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Gastroenterology issues in schizophrenia: why the gut matters

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Abstract

Genetic and environmental studies implicate immune pathologies in schizophrenia. The body's largest immune organ is the gastrointestinal (GI) tract. Historical associations of GI conditions with mental illnesses predate the introduction of antipsychotics. Current studies of antipsychotic-naïve patients support that gut dysfunction may be inherent to the schizophrenia disease process. Risk factors for schizophrenia (inflammation, food intolerances, *Toxoplasma gondii* exposure, cellular barrier defects) are part of biological pathways that intersect those operant in the gut. Central to GI function is a homeostatic microbial community that early reports show is disrupted in schizophrenia. Bioactive and toxic products derived from digestion and microbial dysbiosis activate adaptive and innate immunity. Complement C1q, a brain-active systemic immune component, interacts with gut-related schizophrenia risk factors in clinical and experimental animal models. With accumulating evidence supporting newly discovered gut-brain physiological pathways, treatments to ameliorate brain symptoms of schizophrenia should be supplemented with therapies to correct GI dysfunction.

Keywords

Microbiome; autoimmunity; blood-brain barrier; gluten; autism; synapses

Introduction

Schizophrenia is a complex and debilitating brain disorder that is characterized by a suite of behavioral abnormalities including delusions, psychoses, cognitive dysfunction, apathy and withdrawal [1]. Schizophrenia has a substantial heritable and polygenic component [2, 3], but reasonable expectations that technical progress in genomic tools would translate into etiological insight and more effective medications for psychiatric disease have not materialized. The most consistently supported hypothesis posits that psychopathologies are

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triggered when environmental disturbances interact with genetic predispositions [4, 5]. This causal interface most likely occurs during prenatal or early postnatal brain development when neurons are migrating and synapses are being formed and pruned. Abundant and converging evidence from both genetic and environmental studies points to immune system aberrations as contributing a substantial risk for development of the disorder [6–10].

The largest immune organ in the body is the gastrointestinal (GI) tract. Investigations of GI conditions in the etiology, pathogenesis and pathophysiology of psychiatric illnesses has a long history that predates the earliest versions of our current psychiatric classification systems, the Diagnostic and Statistical Manual of Mental Disorders (DSM; 1952) and the International Classification of Diseases (ICD; 1949) [11, 12]. Today, exploration of the gut-brain link is back in fashion, in part due to a shift in focus toward understanding the environmental contribution to disease and the interacting biological pathways implicated by multiple susceptibility loci. Further propagating this connection are the technological advances that have fueled the burgeoning field of microbiome research. In a series of research reports, we have united conceptually and experimentally a number of risk factors for the development of schizophrenia through a common origin in the gut [13–18]. The disease-associated interaction of such biological variables as humoral immunity to food antigens, intestinal inflammation, exposure to the parasite *Toxoplasma gondii*, endothelial barrier defects and microbial dysbiosis is consistent with a physiological model whereby gut-based processes can create a systemic state of immune dysregulation. The resulting immune response causes the activation of adaptive and innate immunity of molecules and factors that are important to a properly functioning brain [19, 20, 16, 17, 15].

In this review, we present a historical perspective of the association between the GI system and schizophrenia, identify GI issues that are relevant to the practicing psychiatric clinician, and delve into current translational studies that support why understanding immunity and the gut-brain connection is important to understanding schizophrenia. As a review paper, this article does not contain any original research with human or animal subjects performed by any of the authors.

History of GI comorbidities in schizophrenia

The association of digestive disturbances with mental illnesses spans centuries and is the only consistent comorbidity reported in the literature from ancient times to the present. Until the latter half of the 20th century when the current descriptive categories of psychiatric disorders were introduced, generally little distinction was made between mania, depression, bipolar disorder, psychosis and schizophrenia. These disorders were often referred to collectively as “insanity” with some variations that included melancholia, mania, delirium or phrenitis, a term used by Hippocrates to account for inflammation of the brain. Furthermore, first generation antipsychotics did not appear until the 1950s, an important consideration given that antipsychotics are often cited as the culprit behind GI pathologies in schizophrenia, as described in a later section. As such, the early historical documentation of GI comorbidities provides initial evidence that GI conditions are inherent to the disease and that antipsychotics likely compound a pre-existing pathology.

Galen, an ancient Greek physician of enormous influence and popularity (2nd century, C.E.), observed an association between mental disturbance and various GI symptoms including indigestion, flatulence and constipation. Galen's patients were prescribed purgatives, emetics, fasting, moderate wine and diets of simple of foods with known laxative properties in an effort to promote bowel movements, rebalance the body humors and improve the mental state. Galen and his contemporaries stressed the idea of early intervention with the above techniques to reduce or eliminate the mental disturbance [21, 22]. By the middle of the 19th century, it was accepted by many scientists, investigators and practitioners that various forms of mental illness, while manifested as altered brain function, were the secondary result of primary disease of the stomach, liver or other organ system [23]. Inspired by the research work of Louis Pasteur (1822–1895) and Élie Metchnikoff (1845–1916) on anaerobic bacteria, related small-molecule toxins, and the immune system, mid-19th century physicians charged with treating the mentally ill also strongly advocated use of Galen's methods, but towards a different end [24–30]. The new goal of these interventions beyond simple improvement of the tone of the digestive organs and relief of constipation was to remove anaerobic bacteria along with a kaleidoscope of toxic products from the gut, thereby preventing "autointoxication" by small, biologically active, substances. While many positive results were reportedly obtained with acute cases, chronic cases of insanity remained incurable [24–31]. There was a growing feeling among practitioners toward the end of the 19th century that a serious roadblock was reached in the treatment of the chronically mentally ill. Complicating matters was the inability of the physiologically oriented practitioners to provide a unified theory of purgation. The basis for unification, an understanding of bacteriology, digestion, nutrition, metabolism and enzymology required the application of sophisticated chemical, biochemical and biophysical knowledge that was unknown to practitioners during this time period. While anatomists were providing evidence of the structural derangements of the intestinal tract and brain involved in chronic insanity, little else in the way of scientific evidence was available to defend and extend the theory of purgation. Thus, purgation was viewed as only a partial answer to the conundrum of insanity. Since practitioners were not making any therapeutic progress with the treatment of chronic insanity, they looked elsewhere for the answers.

Biochemical and physiological evidence in favor of a GI etiology for psychiatric illness has been accumulating more or less continuously since 1860 [32–35]. Such investigations included those of Herter (1907), who found indication of low stomach acid in patients with mental illness, along with bacterial putrefaction of various amino acids including tryptophan. One function of gastric juices is to maintain a proteolytic environment to enzymatically control proliferation of anaerobic bacteria to the small intestine and prevent the absorption of toxins. Herter's findings have interesting physiological ramifications given that tryptophan and the other aromatic amino acids phenylalanine and tyrosine are precursors of schizophrenia-relevant neurotransmitters including serotonin, dopamine, epinephrine, and norepinephrine. Thus, any interference by putrefactive bacteria would reduce the physical bioavailability of these amino acids and subsequent production of neurotransmitters critical to normal neuronal function. Furthermore, this process of putrefaction would result in the production of highly toxic substances that in theory could be differentially absorbed depending on individual, perhaps genetic, susceptibilities [35, 32].

With these studies laying the historical framework for GI-based issues relevant to the schizophrenia, scientists are now re-conceptualizing the association between dysbiosis-based autointoxication and related processes in relationship to psychiatric disease, cognitive function and neuroinflammation.

GI issues for consideration by psychiatric clinicians

An awareness and understanding of the substantial presence of somatic risk factors including GI conditions associated with schizophrenia aid in designing proper, individualized treatment strategies to improve the comfort and quality of life of people with mental illness. There are currently no FDA approved, alternative therapeutic options to the use of antipsychotics to treat the psychiatric symptoms of schizophrenia; therefore, supplemental palliative care of comorbidities that result from their use must be addressed. As described in this section, it is well-established that the anticholinergic effects of first and second generation antipsychotics, and clozapine in particular, contribute to and compound GI motility issues such as constipation and bowel obstruction. Interestingly, while there exists substantial GI comorbidities in schizophrenia, the reverse may also be true, as increasingly psychiatric comorbidities are being reported in individuals with GI disorders such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and celiac disease [36–40]. In this section, we review the motility effects of psychiatric medications, appraise current information regarding GI inflammation in schizophrenia as an inherent disease pathology and examine the overlapping epidemiology of the autoimmune disorder, celiac disease, and other dietary-based sensitivities with schizophrenia.

GI motility and antipsychotics

GI motility function is a process that is regulated by the parasympathetic cholinergic nervous system. The atypical antipsychotic, clozapine, is a potent effector of decreased intestinal motility due to its strong anticholinergic effects. As such, its use can lead to constipation, bowel obstruction, colitis, paralytic ileus and death. The prevalence of antipsychotic-related constipation has been reported to range from 1.5% to 60% in patients with schizophrenia [41–44]. Other antipsychotics with cholinergic effects, including both agonists and antagonists, and the use of specific cholinergic compounds to counter extrapyramidal side effects of medications prescribed to people with schizophrenia can produce a variety of adverse effects on the gut including anorexia, nausea, vomiting, diarrhea and abdominal pain [45]. Medication side effects that impact the GI tract, however, are not limited to the cholinergic system, as the gut contains numerous other neurotransmitter receptors including dopamine, serotonin and noradrenergic receptors. For example, in addition to its cholinergic effects, clozapine's ability to also antagonize serotonin receptors may further perturb gut function. Dopaminergic blocking agents such as haloperidol and sulpiride have been shown to exhibit varied activity on distal colon motility, with both inhibitions and increases in motility [46]. Lithium and monoamine oxidase inhibitors significantly influence appetite and GI function as well [47]. While medications used to combat the brain effects of psychiatric illnesses are the best available given our current knowledge base, monitoring GI discomfort and nutritional status are often under-addressed endpoints in the care and treatment of people with schizophrenia. In the

conclusions section, we present some GI-relevant therapeutic options to evaluate as supplements to primary medications used to treat psychoses.

GI inflammation

Non-medication-induced GI dysfunction is also evident in psychiatric disorders, and its presence may further contribute to nutritional deficits in people with schizophrenia. In an autopsy study of 82 patients with schizophrenia, it was reported that 50% had gastritis, 88% enteritis and 92% colitis [48, 49]. These are surprisingly high incidence rates, and more modest, but still significant case control differences are evident when narrowing the diagnosis down to specific GI subgroups. For example, in IBS, reportedly 19% of people with schizophrenia had IBS compared to a rate of 2.5% in the control group [37]. In the reverse analysis, up to 54 to 90% of IBS patients may have a psychiatric comorbidity, typically in the form of a mood or anxiety disorder [37, 36]. Biochemical aids for the diagnosis of GI diseases such as Crohn's Disease include the measurement of anti-*Saccharomyces cerevisiae* antibodies (ASCA) [50]. In previous work, we found that an elevated ASCA response indicative of GI inflammation was significantly associated with schizophrenia and particularly in those with a recent onset of the disease compared to controls. Furthermore, in a second cohort, patients with schizophrenia who were antipsychotic-naïve had markedly elevated ASCA levels compared to medicated individuals with schizophrenia [13]. These results echo historical findings of a GI relevance to mental illness in acute vs chronic cases and support that it is in the early stage of schizophrenia where GI inflammation inherent to the disease may be most evident.

Diet-based immune sensitivity

There is an often-replicated association of schizophrenia with celiac disease, an enteropathic autoimmune disorder characterized by interacting genetic and environmental factors and one that can be treated with dietary modifications [51, 52]. In celiac disease, the ingestion of wheat gluten by people with a genetic predisposition triggers the production of autoantibodies directed against tissue transglutaminase and associated molecules, cells and tissues. Tissue transglutaminase is an enzyme that deamidates gluten peptides in the digestive tract, and a classic celiac response is the elevation of anti-gliadin, anti-tissue transglutaminase and anti-endomysial antibodies [53]. F. Curtis Dohan prolifically disseminated the idea that wheat availability was strongly correlated with hospital rates for schizophrenia, with his interest in this area stimulated by his observations of post-war Europe [54, 55]. Mechanistically, Dohan and others have proposed that gluten is broken down into bioactive opioid receptor peptides that may penetrate the GI and brain structural barriers [56, 57]. Implicated by these reports is a separate condition, gluten intolerance or sensitivity that does not have the same autoantigenic profile as celiac disease, but which has also been shown to have associations with schizophrenia [58]. The dietary removal of gluten has met with varied results in schizophrenia and also autism, most likely a reflection of the extreme heterogeneity of both disorders. The most success in improving symptomatology was observed in those instances where inclusion criteria required that candidates have evidence of gluten or diet-related sensitivity [59–61].

By thematic extension, other food antigens such as milk caseins also produce bioactive exorphins and exposure to these peptides are similarly applicable in studies of brain disorders [62, 63, 56]. Elevations in milk casein antibodies are evident in individuals with schizophrenia compared to controls and in some cases, these milk antibodies are increased up to two years prior to diagnosis [64, 14]. It is currently not known whether the pathological brain effect of these food-based antigens are due to direct effects of the food-derived peptides on the brain or of an associated immune activation in response to an antigenic peptide. We discuss in the next section, our findings of antibodies against gluten and casein in CSF samples and suggest that the food-related immune response in the presence of compromised epithelial and endothelial barriers may be a possible pathological mechanism in psychiatric disorders [18]. Others hypothesize that these food-derived opioid peptides may be relevant epigenetically to brain disorders due to their ability to modulate cysteine uptake in neuronal and GI epithelial cells and thus influence the DNA methylation profile of affected cells [65].

The gut-immune-brain interactome in schizophrenia

The GI system is composed of a set of cellular and molecular mechanisms designed to aid digestion, facilitate nutrient absorption and provide initial protection from harmful antigens, toxins and infections. A community of commensal microorganisms, termed the microbiota, is intrinsically a part of such gut-related processes as the maintenance and regulation of metabolism, epithelial barrier integrity, immune system development, and intriguingly, the modulation of host behavior [66, 67]. In this section, we review data in support of a model whereby disruption of proper GI function can impact the brain via immune system pathways. In various iterations of this model, environmental vs genetic predispositions could be interchanged at every stage of each pathway. Residing at the center of these functional interactions is the gut microbiome.

Epithelial and endothelial barrier integrities

Schizophrenia is phenotypically a brain disorder; thus any consideration for a role of the GI system in its etiology or pathophysiology must include a mechanism that impacts the brain. The hypothesis that toxic and bioactive products escape the GI tract, produce an immune response and enter the brain requires the ability of these and associated products to penetrate epithelial and endothelial barriers in both the GI tract and at blood-central nervous system (CNS) interfaces. Daneman and Rescigno (2009) provide an exquisite review of how the gut immune barrier and the blood-brain barrier are functionally and structurally similar [68]. In this section, we will focus on the environmental perturbation of these cytoskeletal architectures, but it is duly noted that a number of genes involved in barrier structures have been identified as susceptibilitiy loci for schizophrenia, such as the tight junction protein claudin-5, actin and other cytoskeletal elements, haptoglobin and nitric oxide synthetase [69–72].

Inflammation, infection and stress are environmental factors that can impact the integrity of epithelial and endothelial barrier structures [73–75]. In two different inflammatory diseases, one that occurs in the gut (IBD) and another that occurs in the CNS (multiple sclerosis, MS), there is a reorganization of tight junction proteins between epithelial cells of the respective

gut (for IBD) and brain (for MS) barriers that results in a heightened permeability [76–79]. Inflammation, particularly of a low-grade nature, is a consistent pathological finding in schizophrenia [80–82], and as described earlier, some of this inflammation is associated with the GI tract [13]. Interestingly, *T. gondii* exposure is a well-documented risk factor for schizophrenia [83, 84], and as a gut pathogen is a tool used in experimental models to produce an inflammatory state in the GI tract. Thus not surprisingly, *T. gondii* infection can drive the dysbiosis of resident microbial communities and bring about a state of increased GI permeability [85–88]. In our studies of clinical samples, we found correlations between levels of *T. gondii* IgG with food antigen IgG in people with a recent onset of schizophrenia, which were not present in control groups [13]. In a rodent model, we verified that GI disruption due to *T. gondii* infection leads to the production of anti-gluten antibodies in infected animals [16]. Thus, once gut barriers have been compromised, bacteria and other bacterial- or food-derived products can be translocated into the general circulation, and a state of low-grade inflammation is initiated and perpetuated. Consistent with this process, we have found that markers of bacterial translocation were indeed altered in schizophrenia, and this finding was independent of antipsychotics [15].

As mentioned, for these associations to be relevant to a brain disease, there must be some physiological connection between the gut and the brain. Studies of cerebrospinal fluid can lend some insight regarding how exogenous or gut-produced factors might gain proximity to the brain in schizophrenia [80, 89–91, 18, 56]. Toward this end, we found that antibodies directed against food antigens in the CSF are highly correlated with serum levels in samples from antipsychotic-naïve people with schizophrenia, a pattern not found in control individuals [18]. These data in conjunction with measurements of relative serum to CSF albumin and total IgG support the possibility of either an anatomical barrier abnormality or reduced CSF flow associated with schizophrenia [89, 92]. These antibodies or their antigenic stimuli thus may have access to the CNS via a CSF route, perhaps through compromised barriers of the choroid plexus or arachnoid membrane.

In a homeostatic GI environment, vast numbers of bacterial cells live in a tightly regulated equilibrium in close proximity to the epithelial surfaces of the host. Commensal gut microbes maintain epithelial barrier integrity via a variety of mechanisms including the downregulation of epithelial inflammatory responses, expression of anti-microbial proteins, defense of epithelial surfaces by mucus production and repair of damaged intestinal tissue [93]. Although proper functioning of the GI system requires a community approach, some roles of specific bacteria in the maintenance of epithelial barrier integrity have been identified [67, 94–98]. For example, *Bacteroides thetaiotaomicron* promotes the upkeep of cadherin desmosomes, a juncture protein that links cells together [94] and inhibits NF-kB function [95]; several *Lactobacillus* strains stabilize tight junctions to preserve epithelial permeability [96, 97]; *Bacteroides fragilis* aids in the correction of gut permeability [67], and; secreted bioactive factors from *Bifidobacterium infantis* enhance epithelial barrier function [98]. A recent and elegant study performed with gnotobiotic mice verified a direct relationship between the presence of gut microbiota and blood-brain barrier permeability [99]. These investigators found that germ-free animals had increased blood-brain barrier permeability compared to animals with normal gut flora. The increased permeability was

maintained in germ-free mice after birth and through adulthood and was associated with decreased expression of tight junction proteins. Upon transplantation with a normal microbiota, blood-brain barrier integrity was recovered.

The immune system, brain and microbiome

The discovery that peripheral immune system components such as complement C1q and the major histocompatibility complex 1 (MHC1) are active in brain synaptogenesis and synaptic pruning greatly strengthened immune-based hypotheses as feasible explanations for how developmental brain disorders such as schizophrenia and autism might arise [100–102]. Various components of the complement pathway are genetically and biologically linked to schizophrenia [103, 20, 19, 104, 105]. For example, we documented an increased abundance of C1q-containing immune complexes with gluten and casein in individuals with schizophrenia compared to controls [20]. We further found that at time of birth, levels of C1q-related antibodies were elevated in mothers whose children developed psychoses as adults compared to controls [19]. This latter study raises the possibility that maternal autoantibodies to C1q could interact with fetal C1q during crucial periods of brain development, such as when synapse formation and pruning is occurring. Within this gut-immune-brain interactome, it would be expected that any products including those that are bacterially-derived will trigger adaptive and innate immune processes including activation of C1q. In particular, anaerobic bacteria anchored along the intestinal lumen are capable of producing a large number of poorly characterized bio-active toxins and toxic metabolites. Absorption of these small molecules over an extended period of time may result in a number of deleterious immunological, nutritional, biochemical, enzymatic, hormonal and epigenetic sequelae. As indicated earlier, some such toxins include the byproducts of aromatic amino acids tryptophan, alanine and tyrosine as well as short-chain fatty acids (SCFAs), butyrate and propionate, produced in the gut during microbe fermentation processes [106]. SCFAs may have immunological effects as well by acting on T cells to regulate their differentiation [107].

As relevant to our proposed model, it is becoming apparent that the gut microbiota have a wide range of key functions in the modulation of maturation and maintenance of the immune system. Among the many documented processes attributed to gut microbiota are the following immune-related specific activities: (1) control of lymphocyte diversity and manipulation of specific T-cell responses [108]; (2) species-specific (*Bacteroides fragilis*, *Lactobacilli spp*, *Clostridia spp*) control of anti-inflammatory responses by promotion of Treg differentiation, IL-10 production and resulting decrease in the pro-inflammatory Th17 response [109–112]; (3) group-specific (segmented filamentous bacteria) induction of Th17 cell growth [113]. The modulation of Th17 cells is interesting because activation of Th17 cells in conjunction with other cytokines and microglia has been shown to lead to the chronic inflammatory response in schizophrenia [114].

Finally, while we rely on information from experimental animal models to guide our knowledge regarding functional interactions between the gut and the brain, microbiome analyses using human samples from people with schizophrenia and controls are beginning to appear [115]. In rodent models, we learned that experimental manipulations of gut

microbiota induce behavioral, biochemical and molecular sequelae, with stunning reversals in phenotype using germ-free animals, vagectomy, probiotics and antibiotics [116, 117, 67, 118–120]. In a new report from our laboratory, we found in microbiome analyses of the oral pharynx of people with schizophrenia that there were significantly differential levels of a bacterial phage, *Lactobacillus* phiadh, and that these levels correlated with the presence of immunological conditions. This phage preferentially infects the bacteria *Lactobacillus gasserri*, a resident member of both the oral and GI mucosae, that is involved in functions related to epithelial cell maintenance and immune system modulation [115].

Conclusions

A multitude of extrinsic and intrinsic factors are known to modify GI function. The interaction of these variables may aggravate adverse effects on an already disturbed gut homeostasis. We do not currently advocate the replacement of antipsychotics with other medications but suggest that GI comfort be examined and supplemental bowel therapy be considered, so that patients will be more likely to continue the medications that are critical to their continued mental health. In response to new information, practicing psychiatrists are beginning to complement traditional treatment approaches with probiotics, herbal medicines, omega-3 fatty acid preparations, b-vitamins and minerals [121]. Dickerson et al (2014) showed that probiotics given once per day improved GI symptoms in individuals with schizophrenia [122].

As etiological evidence accumulates in support of a GI physiological contribution to brain biochemistry, however, it will be necessary to examine other pharmacological mechanisms to better treat this disorder. By combining new information from the fields of microbiology, immunology, and gastroenterology with experimental data from traditional neuroscience fields, a new generation of researchers, using modern biochemical analysis, informed by molecular genetic studies and other advanced laboratory techniques, now have within their possession, powerful, investigative tools to verify and re-integrate the role of GI processes in a wide range of psychiatric disorders. These integrative approaches may provide the basis, for a powerful unified field theory of causation and lead to novel methods for disease prevention and treatment.

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