress, both of which can cause increased enzyme activity. The metabolites produced by this system, particularly kynurenine, can be further transformed into neuroprotective or neurotoxic chemicals, depending on the metabolic situation.[10]

The kynurenine route produces nicotinamide adenine dinucleotide (NAD+), which is an important coenzyme in cellular metabolism. The NAD+ is required for several metabolic activities, including energy production and deoxyribonucleic acid repair. Dysregulation of the kynurenine pathway can result in altered NAD+ levels, influencing cellular metabolism and contributing to metabolic diseases.[11]

The kynurenine pathway is closely associated with inflammatory reactions. Pro-inflammatory cytokines, such as interferon-gamma, can stimulate the expression of IDO, resulting in increased kynurenine synthesis. This mechanism not only alters tryptophan availability but also tips the balance toward the synthesis of neurotoxic metabolites such as quinolinic acid, which can worsen inflammation and contribute to neurodegenerative disorders.[12,13]

The metabolites of the kynurenine pathway, especially kynurenic acid, and quinolinic acid, have a substantial impact on neurotransmitter systems. Kynurenic acid works as an N-methyl-D-aspartate (NMDA) receptor antagonist, giving neuroprotective effects, whereas quinolinic acid is an NMDA receptor agonist, which can cause excitotoxicity. The equilibrium of these metabolites is critical to neuronal health and function.[14]

Dysregulation of the kynurenine pathway has been linked to cognitive deficiencies in a variety of neurological conditions, including depression, schizophrenia, and neurodegenerative diseases.

Quinolinic acid levels have been associated to neuroinflammation and neuronal injury, which can contribute to cognitive impairment. Alterations in kynurenine metabolism have been demonstrated in studies to correspond with the severity of cognitive impairment in illnesses such as Alzheimer's disease and MS.[15-17]

Given the importance of the kynurenine pathway in neurological diseases, it offers prospective therapeutic targets. Modulating the activity of IDO and TDO, as well as the balance of kynurenine metabolites, may provide new treatment options for neuroinflammation and cognitive dysfunction. Inhibiting the formation of quinolinic acid or increasing kynurenic acid levels may give neuroprotective benefits and enhance cognitive results in affected individuals.[18]

The kynurenine pathway is also relevant in cancer, as it can influence tumor growth and immune evasion. Tumors can use the kynurenine pathway to inhibit immune responses, which helps them grow and metastasize. Understanding the relationship between the kynurenine pathway and tumor development could lead to new immunotherapeutic methods that target these metabolic processes.[19]

THE KYNURENINE PATHWAY: DEFINITION AND MECHANISMS OF ACTION

The kynurenine pathway is an important metabolic route for the breakdown of the essential amino acid tryptophan, which is a precursor to the neurotransmitter serotonin. This route is responsible for nearly 95% of tryptophan metabolism, emphasizing its physiological relevance. The route is substantially conserved across species, demonstrating its evolutionary significance in maintaining homeostasis and regulating a variety of biological activities. The kynurenine pathway is also relevant in cancer, as it can influence tumor growth and immune evasion. Tumors can use the kynurenine pathway to inhibit immune responses, which helps them grow and metastasize. Understanding the relationship between the kynurenine pathway and tumor development could lead to new immunotherapeutic methods that target these metabolic processes. The kynurenine pathway is especially important in cancer, as it can regulate tumor growth and immune evasion. Tumors can use the kynurenine pathway to inhibit immune responses, promoting their development and spread. Understanding the relationship between the kynurenine pathway and tumor development may lead to new immunotherapeutic approaches that target these chemical reactions. The IDO and TDO, catalyze the initial and rate-limiting step of converting tryptophan to N-formylkynurenine. This metabolite is then further processed by kynurenine formamidase, which converts it to L-kynurenine, the central intermediate of the pathway. The pathway then bifurcates into distinct branches, each producing a variety of neuroactive and immunomodulatory metabolites, including kynurenic acid, quinolinic acid, and nicotinic acid. The kynurenine pathway is not only involved in the regulation of tryptophan and serotonin levels but also plays a crucial role in modulating the immune system and redox balance within tissues. Dysfunction or dysregulation of the kynurenine pathway has been implicated in the pathogenesis of various diseases, ranging from neurological and neurodegenerative disorders to cancer, and cardiovascular diseases. The wide range of metabolites produced by the kynurenine pathway and their diverse biological roles have made it a focus of extensive research and a potential target for pharmaceutical treatments. The wide array of metabolites generated through the kynurenine pathway, each with distinct physiological and pathological functions, has drawn significant research attention. This metabolic route has emerged as a promising target for potential therapeutic interventions, given its involvement in regulating diverse biological processes, from neurotransmitter balance to immune function and redox homeostasis. The multifaceted nature of the kynurenine pathway and its far-reaching implications in both health and disease have motivated extensive investigations aimed at understanding its underlying mechanisms and exploiting its pharmacological potential.[20-23]

KYNURENINE PATHWAY AND NEURONAL DAMAGE

The kynurenine pathway is a critical metabolic route that plays a fundamental role in the

regulation of various physiological processes, including immune function, neurotransmitter synthesis, and neuronal homeostasis. This pathway is responsible for the conversion of the essential amino acid tryptophan into a diverse array of bioactive metabolites, some of which have potent neuroactive and redox properties that can significantly impact neuronal health and function. Accumulating evidence suggests that alterations in the kynurenine pathway are implicated in the pathogenesis of numerous neurological and neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The imbalance between the neurotoxic and neuroprotective metabolites within this pathway has been identified as a key contributor to the neuronal damage and dysfunction observed in these conditions. One of the primary neurotoxic metabolites generated through the kynurenine pathway is quinolinic acid, an agonist of the NMDA receptor. Quinolinic acid has been shown to induce excitotoxicity, oxidative stress, and neuroinflammation, all of which can lead to neuronal damage and death. In contrast, other metabolites, such as kynurenic acid and picolinic acid, exhibit neuroprotective properties by modulating glutamate receptor activity and reducing oxidative stress. The balance between these neurotoxic and neuroprotective metabolites is tightly regulated by various enzymes and regulatory mechanisms within the kynurenine pathway. Disruptions in the kynurenine pathway, often triggered by neuroinflammation or neuroendocrine imbalances, can shift the metabolic balance towards the production of more neurotoxic metabolites, contributing to the pathogenesis of neurological disorders. Targeting the kynurenine pathway has emerged as a promising therapeutic strategy for mitigating neuronal damage and dysfunction in various neurological conditions. Modulating the enzymes and regulatory mechanisms within this critical metabolic pathway offers the potential to restore the balance between neurotoxic and neuroprotective metabolites, thereby reducing excitotoxicity, oxidative stress, and neuroinflammation that contribute to neuronal injury and degeneration. By developing targeted interventions to selectively enhance the production of beneficial metabolites, such as kynurenic acid and picolinic acid, while limiting the accumulation of harmful compounds like quinolinic acid, researchers aim to develop effective treatments for a range of neurological disorders characterized by neuronal damage.[22-26]

KYNURENINE PATHWAY MODULATORS AND PREVENTION OF NEURONAL DAMAGE

The kynurenine pathway plays a major role in the nervous and immune systems, and its modulators have been investigated for their potential to prevent neuronal damage. Alzheimer's disease, one of the most common causes of dementia, has been shown to be associated with alterations in the kynurenine pathway. Specifically, the pathway has been linked to oxidative stress, glutamate excitotoxicity, and neuroinflammation that characterize the pathogenesis of Alzheimer's disease. The tryptophan-kynurenine pathway is the predominant route for tryptophan catabolism, accounting for approximately 95% of dietary tryptophan degradation. Consequently, immune activation and inflammation can contribute to the accumulation of neurotoxic kynurenine metabolites in the brain, which may exacerbate neuronal damage. Several kynurenine pathway metabolites have been implicated in the pathogenesis of neurodegenerative diseases. The neurotoxic metabolites, such as 3-hydroxykynurenine and quinolinic acid, have been shown to contribute to oxidative stress, excitotoxicity, and neuroinflammation, all of which can lead to neuronal damage and death. In contrast, other kynurenine pathway metabolites, such as kynurenic acid, have demonstrated neuroprotective properties by antagonizing the neurotoxic effects of these compounds and modulating glutamatergic signaling. Pharmacological modulation of the kynurenine pathway, targeting the production or actions of these neuroactive metabolites, has the potential to mitigate the underlying mechanisms of neuronal damage and cognitive impairment. One potential approach for therapeutic targeting of the kynurenine pathway involves increasing the concentration of kynurenic acid, a neuroprotective metabolite that acts as an antagonist at excitatory glutamate receptors, particularly the NMDA subtype. Kynurenic acid

has been shown to have the ability to block the neurotoxic effects of other kynurenine pathway metabolites, such as quinolinic acid, which is an agonist at the NMDA receptor and can induce excitotoxicity. Strategies to enhance kynurenic acid levels, either through the inhibition of enzymes involved in its degradation or the promotion of its synthesis, may therefore represent a viable therapeutic approach for neuroprotection in Alzheimer's disease and other neurodegenerative conditions.[27-29]

RESEARCH ON THE KYNURENINE PATHWAY AND NEW THERAPEUTIC DIRECTIONS

The therapeutic potential of the kynurenine pathway has not gone unnoticed, and there is a growing interest in developing new pharmacological interventions that target this metabolic route. By modulating the balance of the various kynurenine metabolites, researchers hope to harness the beneficial effects while mitigating the detrimental consequences, ultimately leading to novel therapeutic strategies for neurological disorders. One promising approach involves the manipulation of the kynurenine 3-monooxygenase enzyme, which plays a central role in the pathway. By inhibiting this enzyme, it may be possible to redirect the metabolic flux toward the production of neuroprotective kynurenic acid, thereby reducing the accumulation of neurotoxic compounds like quinolinic acid. In addition to the promising therapeutic potential of the kynurenine pathway, the field is not without its challenges and controversies. Researchers have grappled with the complex interplay between the various metabolites, their differential effects on neuronal function, and the intricate regulatory mechanisms that govern the pathway.[30,31]

INNOVATIVE APPROACHES TO PREVENT NEURON DAMAGE

Preserving the integrity and functionality of neurons is a critical challenge in the field of neuroscience, as neuronal damage can lead to a wide range of debilitating neurological conditions. While current treatment options have limitations in halting the progression of neurodegenerative processes, researchers have explored innovative strategies to address this pressing issue. One promising approach involves the utilization of neurotrophic factors, which are essential biomolecules that promote the survival, growth, and regeneration of neurons. These factors have demonstrated significant potential in animal models of various neurological diseases, exhibiting neuroprotective and regenerative effects. However, the translation of this potential to clinical applications has been hindered by factors such as poor blood-brain barrier permeability and short biological half-lives of the neurotrophic factors. To overcome these challenges, researchers have explored alternative methods to harness the neuroprotective capacity of endogenous neurotrophic factors. This includes the development of small molecule inducers that can stimulate the production or activity of these factors within the body, as well as the exploration of cell transplantation strategies that can deliver neurotrophic factors directly to the site of neuronal damage. These innovative approaches have the potential to unlock new avenues for the treatment of neurodegenerative disorders, offering hope for patients and their families.[32-35]

In conclusion, the brain and its constituent cells, the neurons, have an extremely complicated and complex functioning. As a result of disruptions, inadequacies, or complete loss in the functioning of neurons, also known as cells of the nervous system, different and various neurodegenerative diseases are derived. Neuron damage is directly related to the kynurenine pathway. Neuronal health is of utmost importance to ensure that the functioning of neurons is not disrupted or inadequate. Neuronal health may depend on biomolecules or metabolites that exhibit neurotoxic and neuroprotective properties. The metabolites of the kynurenine pathway, especially quinolinic acid, and kynurenic acid, affect the health and functionality of neurons. Neuronal damage is associated with cognitive impairment and neurodegenerative diseases such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, and MS. These associations and neuronal damage occur as a result of kynurenine imbalance. Modulation and optimization of the kynurenenin pathway inspire various therapeutic

strategies. Research suggests that increasing neuroprotective metabolites such as kynurenic acid or suppressing neurotoxic compounds such as quinolinic acid may reduce neuronal damage and slow disease progression.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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