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Review Article

Potential role of amino acids in pathogenesis of schizophrenia

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ABSTRACT

Schizophrenia is a syndrome of inconclusive etiopathogenesis with a prevalence of about 1% in general population. Underlying factors include genetic predisposition and defected neurodevelopment in early stages of life. The role of amino acids has been indicated in some reports. However, very few workers have detailed the effect of each amino acid in the pathophysiology of schizophrenia. Thus, in the present review, we aimed to provide an insight into the potential role of amino acids levels during schizophrenia. Any single amino acid defect cannot lead to the development of the disease. Higher concentration of glycine, serine, glutamate, homocysteine, and arginine are reported by many scientists in blood samples of patients of schizophrenia. Levels of rest of the amino acids show inconsistent results. Involvement of glutamate in pathophysiology of schizophrenia was hypothesized as early as the 1980s. It was demonstrated that dissociative anesthetics which are N-methyl-D-aspartate (NMDA) receptor antagonists can produce all negative, psychotic, cognitive, and physiological features of schizophrenia in healthy controls. This led to the development of hypothesis of NMDA receptor hypofunctioning in the pathophysiology of schizophrenia. Later on, it was also found that agents enhancing functioning of NMDA receptor at glycine modulatory site, improved symptoms in patients of schizophrenia receiving antipsychotic medications. Thus, the relationship of perturb amino acid levels with the biological basis and pathophysiology of schizophrenia is an important area to be further explored for effective management of schizophrenic patients.

Keyword: Amino acids, arginine, glutamate, glycine, homocysteine, N-methyl-D-aspartate receptor, schizophrenia, serine

Introduction

Schizophrenia is a chronic devitalizing disease, affecting around 1% of population.[1] The various factors causing schizophrenia includes genetic predisposition and defected neurodevelopment in early stages of life. There are evidences that some complications in pregnancy and perinatal period can lead to subsequent schizophrenia in life. They may include any infection in second trimester of pregnancy, obstetric complication, starvation of baby in uterus, and decreased nutritional supply to the fetus as in preeclampsia.[2] Its symptoms can be broadly divided to positive and negative ones. Positive symptoms include delusions, hallucinations and paranoia and main negative symptoms are weakened or exhausted speech, decrease motivation, community withdrawal, and blunted effects.[3] Disease starts appearing in early adulthood and symptoms usually persist till later life, despite active treatment.[4-6] Such a prolonged course of illness leads not only to personal disability and distress but also a great burden to society costing about 11.8 billion pounds per annum.[7] Complicating further the situation, the disease is associated with anxiety, depression and addiction,[8] chronic obstructive pulmonary disease, asthma, Type 2 diabetes, and related complications.[9] Mortality in these patients is higher because of high incidence of ischemic heart disease and cancer.[10,11]

Etiology includes genetic factors, some predisposing factors and lifestyle changes. Antipsychotic drugs given to treat the condition further worsen the situation.[12] Dopaminergic pathway is found to be disturbed in these patients but the disease is complicated by the presence of oxidative stress, atypical immune-mediated responses[13] and thyroid disturbances.[14] Such a diversified pathophysiology can be treated by the strategy of adjuvant nutritional therapy along with usual course of treatment.[13]

Schizophrenic patients, mostly live away from home in a very desperate environment. Hence, they have poor physical health[15] and die early because of cardiovascular diseases,[16] poor diet, obesity, physical inactivity, and smoking.[17] Gillman have suggested that an increased intake of fresh fruits plus vegetables can decrease the risk of cardiovascular disease.[18]

Possible three reasons can be given to answer the question of why schizophrenic patients have poor diet. First of all, they are unemployed. Second, mostly they become smokers and even in general population, diet of smokers is worse than that of non-smokers. Third, apathy, a negative symptom of schizophrenia can lead to consumption of less healthy, more convenient food.[17]

It is well known that nutritional status of the patient is very important in etiology of physical diseases such as cardiovascular diseases, diabetes, and cancer but very little research is available regarding relationship of mental illness and nutrition.[19-21] Some previous researchers have reported that there is some relationship between dietary fats and poor outcome in schizophrenic patients.[22,23] It is also reported that dairy products, meat, and intake of saturated fats are associated with adverse outcome in patients of schizophrenia.[22-24] These patients are having severe oxidative stress as there is actually imbalance between production of reactive oxygen species/reactive nitrogen species and antioxidants.[25] This oxidative stress is further complicated by a number of pathophysiological mechanisms such as mitochondrial dysfunction, inflammation, lipid peroxidation, DNA damage, and apoptosis.[26-28] Thus, antioxidant treatment can be adopted as adjuvant therapy in these patients. Glutathione is an important antioxidant; decreased in brains of these patients. N-acetyl cysteine (NAC) has been proven to increase plasma glutathione level in schizophrenic patients.[29] Alpha lipoic acid is another strong antioxidant having similar functions to glutathione, can cross blood–brain barrier. Melatonin is another effective antioxidant can scavenge free radicals ameliorating symptoms of the disease. Researchers have also highlighted the effectiveness of essential polyunsaturated fatty acids supplementation in schizophrenic patients.[13] Among non-enzymatic antioxidants, vitamin C and E are helpful in breaking free radical chain reactions in patients of schizophrenia.[30] L-theanine (a gamma-glutamylethylamide) an important amino acid found in tea plant is an antioxidant as it has ability to inhibit lipid peroxidation.[31] It also reduces adverse effects induced by doxorubicin leading to oxidative damage.[32]

Hypofunctioning of N-methyl-D-aspartate (NMDA) glutamate receptor might be involved in the pathophysiology of schizophrenia.[33,34] Therapeutic administration of certain amino acids, involving NMDA receptor has led to the improvement of symptoms of schizophrenia. For example, glycine, D-cycloserine, D-serine, all of which act as co-agonist at NMDA receptor can lead to improvement in negative symptoms in patients of schizophrenia.[35] Biogenic amines such as norepinephrine, serotonin, dopamine, and histamine are synthesized from their precursors, tryptophan, tyrosine, and histidine.[36] Levels of these amino acids precursors in central nervous system is dependent on blood concentration of phenylalanine, valine leucine and isoleucine, have affinity for tyrosine and tryptophan carriers, to cross blood–brain barrier.[37] Certain other amino acids such as serine, glycine, aspartic, and glutamic acid act as neurotransmitters and aid in neuronal development.[38] An imbalance of these neurotransmitter levels have been reported in patients of schizophrenia. Changes in plasma concentration of these amino acids, might increase susceptibility of such a psychotic disorder, thus can also influence treatment outcome.[39]

From these studies, the role of nutritional status with the genesis of schizophrenia has been indicated in some reports. However, very few workers have detailed the effect of each amino acid in the pathophysiology of schizophrenia. Thus, in the present review, we aimed to provide an insight into the potential role of amino acids levels during schizophrenia. This review may help in developing combination therapies targeting multifactorial schizophrenia pathophysiologies along with normal treatment therapy.

Literature Review

In past few years, increasing interest has been observed in finding out possible role of amino acids in the pathophysiology of schizophrenia. Most of the research is focused on glutamate and gamma amino butyric acid (GABA) but some role is also played by other amino acids as well.[40]

Tyrosine is a non-essential aromatic amino acid, a precursor of nor-epinephrine, epinephrine, and dopamine. Vincenzo *et al.* found a high serum tyrosine concentration in schizophrenic patients treated with clozapine. They also found lower tryptophan concentration also lower tryptophan to large neutral amino acid ratio in the serum of schizophrenic patients.[39] Various studies reported low serum tryptophan levels in patients of schizophrenia.[41,42] It can lead to decreased uptake of tryptophan by neurons of brain leading to decreased serotonin levels in the brain of schizophrenic patients as tryptophan is a serotonin precursor. They also found that with clozapine treatment levels of tryptophan start improving day-by-day with improvement of condition of the patient.[39] Alfredsson *et al.* also found increasing tryptophan levels in early part of their treatment of patients of schizophrenia.[43]

L-serine is another amino acid which acts as cotransmitter to regulate NMDA glutamate receptor. Macciardi *et al.* reported that there is increased level of serine in serum as well as in brain of patients of schizophrenia, they found that there must be a correlation between elevated serine level and pathophysiology of schizophrenia.[44] Some other researchers reported normal serine plasma levels in patients of schizophrenia.[41,45] In contrast, Tortorella *et al*. have reported lower serum serine levels in drug-free schizophrenic patients.[42]

D-serine is another co-agonist at NMDA receptor.[40] To open NMDA receptor, glutamate has to bind to NR2 receptor site. Glycine and serine have to bind to NR1 receptor site. D-serine is more permeable to blood–brain barrier also has more affinity to NMDA receptor compared to glycine. Thus, lesser doses

of D-serine would be more effective.[46] Panizzutti *et al.* have observed increasing activation of hippocampus, enhancement of learning process, increased long-term potentiation after administration of D-serine in patients of schizophrenia.[47] Hashimoto *et al.* found lower levels of D-serine in serum of schizophrenic patients if we compare them with control groups.[48] There can be deficiency of serine racemase enzyme which converts L-serine to D-serine in patients of schizophrenia or overactivity of enzyme D-amino oxidase which leads to increase catabolism of D-serine.[40] Ohnuma *et al.* observed improvement in the levels of D-serine as well as D/L serine ratio in clinically improving patients of schizophrenia.[35] Labrie *et al.* have reported schizophrenia-like behavior in mutant mice, in which there is loss of enzyme serine racemase resulting in decrease D-serine levels in brain.[49]

L-glutamine is a non-essential amino acid. Alfredsson *et al.* found a negative correlation between serum glutamine levels with clinical response to treatment.[43]

L-asparagine: Tortorella *et al.* found lower serum asparagines levels in schizophrenic patients as compared to control group[42] whereas Rao *et al.* reported higher serum asparagines levels in drug-free schizophrenic patients as compared to healthy controls.[41]

L-glutamate is a well-known excitatory, non-essential amino acid. Tortella *et al.* found elevated glutamate levels in serum of patients of schizophrenia which are found to be decreased by treatment with clozapine.[42] Similarly, Macciardi *et al*. also reported higher glutamate levels in the serum of patients of schizophrenia.[44] Tomiya *et al.* have reported rise in serum glutamate levels only in male patients of schizophrenia.[50] According to Evins *et al.,* longterm treatment with clozapine leads to increase in serum glutamate levels.[51] Glutamatergic hypothesis of schizophrenia states that levels of glutamate are lower in patients of schizophrenia and a good antipsychotic medicine can act as enhancer of glutamatergic neurotransmission.[52] According to some researchers, peripheral level of glutamate cannot reflect its level in brain as it is synthesized in central nervous system; however, many others have reported a positive correlation between serum glutamate level with its level in cerebral spinal fluid.[39]

L-aspartate is another non-essential amino acid. Tortorella *et al*. have reported higher serum aspartate levels in drug-free schizophrenic patients.[42] Evins *et al.* have shown that clozapine administration increases basal serum aspartate level (Table 1).[51]

Glycine is a non-essential amino acid, an inhibitory neurotransmitter which regulates the activity of NMDA receptor. Some researchers have reported elevated serum glycine concentration in patients of schizophrenia compared to healthy controls.[44,53] Some researchers have reported decreased plasma glycine levels in schizophrenic patients, seeming to relate the severity of negative symptoms in patients of schizophrenia[54-56] with their response to drugs such as clozapine.[57] Genetic plus drug-induced deficiency in glycine binding as observed in experimental mice leads to certain behavioral changes which appear to be responsible for cognitive and negative symptoms of schizophrenia.[58] According to some researchers, administrating glycine with some antipsychotics or administrating glycine transport inhibitors (GTI), with or without glycine, have promising results in the treatment of schizophrenia.[40] GTI when given together with glycine, less doses of glycine are required because it activates glycine modulatory sites at NMDA receptor, thus inhibits removal of glycine from synaptic cleft region, elevating its levels.[46,59]

L-proline is an essential amino acid. According to Jacquet *et al.*, increased proline level is a risk factor for development of schizophrenia.[60] Raux *et al.* have reported that patients of velocardiofacial-syndrome which is a syndrome associated with schizophrenia, have shown hyperprolinemia.[61]

Table 1: Altered levels of different amino acids are shown in schizophrenic patients

Amino acids	Levels in schizophrenia patients	Authors
Homocysteine	↑	Moustafa *et al*. 2015 Kevere *et al*. 2012 Muntjewerff *et al.* 2006
Glycine	↑	Baruah *et al.* 1991 Macciardi *et al*. 1990
	↓	Hons *et al*. 2010 Neeman *et al*. 2005 Sumiyoshi *et al*. 2004
Tyrosine	↑ (in clozapine treated)	Vincenzo *et al*. 2008
Tryptophan	↑	Vincenzo *et al.* 2008
	↓	Tortorella *et al.* 2001 Rao *et al.* 1990 Alfredsson *et al.* 1990
L-glutamate	↑ (in male pts only)	Tomiya *et al*. 2007
	↑	Tortorella *et al*. 2001 Macciardi *et al*. 1990
L-proline	↑	Jacquet *et a*l. 2005
L-Isoleucine	↑	Tortorella *et al*. 2001
L-aspartate	↑	Tortorella *et al.* 2001
	↑(in clozapine-treated)	Evins *et al*. 1997
L-asparagine	↓	Tortorella *et al.* 2001
	↑	Rao *et al.* 1990
L-serine	↓	Tortorella *et al.* 2001
	↑	Macciardi *et al.* 1990
Histidine	↑	Carl *et al*. 1992
Arginine	↑	Carl *et al*. 1992
Cysteine	↓	Rao *et al.* 1990
Citrulline	↑	Rao *et al.* 1990
L-glutamine	↑	Alfredsson *et al*. 1990

L-isoleucine is also an essential amino acid and competes with tyrosine and tryptophan for binding with transporters to cross blood–brain barrier. Researchers have found higher serum isoleucine levels in patients of schizophrenia.[42] Similarly, Carl *et al.* have reported higher serum histidine and arginine levels in patients of schizophrenia.[45]

Rao *et al.* have reported lower levels of cysteine and higher levels of citrulline in drug-free schizophrenic patients.[41] Similarly, a detailed meta-analysis showed that the levels of homocysteine (Hcy) are higher in patients of schizophrenia as compared to healthy controls.[62] Furthermore, according to Tomiya, serum level of ornithine is positively correlated with duration of illness of schizophrenic patients.[50] Perry *et al.* have reported an irregular high fasting plasma ornithine concentration in patients of acute psychosis.[63]

L-arginine is a precursor of nitric oxide (NO).[40] It effects levels of dopamine, GABA, and Glutamate in prefrontal cortex of brain.[64] It also has a role in memory and learning. NO levels are found to be raised in the brains of awake and mobile animals after phencyclidine (PCP) treatment. If together with PCP a nitric acid synthase inhibitor is administered, it not only reduce brain NO level but also PCP induce behavioral effects.[65] Fejgin *et al.* have also reported that cognitive dysfunction seen in schizophrenia patients may be reduced by using NOS inhibitors as a treatment approach.[66] Contrary to this, some animal studies have reported that under production of NO may have some link with schizophrenia.[40] As for example according to some researchers, NO donors (molsidomine and sodium nitroprusside) can alleviate behavioral effects induced by PCP.[67,68]

A non-protein amino acid, Hcy is also found to be involved in the etiology of schizophrenia. It is produced in the cell during one carbon metabolism. In the past researchers have related raised Hcy levels with a lot of physical diseases (cardiovascular diseases). In recent years, it is found that there is some link between elevated Hcy and psychiatric diseases such as schizophrenia and affective disorders, as raised Hcy causes cognitive impairment, characteristic of most of the psychiatric disorders, especially schizophrenia. It acts by causing oxidative stress in cells by interacting with NMDA receptor leading to vascular damage, mitochondrial dysfunction, and apoptosis. Therapeutic supplementation of folic acid plus vitamin B can effectively reduce raised serum Hcy levels.[69]

Kevere *et al.* also concluded that raised Hcy levels in patients of mood disorders and schizophrenia are linked to course and effect of the disease, suggesting it to be an important prognostic marker of psychiatric disorder, including schizophrenia.[70]

Recently, many authors have emphasized that if schizophrenic patients are treated with amino acids supplements, their symptoms improve. For example, Wass *et al.* suggested that disturbed NO signaling is involved in the pathophysiology of schizophrenia. L-lysine is an amino acid which interferes with NO production. He concluded that 6 g/day treatment of L-lysine for about 4 weeks significantly decreased positive symptoms of schizophrenia.[71] Similarly, according to Giorlando *et al.*, NAC is an important emerging agent which can be used in therapy of different psychiatric disorders such as compulsive and grooming disorders, addiction, schizophrenia, and bipolar disorders. NAC exerts its affects by modulating inflammatory, neurotropic, and glutamatergic pathways. It is also precursor of glutathione which is an important antioxidant for the body.[72]

Many authors have highlighted the role of amino acids and other antioxidants as alternative and complementary treatment for schizophrenia. For example, according to Arroll *et al.,* schizophrenic patients can be given L-theanine (an amino acid of plant origin), NAC, vitamin B12, folic acid, pyridoxine, and essential polyunsaturated fatty acids along with regular medical care. L-theanine will reduce positive symptoms of schizophrenia, vitamin B6, B9, and B12 will reduce Hcy levels and polyunsaturated fatty acid will replenish reduced fatty acid levels in the brain of such patients.[13] Similarly, Lakhan and Vieira suggested that not only tryptophan and glycine would be beneficial for schizophrenic patients but also Veg EPA capsule, containing omega 3 fish oil plus vitamin E as antioxidant, can be helpful in balancing the mood of such patients.[73]

Conclusion

Disturbance in amino acid levels has been linked to pathophysiology of schizophrenia, in many recent studies. Amino acids (glycine, serine, glutamate, cysteine) have important role to play in mitochondria of astrocytes, not only in metabolism of Hcy but also in formation of glutathione. Disturbed Hcy levels can lead to vascular damage, DNA damage, and apoptosis in the brain of schizophrenic patients. Deficiency of glutathione, an important antioxidant can lead to increase ROS, leading to DNA damage and can cause lipid peroxidation of membrane of mitochondria in astrocytes. Increase membrane fluidity will not only disturb membrane transport but also mitochondrial enzymes in the brain of patients of schizophrenia. Thus, relationship of disturbed amino acid levels and schizophrenia is a new era to be further explored to manage schizophrenic patients effectively. As many antipsychotic medicines are having side effects, reducing dosage of these medicines, and adding amino acids, vitamins and other anti-oxidants in regular medical care of these patients would be really beneficial in long term.

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