

The brain-gut axis dysfunctions and hypersensitivity to food antigens in the etiopathogenesis of schizophrenia

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Summary

Despite over 100-year history of research on schizophrenia, its etiology is still not fully understood, which might be due to the significant heterogeneity in terms of both its course, as well as the etiopathogenesis. One of the best-proven mediating mechanisms in the development of schizophrenia is the immuno-inflammatory response, the sources of which are believed to be the dysfunctions of brain-gut axis and pathological processes occurring in the intestines. This paper is a review of the literature on this subject which presents factors both involved in the functioning of brain-gut axis and important for the development of schizophrenia, i.e. 1. intestinal microbiome (intestinal microbiota), 2. permeable intestine (leaky gut syndrome), 3. hypersensitivity to food antigens, including gluten and casein of cow's milk. Research results seem to be very promising and indicate the possibility of improved clinical outcomes in some patients with schizophrenia by modifying diet, use of probiotics, and the implementation of antibiotic therapy of specific treatment groups. However, further research is needed on links between the intestinal microbiome and intestinal function as factors mediating the activation of the immune system and the development and further course of schizophrenia.

Key words: schizophrenia, leaky gut syndrome, gluten sensitivity

Introduction

Despite over 100-year history of research on schizophrenia, its etiology is still not fully understood, which might be due to the significant heterogeneity in terms of both its course, as well as the etiopathogenesis [1]. Research on the causes of schizophrenia is of great importance given the social, economic and cultural context related to

the course of the disease, leading to considerable difficulties in social, professional, and family functioning, personal suffering, as well as the stigma of patients and their exclusion from society [2].

Recently, a huge increase in interest in the importance of the so-called brain-gut axis in the pathogenesis of schizophrenia has been noted [3], including the impact of intestinal microbiome [4] and hypersensitivity to food antigens, particularly gluten [5, 6] and casein of cow's milk [7].

Taking into account historical aspects, the first hypotheses concerning the possibility of a link between impaired gastrointestinal function and psychiatric disorders were presented at the beginning of the twentieth century. In 1910, Dr George Porter Phillips reported that the administration of live lactic acid bacteria to adults suffering from depression reduces their severity of symptoms [8]. A report published in 1923, describing the results of a series of clinical observations made by an independent group of scientists, included recommendations for the use of milk containing *Lactobacillus bacteria* as a factor improving the efficiency of treatment for psychoses [9]. In his publication in 1953, Bender noted the association between celiac disease and juvenile episodes of schizophrenia [10]. Further works on this subject were published in the 1960s, after Dohan had presented his "cereal" hypothesis of etiopathogenesis of schizophrenia, based on the results of an epidemiological study on the risk of developing schizophrenia and the consumption of cereal products [11]. He observed a decrease in hospitalization for schizophrenia in the countries that had been forced to reduce consumption of bread during the Second World War, suggesting a possible link between the level of bread consumption and the incidence of schizophrenia. Singh and Kay described subsequent reports on this topic in the journal "Science" in 1976. They remarked that in people with schizophrenia who were on a gluten and casein-free diet, administration of gluten interrupted the progress of therapy. Upon stopping of the gluten intake, the mental state of patients improved again [12]. In their other study, Dohan et al. showed that only two patients with chronic schizophrenia were found among 65,000 adults who were observed in the Pacific Islands, where cereals had not originally been consumed. As soon as those people partially succumbed to Western influence and began to consume wheat products and barley beer, the prevalence of the disease has reached the European level [13].

Aim

The purpose of this paper is to review the literature on the links between the pathological processes occurring in the intestines and the risk of developing schizophrenia.

Method

Available papers from PubMed and Google Scholar were analyzed using time descriptors: 1995–2015 and key words: schizophrenia, gluten hypersensitivity, cow's milk casein hypersensitivity, celiac disease, microbiota, cytokines, and immune system.

In order to present the analyzed issues in the clearest and most comprehensive way, the article is divided into the following subsections:

- I. Inflammatory (macrophage, cytokine) theory of schizophrenia;
- II. The mechanisms associated with the functioning of brain-gut axis;
- III. Factors affecting the functioning of the brain-gut axis:
 1. Intestinal microbiome (microbiota, formerly the intestinal bacterial flora);
 2. The phenomenon of leaky gut syndrome;
 3. Hypersensitivity to gluten and casein of cow's milk.

Inflammatory (macrophage, cytokine) theory of schizophrenia

Despite the enormous expectations related to resolving the problem of etiopathogenetic schizophrenia through genetic tests, the results show that the cumulative effect of thousands of small single nucleotide polymorphism (SNPs) allows for explaining the genetic risk of schizophrenia in only approximately 30% of cases [14]. Among the analyzed genes, those immune-related genes find the strongest confirmation in GWAS study (Genome-Wide Association Study) [15]. The results also indicate a need for intensive research on mechanisms mediating the genes–environment interaction, including diet or infectious agents [3]. One of the best-proven mediating mechanisms in the development of schizophrenia is immuno-inflammatory response [16]. For the first time this type of pathophysiological mechanism underlying schizophrenia was pointed out by Smith in 1992, by presenting his macrophage (cytokine) theory of schizophrenia [17]. He suggested that chronic activation of macrophages with their subsequent inability to adequately control T-lymphocyte secretion of interleukin-2 and interleukin-2 receptors, underlies a biological mechanism for the development of schizophrenia. He also pointed to the gastrointestinal tract as an area where causes of immune activation in schizophrenia should be looked for. Currently, there is growing evidence from both animal studies and clinical trials, confirming the validity of the cytokine (macrophage) theory of schizophrenia [16].

Cytokines are proteins that play a key role in regulating the immuno-inflammatory response and agents modulating brain development [18]. They can also stimulate and inhibit the body's inflammatory response [19]. It has also been noted that, *inter alia*, pro-inflammatory cytokines directly affect the central nervous system activation by IL-1 receptors in the hypothalamus and hippocampus, manifested by emotional disorders: anhedonia, dysphoria, cognitive impairment, disorders of motor, sleep, and social functions [20]. At present, despite reports on association of schizophrenia with numerous cytokines, it seems that pathways of several cytokines play a key role. The highest congruence research in this area relates to pro-inflammatory interleukins, elevated levels of IL-1RA, sIL-2R and IL-6, and reduced levels of IL-2 [21]. The role of other cytokines at this stage seems unclear [22–24]. One of the possible explanations for this phenomenon is to treat schizophrenia as a disorder of heterogeneous causes and course.

In the context of the cytokine theory of schizophrenia, the importance of brain-gut axis dysregulation has recently been stressed more and more often as a trigger of immuno-inflammatory processes important for the development of schizophrenia [3].

The mechanisms associated with the brain-gut axis functioning in schizophrenia

The brain-gut axis is a network of autonomous neurons connecting the central nervous system (CNS) with the gastrointestinal tract, liver and pancreas. Its first anatomical descriptions were mentioned in very early written records. Galen already knew about the vagus nerve. However, the exact anatomy of the axis remained undisclosed until the mid-nineteenth century when Auerbach and Meissner found postganglionic fibers forming enteric nervous system in the intestinal wall [25]. Subsequent research studies in this field are even more important when we realize that the intestines form the largest surface through which our body contacts with the outside world and which is, according to the latest sources, about 32 square meters [26]. Information between the CNS and the intestines is transferred in both directions using different routes of communication, such as endocrine, metabolic, neural, immunological pathways [4, 27–29].

Endocrine factors that regulate the axis include, *inter alia*, cortisol, which is released under conditions of stress, and the secretion of which is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. It may affect the immune cells by modulating the secretion of cytokines, and the composition and activity of the microbiota [27].

The metabolic route is formed, *inter alia*, by short-chain fatty acids (SCFA), which are a product of bacterial fermentation occurring in the large intestine. Changes in their contents in the feces have been described in children with autism [29]. These relationships have also been confirmed in animal studies. Propionic acid, belonging to the SCFA, infused into the CNS of rats caused an occurrence of autistic behaviour and aggression [30]. Furthermore, vancomycin (a broad-spectrum glycopeptide antibiotic used in severe infections) has been reported to have beneficial therapeutic effects on symptoms of aggression in people with autism [31].

Regulation of brain-gut axis also takes place through the neuronal pathway, which is created by the enteric nervous system (ENS) producing neurotransmitters and neuromodulators. Particularly important is the role of corticotropin-releasing hormone (CRH) which contributes to increases in the permeability of the intestinal barrier when under stress [28]. In addition, the bacteria present in the guts can secrete a variety of neurotransmitters such as serotonin, melatonin, GABA, catecholamines and histamine, which are likely to affect the communication between various components of the microbiota through both peripheral and central activities [27]. The neuronal route also includes sympathetic and parasympathetic branches, especially the vagus nerve. It creates a communication route between the microbiota and the CNS [32]. The direct effect of inflammatory cytokines on the CNS through activation of afferent nerve fibers that transmit impulses to the corresponding regions of the brain, e.g. the solitary tract nucleus, deserves attention [20]. Efferent innervation, however, can participate in the anti-inflammatory response by acting on the $\alpha 7$ -nicotinic receptors in many cells of the immune system, re-

ducing the secretion of proinflammatory cytokines [33]. It has also been found that stimulation of the vagus nerve has an antidepressant effect and normalizes the HPA axis activity in patients treated for recurrent depression [34, 35].

Cytokines form an immunological route of communication between the intestines and the CNS. Their concentration is affected by microbiota. It has been confirmed that intestinal bacteria can both decrease the concentration of inflammatory cytokines (TNF-alpha, IFN-gamma, IL-6) and also modulate concentrations of anti-inflammatory cytokines, e.g. IL-10 [4]. Cytokines may directly influence CNS, among others, entering through leaky regions in the blood-brain barrier by using specific carriers or by activation of afferent nerve fibers, such as vagus nerve [36].

Factors affecting the functioning of the brain-gut axis

The important factors that both affect the functioning of the axis and are associated with the pathophysiology of schizophrenia, include:

1. Intestinal microbiome (microbiota, formerly the intestinal bacterial flora);
2. The phenomenon of permeable intestine (leaky gut syndrome);
3. Hypersensitivity to food antigens, including gluten and casein of cow's milk.

Intestinal microbiome

The microbiome is one of the key elements of the brain gut-axis. Its condition is influenced by diet, stress, a history of infections, personal hygiene and use of medication, including e.g. antibiotics [37]. Because of great numbers of resident flora (which outnumbers cells in the human body) and the complexity of functions, it is often referred to as “a forgotten organ” [38]. Its environment essentially consists of anaerobic bacteria belonging to four types – *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*. The primary function of the microbiota is its contribution to digestive processes. It is involved in the decomposition of complex carbohydrates, SCFA production and synthesis of vitamins [37].

Apart from influencing the digestive processes, the microbiome plays a key role in the development of the CNS. The microbiota affects a wide range of neurotrophins and proteins such as brain-derived neurotrophic factor (BDNF), synaptophysin and postsynaptic density protein 95 (PSD-95), which are involved in brain development and neuroplasticity [39]. Decreased levels of BDNF and NMDA receptor expression in the hippocampus and cortex was observed in germ-free animals [40].

The state of the intestinal microbiome directly affects the functioning of the innate and acquired immune system [41]. Communication between the microbiome and mucosal cells is regulated by the production of different cytokines and chemokines, both inflammatory (IL-8 and IL-1) and anti-inflammatory (IL-10 and TGF- β) [42]. This is confirmed by the findings of other authors who show that the microbiota may decrease the concentrations of proinflammatory cytokines: TNF-alpha, IFN-gamma, IL-6, and modulate the concentration of anti-inflammatory cytokines, e.g. IL-10 [4]. Investigations carried out on rats, aiming at examining the potential antidepressant ac-

tion of *Bifidobacterium infantis*, also shows a significant decrease in the concentrations of pro-inflammatory cytokines: IFN-gamma, TNF-alpha and IL-6 as well as a reduction in the levels of IL-10 in the group receiving the probiotic compared to the control group receiving placebo. Moreover, the probiotic increased the content of tryptophan and its metabolite – kynurenine acid (KYNA) having a neuroprotective effect by its antagonism to NMDA receptors [4]. Disturbances in the metabolic pathway of KYNA are considered one of the central factors in the development of schizophrenia [43].

It should be mentioned, however, that there are also reports showing that changes in microbiota can lead to neuropsychiatric disorders through the production, by bacteria, of harmful compounds such as P-cresol, which disrupt the intestinal barrier and allow bacterial products or proteins with neuroactive properties enter the bloodstream [44].

Leaky gut syndrome

The mechanism of permeable intestine (leaky-gut) seems to play an important role, inter alia, in the activation of the immune system [45]. Its occurrence is related to the activity of various modulators of the intestine permeability, including occludin and endogenous protease called zonulin. Its mechanism of action is similar to that of the ZOT toxin (Zonula occludens toxin) produced by *Vibrio cholerae*. The activation and expression of zonulin is influenced by, among others, gluten, antibiotics, bacteria and drugs. This results in increased permeability of the intestinal wall and destruction of epithelial tight junction between mucosal cells, which in turn leads to penetration of antigens into the circulatory system, and thus to activation of the immune system and an immune response [45]. It seems important that some schizophrenic patients exhibit increased expression of inflammatory markers, including haptoglobin, the precursor of which is zonulin and whose receptors are also found in the human brain [46]. It has been suggested that zonulin can modulate the permeability of the blood-brain barrier and thereby form the biological gate for inflammation, autoimmune and neoplastic processes [45].

Evidence for the structural damage of the intestinal barrier in patients with schizophrenia are derived from three types of studies:

- 1) Autopsy studies. The study on 82 schizophrenic patients showed that colitis was found in 92% of them, enteritis in 88% and gastritis in 50% [47, 48];
- 2) Research on markers of intestinal inflammation and bacterial translocation in schizophrenia. The results of the research by Severance et al. indicate elevated levels of antibodies against *Saccharomyces cerevisiae*, both in the group of people recently diagnosed with schizophrenia as well as in chronically ill patients [49]. The second marker, the elevated levels of which were found in patients with treated and untreated schizophrenia, is soluble cell differentiation antigen (sCD14). This is one of the markers of bacterial translocation. In addition, its elevated levels were strongly correlated with the CRP level and antibodies against gluten IgG, which suggests a relationship with inflammation, increased intestinal permeability and hypersensitivity to food allergens [50];

- 3) Research on pathogenic antigens. These studies concern the possibility of penetration of antigens into the circulatory system that results in inducing an immune response against its own tissues and cells by molecular mimicry [51]. This process plays a central role in the development of autoimmune diseases. In schizophrenic patients and their families, a higher incidence of these diseases, in comparison with the control group, was found [52].

Hypersensitivity to food antigens, including gluten and casein of cow's milk

In sensitive individuals, gluten can cause reactions which vary both in type and severity. In 2012, a team of experts in the field suggested a new classification of gluten-dependent disorders [53]. Due to pathogenesis, disorders associated with gluten were divided into three main groups: autoimmune, allergic and non-autoimmune and non-allergic (innate immunity). The first group (autoimmune reactions) include celiac disease (symptomatic, silent and potential), gluten ataxia and dermatitis herpetiformis. In the second group (allergic reactions), there is wheat allergy, which can be expressed in the following forms: food allergy, respiratory allergy, contact urticaria and WDEIA (wheat-dependent exercise-induced anaphylaxis). The third group includes disorders, the pathogenesis of which is connected with hypersensitivity to gluten in non-allergic and non-autoimmune ways. According to recent reports, a whole range of diseases can be associated with it, ranging from a variety of ailments associated with the digestive system, through various neurological diseases, ending with the psychiatric disorders such as schizophrenia, depression, bipolar disorder, autism [53].

Sensitivity to gluten is defined as the presence of antibodies against gliadin in IgA and IgG class, with rarely present antibodies specific to celiac disease, i.e. against deamidated gliadin, tissue transglutaminase, endomysium [54]. According to recent studies, both diseases also differ in activation of the immune system. The gluten-sensitive immune response is independent of the presence of antigens HLA-DQ2/DQ8. In celiac disease, they play a key role in the presentation of immunogenic peptides included in the gluten specific T-lymphocytes in the small intestine [55]. In celiac disease, the prevalence of HLA-DQ2/DQ8 is 95%, while in case of sensitivity to gluten, their presence is confirmed in only about 50% of cases, which is a value slightly higher than in the general population (30%) [53]. The differentiating factor is also the expression of the gene for IL-17a in biopsy specimens of patients with celiac disease. Compared to controls, it was found that patients with celiac disease had significantly elevated levels of IL-17a in the mucosa. In gluten-hypersensitive patients, IL-17a levels were similar to those of the control group [56]. The expression of membrane receptors TLRs (Toll-like receptor), which play a key role in the activation of the innate immune system, was also examined. Gluten-sensitive individuals presented considerably elevated levels of TLR2 transcripts and higher levels of TLR1 and TLR4 transcripts than the control group, but for the last two without reaching significance. In the celiac disease, however, increased levels of TLR1 and TLR2 transcripts (but not of TLR4), were observed compared to the control group, but neither of them reached significance. Thus, it seems that in gluten-sensitivity the

key role in the activation of the immune response is played by the innate immune system, while in celiac disease the acquired immune system is crucial, but this finding requires further confirmation [57].

The results of studies on schizophrenic patients seem to show that at least some of them had antibodies against gluten [6, 58–61]. However, this applies only to antibodies associated with gluten-hypersensitivity, because there were no antibodies specific to celiac disease and their prevalence was at the level of the control group [54]. However, the results were significantly inconsistent, as illustrated in the Table 1.

Table 1. Comparison of the levels of IgA and IgG antibodies against gliadin in patients and the control group

Authors, year	IgG antibodies against gliadin					IgA antibodies against gliadin					Description
	Patients		Controls		Odds ratio	Patients		Controls		Odds ratio	
	N	%	N	%		N	%	N	%		
Reichelt et al. 1995						48	18.75	13	0.00	6.33 (0.34–116.53)	Age: 16–52; gender: 36M + 12F; 12M untreated, 12M untreated for over 3 months; exclusion due to alcohol, SPA, celiac disease, asthma
Cascella et al. 2011	1401	1.43	900	3.33	0.42 (0.24–0.74)	1401	23.05	900	3.11	9.33 (6.28–13.87)	Age: 18–65; mean age 40.6 ± 11.1; 74% M + 26% F; treated with oral neuroleptics
Jin et al. 2012	419	17.90	478	14.23	1.32 (0.92–1.88)	473	27.06	478	17.80	1.72 (1.25–2.35)	Age: 38.9 ± 12.5, IgG: 173M + 246F; IgA: 227M + 246F
Sidhom et al. 2012	47	59	41	23.90	4.57 (1.82–11.47)	47	4.47	41	10.49	0.41 (0.07–2.37)	Age: 42.38 ± 13.48; gender: 35M + 12F; first episode age: 25.89 ± 8.41; duration: 16.54 ± 12.77
Okusaga et al. 2013	950	21.90	1000	10	2.13 (1.57–2.91)						Age: 18–60; mean age: 38.0 ± 11.6; gender: 600M + 350F

As the data presented in Table 1 show, although in most studies a higher prevalence of IgA or IgG antibodies against gliadin is reported, there are considerable differences

between studies in terms of their distribution. Additionally, in the work published in 2014, in 44 patients with a diagnosed presence of IgG antibodies against gliadin, a 6-month gluten-free diet was implemented. After this period, the antibodies remained in only 3 patients [62]. These results are even more important when compared with various reports mentioning cases of improvement or even complete remission of psychotic symptoms after the introduction of a gluten-free diet [63].

It is worth to mention an interesting clinical case of a patient with diagnosed schizophrenia accompanied by chronic diarrhoea and weight loss, as well as hypoperfusion in the frontal cerebral anterior region, demonstrated in SPECT test, which was not accompanied by structural changes in the CNS. The introduction of a gluten-free diet resulted in an disappearance of symptoms of psychosis and full normalization of cerebral perfusion [64].

Another food antigen related to the etiopathogenesis of schizophrenia is cow's milk casein. This seems to be confirmed by a study published in 2015 by Severance and et al. [65]. They found elevated levels of antibodies against casein and gluten in the cerebrospinal fluid of people suffering from schizophrenia. It was also observed that in the control group, a high level of IgG antibodies against casein and gluten in the serum did not correlate with elevated levels of IgG in the cerebrospinal fluid and was different from the results in the group of patients. This confirms the reports of possible dysfunction of the blood-brain barrier in patients with schizophrenia [66].

It is also noteworthy that food antigens, such as cow's milk casein and gluten contained in cereals, may be included in the immune complexes with complement protein C1q [7]. A considerably elevated level of antibodies was observed in patients with newly diagnosed schizophrenia: odds ratio (OR) = 8.02, while in patients with a long course of the disease the odds ratio was lower: OR = 3.15. An important role is played by the C1q complex of complement system that is responsible for binding and removing of antigen-antibody complexes from the circulation system. It has been shown that C1q is also responsible for the elimination of synapses (pruning) during the neurodevelopmental period. Its subsequent reactivation probably occurs in the neurodegeneration. Its elevated level was also confirmed in schizophrenic patients compared to controls. Based on the obtained results, the authors suggest usefulness of measuring the activation of C1q as a marker of early psychosis. However, this requires further research, which should also include links to other potential antigens.

The relationship between food antigens and the prevalence of psychoses also seems to be confirmed by the presence of exorphins in the urine of untreated patients diagnosed with schizoaffective disorder – depressive type, the sources of which might be gluten and casein [67].

Recapitulation

One of the many ways that lead to schizophrenia development appears to be activation of inflammation. According to the results of studies presented in this article, the brain-gut axis and the pathological processes occurring in the intestines may play a key role in activation of this condition. It appears that as a result of diet

modification, the use of probiotics and antibiotics from certain treatment groups, a significant number of patients could expect improvement in the clinical condition, and even obtain full remission [3]. However, despite substantial evidence for the existence of links between schizophrenia prevalence and the digestive system disorders, at this stage of the investigation it is not possible to know exactly the mechanisms linking the two disorders. Further studies are needed on the links between intestinal microbiome, hypersensitivity to food antigens and the functioning of the intestines, as intermediary elements in the activation of the immune system, and development and further course of schizophrenia.

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