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Review

Autoimmune diseases, gastrointestinal disorders and the microbiome in schizophrenia: more than a gut feeling

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ABSTRACT

Autoimmunity, gastrointestinal (GI) disorders and schizophrenia have been associated with one another for a long time. This paper reviews these connections and provides a context by which multiple risk factors for schizophrenia may be related. Epidemiological studies strongly link schizophrenia with autoimmune disorders including enteropathic celiac disease. Exposure to wheat gluten and bovine milk casein also contribute to non-celiac food sensitivities in susceptible individuals. Co-morbid GI inflammation accompanies humoral immunity to food antigens, occurs early during the course of schizophrenia and appears to be independent from antipsychotic-generated motility effects. This inflammation impacts endothelial barrier permeability and can precipitate translocation of gut bacteria into systemic circulation. Infection by the neurotropic gut pathogen, *Toxoplasma gondii*, will elicit an inflammatory GI environment. Such processes trigger innate immunity, including activation of complement C1q, which also functions at synapses in the brain. The emerging field of microbiome research lies at the center of these interactions with evidence that the abundance and diversity of resident gut microbiota contribute to digestion, inflammation, gut permeability and behavior. Dietary modifications of core bacterial compositions may explain inefficient gluten digestion and how immigrant status in certain situations is a risk factor for schizophrenia. Gut microbiome research in schizophrenia is in its infancy, but data in related fields suggest disease-associated altered phylogenetic compositions. In summary, this review surveys associative and experimental data linking autoimmunity, GI activity and schizophrenia, and proposes that understanding of disrupted biological pathways outside of the brain can lend valuable information regarding pathogeneses of complex, polygenic brain disorders.

Contents

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1. Introduction

Schizophrenia is a complex brain disorder with lifetime prevalence rates estimated to range from 1.6–12.1/1000 persons, with some variability according to age and sex (Eaton et al., 2011; Pedersen et al., 2014). The disorder is characterized by behavioral abnormalities and is diagnosed by a set of criteria defined in the Diagnostic and Statistic Manual of Mental Disorders, 5th edition (DSM-5) (APA, 2013). Among the criteria used to diagnose schizophrenia are the presence of psychotic symptoms, such as delusions and hallucinations, as well as cognitive disorganization, apathy and withdrawal (APA, 2013). The causes of schizophrenia have not been fully defined, but prevailing evidence supports an interaction of genetic and environmental variables as central to its etiology (Tsuang, 2000; Demjaha et al., 2012; Modinos et al., 2013).

The relationship between autoimmune diseases and schizophrenia has been studied for more than half a century. In the past decade, the focus of this autoimmune research has been narrowed to a certain extent to gastrointestinal (GI) disorders, while at the same time has broadened somewhat to include dysfunctions of the immune system. As the largest immune organ in the body, the GI tract is a plausible junction to reconcile hypotheses regarding how the autoimmune response and GI-related products can become neuropathogenic. This paper traces some of these developments and, following the logic of translational research, links the epidemiologic observations to molecular studies of the gut-brain axis and the gut's main bio-processor, its resident microbiota. An overview of the interactions described in this review is depicted in Fig. 1.

2. Autoimmunity and schizophrenia

2.1. Origins

The earliest interest connecting autoimmunity and schizophrenia stems from a repeated finding of a low prevalence of rheumatoid arthritis in individuals with schizophrenia, beginning with studies in the 1950's and including analyses up to the present (Trevathan and Tatum, 1953; Pilkington, 1955; Vinogradov et al., 1991; Eaton et al., 1992; Oken and Schulzer, 1999; Sellgren et al., 2014). The finding was replicated more than a dozen times, and various explanations were offered, such as that neuroleptic medications had a protective effect; or that persons with schizophrenia were less likely to report pain; or that life as an inpatient was less physically active and thereby less prone to raising risk for rheumatoid arthritis. Each of these hypotheses was evaluated in studies with research designs that effectively discounted those explanations (Trevathan and Tatum, 1953; Pilkington, 1955; Mellsop et al., 1974; Mohamed et al., 1982). There have been several studies of genes, immune-related factors, and common infections which might explain the inverse association (Taylor, 1978; Hopkins et al., 1988; Wright et al., 1998; Torrey and Yolken, 2001; Genevay et al., 2002; de la Fontaine et al., 2006), including a compelling meta-analysis showing that the antagonist to the receptor of the inflammatory cytokine IL-1 was more prevalent in individuals with schizophrenia, thus protecting them from rheumatoid arthritis (Potvin et al., 2008).

2.2. Autoimmunity and the GI tract

Autoimmune disorders can be triggered by dietary components and antigens derived from the GI tract. One such autoimmune condition characterized by altered GI structure and functioning is celiac disease, a disorder that arises from the interaction of gene and environmental factors. Upon the ingestion of wheat gluten by people who are genetically susceptible, an immune reaction is launched that damages the epithelial lining of the small intestine (Green et al., 2005; Guandalini and Assiri, 2014). During digestion, the gluten protein in wheat is broken down into toxic peptides that are modified through deamidation and/or transamidation by tissue Transglutaminase (tTG), so that the modulated peptide might stimulate the immune system more effectively and thus be more easily cleared. Through the process of molecular mimicry, tTG becomes the target of a T-cell-mediated immune attack, and resulting inflammation causes extensive histopathological changes in the small intestine (van Heel and West, 2006; Alaedini and Green, 2008; Di Sabatino et al., 2012). Clinically-defined celiac disease will be the focus of this portion of this discussion, and this condition differs in diagnosis from non-celiac disease gluten sensitivity, which will be discussed later.

The GI system connection with autoimmune issues in schizophrenia came about with clinical observations of co-associations of celiac disease and schizophrenia, starting with Bender in 1953 (Bender, 1953), and later in 1961, when two residents in psychiatry reported a higher number than expected of people with celiac disease among their psychiatric patients (Graff and Handford, 1961). This finding interested F. Curtis Dohan who spent the remainder of his career focusing on a link between wheat consumption and schizophrenia (Dohan, 1970, 1973, 1980). His first epidemiologic study of wartime admissions for schizophrenia showed that populations in countries whose consumption of wheat had decreased during the war saw a decrease in hospital admissions for schizophrenia, whereas those populations in countries with an increase in consumption of wheat during the war had an increase in hospital admissions for schizophrenia (Dohan, 1966a,b). Dohan analyzed other epidemiologic data consistent with the hypothesis that eating wheat was linked to higher rates of schizophrenia, as evident by areas of the south Pacific region where consumption of wheat was low having lower rates of schizophrenia than areas where wheat consumption was high (Dohan et al., 1984). He also conducted several controlled trials removing gluten from the diet (Dohan et al., 1969; Dohan and Grasberger, 1973), the results of which supported the hypothesis that celiac disease was related to schizophrenia. Clinical trials conducted by others were sometimes supportive of the idea (Singh and Kay, 1976; Rice et al., 1978; Vlissides et al., 1986), and sometimes failed to replicate it (Potkin et al., 1981; Storms et al., 1982). One explanation for the diverse results is the effect of random sampling in a population of persons with a heterogeneously complex disease such as schizophrenia, of whom only a small proportion might actually have celiac disease (King, 1985). Thus, some studies might have had enough persons with schizophrenia to detect an effect, but other samples would have few or none with celiac disease, with no possibility of a positive effect of removal of gluten from the diet. There are several case studies