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Nutrients in schizophrenia: a focus on the pathophysiological pathway

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SUMMARY

Objectives

The aim of this article is to explain the nutrients that play an active role in the pathophysiology of schizophrenia.

Methods

This paper is a narrative literature review of relevant articles and prior works that have been central to the topic including the active nutrients in the pathophysiology of schizophrenia.

Results

The findings are compiled under six headings. The changes in the antioxidant defense system, dopamine pathway, serotonin pathway, gamma-aminobutyric acid (GABA) pathway, glutamate pathway, the endocannabinoid system, and metabolomic profile were investigated in relation to nutrients.

Conclusions

This review provides an update of scientific knowledge on the growing role of nutrition in schizophrenia. Nutrient deficiencies that occur frequently in these patients should be followed and eliminated to ensure the correct functioning of the pathophysiological pathways of the disease.

Key words: endocannabinoids, neurotransmitter agents, nutrients, schizophrenia

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Introduction

Schizophrenia is a type of psychosis with many mental signals, such as positive symptoms as hallucinations and delusions, or negative symptoms as motivation and social communication problems. Over time, cognitive problems such as attention deficit and speech disorders also appear [1]. Schizophrenia is a complex neurodevelopmental disorder in which environment and genetics play a role. It can be said that risk alleles (SNPs), de nova hereditary mutations, or a combination of variants together with environmental factors affect brain development. However, it usually does not show symptoms until the adolescent period [2]. Different possible etiological factors are effective in Schizophrenia. While explaining the pathophysiological processes, different mechanisms such as neurotransmitter pathway and oxidative stress are emphasized [3-5]. Vitamins, minerals, and other nutrients are important for reducing symptoms of schizophrenia by decreasing oxidative stress or modulating neurological pathways [6]. This review will focus on the nutrients involved in these pathways while emphasizing the pathophysiological processes associated with schizophrenia (Fig. 1). This review provides an update of scientific knowledge on the growing role of nutrition in schizophrenia. To do so, the pathophysiological pathways of schizophrenia have been reviewed as well as the efficacy of specific nutrients on these pathways were reviewed.

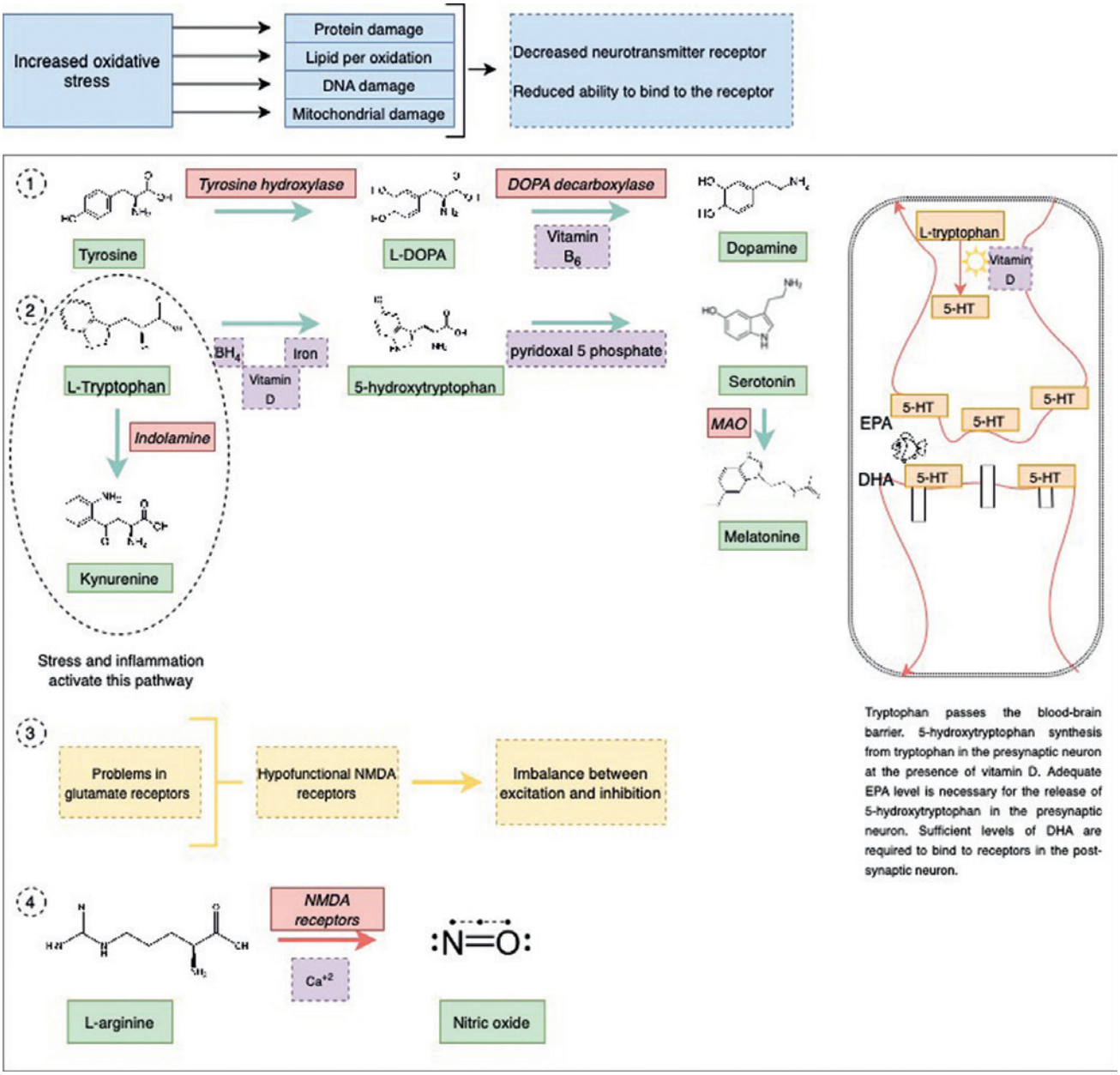

FIGURE 1. *The pathways that are effective in the pathophysiology of schizophrenia and the nutrients that regulate these pathways.*

Antioxidant defense system

It is thought that inflammation and oxidative stress play an important role in the etiology of schizophrenia. Free radical production has increased in schizophrenia and proinflammatory cytokine release has also increased due to disorders in detoxifying ability. Increased pro-inflammatory cytokines are known to be important for normal central nerve development and the proper functioning of neural networks and neurotransmitters. Increased immune system activation causes increased proinflammatory cytokine release and disorders in neurotransmitter balance. Inflammation and oxidative stress trigger psychotic symptoms [7,8]. In a study, it was emphasized that the severity of the neurological signals of patients increased four times compared to the healthy control group and important enzymes for oxidative stress, such as glutathione peroxidase and superoxide dismutase, have been found to be reduced [9].

Many nutrients are known to have anti-inflammatory and antioxidant functions by various mechanisms in our

body [8]. Omega-3 polyunsaturated fatty acids (PUFAs) form about 20% of the dry weight of the brain and 1/3 of all fat in the central nervous system. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the two most specific omega-3 PUFAs known to have therapeutic antioxidant and anti-inflammatory effects in mental health [9]. In addition, it has been shown to have anti-excitotoxic effects on brain tissue by preventing neuron damage as a result of excessive release of excitatory neurotransmitters such as glutamate [10]. However, it has been found that undesirable fats in the structure of the Western Diet, which is high in saturated and trans-fatty acids, may aggravate the symptoms of schizophrenia by entering into the structure of phospholipids and competing with omega-3 PUFA. Studies have found that individuals with schizophrenia have lower levels of omega-3. Omega-3 supplementation is effective in improving symptoms of schizophrenia, especially positive symptoms [8].

Homocysteine, an oxidative stress agent, increases in schizophrenia. Homocysteine turns into glutathione, one of the important components of the antioxidant defense system, from the presence of pyridoxal 5 phosphates. Vitamin B_2 is required for the formation of pyridoxal 5 phosphate from pyridoxine. While vitamin B_2 is indirectly involved in this path, vitamin B_6 is directly involved. In a study, impaired glutathione function was detected in schizophrenia and it was emphasized that there may be glutathione deficits and abnormalities in patients with schizophrenia in the glutathione redox cycle [11]. Another pathway of homocysteine metabolism is the formation of methionine. Vitamin B_{12} is a cofactor in this pathway. Folic acid acts as a methyl supplier. Another pathway in which homocysteine is converted to another metabolite is the formation of cysteine. Vitamin B6 is also involved in the formation of cysteine from homocysteine [12,13]. Studies have shown that in cases of B_2, B_6, B_{12}, and folic acid deficiency, the level of homocysteine increases, and oxidative stress increases accordingly. This situation causes increased DNA damage and exacerbation of psychotic attacks due to schizophrenia [14,15].

Dopamine pathway

Dopamine regulates the formation of emotional learning, perception, and memory. It is known that dysregulation of dopaminergic neuron activities is effective for the appearance of symptoms of schizophrenia [16]. It is known that dopamine release increases in schizophrenia. It has been revealed that imbalance that occurs as a result of excessive subcortical dopamine release and deficiency in cortical dopamine has played an important role in the pathogenesis of schizophrenia [17]. It is thought that excessive activation of dopaminergic neurons plays a role in the formation of positive symptoms of psychosis such as hallucination. Negative symptoms are thought to be related to a deficit in dopaminergic neuron activity in a mesocortical area extending to the ventromedial prefrontal cortex. The studies emphasize that dopamine dysregulation leads to symptoms of schizophrenia [18]. One of the reported neurochemical abnormalities in a patient with schizophrenia is an increase in the synthesis of dopamine and the release of dopamine in the dorsal striatum [19]. There are some enzymes and hormones which are affected by releasing of dopamine. One of these is estrogen. It is known that estrogen regulates the expression of dopamine receptors and carriers and activities of the monoamine oxidase enzyme [20]. Tyrosine is an essential amino acid that readily passes the blood-brain barrier. Once in the brain, it is a precursor for dopamine. The concentration of dopamine in the brain depends on the amount of dietary tyrosine. Tyrosine is rapidly metabolized and folic acid, copper, and vitamin C are cofactor nutrients of these reactions (http://www.dcnutrition.com). Studies have emphasized that the deficiency of tyrosine hydroxylase enzyme activation increases the loss of the neuron and affects the dopaminergic pathway and causes decreases in tyrosine synthesis. The result of the lack of tyrosine, psychotic attacks exacerbates [21]. Tyrosine is an essential amino acid and is abundant in protein-rich foods. Nutrition affects tyrosine intake and hence dopamine release [22,23]. Impairment of dopaminergic transmission due to deficiency of tyrosine can be broke cognitive function. Therefore, abnormal tyrosine kinetics in patients with schizophrenia may be associated with cognitive dysfunction [24].

Serotonin pathway

Serotonin is found in many organs, like the brain. serotonin, which is located in the brain, plays an important role in homeostatic balance. It is synthesized by the tryptophan hydroxylase enzyme in the presence of oxygen [25]. 5-hydroxy tryptophan is synthesized from tryptophan in the presence of tetrahydrobiopterin and iron and vitamin D. Then, in the presence of pyridoxal 5-P, serotonin synthesis takes place. In inflammation and stress indolamine 2,3-dioxygenase and tryptophan2,3-dioxygenase enzymes are activated and kynurenine is synthesized from tryptophan [26,27]. Additionally, tryptophan is metabolized by the tryptophan hydroxylase 1 enzyme and 5-hydroxytryptophan is produced. Tetrahydrobiopterin and iron are cofactors in the pathway5-hydroxytryptophan are metabolized by l-amino acid decarboxylase and pyridoxal 5 phosphatase plays a role as a cofactor. tryptophan must be passed the blood-brain barrier for the production of serotonin in the brain. This transfer is influenced by the ratio of tryptophan and branched-chain amino acid. In the situation which removes the branched-chain amino acid in the circulation like exercise, passed tryptophan from the blood-brain barrier can be increased. An adequate EPA

level is necessary for the release of 5-hydroxy tryptophan from the presynaptic neuron. Sufficient levels of DHA are required to bind to receptors in the postsynaptic neuron [28,29]. Insufficent EPA, DHA, and vitamin D will cause problems in the nervous system in the pathway of serotonin synthesis. This will bring abnormal serotonin levels and behavioral problems [29]. Studies have found that individuals with schizophrenia have low vitamin D levels and their supplementation is associated with a decrease in proinflammatory cytokines such as Tumor necrosis factor-alpha (TNF-a), Interleukin 6 (IL-6) [30].

Gamma-aminobutyric acid (GABA) pathway

GABA is the main inhibitory effect neurotransmitter in the brain. A decrease in GABA cell density or loss of activity causes to decrease of regulatory inhibitory effect on dopaminergic and glutamatergic neurons of GABA [31]. In schizophrenia, GABAergic neurons are inhibited. Accordingly, there are imbalances between excitation and inhibition in the brain cortex [32]. Increased norepinephrine levels in schizophrenia cause an increase in sensitivity to emotional input. Second-generation antipsychotics increase norepinephrine levels by 5HT2C blockade in GABA interneurons. Increased norepinephrine and dopamine are also thought to have a positive effect on cognitive and affective symptoms in schizophrenia [18].

Glutamate pathway

Glutamate is a non-essential and excitatory neurotransmitter of the central nervous system. It is a neurotransmitter with adverse effects, and it has an “activator” effect on release towards dopamine and an “inhibitory” effect on release towards GABA. It has two types of receptors: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA). In resting potential, the NMDA receptor is blocked both by a passage and by the magnesium ion side. Phencyclidine, which acts by blocking NMDA, a glutamate receptor, causes a clinical picture with symptoms similar to the positive and negative symptoms of schizophrenia and exacerbates the role of the glutamate system in schizophrenia. NMDA receptors are hypofunctional in untreated schizophrenia [18,33]. Studies have found that l-theanine, which is abundant in the structure of green tea, is effective in stabilizing the concentration of glutaminergic neurotransmitters (34). Nitric oxide (NO) is produced by a reaction catalyzed by the nitric oxide synthase (NOS) enzyme from L-arginine. NO synthesis in neurons is activated by the leakage of Ca^{+2} into the cell. NMDA receptors are important for the Ca^{+2} leaks. NO, which is present at high levels in neurons, modulates neuronal functions as a secondary messenger. Studies have reported that nitrite plasma level, which is the stable last product of NO metabolism, is higher in schizophrenia patients than in healthy controls [32].

Endocannabinoid system in schizophrenia

The endocannabinoid signal is a lipid signal system that has regulatory functions in many different pathways in the central nervous system [34]. The endocannabinoid system is a recently discovered signaling system consisting of cannabinoid receptors (CB1 and CB2 receptors), endocannabinoids (Anandamide, cannabinoids, virodhamin, noladin, and n-arachidonoyl dopamine (NADA)), and enzymes (fatty acid hydrolase (FAAH) and monoacylglycerol lipase (MAGL)) on the surface of the cell wall [34-36]. The Endocannabinoid system regulates glutamatergic, GABAergic, and dopaminergic synaptic functions [37]. Increased endocannabinoids in the body fluids and increased CB1 receptor levels in postmortem brains of patients with schizophrenia were detected [38,39]. In schizophrenia, as a result of excessive activation of the endocannabinoid system, disturbances in balance in glutaminergic and dopaminergic neurons occurred. Psychotic symptoms (delusions, hallucinations, cognitive disorders) increase after an overdose of tetrahydrocannabinol (THC) in healthy individuals. Similarly, psychotic symptoms were found to increase even more in schizophrenia [40]. Cannabis use has been found to increase psychotic attacks in patients with schizophrenia [35]. Caspi et al. found that cannabinoid use leads to polymorphism on catechol-O methyltransferase (COMT), which encodes an important dopamine degradation enzyme and this causes increases the risk of psychosis [41].

Cannabinoid type-1 (CB1) receptors have a large expression on the cortical glutaminergic neurons of the main olfactory bulb in the brain. This increases the smell sensation and the food intake increases [42]. Studies have shown that blocking CB1 receptors reduces food intake [43]. Overactivity of the endocannabinoid system in patients with schizophrenia is thought to be associated with increased nutrient intake in these patients [44].

Metabolome in schizophrenia

Metabolomics is a technology based on the determination of metabolites from lipids, carbohydrates, vitamins, and minerals in body tissues and fluids [45]. Pathogenic processes in the body can cause changes in circulating concentrations of metabolites. Metabolomics can be used in psychiatric research to investigate disease susceptibility and response to treatment [46]. Findings from studies show that metabolic deviations detected in plasma can be used as potential biomarkers to help diagnose schizophrenia [47].

Obesity, impaired glucose tolerance, and impaired lipid profile are common in patients with schizophrenia. Studies have found that saturated fatty acids are high in the metabolic profiles of patients with schizophrenia. Therefore, specific metabolic abnormalities associated with glucoregulatory markers and proline metabolism indicate that metabolomics can be used in patients with schizophre-

nia [47]. Another study revealed abnormalities in biosynthetic pathways due to glutamine and arginine metabolism in patients with schizophrenia. It is thought that the follow-up of these components in the blood profile may be important for monitoring the prognosis of the disease [15]. Kynurenine is also considered metabolomic in schizophrenic patients. Kynurenine occurs from the l-tryptophan presence of indolamine in cases plasma iron, vitamin D and pyridoxal 5 phosphate levels are not sufficient [48,49].

Final consideration

Nutritional factors in psychiatric diseases should be evaluated with a multidisciplinary approach in order to achieve better results in patients' health status and quality of life. Many different pathways can be mentioned that affect the nutritional status of patients. However, it is difficult to make the desired changes in the diet of these patients [50]. However, the association between schizophrenia and nutritional deficiency does not imply a causal relationship, and studies related to dietary supplements do not always show proven effects. Therefore, more studies are needed on the effectiveness of nutrition in schizophrenia and other psychotic diseases. Although the results are not entirely consistent, omega-3, vitamin D, and group B vitamins have activity on pathophysiological pathways associated with schizophrenia, which may be useful as complementary strategies. Patients with schizophrenia have low antioxidant and anti-inflammatory component levels. This situation causes problems in neurotransmitter pathways and increases positive and negative symptoms. The results obtained from the studies indicate that the deficiency of nutrients is effective in the pathophysiology of schizophrenia. Nutrient deficiencies that occur frequently in these patients should be followed and eliminated to ensure the correct functioning of the pathophysiological pathways of the disease.

Ethical consideration

The articles that contributed to this review were reviewed by considering international ethical standards.

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Conflict of interest

The Authors have no conflict of interest to declare.

Author contributions

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