ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

COMMENTARY

Tryptophan metabolism in schizophrenia

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This commentary aims to emphasize the molecular mechanisms involved in the pathophysiology of schizophrenia and in the onset of the disease addressed in an article recently published by Carvalho *et al.*[1] In addition, it is necessary to gather recent and updated information on the role of tryptophan and its metabolites, emphasizing the relationship of this amino acid and its metabolites in the pathophysiology of schizophrenia, with a focus on the kynurenine pathway and, above all, its possible associations with the mental illnesses[2].

Carvalho *et al.* reported that when tryptophan crosses the blood–brain barrier, its metabolites exert different actions on the central nervous system (CNS)[1]. Important neuroactive metabolites resulting from tryptophan metabolism, including serotonin, melatonin, 3-hydroxykynurenine (3-HK), quinolinic, and kynurenic acid (KYNA), have been associated with neuropsychiatric diseases such as schizophrenia[2].

Schizophrenia is a disorder that shows a functional imbalance of the dopaminergic system, causing cognitive and emotional functions to be altered due to changes in the dopaminergic response. These changes can be divided into two subgroups of symptoms: positive and negative[3]. Positive symptoms, such as delusions, hallucinations, psychoses, paranoia, disordered thinking, and disorganized speech, occur as a result of dopaminergic hyperactivity in the mesolimbic area. Negative symptoms, such as demotivation, violent emotional behavior, social isolation, cognitive impairment, and slow speech, occur due to dopaminergic hypoactivity in prefrontal cortex projections[3].

Tryptophan is an essential amino acid that is not synthesized by the body and, therefore, needs to be obtained from the diet; it is present in the vast majority of foods. About 90% of ingested tryptophan is bound to plasma albumin and only 10% is found in free form in the bloodstream[4]. Non-esterified fatty acids are essential for the balance between the tryptophan in free form and the tryptophan bound to albumin, as they compete with this amino acid for binding to plasma albumin, consequently increasing the level of free tryptophan in plasma[5].

This acid amine is a substrate for the production of several neuroactive molecules with biological activities, such as serotonin (5-hydroxytryptamine [5-HT]), melatonin, 3-HK, quinolinic acid (QA), and KYNA, among others[6]. The two main known pathways of tryptophan metabolism are 5-HT and kynurenine. About 95% of tryptophan obtained from the diet is metabolized through the *kynurenine* pathway, and only about 1% of tryptophan is converted to 5-HT in the CNS, while the rest is converted to proteins and melanin[6].

As shown in Figure 1, tryptophan is a substrate for the synthesis of 5-hydroxytryptamine, also known as serotonin (5-HT), in the CNS. Tryptophan

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Citation: Júnior DST, da Silva HT, Ribeiro AM, *et al.*, (2023), Tryptophan metabolism in schizophrenia. INNOSC Theranostics and Pharmacological Sciences, 6(2): 0435. https://doi.org/10.36922/itps.0435

Received: April 13, 2023

Accepted: July 19, 2023

Published Online: August 4, 2023

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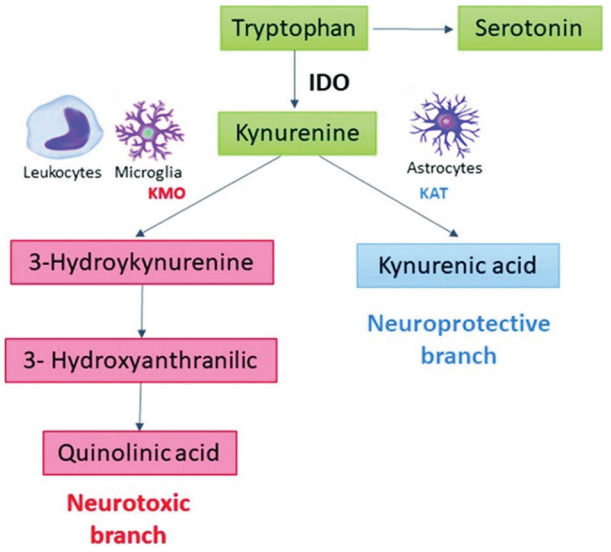


Figure 1. Tryptophan metabolism pathway.

availability may have rate-limiting effects on 5-HT synthesis[7]. Tryptophan is hydrolyzed by the action of tryptophan hydroxylase into 5-hydroxytryptophan, which is rapidly metabolized into 5-HT. 5-HT is stored in synaptic vesicles, in serotonergic neurons, until it is used and/or metabolized to 5-hydroxyindoleacetic acid[8].

5-HT produced from tryptophan, which belongs to the class of small-molecule and fast-acting neurotransmitters, is responsible for acute responses of the CNS and one of its characteristics is to intensify satiety[9]. In addition, low levels of 5-HT can lead to psychopathologies, such as depression, suicide, aggression, anxiety[10], anorexia, and bulimia. Elevated levels of tryptophan result in inhibition of gluconeogenesis, increase in blood glucose level and glucose release to the brain, thereby reducing appetite[11]. Variation in brain serotonergic activity (tryptophan and 5-HT) has been implicated in the regulation of appetite, anxiety and impulse/binge control. 5-HT inhibits neuropeptide Y, resulting in the suppression of hunger and food intake[11].

Eventually, tryptophan can still be converted into melatonin, which is a hormone synthesized by the pineal gland, and is a hormone related to sleep regulation in humans[9]. It is also important to mention that, although it is known to be found in lower concentrations in patients with schizophrenia, the importance of melatonin for some specific symptoms of schizophrenia and in inhibiting some side effects of antipsychotics is still underestimated[9]. Interestingly, the melatonin pathway, which is recognized as a genetic susceptibility factor for bipolar disorder, contributes to the increased risk of cardiovascular complications and decreased life expectancy, and is also frequently reported in schizophrenia[9].

When there is a deficiency of niacin (vitamin B3) in the body, tryptophan can be used for the synthesis of the essential cofactor nicotinamide adenine dinucleotide (NAD^+), which is an important carrier of electrons and fundamental in the production of energy for the cell[12].

Kynurenine pathway is the main route of tryptophan metabolism (Figure 2), responsible for metabolizing more than 95% of this acid amine in the human body, and the catabolic action of some important enzymes in this pathway is dependent on the presence of vitamins B2 and B6, which act as cofactors[10].

However, it is already known that the degradation of tryptophan and the activation of the kynurenine pathway generates several neuroactive compounds, such as KYNA, which is an antagonist of the N-methyl-D-aspartate (NMDA) receptor and the alpha-7-nicotinic cholinergic receptor[13]. It is also known to have a neuroregulatory role in contrast to other kynurenine products[14]. The effect of KYNA on schizophrenia can be explained by its blocking action on glutamate receptors, which are found at elevated levels in patients with schizophrenia. Recent findings have specifically supported the neuroregulatory role of KYNA[15]. KYNA impairs glutamatergic and dopaminergic neurotransmission, and its elevation in the brain is related to psychotic symptoms and cognitive impairments[16].

QA is a selective agonist of NMDA-sensitive ionotropic glutamate receptors[17]. The known neurotoxic role of QA is executed by triggering excitotoxicity and neurodegeneration. Besides, an increase of QA production, which is detrimental to other pathways, elevates the risk for neurological and psychiatric disorders, including depression and schizophrenia[17]. The balance between QA and KYNA, which act as agonist and antagonist, respectively, can be controlled by the relative expression and activity of kynurenine aminotransferases, kynureninase, and kynurenine-3-mono-oxygenase, perhaps indicating a significant physiological or pathological relevance of the quinolinate/Kynurenate relationship. Likewise, disturbances in cognition are associated with high levels of kynurenate and attributed to the slowing down or suppression of excitatory neurotransmission by this compound[13].

There is evidence that dysregulation of the tryptophan-kynurenine pathway can culminate in certain psychiatric disorders such as schizophrenia with increased tryptophan degradation that can induce serotonin depletion and depressed mood[18]. The downstream metabolites from this pathway, such as 3-HK, QA, and KYNA[18], are neuroactive components that can modulate several neurotransmissions, such as glutamatergic, GABAergic, dopaminergic, and noradrenergic neurotransmissions.

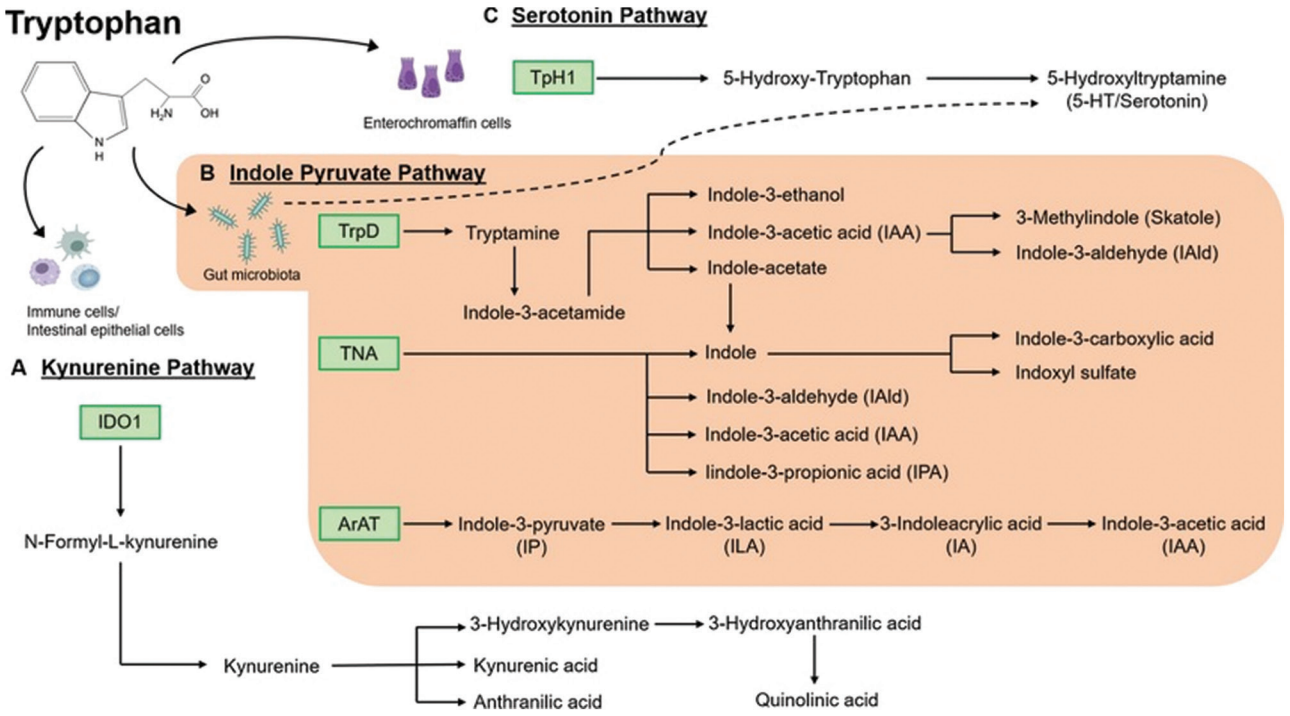


Figure 2. Tryptophan metabolism. Kynurenine (A), indole pyruvate (B), and serotonin pathways leading to different secondary metabolites.

In turn, these neurotransmissions can induce changes in the neuronal-glial network and result in neuropsychiatric consequences[19]. Myint and Kim[19] have shown that upregulation of tryptophan pyrrolase results in increased kynurenine/tryptophan ratio and decreased serotonin/tryptophan ratio in the bilateral hippocampus of the brain. Either tryptophan pyrrolase gene knockout or pharmacological inhibition of hippocampal tryptophan pyrrolase activity attenuates both nociceptive and depressive behavior[20].

Although the data from the studies are not sufficient to identify the mechanisms involved, it is possible to suggest that the low level of tryptophan is related to the decrease in the supply and the increase in the catabolism of this amino acid, which is, therefore, able to promote greater vulnerability to white matter lesions in patients, by activation of neuroinflammation, neurovascular, and neuroendocrine pathways[2].

From an etiological point of view, it is difficult to establish a single potential pathway involved in the pathophysiology of schizophrenia. Nevertheless, there is a general consensus that the development of schizophrenia is dependent on both predisposing factors (genetic, constitutional, and biochemical) and environmental factors. The dopaminergic hypothesis is widely accepted as it associates dopaminergic stimuli with the symptoms of schizophrenia. Dopamine is a central neurotransmitter released in vesicles at synapses in the CNS; in schizophrenia, the mesolimbic and mesocortical systems are involved. The dopaminergic hypothesis is based on the fact that mediation antipsychotic blocks postsynaptic dopamine receptors of the D2 subtype, resulting in an improvement in symptoms. On the other hand, the administration of dopamine agonists worsens the symptoms of schizophrenia. The emerging "second-generation" atypical antipsychotics, which have a broader profile in addition to drug blockade dopamine receptors, block type 2 serotonin receptors, suggesting a role for serotonin in the pathophysiology of schizophrenia[21].

Another neurotransmitter, glutamate, is also linked to the development of schizophrenia. According to glutamatergic hypothesis, excessive amounts of this neurotransmitter are released and exert a neurotoxic effect that triggers the symptoms of schizophrenia. Therefore, in recent years, it remains controversial whether the dopaminergic hypothesis is the only dysfunction related to schizophrenia. Current studies on the neurobiology of schizophrenia evaluate the multiplicity of factors, including genetics, anatomy (mainly through structural neuroimaging examinations), functional circuits (by functional neuroimaging examinations), neuropathology, electrophysiology, neurochemistry, neuropharmacology, and neurodevelopment[22].

In summary, schizophrenia is one of the most intriguing and well-studied psychiatric conditions. The

psychopathological richness and the clinical characteristics, such as its onset in adolescence and the deteriorating course without major neurological alterations, arouse curiosity and generate a considerable number of studies on the neurophysiological processes involved in the disease. Furthermore, increased KYNA can have several important adverse consequences in schizophrenia. Dysfunctions of these receptors have been associated with cognitive impairments and symptom manifestations seen in people with schizophrenia[3].

Many advances have made it possible to better understand the pathophysiology of schizophrenia. However, much is yet to come. Several research groups around the world, using the wide array of methodologies, are working hard to deepen our understanding of the processes involved in the disease. It is expected that the in-depth knowledge of the pathophysiological mechanisms involved will allow the development of even more effective treatments for the control and eventually the prevention of schizophrenia.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the commentary.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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