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Mini Review

Kynurenine Pathway and Human Diseases: Potential Therapeutic Agents Against Such Diseases

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Abstract

Tryptophan is one of the essential amino acids. Kynurenine pathway is the major pathway in the metabolism of tryptophan. The objective of the study was to provide information on human diseases associated with kynurenine pathway as well as potential therapeutic agents that could combat such diseases.

The methodology involved gathering information from scientific journals, official books, as well the internet websites.

The results show that elevation of kynurenine-3-monooxygenase, quinolinic acid and 3-hydroxykynurenine in the central nervous system leads to a number of neurological and non-neurological human diseases.

In conclusion, the study has shown that the disorder of kynurenine pathway is associated with a number of neurological and non-neurological diseases.

Keywords: *Kynurenine Pathway; Human Diseases; Potential Therapeutic Agents*

Introduction

The kynurenine pathway accounts for the catabolism of about 99% of consumed tryptophan not employed for protein synthesis [1]. It is the principal pathway in tryptophan metabolism. Such metabolism occurs in peripheral tissues (kidney, liver) and central nervous system (astrocytes, microglia). The kynurenine pathway present in the central nervous system (CNS) vary in amounts in most cell types, such as astrocytes, neurons, macrophages and microglia, oligodendrocytes and endothelial cells [2, 3]. Tryptophan (free form) in the central nervous system acts as a precursor to several metabolic pathways, namely the synthesis of kynurenine (KYN), serotonin, melatonin and protein [4]. The oxidation of tryptophan initiates the kynurenine pathway. The first and rate-limiting step of the kynurenine pathway is catalyzed by tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO) [5,6]. These heme-dependent enzymes (IDO, TDO respectively) insert molecular oxygen across the 2,3 bond of the indole moiety of tryptophan [7]. Kynurenine pathway activation by alpha-interferon (IFN-a) results in increasing amounts of kynurenine pathway metabolites, namely kynurenine, kynurenic acid and quinolinic acid concentrations in cerebrospinal fluid [8]. Three metabolic pathways are associated with the metabolism of kynurenine.

Kynurenine-3-monooxygenase (KMO), kynurenase (KYNU), and 3- hydroxyanthranolic acid dioxygenase (3-HAO) are the enzymes involved in the first metabolic pathway. One of the products of this first pathway is quinolinic acid (QUIN). The second pathway gives kynurenic acid (KYNA), having kynurenine aminotransferase (KAT) as the catalyzing enzyme. Anthranilic acid is the product of the third

pathway catalyzed by kynurenase. Kynurenine-3-monooxygenase the major enzyme of the kynurenine pathway relies on nicotinamide adenine dinucleotide phosphate (NADP) in playing vital role in many human diseases [9]. Furthermore, enhanced quinolinic acid levels following the activation of the kynurenine pathway are associated with numerous neurological diseases (anxiety, depression, human immunodeficiency virus-associated neurocognitive disorders, epilepsy, Alzheimer's disease and Huntington's disease) [10-13].

In this context, the objective of this article was to examine human diseases associated with kynurenine pathway and the potential therapeutic agents that could be utilized in the management such diseases.

Neurological diseases

(a) Alzheimer's disease

Alzheimer's disease (senile dementia) is a progressive neurological degenerative disease. Potential therapeutic agents are (i) clioquinol (quinoline metal chelator)- dissolves beta amyloid (Aβ) aggregates implicated in Alzheimer's disease by chelating copper and zinc ions [14], (ii) nicotinylalanine- quinolinic acid synthesis inhibitor. Increased level of quinolinic acid has been reported in Alzheimer's disease patients [15].

(b) Parkinson's disease

Parkinson's disease is associated with the degeneration of dopamine neurons in substantia nigra and Lewy body in the cytoplasm of the remaining neurons. Potential therapeutic agents are:

- Clioquinol- reduce the elevated levels of iron in the substantia nigra by chelation and capable of antagonizing the action of the Parkinson's inducing agent 1-methyl-4-phenyl-1,2,3,6-tetra-pyridine (MPTP) [16],
- KMO potent inhibitors (diclofenac and Ro61-8048 (3,4-dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl] benzenesulfon-amide)- acts by elevating.

kynurenine acid (KYNA) levels in the CNS [17].

(c) Huntington's disease

Huntington's disease (HD) is a neurodegenerative disease caused by the increase of the polyglutamine bundle in Huntington's protein (HTT), resulting in the accumulation of the protein in nuclear and cytoplasmic inclusions. Potential therapeutic agents are: (i) clioquinol- acts by reducing iron, copper and zinc that have been implicated in the brain of Huntington's disease patients [18], (ii) Ro61-8048 (3,4-dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl] benzenesulfon-amide)- reduces the levels of quinolinic acid and 3-hydroxykynurenine (3-HK) in the CNS [19].

(d) Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease with increased levels quinolinic acid in cerebrospinal fluid (CSF) and serum [20]. Potential therapeutic agents are: (i) methyl-thiohydantoin-tryptophan, (ii) nicotinylalanine, (iii) meta-nitrobenzoylalanine (iv) Ro61-8048. The first three agents are kynurenine pathway inhibitors [21,22].

(e) Epilepsy: a tendency to have recurrent seizures unprovoked by any systemic or acute neurologic insults. Potential therapeutic agents are: (i) Nicotinylalanine- acts by increasing the amount of KYNA produced in the brain [23], (ii) meta-nitrobenzoylalanine- inhibits KMO and such inhibition results in sedation and anticonvulsant effects because of increased KYN and KYNA in the brain [24].

Non-neurological disease

KMO is widely scattered in non-neural tissues such as kidney, liver, macrophages and monocytes and has been implicated in a number of non-neurological diseases [25].

(a) Acute pancreatitis (AP)

Elevation of KMO and 3-HK levels, are found to be proportional to disease severity in acute pancreatitis patients. [26, 27]. Potential therapeutic agents are: (i) Ro61-8048 (3,4-dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl] benzenesulfon-amide) and (ii) meta-nitrobenzoylalanine. Both agents are KMO inhibitors. The inhibition results in an increase in KYN and KYNA as well as significant reduction in the neurotoxic levels of 3-HK and QUIN in the CNS [28, 29, 30].

(b) Hepatocellular carcinoma (HCC)

Report has shown that KMO can absolutely regulate the proliferation, migration, and invasion of HCC cells [31]. Potential therapeutic agents are: (i) leflunomide- an immunosuppressive agent (ii) tranilast- a synthetic anthranilic acid derivative agent with immunosuppressive property [32], (iii) KMO inhibitors- inhibited cell proliferation of tumor cells [33]. (iv) methyl-thiohydantoin-tryptophan (tryptophan 2,3-dioxygenase inhibitors)- found to potentiate the efficacy of chemotherapy drugs and also promote tumour regression without increasing the side effects [34].

(c) Inflammation: A localized reaction which generates redness, warmth, swelling, and pain arising from irritation, infection and injury. It can be external or internal. Potential therapeutic agent is: (i) leflunomide- kaynurenine pathway inhibitor [35].

Although we have listed a number of potential therapeutic agents against neurological and non-neurological diseases associated with this pathway, a vast majority of such agents are yet to be discovered either as enzyme inhibitors or chemical compounds (metabolites) antagonists or blockers since they are many enzymes and metabolites involved in kynurenine pathway.

Conclusion

The generation of quinolinic acid is believed to be the major link between the kynurenine pathway and inflammatory response. Quinolinic acid concentrations increase in cerebrospinal fluids has been observed in several neurodegenerative diseases. The current interest in kynurenine pathway is because of apparent links of the pathway with neurodegenerative diseases, tumor proliferation, inflammation and depression.

Finally, it is hoped that by targeting the kynurenine pathway, more effective therapeutic agents, acting in synergy with other agents, may provide a better treatment for neurological and non-neurological diseases.

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