What's new in KYNA? A review of current literature

Co nowego w KYNA? Przegląd aktualnego piśmiennictwa

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Abstract

The present article reviews current research on the role of the metabolites and enzymes of the kynurenine pathway in the pathogenesis, and potential new trends in the therapy, of diseases of the central nervous system. The authors present reports on the regulatory role of the kynurenine pathway in the activity of the immune system and the relationships between the activity of the kynurenine pathway and parameters of inflammation. Also discussed is the role of the kynurenine pathway in the pathomechanisms underlying the development of neurodegenerative diseases, schizophrenia, bipolar disorder and migraine. The article presents research on the role of the kynurenine pathway in the body's response to the action of antipsychotic drugs. An interesting line of research in this area concerns the possibilities of influencing the activity of the kynurenine pathway using synthetic compounds. Another new problem in KYNA research is related to changes in the expression of kynurenine 3-monooxygenase, which may turn out to be a risk factor for neurocognitive deficits in schizophrenic patients. Increased prenatal levels of KYNA may be associated with an increased risk of cognitive deficits in adult life. The kynurenine pathway may also play a regulatory role in the physiology of behavior.

Keywords: kynurenic acid, mental disorders

Streszczenie

Artykuł przedstawia aktualne badania naukowe na temat roli metabolitów oraz enzymów szlaku kynureninowego w patogenezie i potencjalnych nowych kierunkach terapii chorób ośrodkowego układu nerwowego. Autorzy przedstawiają doniesienia mówiące o regulacyjnej roli szlaku kynureninowego w odniesieniu do aktywności układu immunologicznego oraz powiązania między aktywnością szlaku kynureninowego i parametrami stanu zapalnego. Podnoszą również znaczenie szlaku kynureninowego w patomechanizmach stojących za rozwojem chorób neurodegeneracyjnych, schizofrenii, choroby afektywnej dwubiegunowej migreny. W artykule przedstawiono również badania nad rolą szlaku kynureninowego w odpowiedzi organizmu na działanie leków przeciwpsychotycznych. Interesujące wydają się również nowe możliwości wpływania na aktywność szlaku kynureninowego za pomocą związków syntetycznych. Zmiany ekspresji 3-monooksygenazy kynureniny mogą okazać się z kolei czynnikiem ryzyka deficytów neuropoznawczych u chorych na schizofrenię. Zwiększony poziom KYNA w życiu wewnątrzmacicznym, może być związany ze zwiększonym ryzykiem deficytów poznawczych w okresie dorosłości. Szlak kynureninowy może także odgrywać rolę regulacyjną w zakresie fizjologii zachowania.

Słowa kluczowe: kwas kynureninowy, zaburzenia psychiczne

Introduction

It has been known since the beginning of the previous century that kynurenic acid (KYNA) is a product of metabolism of the exogenous amino acid, tryptophan. This is because the main pathway of tryptophan metabolism encompasses kynurenine and its derivatives. Kynurenine can be metabolized to anthranilic acid or KYNA or it can be transformed into 3-hydroxykynurenine, and then into quinolinic acid. The reaction of production of KYNA from L-kynurenine is catalyzed by three isoforms of kynurenine aminotransferase [1]. KYNA is, so far, the only known unselective endogenous antagonist of all subtypes of ionotropic glutamatergic receptors [28]. It has been found that these receptors can only be blocked by high, hyperphysiological concentrations of KYNA; lower concentrations exert a strong competitive blocking action on the strychnine-insensitive glycine site in the NMDA receptor complex, as well as a non-competitive blocking action on alpha 7 nicotinic acetylcholine receptor [2]. The study of presynaptic NMDA receptors that respond to physiological, low concentrations of KYNA was the starting point in KYNA research. The above-described properties of KYNA inspire growing interest in the metabolites and enzymes of the kynurenine pathway in relation to schizophrenia [3,4, 5], bipolar disorder, [6], inflammatory processes in the brain and spinal cord [22], depression [7,8], brain strokes [9], migraine, and neurodegenerative processes [10]. In the era of rapidly developing research on KYNA, there is increasing interest in the possibility of its clinical use, both in terms of predicting the

effects of treatment, as well as new possibilities in the treatment of CNS disorders [11].

Changes in the expression of kynurenine 3-monooxygenase as a risk factor for neurocognitive deficits in schizophrenia

Cognitive deficits aggravate the quality of life and the productivity of people suffering from schizophrenia, however, no fully effective therapies against those deficits have yet been found. Preclinical data point to the kynurenine pathway of tryptophan metabolism as a target in the design of pro-cognitive drugs. Previous studies have shown a link between the presence of a kynurenine 3-monooxygenase (KMO) gene variant with reduced KMO gene expression in *postmortem* studies and neurocognitive endophenotypic deficits in a clinical sample [29]. Kynurenine 3-monooxygenase is a microglial enzyme that regulates the rate of kynurenine metabolism in the cortex. Changes in the expression of the KMO gene might be the cause of impaired cortical kynurenine metabolism observed in schizophrenia. Wonodi et al. have confirmed that the KMO gene allele rs2275163C> TC is associated with deficits in general neuropsychological performance and that this effect is more pronounced in patients suffering from schizofrenia than in healthy controls. The relationships between the occurrence of the KMO Arg452Cys allele and the severity of cognitive deficits in patients with schizophrenia also arouse the interest of researchers [3].

Relationships between KYNA and the immune system

Evidence gathered so far suggests that the pathogenesis of schizophrenia is associated with brain immune activation. Numerous reports suggest that patients with schizophrenia have elevated levels of pro-inflammatory cytokines; it should be noted, however, that some of those studies have limitations resulting from the fact that cytokine levels were only determined at the periphery and that various antipsychotic therapies were used [30].

Schwieler et al. have looked for a correlation between the level of pro-inflammatory cytokines in the cerebrospinal fluid and the concentrations of kynurenine metabolites in a cell culture of human cortical astrocytes. The levels of pro-inflammatory cytokines were determined using electrochemiluminescence detection, and the kynurenine pathway metabolites were analyzed using high performance liquid chromatography or liquid chromatography/mass spectrometry. The study included patients with schizophrenia receiving olanzapine treatment and healthy controls. Patients with schizophrenia had elevated levels of interleukin-6, compared with the control group. Moreover, in the patients, there was a positive correlation between IL-6 and the tryptophan/KYNA ratio, which indicates that IL-6 activates the kynurenine pathway. In line with the above results, the administration of Il-6 to the culture of human astrocytes increased cell medium concentration of KYNA. As limitations to their study, the authors reported the fact that the cerebrospinal fluid samples had been frozen and thawed twice prior to analysis and that the median age differed between the patients and the controls [4].

Increased prenatal levels of KYNA and the risk of cognitive deficits in adult life

A study by Pershing et al. suggests that increased levels of brain KYNA in rats, induced by exposure to its precursor, kynurenine, from embryonic day 15 to postnatal day 21, result in neurochemical and cognitive deficits in adulthood. The study assessed how exposure to kynurenine affected the parameters of prefrontal cortex activation. Administration of kynurenine with food increased maternal and fetal plasma levels of kynurenine and elevated fetal KYNA levels on embryonic day 21 by compared with the control group. Elevations in forebrain KYNA disappeared after termination of exposure to kynurenine, but KYNA levels in the prefrontal cortex of the subjects proved unexpectedly elevated again when measured in adulthood. Additionally, several other markers of prefrontal excitability were observed, including expression of the α7nAChR, expression of mGluR2, dendritic spine density. These results highlight the deleterious effect of elevated KYNA levels during the difficult period of early development. This is a kind of pathophysiological model of the cognitive deficits observed in schizophrenia [5].

The role of the kynurenine pathway in bipolar disorder

Inflammation-associated changes in the concentrations of kynurenic acid have been reported for depression secondary to other medical conditions, and also in patients with bipolar disorder [31]. The discrepancies in the reports may have been related to the presence or absence of psychotic symptoms as well as the effect of medication. Savitz et al. have investigated whether concentrations of the putatively neuroprotective metabolites of the kynurenine pathway (kynurenic acid) and neurotoxic metabolites of this pathway (3-hydroxykynurenine and quinolinic acid) are altered in a primary disease such as bipolar disorder and whether changes in serum concentrations of these metabolites are associated with hippocampal and amygdalar volumes. Those authors compared three groups of subjects: moderately-to-severely depressed unmedicated subjects, medicated subjects with a diagnosis of moderate-to-severe depression in bipolar disorder, and healthy controls. Their results have shown that

the abnormalities in kynurenine metabolism observed in patients with bipolar disorder may affect the structure of the hippocampus and amygdala, highlighting a pathway through which inflammation may induce neuropathological changes in depressed patients [6]. There is some new interesting perception about the role of KYNA and the kynurenic pathway in endogenous depression which say that before the electroconvulsive therapy the KYNA level in patients with depression is lower than the healthy people [16].

Relationships between AHR and IDO

Aryl hydrocarbon receptor (AHR) is considered to be an important factor in the regulation of immune responses. Many AHR-mediated mechanisms have been discovered which regulate the immune system response, and this knowledge can enhance our understanding, at the molecular level, of autoimmune inflammatory syndromes such as collagen-induced arthritis, experimental autoimmune encephalomyelitis or experimental colitis. Recent discoveries have shed light on the critical link between AHR and indoleamine 2,3-dioxygenase (IDO) in the development of regulatory T cells and Th17 cells, which are key factors in a variety of autoimmune diseases [29,32]. Induction of IDO and IDO-mediated tryptophan metabolism, along with its downstream products, such as kynurenine, is an important immunoregulatory mechanism underlying immunosuppression, immune tolerance and immunity. Recent studies have revealed that the induction of IDO expression is dependent on AHR. An important role also seems to be played by the relationships between AHR and the products of IDO-mediated tryptophan metabolism and the involvement of several factors, such as microRNA, in the development of autoimmune diseases. These novel factors may represent potential therapeutic targets for the treatment of autoimmune diseases [9].

The role of the kynurenine pathway in migraine and neurodegenerative diseases

Although migraine and neurodegenerative disorders have a major socio-economic impact, no comprehensive methods of treatment have so far been developed for them. The pathomechanisms of these diseases are not fully understood, but current research indicates that crucial roles are played by glutamate-induced excitotoxicity, mitochondrial disturbances and oxidative stress [33,34]. Overactivation of glutamate receptors contributes to the hyperexcitability of the structures of the central nervous system observed in patients suffering from migraine, and to the initiation of neurodegenerative processes. The kynurenine pathway of tryptophan metabolism leads to the synthesis of the only known endogenous N-methyl-D-aspartate antagonist, kynurenic acid, which is believed to exert neuroprotective effects, as determined in various preclinical studies. Influencing the kynurenine pathway may have a beneficial effect in migraine and neurodegenerative diseases, and the normalization of glutamatergic neurotransmission can prevent excitotoxic neuronal damage. The synthesis of kynurenic acid analogues may lead to the development of new pharmacotherapies [10].

KYNA and the physiology of behavior

There are reports, based on studies of *C. elegans*, that kynurenic acid can function as a regulator of food-dependent behavioral plasticity. Fasting alters a variety of behaviors, including feeding rate. Levels of neurally produced kynurenic acid are depleted by fasting, which leads to an increased expression of genes for the NMDA receptor located on interneurons and initiation of a neuropeptide-y-like signaling axis, which promotes an increase in the concentration of serotonin by increased release into the synaptic cleft when food is re-encountered. When the animals obtain food again, kynurenic acid levels are replenished by neurons, which ends the period of elevated feeding. As tryptophan is an essential amino acid, these results suggest that a physiological role of kynurenic acid is to directly link metabolism to the activity of NMDA and serotonergic circuits, which regulate a broad range of behaviors and physiologies [12].

Selective inhibitors of kynurenine monooxygenases

Toledo-Sherman et al., have drawn attention to the discovery of a series of pyrimidine carboxylic acid derivatives that are potent and selective inhibitors of kynurenine monooxygenase (KMO) and competitive inhibitors of kynurenine. Those authors have described the SAR for the new series and inhibition of KMO activity in biochemical and cellular assays as well as their selectivity against other enzymes in the kynurenine pathway. They have also presented an optimization process that leads to the identification of compounds with a suitable ADME/PK profile, which can be used to expand the existing therapeutic methods. The authors emphasize that systemic inhibition of KMO in vivo using these types of compounds provides the possibility of pharmacodynamic modulation of the formation of kynurenine pathway metabolites both in the periphery and in the central nervous system [13].

The kynurenine pathway and the mechanisms of action of antipsychotic drugs

Two kynurenine metabolites, 3-hydroxykynurenine and 3-hydroxyanthranilic acid, are known to have an inhibiting effect on melanin polymer formation in *in vitro* reactions catalyzed by tyrosinase [14]. Miller has made an attempt to expand this line of research by trying to answer the question whether kynurenine metabolites inhib-

it chlorpromazine-, olanzapine- and minocycline-stimulated reaction of melanin formation from the endogenous melanin precursor, adrenochrome Some kynurenine metabolites, such as tryptophan, kynurenine, kynurenic acid, quinolinic acid and nicotinic acid had no measurable effect on the reaction. However, the 4 3-hydroxykynurenine reduced the amount of the products formed and the 3-hydroxyanthranilic acid suppressed the reaction completely. 3-hydroxyanthranilic acid exerted an inhibitory action on both olanzapine- and minocycline-stimulated reactions, and 3-hydroxykynurenine inhibited product formation only in the minocycline-stimulated reaction. These results are important, given the upregulation of the kynurenine pathway in psychotic disorders; they provoke reflection on how the metabolites of this pathway influence the mechanism of action and, hence, the effectiveness of antipsychotic drugs [14]. The development of research in psychopharmacology allowed the perception of potential new directions antipsychotic drugs action among which certainly deserves credit for glutamatergic pathways system, very important in the activity of the central nervous system. For some time it is known that the cortico-truncalis projections have links with the trail of dopaminergic neurons in mesolimbic area through a system of interneurons, which are dependent on the action of gamma-aminobutyric acid located in the area of abdominal field cap, under physiological conditions, it allows to execute the tonic stimulation [15]. Reducing the activity of NMDA receptors in cortico-truncalis projections cause the atrophy of tonic stimulation, according to this changes the activity of mesocortical dopamine pathway is reduced. With regard to the early stages of schizophrenia we considered the hypothesis which says that it can be excessive activity of the glutamatergic excitotoxicity. Excitotoxicity maintained in subsequent stages of the disease is combined with progression. It should be taken into account that in schizophrenia there may be a combination of excitotoxicity, especially in the early phase of the disease and reduced NMDA receptor activity in a later stage of the disease, which complicates the use of drugs which block NMDA receptors. The compounds strongly block NMDA receptors are expected to inhibit the phenomenon of excitotoxicity, but in addition will also cause or exacerbate a wide range of symptoms of schizophrenia. These observations are confirmed by tests carried out using phencyclidine and ketamine [35]. It is believed that the therapeutic benefits in the treatment of schizophrenia can be achieved using substances with weaker antagonistic properties of NMDA receptors. Examples of such substances are memantine and amantadine which only partially block the transmission via NMDA receptors. Some possibilities may be open because of the substances blocking the presynaptic release of glutamate. Lamotrygine or riluzol could be an example of this substances. In the researches of a new treatment options for schizophrenia there is also some place for substances affecting the cholinergic system. Agonists of nicotinic cholinergic receptor alpha-7 may play a role in enhancing cognitive function in schizophrenic patients, since deficits in activity of this receptor could be responsible for the difficulties which patients may have in effective learning, and also could be responsible for developing the delusional thinking [15]. Substances with respect to nicotinic partial agonist of alpha-4 beta-2 for example varenicline can help people with schizophrenia in giving up the habit of smoking cigarettes. Many patients smoke, which worsens their overall health and shortens life expectancy, which anyway is changed because of illness. A receptor alpha-4 beta-2 located in the mesolimbic reward pathway may be involved in reward mechanism behind smoking. Muscarinic M1 receptor agonists may prove to be helpful in combating sedation and cognitive dysfunction in schizophrenia. It was confirmed that the antagonistic effect of drugs according to these receptors contributes to the cause of these problems. Clozapine metabolite (which is a muscarinic receptor antagonist) -ACP104 as an agonist of these receptors, and may be a partial dopamine agonist, is currently under investigation for its use in schizophrenia [15].

Studies of the role of the kynurenine pathway in brain stroke

AHR is a transcription factor belonging to the PAS (Per-Arnt-SIM homology domain) family, which mediates the toxic and carcinogenic effects of xenobiotics. Interestingly, AHR is broadly expressed in the central nervous system [17], but its physiological and pathological role still remains unclear. To determine the role of AHR in the pathophysiology of stroke, Cuartero et al. used middle cerebral artery occlusion in mice and oxygen and glucose deprivation in rat cortical neurons. The results of their study show that ischemia causes an increase in total and nuclear AHR levels and transcriptional activity of AHR in neurons *in vivo* and *in vitro*. They also demonstrate the causal role of AHR in acute ischemic brain damage because pharmacological or genetic modifications of its activity may have a neuroprotective effect. Inhibition of cAMP response element-binding protein-dependent signaling may play a role in reducing the activity of AHR. Furthermore, the authors have found that L-kynurenine, a metabolite of tryptophan with AHR agonistic properties, is an endogenous ligand that mediates the activation of AHR in the brain after middle cerebral artery occlusion [17]. Ormstad et al. have reported a lower bioavailability of tryptophan, the substrate for the synthesis of serotonin in the acute phase of ischemic stroke, in patients with post-stroke fatigue syndrome (poststroke fatigue syndrome). At the same time these patients were observed to have a greater neuroprotective

potential due to an increase in the level of serum KYNA. In turn, no potential risk factors were observed with regard to post-stroke depression [18].

The impact of exogenous kynurenine on aura symptoms in migraine

The aura symptoms of migraine are most likely caused by cortical spreading depression (CSD). CSD is promoted by NMDA receptor activation and increased cortical excitability [19]. This finding probably explains why migraine with aura presents when estrogen levels are high, e.g., during pregnancy. Chauvel et al. have investigated whether the administration of exogenous L-kynurenine could affect the occurrence of KCl-induced cortical spreading depression, and, if so, whether the effect was sex-dependent and whether it varied depending on the phase of the estrous cycle. It was found that the administration of L-kynurenine suppressed CSD, probably by increasing KYNA levels in the cerebral cortex. Females were more sensitive to this suppressive effect of L-kynurenine than males. The suppressive effect of L-kynurenine on CSD in females was the strongest in the luteal phase. These results highlight the role of sex hormones in the pathogenesis of migraine and open up the prospect of exploring novel directions in its preventive treatment [19].

Studies of the effects of anti-inflammatory medication on kynurenine pathway activity and immune function

Immune activation induces a pro-inflammatory state, which increases the degradation of tryptophan to kynurenine (KYN). The involvement of kynurenine has been demonstrated in patients with major depression [16]. Krause et al. have evaluated the effects of anti-inflammatory drugs (celecoxib) and antidepressants (venlafaxine, reboxetine, imipramine and fluoxetine) on changes in cytokine and tryptophan metabolite levels in blood culture upon proinflammatory activation with a lipopolysaccharide. The authors found that LPS stimulation induced an increased production of proinflammatory and anti-inflammatory cytokines in both groups, with a stronger response observed in the control group.

The lower cytokine production in patients with depression indicated that their immune cells were in a refractory phase induced by a pre-existing pro-inflammatory state. For substances produced in the kynurenine pathway, the whole metabolism was enhanced by LPS; however, an imbalance in favor of neuroprotective metabolites (KYNA/KYN ratio) was observed only in the control group.

The effect of medication was only observed for imipramine and celecoxib, which were beneficial in terms of re-balancing the immune system, but did not affect the balance of neuroactive metabolites [20].

The role of inflammatory cytokines and microglial cells in the pathogenesis of mental disorders

Markers of inflammation, such as pro-inflammatory cytokines, are well known as aetiological factors in psychiatric disorders, including schizophrenia. Inflammatory states in the central nervous system are closely related to neurodegeneration [36]. In addition to proinflammatory cytokines, an important role in inflammatory processes in the CNS is played by microglial cells. Uncontrolled activity of proinflammatory cytokines and microglia together with the factors determining genetic susceptibility and impaired glutamatergic transmission can create the conditions for the development of schizophrenia. Several studies have assessed the potential effects of antipsychotic treatment on inflammation and neurogenesis. In addition, anti-inflammatory treatment has been considered as complementary treatment in the therapy of schizophrenia. Further research should investigate the role of systemic factors, such as metabolic syndrome and smoking in the pathogenesis of mental disorders [21].

The role of aminotransferase II gene polymorphism in the regulation of immune function

Bacterial meningitis is characterized by an intense inflammatory response, which contributes to the development of brain damage and neural sequelae. Activation of the kynurenine pathway has been reported to be a consequence of inflammation in various neurological disorders. Previous studies of animal models have shown that the kynurenine pathway is activated in bacterial meningitis, and that there is a relationship between the variant allele of the kynurenine aminotransferase II gene and the immune response to bacterial meningitis [22]. Coutinho et al. have observed increased levels of kynurenine, kynurenic acid, anthranilic acid and cytokines, and an increase in the activity of indoloamine 2,3-dioxygenase (IDO) in the CSF of patients with bacterial meningitis.

IFN-γ and IL-1Ra levels showed a positive correlation with the activity of IDO and the levels of TNF-α and IL-10 were positively correlated with the levels of kynurenine and kynurenic acid. Moreover, the highest levels of kynurenic acid were found to be associated with the presence of the variant allele AADAT + 401 C / T [22]. De Souza et al. have reported that single nucleotide polymorphism in this allele may affect the ability of the host to recruit leukocytes to the infection site [23].

The therapeutic potential of KYNA in counteracting the effects of hepatic encephalopathy

KYNA regulates glutamatergic neurotransmission by controlling neuronal glutamate release. Hilgier et al. have studied the potential of the KYNA precursor, kynurenine, to counter the increase in extracellular glutamate associated with the pathogenesis of hepatic encephalopathy accompanying acute liver failure (ALF) Extracellular KYNA was elevated in the cerebral cortex of ALF rats not treated with kynurenine, which was in line with the previously observed increase in cerebral cortical activity of kynurenine aminotransferase II. Single intraperitoneal administration of kynurenine led to a considerable increase in extracellular KYNA along with a drop in extracellular glutamate. In cultured cerebral cortical astrocytes, which are the primary target of blood-derived ammonia and other toxins released in the course of ALF, an increase in kynurenine aminotransferase II mRNA expression was recorded upon their incubation with kynurenine and the kynurenine precursor, tryptophan, just as is normally the case in ALF [24].

Kynurenine pathway in the pathogenesis of sleep disorders

Extremely interesting is the role of the kynurenine pathway compounds in the pathogenesis of sleep disorders. Yamashita and Yamamoto have developed an animal model of central fatigue induced by chronic sleep disorder (CFSD). Their results showed that while plasma concentrations of 5-hydroxytryptamine did not differ between control rats and CFSD rats, tryptophan and KYNA levels in CFSD rats were, respectively, about 2 and 5 times higher in the hypothalamus and 2 and 3.5 times higher in the hippocampus. In addition, the animals suffering from CFSD showed abnormal running performance (on treadmill test) and social interaction deficits (on social-interaction test) [25].

KYNA level and distress tolerance

People with schizophrenia are often affected by distress intolerance. Chiapelli et al. used 'quitting the stressful task early' as a behavioral marker of distress intolerance. The study included 64 patients with schizophrenia and 64 healthy controls. Salivary KYNA levels increased significantly during the 20 minutes of performing the stress task in both patients and controls. Patients who discontinued the task early had significantly higher salivary levels of KYNA compared with the patients who continued the task and the healthy controls. In patients with distress intolerance, the increase in KYNA clearly correlated with the severity of clinical symptoms [26].

The role of the kynurenine pathway in the development of addictions co-occurring with schizophrenia

It is believed that changes in brain reward systems contribute to the development of cognitive and behavioral disorders present in patients with schizophrenia and the tendency to develop co-occurring substance abuse disorders. Still little is known about the neural substrates that underlie co-occurring schizophrenia and substance abuse. De Angeli et al., have shown in their experiment that rats which received L-kynurenine, the precursor of KYNA, throughout adolescence, in adulthood presented a pattern of behavior that attested to addiction – lever pressing that had previously been associated with delivery of food. In addition, the researchers assessed the effects of exposure to KYNA in adolescence on long-term potentiation in the hippocampus. Rats which received L-kynurenine during adolescence did not exhibit LTP after a burst of high-frequency stimulation that was sufficient to produce LTP in rats fed a standard diet [27].

Conclusion

A better understanding of the biological role of the kynurenine pathway metabolites and enzymes seems, in the light of current knowledge, indispensable for a proper understanding of the pathogenesis of the diseases of the central nervous system and the optimization of the existing and creation of new treatments for these diseases. What seems particularly important is the regulatory role of the kynurenine pathway in the activity of the immune system and the relationships between the activity of the kynurenine pathway and parameters of inflammation. The kynurenine pathway is a critical element of the pathomechanisms of such medical conditions as neurodegenerative diseases, schizophrenia, bipolar disorder and migraine. It is also necessary to delve deeper into the role of the kynurenine pathway in the body's response to the action of antipsychotic drugs. An interesting line of research in this area concerns the possibilities of influencing the activity of the kynurenine pathway using synthetic compounds. Changes in the expression of kynurenine 3-monooxygenase, on the other hand, may turn out to be a risk factor for neurocognitive deficits in schizophrenic patients. Increased prenatal levels of KYNA may be related to an increased risk of cognitive deficits in adult life. The kynurenine pathway also seems to play a regulatory role in the physiology of behavior.

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