Cite as: Sadko KG, Wichowicz H, Jabłońska P, Wolszczak A: Schizophrenia and amino acids in diet – it is possible to enhance treatment through nutrition? Psychiatr Psychol Klin 2025; 25 (2): 162–168

Received: 29.01.2024
Accepted: 24.01.2025
Published: 31.07.2025

Krzysztof Grzegorz Sadko[1], Hubert Wichowicz[1,2], Patrycja Jabłońska[3], Anna Wolszczak[1]

Schizophrenia and amino acids in diet – it is possible to enhance treatment through nutrition?

Schizofrenia a aminokwasy w diecie – czy można usprawnić leczenie żywieniem?

[1] Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland
[2] Institute of Health Sciences, Pomeranian University in Słupsk, Słupsk, Poland
[3] Department of Biochemistry, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland
Correspondence: Krzysztof Grzegorz Sadko, Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Smoluchowskiego 17, 80-214 Gdańsk, Poland, e-mail: krzysztof.sadko94@gmail.com

https://doi.org/10.15557/PiPK.2025.0020

ORCID iDs
1. Krzysztof Grzegorz Sadko https://orcid.org/0000-0003-0777-5741
2. Hubert Wichowicz https://orcid.org/0000-0002-2631-0539
3. Patrycja Jabłońska https://orcid.org/0000-0001-5633-2328

Abstract

This study presents current knowledge about the possibilities for modulating the course of schizophrenia through dietary amino acids levels. Both the results of basic research (data regarding the level of amino acids in patients' serum) and recent clinical evidence are presented. Results based on serum amino acids levels indicate the possibility of influencing the course of schizophrenia via amino acid supply. The suggested amino acids are related primarily to dopaminergic and glutamatergic neurotransmission (L- and D-tyrosine, glutamate, gamma-aminobutyric acid, glycine, serine, aspartate, and alanine). The remaining data is too scarce to draw definitive conclusions. Clinically, in addition to the amino acids listed above, an impact of amino acids related to the synthesis of glutathione (glutamic acid, cysteine, glycine, and serine) is also possible. The third possibility, affecting not the core symptoms of schizophrenia but the accompanying ones (e.g. affective symptoms), involves regulating the levels of tryptophan and other amino acids implicated in its absorption (valine, isoleucine, leucine, and phenylalanine). While some hypothetical premises are supported by clinical data, current evidence remains limited. The presented problem certainly requires further research, including a full assessment of patients' amino acid profiles.

Keywords: schizophrenia, diet, amino acids

Streszczenie

Celem pracy było przedstawienie potencjalnych możliwości modulacji przebiegu schizofrenii poprzez dietę, z uwzględnieniem zawartych w niej aminokwasów. Przedstawiono zarówno wyniki badań podstawowych (stężenie aminokwasów w surowicy), jak i uzyskane dane kliniczne chorych. Dane dotyczące stężenia aminokwasów w surowicy potencjalnie wskazują na możliwość wpływu na przebieg schizofrenii poprzez modyfikację zawartości w diecie aminokwasów, związanych przede wszystkim z przewodnictwem dopaminergicznym (głównie tyrozyną, która jest substratem syntezy dihydroksyfenyloalaniny i docelowo dopaminy oraz D-tyrozyny, która odgrywa rolę w transmisji dopaminergicznej jako inhibitor tyrozynazy) i glutaminergicznym (glutaminian, kwas gamma-aminomasłowy, glicyna, seryna, asparaginian i alanina). Pozostałe dane są zbyt skąpe, aby na ich podstawie formułować dalej idące wnioski. W zakresie badań klinicznych uzyskane rezultaty wskazują na potencjalny wpływ na przebieg schizofrenii via wymienione aminokwasy oraz – dodatkowo – na działanie poprzez regulację stężenia aminokwasów związanych z syntezą glutationu (kwas glutaminowy, cysteina, glicyna, seryna). Trzecia droga, wpływająca już nie na objawy schizofrenii per se, ale na objawy jej towarzyszące (np. afektywne), może obejmować regulację stężeń samego tryptofanu i innych aminokwasów uczestniczących w jego wchłanianiu (waliny, izoleucyny, leucyny i fenyloalaniny). Dlatego niektóre hipotetyczne przesłanki zostały potwierdzone danymi klinicznymi, choć na obecnym poziomie mają one słabą wartość dowodową. Z pewnością poruszany temat wymaga dalszych badań, obejmujących pełną ocenę profilu aminokwasów pacjenta.

Słowa kluczowe: schizofrenia, dieta, aminokwasy

INTRODUCTION

Schizophrenia is a serious illness associated with the loss of at least 13–15 years of potential life (Hjorthøj et al., 2017). The pathogenesis remains unclear. Among the theories and hypotheses concerning its causes and pathophysiology, the oldest and most established are those focusing on the dopaminergic and glutamatergic systems (McCutcheon et al., 2020). Both neurotransmitters are chemically amino acids (AAs). To date, there are only a few studies on the supply, absorption, and serum levels of AAs in schizophrenia.

In contrast, the situation is quite different for cardiovascular diseases. The homocysteine (Hcy) level is a prognostic factor, and knowledge about its role in the diet is extensive. By comparison, there are only a few studies showing correlations between diet and schizophrenia (McCreadie, 2003; Peet, 2004a; Ryan and Thakore, 2002; Saleem et al., 2017). Those studies are so scarce that it is impossible to form a coherent picture from them. Moreover, to the best of available knowledge, there is no publication examining the full biochemical profile of AAs in the serum of patients with schizophrenia. There are only papers examining individual AAs.

SELECTED STUDIES ON AMINO ACID SERUM LEVELS IN PATIENTS WITH SCHIZOPHRENIA

To illustrate the potential impact of diet on the course of schizophrenia, it is worth starting with papers examining the level of AAs in blood serum; even if they are only a few. Those papers can be divided into three types:

- related to the glutamatergic receptor, the most numerous;
- associated with other neurotransmitters;
- without the above-mentioned associations.

Most studies focus on glutamate and gamma-aminobutyric acid (GABA), in line with the glutamatergic theory of schizophrenia. The simplified framework of this theory suggests reduced glutamate transmission in schizophrenia. The *N*-methyl-D-aspartate receptor (NMDA)-type receptor is being studied especially intensively. However, the correlation between the level in the central nervous system and serum levels remains unclear. Some authors point out that the peripheral glutamate level cannot reflect the level of glutamate in the brain, the place of synthesis; others, however, have reported a positive correlation between the level of glutamate in the serum and its level in the cerebrospinal fluid (De Luca et al., 2008). Generally, in schizophrenia, an increased level of glutamate was observed in the serum (Saleem et al., 2017; Tortorella et al., 2001), although in some cases this finding is restricted to males only (Saleem et al., 2017). Even less clear is the effect of treatment. Some researchers claim that long-term treatment with clozapine leads to an increase in serum glutamate concentrations (Evins et al., 1997), while others find completely contrary results (Tortorella et al., 2001).

Another AA associated with NMDA activity as a cofactor, potentially affecting the pathogenesis of schizophrenia, is glycine. Again, some papers report an increased concentration of glycine, while others report a decreased level in the serum, which is probably related to the intensification of negative symptoms in individuals with schizophrenia as well as their reaction to medication, mainly clozapine (Hons et al., 2010; Neeman et al., 2005; Sumiyoshi et al., 2005). It is worth mentioning that both genetic and drug-induced glycine deficiency leads to behavioural changes that resemble cognitive and negative symptoms of schizophrenia (Saleem et al., 2017).

Moreover, L-serine, which acts as a co-transmitter at the NMDA receptor, and D-serine, a form that more easily crosses the blood–brain barrier (BBB), regulate the NMDA glutamate receptor function (Saleem et al., 2017). Panizzutti et al. (2005) reported an increase in hippocampal activity and improved learning performance in patients after the administration of D-serine. A decreased D-serine serum level in schizophrenic individuals was observed in the study by Cho et al. (2016). This could be explained by a deficiency of serine racemase, the enzyme converting L-serine to D-serine, or by the overactivity of the D-amino acid oxidase enzyme, which breaks down the latter (Saleem et al., 2017).

When considering the AAs not directly associated with the NMDA receptor, L-isoleucine should also be taken into account. L-isoleucine competes with tyrosine and tryptophan in binding to transporters in the BBB. Tortorella et al. (2001) demonstrated its increased concentration in the blood serum in patients with schizophrenia based on a group of 11 individuals resistant to neuroleptics. The authors analysed changes in concentrations before and after a 12-week course of treatment with clozapine. The administration of clozapine significantly lowered the concentration of serum glutamate, but did not affect the concentrations of other amino acids (Tortorella et al., 2001).

Recent studies have also demonstrated the role of other D-amino acids. For example, D-tyrosine, acting as a tyrosinase inhibitor, prevents the synthesis of melanin (Saleem et al., 2017). This fact is of interest to both clinicians and scientists because tyrosinase is also involved in the pathomechanism of other neurodegenerative disorders, such as Alzheimer's disease or Parkinson's disease, as well as conditions affecting other organs, e.g. melanoma in the skin. It has been suggested that tyrosinase inhibitors may have a neuroprotective effect by preventing the overproduction of dopamine (DA) which seems to be significant in diseases such as schizophrenia, where excess DA triggers neuroprotective symptoms in patients (Saleem et al., 2017). The cited role of D-tyrosine in combination with the activity of other D-amino acids, such as stimulation of the release of D-serine without impairing cognitive functions (D-isoleucine), antiepileptic effect (D-leucine), strengthening the activity of the hippocampus (D-threonine), or the ability of D-phenylalanine to inhibit carbonic anhydrase, may suggest a broader neuroprotective role of D-amino acids in neurological and mental disorders (Seckler and Lewis, 2020).

 DOI: 10.15557/PiPK.2025.0020

Homocysteine, primarily known for its association with cardiovascular diseases, probably plays a role in the pathophysiology of schizophrenia as well. There is a relationship between elevated concentrations of Hcy and schizophrenia (Saleem et al., 2017). An increase in Hcy level is responsible for the impairment of cognitive functions and is characteristic of multiple mental diseases, including schizophrenia (Muntjewerff, 2006). This claim is confirmed by meta-analyses. For example, an increased risk of schizophrenia is associated with the homozygous genotype of the *MTHFR* 677C4T polymorphism, which increases the level of Hcy (Muntjewerff, 2006). Hcy causes oxidative stress in cells by interacting with NMDA receptors, damaging blood vessels and mitochondria, and leading to cellular apoptosis (Saleem et al., 2017). Therapeutic supplementation with folic acid and vitamin B effectively reduces serum Hcy levels (Moustafa et al., 2014). Due to the correlations of altered Hcy levels in the course of the disease, Kevere et al. (2012) proposed that Hcy might serve as a prognostic factor in certain mental disorders, including schizophrenia.

Not all abnormalities in AA levels observed in schizophrenia could be explained in the scope of the currently known theories. Tortorella et al. (2001) found a higher concentration of aspartate in the blood serum of patients suffering from schizophrenia. Evins et al. (1997) showed that treatment with clozapine increases the baseline level of aspartate in the blood serum. Referring to other studies and analyses of amino acid concentrations, Rao et al. reported lower cysteine concentrations and higher citrulline levels in drug-naive patients with schizophrenia. According to Tomiya, the level of ornithine in the serum is positively correlated with the duration of the disease, while Perry et al. noted irregularly high fasting plasma ornithine concentrations in patients with acute psychosis (Saleem et al., 2017). Recently, some studies have shown that supplementation with amino acids may help reduce schizophrenia symptoms. Wass et al. (2011) considered the role of L-lysine in aberrant NO signalling that contributes to the pathophysiology of schizophrenia. According to the results of their study, treatment with L-lysine significantly reduced the positive symptoms of the disorder.

At the level of fundamental knowledge, current data remains fragmentary and unclear. Only the regulation of glutaminergic transmission appears to offer a preliminary indication that dietary modification might influence the course of schizophrenia.

SELECTED STUDIES SUGGESTING THE INFLUENCE OF DIET ON POSITIVE AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Stepping from pathophysiology to practical data, the impact of diet on the course of the disease reveals an interesting finding. It turns out that the literature reports a potential impact of other AAs, not only the discussed above. Most of them are connected with antioxidant mechanisms.

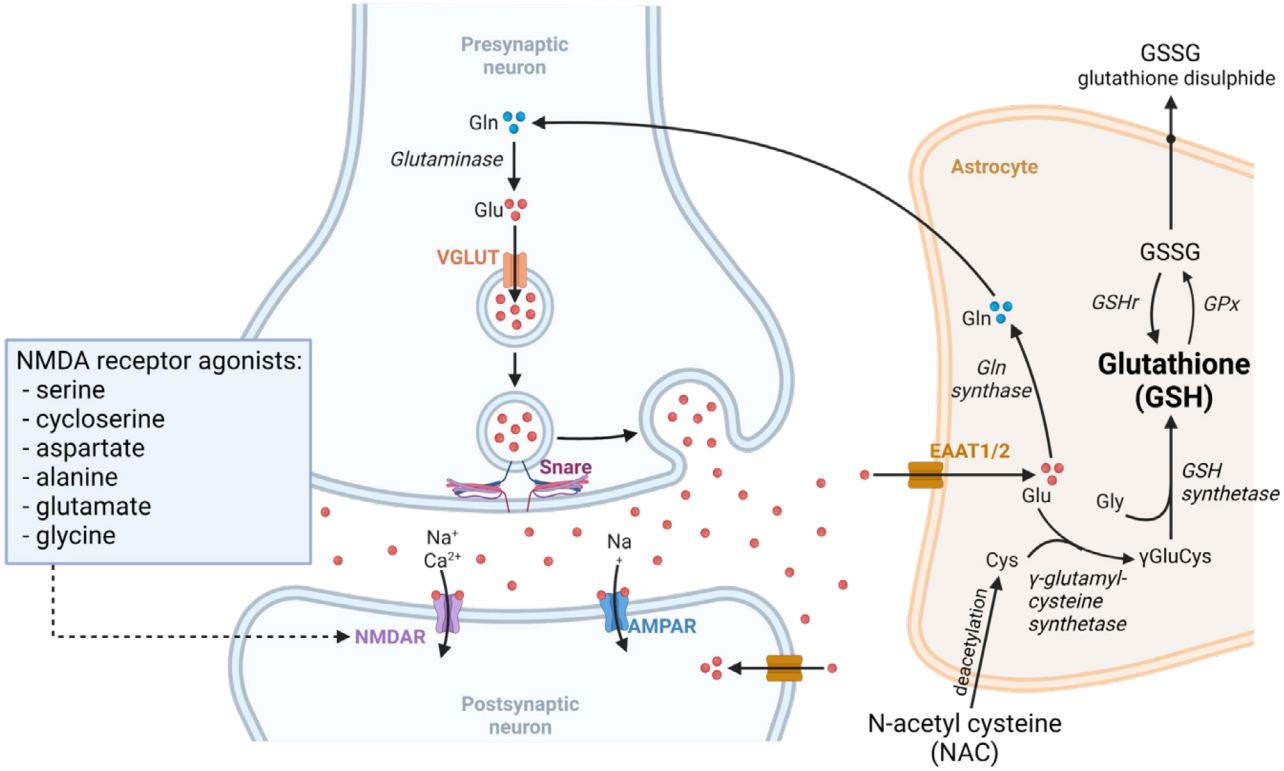
As a result of an imbalance between the systemic manifestation of reactive oxygen species and the body's ability to detoxify the reactive intermediates or repair the resulting damage, oxidative stress may develop. It causes mitochondrial dysfunction, inflammation, lipid peroxidation, DNA damage, and cellular apoptosis (Bitanihirwe and Woo, 2011; Peet, 2004a, 2004b). It can be concluded that antioxidant treatment can be used as a complementary strategy to pharmacotherapy of schizophrenia. They are partially related to the influence of AAs because some of them are polypeptides.

The most important antioxidants in the human body are glutathione (GSH) and alpha-lipoic acid, both of which can penetrate the BBB. Melatonin also plays a key role. These compounds act by preventing oxidation reactions or the accumulation of free radicals, which alleviates the symptoms of the disease. In addition, vitamins C and E, which are non-enzymatic antioxidants, can interrupt free radical chain reactions, also in patients with schizophrenia (Onhuma et al., 2008; Saleem et al., 2017). L-theanine (gamma-glutamylethylamide), an AA found mainly in tea, is an antioxidant with the ability to inhibit lipid peroxidation (Yokozawa and Dong, 1997).

Glutathione synthesis takes place in a two-stage biochemical reaction, in the mitochondria of astrocytes (Fig. 1). It is a tripeptide composed of glutamic acid, cysteine, and glycine. Cysteine is a sulphur-containing AA, which may suggest that consuming foods rich in sulphur AAs may support GSH synthesis. In addition, glycine may be as important as cysteine in the production of GSH, especially when simultaneously supplemented with *N*-acetylcysteine (NAC) (McCarty et al., 2018). Lavoie et al. (2008) demonstrated that NAC could increase the level of GSH in the blood plasma of patients diagnosed with schizophrenia; however, there is still no direct data on the impact of this phenomenon on the condition of patients (Saleem et al., 2017). GSH deficiency causes an increase in reactive oxygen species and, consequently, damage to cellular DNA and lipid peroxidation of mitochondrial membranes in astrocytes. This may not only disrupt intracellular membrane transport but also affect the function of mitochondrial enzymes in the brains of patients diagnosed with schizophrenia (Peet, 2004a).

The dose-dependent effects of NAC were assessed in rats raised in social isolation. Isolation profoundly alters the corticostriatal DA, serotonin (5-HT), and norepinephrine (NA) pathways that are analogous to those observed in schizophrenia. These changes are reversed or eliminated in a dose-dependent manner by NAC supplementation. The modulating effect of monoamines on the corticostriatal region may explain the therapeutic use of NAC in schizophrenia and probably other mental disorders where redox disorders or oxidative stress are the causative factors (Möller et al., 2013). In another study, NAC supplementation normalised GSH concentrations within the typical range (Sekhar et al., 2011). Such an intervention could potentially have implications also in the group of patients with

DOI: 10.15557/PiPK.2025.0020



AMPAR – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **Cys** – cysteine; **EAAT1/2** – excitatory amino acid transporters; **Gln** – glutamine; **Glu** –glutamic acid; **Gly** – glycine; **GPx** – glutathione peroxidase; **GSHr** – glutathione-disulfide reductase; **NMDAR** – *N*-methyl-D-aspartate receptor; **Snare** – transmembrane proteins; **VGLUT** – vesicular glutamate transporter; **γGluCys** – gamma-glutamylcysteine.

Fig. 1. Synthesis of glutathione

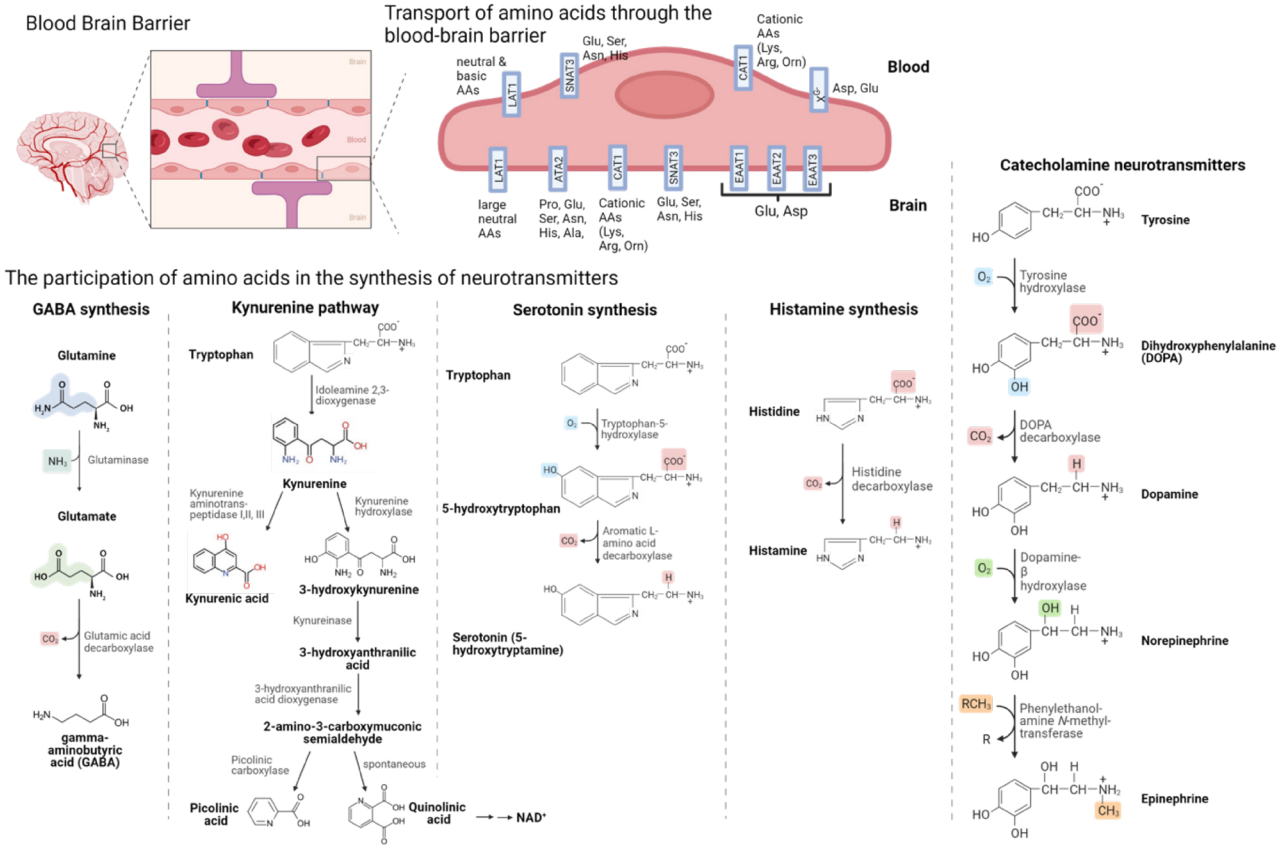
schizophrenia and other mental disorders, but this requires further investigation.

Genetic variations may also modulate GSH levels. Nucifora et al. (2017) presented evidence that schizophrenia is characterised by a decrease in the concentration of peripheral GSH and associated with the occurrence of oxidative stress. They also showed a significant reduction in plasma GSH levels in patients with schizophrenia compared to the control group. Additionally, they assessed the possible impact of clinical features on GSH levels, showing that a decrease in GSH levels correlated with Positive and Negative Syndrome Scale scores: full and positive symptoms subset (Nucifora et al., 2017). Among the studies exploring ways to increase GSH production through nutrition, oral administration of GSH in the form of ready-made mixtures seems most promising for overcoming the effects of potentially ineffective single nucleotide polymorphisms and related enzymes. However, there are conflicting studies on the effectiveness of this therapy due to the risk of GSH degradation by digestive peptidases (Allen and Bradley, 2011; Sinha et al., 2018).

A second mechanism by which diet may affect the course of schizophrenia is linked to precursors of neurotransmitters or neurotransmitters themselves. An example of a potential dietary intervention is addressing insufficient activation of the NMDA glutamate receptor (Balu, 2016). Ohnuma et al. (2008) found that the administration of glycine, D-cycloserine, and D-serine led to an alleviation of negative symptoms of schizophrenia. However, the potential scope of dietary influence remains complex. Tryptophan, tyrosine, and histidine are precursors of biogenic amines such as norepinephrine, 5-HT, DA, and histamine, and their levels in the central nervous system depend on the blood concentration of other AAs (phenylalanine, valine, leucine, and isoleucine) which cross the BBB (Saleem et al., 2017). The synthesis pathways of these biogenic amines are presented in Fig. 2. These are not the only AAs that affect the development and proper functioning of the brain. Serine, glycine, aspartic acid, and glutamic acid also act as neurotransmitters and support neuronal development (Maycox et al., 1990). Patients suffering from schizophrenia may potentially have altered levels of these neurotransmitters, which results from changes in the concentration of aforementioned AAs in blood plasma and may increase the tendency and predisposition to develop psychotic disorders (De Luca et al., 2008).

The third way through which AAs in the diet may influence the course of schizophrenia is through D-amino acids. This is again related to glutamatergic transmission. A significant number of papers report the influence of gut bacteria, which are a potential source of D-amino acids and are responsible for their production, use, and metabolism (such as *Acetobacter*, *Lactobacillus*, *Micrococcus*, and *Streptococcus*), as well

 DOI: 10.15557/PiPK.2025.0020



AAs – amino acids; **Arg** – arginine; **Asn** – asparagine; **Asp** – aspartic acid; **ATA2 (SNAT2)** – amino acid transport system A 2; **CAT1** – chloramphenicol acetyltransferase 1; **EAAT1/2/3** – excitatory amino acid transporters 1/2/3; **Glu** – glutamic acid; **His** – histidine; **LAT1** – L-type/large neutral amino acid transporter 1; **Lys** – lysine; **Orn** – ornithine; **Ser** – serine; **SNAT3 (ATA3)** – amino acid transport system A 3; **X^{G-}** – blood group antigen proteins.

Fig. 2. Neurotransmitter synthesis and amino acid transport

as their role in the development and progression of schizophrenia (Kepert et al., 2017; Quigley, 2017). This effect again focuses mainly on NMDA receptor agonists, i.e. amino acids such as D-aspartate, D-serine, D-alanine, and D-glutamate (Genchi, 2017; Seckler and Lewis, 2020).

The activity of serine racemase (SR) (synthesis of D-serine, MDMA receptors "gate-keeper") potentially plays a role in the pathophysiology of schizophrenia (Cheng et al., 2021). D-serine deficiency contributes to the blockade of the glutamate receptor, which may be one of the proposed causes of schizophrenia symptoms (Cheng et al., 2021). Mice used as animal models for schizophrenia, in which SR deficiency was induced, showed loss of cortical grey matter, reduction of cortical glutamatergic synapses, downregulation of parvalbumin-positive cortical GABA-ergic neurons, and cognitive impairment (Balu et al., 2013; Cheng et al., 2021; Puhl et al., 2015).

Among multiple strategies proposed to address drug-resistant patients, especially clozapine non-responders, D-amino acids (i.e. D-serine, D-alanine, and D-aspartate) and related proxy molecules (such as D-cycloserine) have been tested. All D-amino acids and proxy molecules were used as augmentation strategies. They presented a significant capability to decrease the severity of the overall or subsets of symptoms in schizophrenia individuals (Sumiyoshi et al., 2001a).

STUDIES SUGGESTING THE POTENTIAL INFLUENCE OF DIET ON SYMPTOMS CO-OCCURRING WITH SCHIZOPHRENIA

Apart from positive and negative symptoms, schizophrenic individuals often present with several other dysfunctions, such as elements of compulsive-obsessive or mood disorders, or cognitive dysfunctions. Serotonergic transmission plays a significant role in these symptoms, which has led to the potential impact of its precursor – tryptophan – in the diet. Stimulation of the 5-HT_{1A} receptor likely improves the course of schizophrenia (Sumiyoshi et al., 2001a, 2001b). 5-HT levels in the brain depend directly on the amount of exogenous tryptophan available for its synthesis. Thus, diet can potentially regulate 5-HT levels in the brain. Tryptophan supplementation has been suggested in schizophrenia, as its deficiency is probably involved in schizophrenia pathogenesis.

DOI: 10.15557/PiPK.2025.0020

However, study results are incongruous, and there are a few problems in drawing conclusions. The first is clinical: schizophrenia is a set of symptoms, sometimes even of opposing nature (e.g. mental retardation/agitation). The next issue is biochemical: other large neutral AAs, such as valine, isoleucine, leucine, and phenylalanine, also affect the availability of 5-HT precursors by competing with tryptophan and tyrosine for the same transport system across the BBB.

The necessity of high tryptophane intake in schizophrenic individuals is stressed by many investigations. Short-term administration of L-tryptophan is an effective way to increase the concentration of both tryptophan itself and its metabolite (5-HT). In patients with schizophrenia, a significant improvement was observed in visuospatial memory, working memory, psychomotor speed, and visual-motor coordination. This memory improvement was probably related to the effect of tryptophan on serotonergic activity and an indirect effect on the cholinergic or dopaminergic system (Levkovitz et al., 2003). Tryptophan has also been found to have a mood-stabilising effect in patients with schizoaffective disorder (Brewerton and Reus, 1983; Chandramouli and Subrahmanyam, 1981), but there is no clear evidence for this effect in schizophrenic individuals. In another study, the effects of acute dietary tryptophan depletion led to a statistically significant worsening of negative symptoms (Sharma et al., 1997), which also supports higher tryptophan consumption in these patients.

Yet, a paper with opposite findings exists. In Rosse et al.'s (1992) study, participants were on a 4-day tryptophan-deficient diet. Plasma tryptophan levels were reduced, which was associated with improved results of the Stroop test – colour and word scores. Colour naming is related to frontal lobe function, which is less efficient in schizophrenia. Interestingly, depressive symptoms did not appear in the tryptophan-deficient diet, despite the lowered total plasma tryptophan levels. There was also a small improvement in objective assessments of the severity of psychotic symptomatology. The results of this study suggest the opposite hypothesis: some adjuvant potential for a low tryptophan diet in the treatment of schizophrenia, and that schizophrenia or antipsychotic drugs may offer some protection against the depressive effects of a tryptophan-deficient diet (Rosse et al., 1992).

Among other dietary strategies linked to AAs' augmentation of antipsychotic therapy, using L-theanine (a unique amino acid present almost exclusively in the tea plant), was also suggested (Ritsner et al., 2011). The results, particularly the good therapeutic response on the Hamilton Anxiety Rating Scale, are promising. However, the cited paper, based on 60 patients, highlights several typical problems: heterogeneity, a small sample, and the need for further evaluation.

CONCLUSIONS

There is still a long way to go to find the answer to the question posed in the title. The results regarding the possibility of preventing, mitigating, or treating schizophrenia through dietary management are extremely fragmentary. Only scarce clinical data exists, and it is usually based on small patient samples. Possible hypotheses are supported by data based on animal models, in which only certain elements of the disease can be mapped. In addition, the unusual polymorphism of the disease, with its numerous forms and a wide variety of symptoms, sometimes of opposing nature (e.g. affective, anxiety, cognitive) is another obstacle to drawing definitive conclusions. Finally, a completely neglected issue is the problem of absorption.

There are some possibilities for using diet to enhance the treatment of schizophrenia. The following AAs in the diet can have a hypothetical impact: glutamic acid, cysteine, glycine, and serine (as they impact the synthesis of GSH); tryptophan, tyrosine, histidine, phenylalanine, valine, leucine, and isoleucine (as precursors of neurotransmitters and agents influencing their transport); serine or selected D-amino acids (as transmission facilitators); and Hcy (as an amino acid associated with the destruction of mitochondria in astrocytes). The strongest clinical data concerns glycine, serine, glutamate, Hcy, and arginine, which confirms some hypothetical premises, but at the current level, their evidentiary value remains limited. The discussed topic certainly requires further research, including a full assessment of patients' AA profiles.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study; writing of manuscript: KGS. Collection, recording and/or compilation of data: KGS, AW. Analysis and interpretation of data: KGS, PJ, AW. Critical review of manuscript; final approval of manuscript: HW.

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DOI: 10.15557/PiPK.2025.0020