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From Leaky Gut to Central Nervous System Autoimmunity: Cross-Reactivity and Molecular Mimicry in Schizophrenia

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Abstract

Background and Aim: Traditional schizophrenia models relying on neurotransmitter dysfunctions are giving way to new perspectives. Stepping beyond the conventional gut-brain axis paradigm, this review emphasizes a fresh autoimmune hypothesis: molecular mimicry and cascading tissue barrier breakdowns as direct triggers of central nervous system (CNS) pathology.

Materials and Methods: We analyze recent clinical studies concerning intestinal and blood-brain barrier (BBB) integrity, focusing on specific mechanisms: the kynurenine pathway, cross-reactivity to food antigens (wheat gluten, bovine casein), and NMDA receptor autoantibodies in schizophrenia.

Results: Schizophrenia-associated dysbiosis, marked by a depletion of butyrate-producing bacteria, compromises the intestinal barrier, leading to metabolic endotoxemia. Crucially, the pathology is driven by immune deception. Given the structural homologies between foreign or dietary antigens and host tissues (molecular mimicry), cross-reactive lymphocytes and autoantibodies are generated. These penetrate the compromised BBB - sometimes via a macrophage-mediated "Trojan Horse" mechanism - and directly attack host brain structures, including myelin and NMDA receptors. Concurrently, systemic inflammation pathologically redirects tryptophan metabolism, producing neurotoxic kynurenic acid.

Conclusions: Schizophrenia's pathophysiology is inextricably linked to immune autoaggression initiated by molecular mimicry. Shifting focus from general microbiome presence to the mechanisms of cross-reactivity and cascading barrier hyperpermeability reveals novel avenues for antigen-specific therapies. Addressing these root causes offers substantial hope for profound clinical improvement or even full remission.

Keywords: schizophrenia; molecular mimicry; cross-reactivity; dysbiosis; gut-brain axis; autoimmunity.

1. Introduction

Schizophrenia is a mental disorder that is still quite poorly understood, yet keenly employed and vividly depicted in media, such as film, fascinating and provoking unease in the general audience. However, schizophrenia is a real issue, affecting real people, as much as around 1% of our population [1]. Schizophrenia is linked to significant health, economic and social concerns, being one of the main causes of disability and increasing the risks of premature mortality [2].

Throughout the years different hypotheses on schizophrenia's etiology have been proposed. These include the prominent dopaminergic theory, as well as less popularized ideas, such as dysfunctions within the glutamatergic, serotonergic, and gamma-aminobutyric acid (GABA) signaling [1], and various environmental factors including obstetric complications, infections or marijuana use [3]. However, an extremely interesting take on the matter is the approach concerning the role of autoimmune processes and resulting inflammation in the etiopathogenesis of different mental disorders, including schizophrenia [4]. The main purpose of this paper is to delve into that hypothesis,

focusing specifically on the mechanisms of intestinal dysbiosis and molecular mimicry, which lead to the host's immune system attacking brain tissue and causing symptoms specific to schizophrenia.

2. The Gut-Brain Axis

It is well established that the enteric nervous system (ENS) guards a proper gut function, but evidence shows that the ENS also connects to the central nervous system (CNS) and does so in a bidirectional manner. One of the main pathways for this connection seems to be the vagus nerve – a part of the CNS branching throughout the body, bringing sensory information from the gut to the brain and sending back motor signals [5] [6].

Another critical component is the intestinal microbiota. The human microbiome is vast and plays a major role in regulating our physiology; while it inhabits different parts of the body, the majority of it is located in the gut [7]. Bacterial metabolites and toxins, neuroactive molecules, hormones, as well as pro-inflammatory cytokines emerging from a general immune response triggered by bacterial lipopolysaccharides (LPS) can travel through the bloodstream and potentially pass through the blood-brain barrier. Among the metabolites of great significance are those derived from tryptophan, like serotonin and kynurenine. Moreover, the gut microbiota provides us with crucial neurotransmitters regulating the CNS function, including acetylcholine, glutamate or GABA [8] [9].

Two important mechanisms – the intestinal barrier and the blood-brain barrier – serve to guard the brain against a gut bacteria-induced invasion of harmful substances, while allowing the crucial regulatory ones to pass. The physical component cooperates with the immune response, involving lymphocytes and dendritic cells of the intestine, as well as perivascular macrophages and mast cells of the blood-brain barrier [10].

However, specific pathogens have developed mechanisms to disrupt and bypass the regulatory pathways, increasing the permeability of these barriers and ultimately managing to access the central nervous system [10].

3. From Dysbiosis To Autoimmunity

3.1. Microbiome Composition in Schizophrenia

The microbiome of the human gastrointestinal tract plays a significant role in maintaining homeostasis and regulating the immune system. Recently conducted studies have pointed at the significance of observed dysbiosis in the gut microbiome in schizophrenia patients compared to healthy controls. Results show that patients diagnosed with schizophrenia exhibit an increased number of potentially

pathogenic gut bacteria, such as those of Proteobacteria and Enterobacteriaceae family or those of genus *Prevotella* and *Lactobacillus*. Simultaneously, they present a reduced abundance of beneficial bacteria of genera *Roseburia* and *Coprococcus*, which are responsible for producing short-chain fatty acids (SCFAs) - molecules essential for maintaining a healthy intestinal barrier, as well as exhibiting anti-inflammatory properties [11] [12]. Consequently, this shift in the microbiome's structure serves as a trigger for inadequate inflammation within the gut, aligning well with previous findings reporting an elevated prevalence of intestinal inflammation among schizophrenia patients [11].

Schizophrenia frequently co-occurs with gastrointestinal disorders driven by imbalances in the gut microbial pattern. A study conducted by Hemmings demonstrated that among 82 schizophrenia patients 92% suffered from colitis, 88% from enteritis and 50% from gastritis [13]. To further support the connection between perturbations in the gut microbiome composition and schizophrenia, studies have shown that transplanting fecal microbiota from individuals diagnosed with schizophrenia into germ-free mice resulted in the mice developing schizophrenic-like behaviors, including locomotor hyperactivity or increased startle response [14].

3.2. Intestinal Barrier Dysfunction

The intestinal barrier ensures that ingested pathogens are not permitted to pass further into the bloodstream. The gut's mucus layer and epithelial cells form a barrier regulating the movement of substances from the gut lumen to the rest of the organism. The epithelial cells are connected by tight junctions with their permeability regulated by proteins, such as occludin, claudin and zonula occludens [15].

The aforementioned increased count of pathogens and depleted number of protective bacteria in schizophrenia patients contribute to the compromised integrity of the epithelial barrier, leading to products of intestinal inflammation making their way into the bloodstream [11].

Research conducted by Severance et al. demonstrated structural damage to the integrity of the gastrointestinal barrier in schizophrenia patients by assessing markers of bacterial translocation and intestinal inflammation. Both recent-onset as well as chronic schizophrenia individuals exhibited elevated levels of antibodies against *Saccharomyces cerevisiae* – a commensal fungus – hence pointing to an above-average immune reactivity towards gut antigens [13].

Because the number of short-chain fatty acids (SCFAs) producing bacteria is depleted in schizophrenia, consequently particular SCFAs, like butyrate, exhibit a decreased abundance [11]. Butyrate's role incorporates lowering bacterial translocation and affecting tight junction proteins in a

way that supports barrier's integrity. Hence, butyrate deficiency can be seen as a factor connected to the disruption of the intestinal barrier [16] [17].

3.3 Metabolic Endotoxemia

Research utilizing rat models has indicated that enhanced intestinal permeability allows dietary antigens, microbes, and lipopolysaccharides (LPS) to enter the bloodstream - a mechanism connected to systemic inflammation [18]. The intestinal microbiome, heavily populated by Gram-negative bacteria, most notably the *Bacteroidetes* phylum, acts as the primary origin for this circulating LPS. Compromises to the gut barrier create increased porosity, promoting the translocation of LPS molecules [18] [19].

The phenomenon of LPS circulating in the bloodstream without an active Gram-negative infection is defined as metabolic endotoxemia. Dysbiosis within the gut is hypothesized to be a key contributor, or potentially the initiating trigger, for this condition. Even minor increases in systemic LPS correlate with chronic, low-grade inflammation - a state frequently identified in neurodegenerative disorders such as schizophrenia [18].

However, it is important to note that LPS translocation also occurs in healthy populations, with post-meal elevations in LPS not typically coinciding with a rise in inflammatory markers. Furthermore, recent evidence indicates that standard Limulus Amebocyte Lysate (LAL) assays fail to detect the majority of circulating LPS, since it is protein-bound. Consequently, numerous prior investigations may exhibit methodological bias, as they only quantified the unbound fraction of LPS [18].

3.4 Blood-Brain Barrier Disruption by Bacterial Toxins

The blood-brain barrier functions as a strictly regulated, semi-permeable interface dividing the systemic circulation from the neural tissue and extracellular fluid of the central nervous system. It consists of specialized blood vessels meant to prevent pathogens or toxins already circulating in the bloodstream from accessing the CNS [10]. The principal role of this structure is to shield the brain against toxic substances and infectious agents, while simultaneously facilitating the transit of vital gases and nutrients [11]. Various supportive components, like astrocytes, the basement membrane, smooth muscle cells or the pia mater along with oligodendrocytes, play a collective role in modulating cerebral hemodynamics and preserving neurovascular equilibrium [11].

Bacterial translocation entails the migration of microbes from peripheral locations, such as the gastrointestinal tract, into environments that are typically sterile, like the CNS. Specific bacterial

strains have developed adaptive strategies to penetrate the blood-brain barrier (BBB), activating microglia which in turn leads to inflammation spreading within the central nervous system, contributing to the risk of developing schizophrenia symptoms [11].

There are multiple mechanisms that enable the infiltration of these microorganisms into the cerebral environment. Such pathways include the synthesis of enzymes capable of dismantling tight junction proteins, the utilization of receptor-mediated transcytosis, and the instigation of inflammatory cascades that compromise the structural integrity of the BBB. Additionally, a particularly notable strategy is the "Trojan Horse" mechanism, wherein pathogens evade detection by co-opting immune cells, such as macrophages, to covertly traverse the barrier [20].

4. Molecular Mimicry And Cross-Reactivity

4.1. The Mechanism of Molecular Mimicry

Molecular mimicry represents a primary pathway through which microorganisms ensure their survival within a host, simultaneously acting as a foundational trigger for autoimmune diseases [21]. This phenomenon occurs when there is a sequence or structural resemblance between the host's self-antigens and foreign antigens, such as those originating from gut microbiota, viruses, or dietary elements [22]. Extensive research indicates that this structural homology is a key factor in the pathogenesis of numerous autoimmune conditions [21] [23].

When genetically susceptible individuals are exposed to these pathogens—either through active infection or general microbiota stimulation—the body mounts an immune defense involving B cells and T cells. The immune system produces cross-reactive lymphocytes that mistakenly target the host's own tissues alongside the invading microorganisms, thereby setting the stage for widespread autoimmunity [22].

The effects of this immune system misdirection are particularly severe when targeted at the central nervous system. Self-reactive lymphocytes migrate into the CNS, where they attack critical structural components, specifically myelin basic proteins, proteolipid proteins, and myelin oligodendrocyte glycoproteins. This process initiates a destructive cascade of autoimmune demyelination and subsequent neurodegeneration [22].

4.2. Specific Targets: NMDA Receptors

A convergence of multidisciplinary research indicates that dysfunctions in excitatory signaling, specifically the hypofunction of the N-methyl-D-aspartate receptor (NMDAR), play a fundamental role in the pathogenesis of schizophrenia [24] [25]. As ligand-gated ion channels, NMDA receptors

are essential for plasticity, and excitatory neurotransmission, but can also be a part of the pathological process of excitotoxicity [1].

Their diminished activity is theorized to drive the emergence of schizophrenia. This hypothesis is corroborated by instances of NMDA-R encephalitis, a condition frequently characterized by initial psychotic manifestations before rapidly advancing to other clinical symptoms. Investigations reveal that between 4% and 10% of patients present with NMDA-R autoantibodies during their first episode or acute stages of schizophrenia, with recent findings further suggesting that seropositivity aligns with the acute phases of chronic psychoses [25].

Interestingly, another study detected NMDA-R antibody seropositivity in 10.5% of its cohort, noting no discrepancy in prevalence rates between individuals with schizophrenia and healthy controls. Addressing this phenomenon, the same investigators presented via animal models that NMDA-R autoantibodies only elicit behavioral alterations in rodents possessing a compromised blood-brain barrier. Therefore, they proposed the hypothesis that a breach in BBB integrity among schizophrenic patients is what permits a higher volume of NMDA-R autoantibodies to infiltrate the brain in comparison to healthy populations [25].

4.3. Specific Targets: The Kynurenine Pathway

Tryptophan, an essential amino acid derived from dietary sources, acts as a foundational precursor for intestinal serotonin synthesis. Physiologically, tryptophan metabolism bifurcates into two primary trajectories: serotonin synthesis and kynurenine production. While serotonin functions as a principal neurotransmitter responsible for mood modulation, the kynurenine pathway yields neuroactive metabolites that modulate immunological responses and cerebral function.

Under homeostatic conditions, tryptophan is predominantly metabolized into serotonin, which facilitates cognitive processes and mood stability. Conversely, under conditions of stress or inflammation, this metabolic routing is diverted toward the kynurenine pathway. Such a shift culminates in the generation of quinolinic acid, a recognized neurotoxin implicated in neurodegenerative disorders and neuroinflammation. The gut microbiome modulates the metabolism of tryptophan, thereby dictating the equilibrium between serotonin generation and the activation of the kynurenine pathway, this balance being of critical importance [26].

Kynurenic acid (KYNA), synthesized from astrocytes, is generated via the kynurenine (KYN) pathway of tryptophan (TRP) metabolism. This specific metabolic route is responsible for more than 90% of the breakdown of TRP. KYNA acts as an endogenous antagonist at NMDA receptors. Current evidence indicates that hyperactivation of the KYN pathway leads to imbalances in glutamatergic

transmission secondary to NMDA receptor hypofunction. Consequently, this mechanism is proposed to play a role in the pathophysiology of schizophrenia. Furthermore, the central and peripheral KYN pathways are closely integrated; while approximately 40% of kynurenine is produced locally within the brain, the remaining 60% originates from peripheral sources and subsequently permeates the blood-brain barrier [27].

Preclinical investigations involving the experimental modulation of KYNA concentrations reveal its impact on both behavioral phenotypes, such as cognitive function, and neurotransmitter systems, including glutamatergic and dopaminergic pathways, which are typically dysregulated in schizophrenia. Additionally, clinical assessments frequently demonstrate that KYNA concentrations in cohorts of patients with schizophrenia diverge from those observed in healthy controls [28].

Evidence indicates that inflammatory processes and elevated concentrations of pro-inflammatory cytokines in patients with psychotic disorders can stimulate tryptophan metabolism via the kynurenine pathway, leading to an overproduction of kynurenic acid. This phenomenon appears congruent with previously noted indications of potential blood-brain barrier dysfunction in individuals experiencing first-episode psychosis [29].

4.4. Specific Targets: Food Antigens

The production of antibodies against dietary components is triggered as these antigens infiltrate the systemic bloodstream, a process hypothesized to stem from gastrointestinal inflammation or a breakdown in the gut's epithelial or endothelial defenses. In the context of neuropsychiatric conditions, wheat gluteins and bovine milk caseins are of special significance, as the peptides generated from these proteins can bind to opioid receptors within both the central and peripheral nervous systems [30].

Research conducted by Severance et al. in 2015 demonstrated increased concentrations of anti-casein and anti-gluten antibodies within the cerebrospinal fluid of individuals diagnosed with schizophrenia. Furthermore, the study noted that for the control cohort, elevated serum IgG antibodies targeting these proteins did not correspond to higher CSF IgG levels, marking a significant divergence from the patient group's outcomes. These findings corroborate existing hypotheses regarding potential blood-brain barrier impairment in patients with schizophrenia [31].

The association between dietary antigens and the prevalence of psychotic conditions appears to be supported by the detection of exorphins—potentially originating from gluten and casein—in the urine of unmedicated patients diagnosed with the depressive subtype of schizoaffective disorder. Additionally, gastrointestinal epithelial defenses may be breached during intestinal infections caused by enteric viruses or alternative microorganisms introduced via oral ingestion [30].

5. Discussion

The integration of the gut-brain axis, barrier dysfunction, and molecular mimicry presents a compelling new paradigm for understanding the pathogenesis of schizophrenia. As the reviewed studies indicate, the gut microbiome of patients with schizophrenia possesses the capacity to modulate neurochemical balance and neural activity in ways directly linked to the disorder's pathology. The dysbiotic shift in the gastrointestinal tract, marked by an overrepresentation of pathogens and a deficit in protective, butyrate-producing bacteria, acts as a primary catalyst for local inflammation and subsequent epithelial barrier breakdown.

This increased intestinal permeability initiates a cascade of systemic consequences. The translocation of lipopolysaccharides (LPS), dietary antigens, and microbes into the bloodstream triggers chronic, low-grade inflammation. Emerging evidence suggests that this impairment in peripheral immunity and its interaction with the brain is a contributory factor to the development of schizophrenia, particularly aligning with indications of BBB impairment observed in individuals with first-episode psychosis (FEP). Consequently, the CNS becomes exposed to neurotoxic metabolites, such as the kynurenic acid resulting from the hyperactivation of the kynurenine pathway, which drives glutamatergic imbalances through NMDA receptor hypofunction.

Molecular mimicry serves as a plausible explanation for the onset of autoimmune processes subsequent to microbial imbalances. Because foreign antigens from gut microbiota or dietary elements, like wheat gluteins and bovine milk caseins, share structural homologies with host self-antigens, genetically susceptible individuals may develop cross-reactive lymphocytes. These immune cells, along with autoantibodies, can infiltrate the compromised BBB—sometimes utilizing a "Trojan Horse" mechanism—and attack vital CNS targets, including myelin components and NMDA receptors. While methodological biases in past research, such as LAL assays failing to detect protein-bound LPS, must be acknowledged, the convergence of these findings highlights that pathology occurring in the intestines possibly plays a significant role in the activation of the immune system and the subsequent development of schizophrenia.

6. Conclusions

Based on the evidence reviewed in this paper, it can be concluded that the activation of inflammation, driven by intestinal pathology and disruptions in the bidirectional gut-brain axis, is an important intermediary element in the development and course of schizophrenia.

The gastrointestinal microbiome in schizophrenia patients is significantly altered, leading to dysbiosis that compromises epithelial barrier integrity, triggers metabolic endotoxemia, and promotes systemic immune activation.

Building upon this state of systemic vulnerability, molecular mimicry offers a highly plausible explanation for how gut-derived and food-specific antigens trigger an autoimmune response against CNS structures, including NMDA receptors. Better comprehension of mimicry pathways could ultimately enable advancements in disease prediction and monitoring, as well as development in antigen-specific therapeutic strategies.

Consequently, addressing the underlying gastrointestinal dysbiosis holds a substantial clinical promise. Targeted interventions, such as diet modifications, the administration of probiotics, and specific antibiotic treatments, may allow a considerable number of patients to experience clinical improvement or even achieve full remission.

While the theoretical framework seems very compelling, solid clinical evidence conforming an autoimmune causation in humans is still limited. Further studies are crucial in order to establish the links between the intestinal microbiome, hypersensitivity to food antigens, barrier permeability, and the resulting etiology of schizophrenia.

Disclosure

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