New prospects for antipsychotic treatment – the role of the kynurenine pathway

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Summary

The mechanism of action of antipsychotic drugs is mainly associated with changes in dopaminergic system. The application of antipsychotic agents simultaneously produces changes in concentrations of metabolites (e.g. kynurenic acid – KYNA, 3-hydroxykynurenine – 3-OHKYN, kynurenine – KYN) of the kynurenine pathway, the pathway engaged in glutamatergic transmission. The increase in KYNA levels in certain areas of the central nervous system results in inhibition of glutamatergic transmission. Pharmacologically induced elevation of KYNA levels produces effects similar to those observed after administering ketamine or phencyclidine (the noncompetitive NMDA receptor antagonist), concerning increased activity of mesolimbic dopamine neurons, as well as reduction in dopamine release from the prefrontal cortex. Recent research results confirm the predictive value of changes in concentrations of kynurenine pathway metabolites for assessment of effectiveness of antipsychotic treatment. Significant relationships were found 1) in schizophrenia between the reduction of psychopathological symptoms and variations in 3-OHKYN levels as well as changes in KYNA/3-OHKYN and KYN/KYNA ratios, 2) in mania between varying tryptophan concentrations and the reduction in manic symptoms achieved with antipsychotic treatment. The research as well presented the possibilities of kynurenine pathway modifications, raising high hopes for their future application as target points for the action of novel antipsychotic agents.

Key words: kynurenic acid, 3-hydroxykynurenine, antipsychotics

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Introduction

The discovery of the involvement of kynurenic acid (KYNA) and other compounds formed in the course of kynurenine transformation in the brain activity, either in physiological or pathological conditions, resulted in determination of new goals for the pharmaceutical research, i.e. searching to find compounds fully exploiting the therapeutic potential of the kynurenine pathway metabolites. Those include substances exhibiting neuroprotective effects confirmed on animal models, and the extensive research on the subject concerning possibilities of kynurenine pathway modifications raise hope for their future clinical application.

The kynurenine pathway is one of possible routes of tryptophan conversion in a human organism, leading to formation of neuroactive metabolites in CNS, i.e. 3-hydroxy-kynurenine, quinolinic acid and KYNA. The last two seem to be of particular importance, as they produce opposite effects on the NMDA excitatory amino acid receptors [1].

The evidence supports anticonvulsant [2] and neuroprotective [3] properties of KYNA. Differences in KYNA concentrations are described in the course of such disorders as: Alzheimer’s disease [4], Parkinson’s disease [5], Huntington’s disease [6, 7], epilepsy [2, 8], bipolar disorder [9], depression [10, 11] and schizophrenia [12]. Due to poor penetration of the blood-brain barrier by KYNA and difficulties in reliable measurement of serum KYNA concentrations, the remaining metabolites of kynurenine pathway have also become the objects of scientific examination. There are publications illustrating changes in concentrations of KYNA and other metabolites of the kynurenine pathway in the course of treatment of both neurological and mental disorders [13, 14]. Recent studies focus on modifications of the kynurenine pathway in terms of new therapeutic possibilities for CNS disorders [15-17].

This study aimed to demonstrate the association between the KYNA and the remaining kynurenine pathway metabolites, and antipsychotic agents, as well as the promising role they could play in predicting the effectiveness and optimization of the treatment.

KYNA – biochemical description, function and role in the human body

Kynurenic acid is a nonselective antagonist of the three types of ionotropic receptors for excitatory aminoacids: N-methyl-D-aspartate (NMDA) receptor, kainic acid receptor and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. In addition, KYNA acts as an antagonist of strychnine-insensitive glycine recognition site of the NMDA receptor complex [2]. Inhibition of glutamate release by KYNA may occur via blockade of NMDA autoreceptors located on presynaptic nerve endings, or by noncompetitive blockade of nicotinic receptors [18]. The presence of KYNA is observed in brains of humans and many other animal species, however, the highest concentration has been found in human cerebral tissue, through which KYNA is distributed in an irregular manner [19, 20]. The greatest KYNA concentrations have been reported to be present in the caudate nucleus and thalamus,
lower concentrations have been detected in the hippocampus and cerebral cortex, with the lowest ones registered in the cerebellum [20]. The animal-based research proved that brain levels of KYNA undergo changes during individual development – in rats, high KYNA concentrations are noted during foetal life, then they suddenly drop after birth, to finally rise in aging individuals [21].

KYNA is a neuroactive product of metabolism of tryptophan, which may undergo three distinct reactions in the human body: decarboxylation to tryptamine, hydroxylation to 5-hydroxytryptophan, or indole ring opening, resulting in production of kynurenine. Tryptamine and 5-hydroxytryptophan are further converted to serotonin, nevertheless, over 95% of tryptophan is metabolized to kynurenine. Among the enzymes responsible for activation of the kynurenine pathway, there are tryptophan 2,3-dioxigenase (TDO) and indoleamine 2,3-dioxigenase (IDO) [1].

KYNA is mainly synthesized de novo, in the brain, in an enzymatic reaction catalyzed by kynurenine aminotransferase (KAT) [22]. The substrate for this reaction is kynurenine – provided from external supplements or derived from tryptophan metabolism occurring outside the CNS, as in the brain tryptophan is mainly converted to serotonin [23]. Kynurenine easily penetrates the blood-brain barrier, in contrast to KYNA, which crosses the barrier only to a small extent [24]. The produced KYNA is not stored inside cells, but released by diffusion. It is rapidly distributed from the brain to blood circulation and then to urine, with which it is further excreted. All of the stages of the kynurenine pathway may occur inside the brain [25], therefore, the remaining kynurenine metabolites, i.e. neurotoxic 3-hydroxykynurenine [26, 27], as well as quinolinic acid – the agonist of NMDA receptor for excitatory aminoacids [1], may be also present in the brain tissue. The injection of this compound into rat’s brain results in seizures [28], whereas in humans it is responsible for evoking complex partial seizures, producing neurological disorders in the course of numerous ischemic and inflammatory diseases [29]. The concentration of quinolinic acid substantially increases with the aging process [1].

The synthesis of KYNA in the brain is regulated by a number of factors, e.g. kynurenine supply, mitochondria damaging toxins, hypoxia, hypoglycemia, hyperglycemia [1].

**KYNA and the mechanisms of action of antipsychotic drugs**

Introduction of the antipsychotic agents was undoubtedly of great importance for the therapy of mental disorders. The mechanism of their action was mainly associated with the reduction in dopaminergic transmission, which is consistent with the classical Carlsson’s dopamine hypothesis [30] that proposed the connection between schizophrenia and the hyperactivity of dopaminergic system. Application of new atypical antipsychotic drugs, also affecting the serotonergic system, drew attention to other neurotransmitter systems, which could be involved in the development of psychotic symptoms as well. Subsequently the impact of GABA and glutamatergic transmission was investigated [31]. The inhibition of glutamatergic transmission which may lead to disturbances of thalamic functions related to filtering sensory impressions and, in consequence, resulting in the uncontrolled flooding of the cerebral cortex with tho-
se impressions further producing the psychotic symptoms, also seems to be of great importance [32]. Confirmation of the hypothesis may be found in the resemblance between the symptoms of schizophrenia and the mental disturbances occurring after administration of ketamine or phencyclidine – the noncompetitive antagonists of glutamate NMDA receptors [33].

It is known that the majority of the antipsychotic agents may, aside from exhibiting their regular antagonistic action on dopaminergic and serotonergic receptors, exert the adrenolytic, antihistaminic or anticholinergic effects [31]. However, the latest research on clozapine – the antipsychotic agent very effective also in the treatment of refractory schizophrenia – indicates the direct action of the drug on the glycine recognition site of the NMDA receptor complex [34]. The same research also showed that the response of ventral tegmental area dopaminergic neurons to clozapine administration depends on the brain concentrations of the endogenous KYNA. The influence on glutamatergic transmission seems to be the link between KYNA and the action of antipsychotic drugs, in terms of positive and negative symptoms alike. Research evidence indicates the role of KYNA in regulation of glutamatergic transmission [35], and some mechanisms are known by which KYNA inhibits glutamate release (blocking the NMDA autoreceptors located on presynaptic nerve endings and the noncompetitive blockade of nicotinic receptors).

The pharmacologically induced elevation of KYNA concentrations produces the effect similar to that observed after administration of ketamine or phencyclidine, which indicates the psychotomimetic action of the KYNA [33]. A growing body of research evidence depicts the elevation of KYNA levels in the cerebrospinal fluid (CSF) of patients requiring antipsychotic treatment in the course of schizophrenia and bipolar disorder, where the psychotic symptoms may be also observed during the manic episodes. Research by Olsson et al. [9] demonstrates the increase in KYNA concentrations in the CSF fluid of euthymic patients with bipolar disorder, while Erhardt et al. [12, 33, 36] indicate in their papers the elevation of KYNA levels in CSF of patients suffering from schizophrenia and reveal the relationship between pharmacologically-induced KYNA concentrations and the increasing activity of the ventral tegmental area dopaminergic neurons in rats. The numerous post-mortem examinations confirmed high CSF and cerebral cortex concentrations of KYNA in patients with schizophrenia or bipolar disorder [37].

Antipsychotic agents exert their effects by affecting neurotransmitter systems, the functioning of which is impaired in the course of illnesses with psychotic symptoms. KYNA is involved in the modulation of dopaminergic and glutamatergic transmission [34, 35]. Therefore, a thorough investigation of the connections between the antipsychotic agents, and KYNA along with the remaining metabolites of the kynurenine pathway is essential, especially in the context of predicting the effectiveness of antipsychotic treatment.
KYNA and the antipsychotic agents – animal models

Among studies on CSF and cerebral cortex KYNA levels conducted on animal models, there are those that provide particularly valuable data on mechanisms of action of the antipsychotic drugs.

Caresoli-Borroni et al. [38] show in their research that the long-term (rated after 4 weeks and 12 months) administration of the antipsychotic drugs (haloperidol, clozapine, raclopride) produced a substantial decrease of KYNA concentration in rats’ brains. On the other hand, the acute application or one-week drug exposure resulted in no changes in brain KYNA levels. All of the antipsychotic agents that were used during the studies had a comparable effect on KYNA concentrations [38]. The lack of response to short-time treatment with antipsychotics proves that the mechanisms underlying the therapeutic effects of long-term treatment with neuroleptics are not directly related to dopamine receptor blockade, reduced glucose uptake [39] or other documented acute effects of antipsychotic medications [40]. The authors suggest that the therapeutic effect of a long-term treatment with antipsychotics may depend on the ability of the drug to decrease KYNA levels, and therefore enhance the cholinergic and glutamatergic neurotransmission.

There are also research studies available depicting the influence of the initial KYNA concentration in the rat brain on response to the administration of antipsychotic drugs. The studies of Schwieler [34] prove that the response of the ventral tegmental area dopaminergic neurons in rats to clozapine administration depends on the brain concentrations of the endogenous KYNA. The pharmacological induction of the increase in brain KYNA levels tends to convert the originally stimulating effect of clozapine into the inhibitory one, whereas lowering KYNA concentration results in enhanced activity of the neurons in response to clozapine. The research results indicate the potential of clozapine to interact directly with the glycine recognition site of the NMDA receptor complex.

The elevation in levels of KYNA – the endogenous antagonist of the glycine site of the NMDA receptor complex, might have led to weakening of glutamatergic transmission, the role of which in the pathogenesis of schizophrenia has been recently emphasized [32, 33]. In that situation, clozapine decreased dopaminergic neuronal activity in the ventral tegmental area in rats, presumably by acting as the agonist of the glycine site of the NMDA receptor [34]. However, the antagonistic role of clozapine, leading to activation of dopaminergic neurons, is well observed at decreased initial levels of KYNA. These studies provide further evidence for the participation of glutamatergic transmission in the process of modulation of the response of dopaminergic neurons to the effects of antipsychotic agents.

The studies on animal models provide more information on new therapeutic options for the treatment of CNS disorders in terms of modification of the kynurenine pathway. In a recent study in this area, mice were administered a KYNA analogue (the KYNA-amide) in a dose that produced neuroprotective effects, but simultaneously not resulting in worsening of the cognitive function of the brain [15]. Previous studies suggested that the increase in KYNA levels led to deterioration of spatial working
memory in rats [41]. This was associated with the action of KYNA on the glycine site of the NMDA receptor and on the α-7 nicotinic receptor. The variations in KYNA levels within the prefrontal cortex (PFC) of rats were responsible for modulation of extracellular concentrations of 3 neurotransmitters, i.e. glutamate, dopamine and acetylcholine, regulating cognitive functions. However, the possibility of determination of a dose of the KYNA analogue that would produce therapeutic effects without causing side effects, even if only in mice, raises high hopes for the future, regarding the role that KYNA may play in treatment of CNS disorders.

**Kynurenine pathway metabolites and the treatment of schizophrenia and bipolar disorder with antipsychotic medications**

KYNA has been the subject of many studies aimed at establishing its role in physiology and pathology of the human organism [2]. When its presence in the brain was confirmed, the interest in KYNA was also transferred to the field of neurophysiological studies. The differences in KYNA concentrations in the course of numerous neurological and mental disorders were then discovered, i.a. an increase in CSF KYNA levels was noted in patients with schizophrenia [12] and affective bipolar disorder [9]. The remaining metabolites of the kynurenine pathway – their interrelationships and changes they undergo under the influence of administered antipsychotic agents – have now become the focus of research.

The kynurenine pathway leads to production of many neuroactive metabolites, e.g. quinolinic acid (a selective agonist of the NMDA receptor, which intracerebral administration results in neuronal damage with axon preservation, KYNA (an antagonist of the glycine site of the NMDA receptor that exhibits neuroprotective properties and may counteract the neurotoxic and proconvulsant effects of the quinolinic acid [42]), 3-hydroxykynurenine (a neurotoxic metabolite which induces neuronal apoptosis by generation of reactive oxygen species [26, 27]).

Research attention was directed towards 3-hydroxykynurenine, one of the most toxic metabolites. The study published recently by Condray et al. [43], concerning the first-episode schizophrenia patients who were never subjected to the effects of antipsychotic medications, revealed the relationship between serum levels of 3-OHKY and severity of clinical symptoms. In addition, the reassessment of the 3-OHKY concentration and patients’ clinical status after a four-week antipsychotic treatment (different types of antipsychotic drugs were used, both typical and atypical) indicated the predictive value of 3-hydroxykynurenine in relation to reduction of psychopathological symptoms in the treatment of first-episode schizophrenia patients.

The imbalance between kynurenine pathway metabolites in patients with schizophrenia was the subject of research by Myint et al. [13], in which the role of relationship between KYNA and 3-OHKY in blood serum is highlighted in the context of clinical manifestation and response to treatment. The study group consisted of drug naïve patients and those, in whom the antipsychotics were not used for at least four months prior to the study. Levels of kynurenine pathway metabolites and clinical status of the patients were assessed before starting the treatment and after six weeks
of therapy with antipsychotics (only atypical antipsychotics were used in this research). According to the published results of this study, the KYNA/3-OHKY ratio tends to be lower in the patients suffering from schizophrenia than in the control group. The treatment resulted in a decrease in serum 3-OHKY levels and elevation in serum KYNA levels, thus producing a higher KYNA/3-OHKY coefficient. The relationship between the levels of KYNA and KYN were also investigated, with reference to the patients’ results obtained with the use of mental state reference scales. It was proved, among other things, that a higher serum KYNA level at admission, together with greater increase in the KYNA/KYN ratio after completion of the therapy, are associated with reduction in symptom rating scale scores at discharge. The quoted research indicates the imbalance between kynurenine pathway metabolites and confirms the potential of antipsychotic agents to restore, at least partially, the balance between them, which in turn may affect clinical response to the treatment.

There are also studies in progress on groups of patients that differ in their response to the treatment with antipsychotic medications. Among the patients suffering from schizophrenia, the studies revealed a substantially lower serum tryptophan level in treatment-resistant patients, as compared to the patients undergoing antipsychotic therapy, in whom the improvement of clinical status was observed, and with reference to the control group [44].

Tryptophan, the substantial portion of which is metabolized via the kynurenine pathway, was the subject of study by Myint et al. [14], which was also conducted on the serum of patients with bipolar disorder in their first or consecutive episode of mania, provided that the antipsychotic treatment was discontinued at least for a 4-month period. It was proved that serum tryptophan levels were reduced in patients on admission in comparison with the control group. However, the comparison of the measurements of tryptophan levels and its consumption before and after 6 weeks of therapy (with the use of normothymic and antipsychotic drugs) with the results of clinical assessment of the patients indicates the involvement of tryptophan and the kynurenine pathway in the pathophysiology of the disorder, as well as in the treatment response of patients in the manic phase of affective bipolar disorder.

**Treatment prospects**

Due to the effect of KYNA on the levels of diverse neurotransmitters engaged in pathophysiology of disorders with psychotic symptoms, modification of its level appears to be a promising target point for the action of new antipsychotic agents.

The effects of elevated KYNA levels could be limited directly through pharmacological interventions in the kynurenine pathway, also at the peripheral level. This group of medications may be represented by TDO and/or IDO inhibitors which, by lowering the level of circulating kynurenine, contribute to the reduction of amounts of the KYNA precursor crossing the blood-brain barrier, ultimately leading to the decrease in brain KYNA concentration [16, 45]. The level of circulating kynurenine may be as well reduced by activation of kynurenine 3-monoxygenase (KMO), but this would simultaneously result in elevated levels of neurotoxic metabolites, e.g. 3-OHKY [45]. Still,
the most promising group of substances causing reduction in brain KYNA levels tend to be the inhibitors of KAT II [46] – one of at least four of the kynurenine transaminases that act preferentially on controlling the KYNA pool which can be rapidly stored in the brain. The results of rat experiments indicate the reduction in brain KYNA levels of the rodents, following the administration of the selective KAT II inhibitor directly into the prefrontal cortex [17]. Simultaneous elevation of glutamate, dopamine and acetylcholine concentrations was also noted [47-49].

The above-mentioned attempts of modifying the kynurenine pathway still require further in-depth biochemical, neuropsychological and neurophysiological studies on animals and eventually on humans, before they find clinical application in the treatment of CNS disorders.

However, there have been studies conducted on therapeutic application of the compounds directly reacting with the glycine recognition site of the NMDA receptors, and the results are promising. The initial study by Strzelecki et al. indicates that augmentation of the antipsychotic treatment with glycine may decrease the intensity of depressive and extrapyramidal symptoms in schizophrenic patients [50].

With rapidly developing research on KYNA, its clinical application is gaining more and more attention, both in the aspect of predicting the treatment results and new possibilities in therapy of CNS disorders. There are research results that highlight the meaning of KYNA and the remaining metabolites of the kynurenine pathway in prediction of the antipsychotic treatment, and thus in its optimalization. Therefore, a need exists to continue and expand the research conducted in this particular area, which in the future may allow introduction of more effective and less aggravating treatment plans, cost reduction, and above all improvement of the quality of life of the patients.

References

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