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Review

Inflammation and the two-hit hypothesis of schizophrenia

Keith A. Feigenson[a,*], Alex W. Kusnecov[b], Steven M. Silverstein[a,c]

[a] Robert Wood Johnson Medical School at Rutgers, The State University of New Jersey, 675 Hoes Lane, Piscataway, NJ 08854, USA
[b] Department of Psychology, Behavioral and Systems Neuroscience Program and Joint Graduate Program in Toxicology, Rutgers University, 52 Frelinghuysen Road, Piscataway, NJ 08854-8020, USA
[c] University Behavioral Health Care at Rutgers, The State University of New Jersey, 671 Hoes Lane, Piscataway, NJ 08855, USA

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ABSTRACT

The high societal and individual cost of schizophrenia necessitates finding better, more effective treatment, diagnosis, and prevention strategies. One of the obstacles in this endeavor is the diverse set of etiologies that comprises schizophrenia. A substantial body of evidence has grown over the last few decades to suggest that schizophrenia is a heterogeneous syndrome with overlapping symptoms and etiologies. At the same time, an increasing number of clinical, epidemiological, and experimental studies have shown links between schizophrenia and inflammatory conditions. In this review, we analyze the literature on inflammation and schizophrenia, with a particular focus on comorbidity, biomarkers, and environmental insults. We then identify several mechanisms by which inflammation could influence the development of schizophrenia via the two-hit hypothesis. Lastly, we note the relevance of these findings to clinical applications in the diagnosis, prevention, and treatment of schizophrenia.

Contents

* Corresponding author at: 151 Centennial Avenue, Piscataway, NJ 08854, USA. Tel.: +1 732 235 2864; fax: +1 732 235 9293.
E-mail addresses: Feigenka@rwjms.rutgers.edu (K.A. Feigenson), Kusnecov@rci.rutgers.edu (A.W. Kusnecov), Silvers1@ubhc.rutgers.edu (S.M. Silverstein).

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1. Introduction

Schizophrenia is a serious mental illness characterized by psychotic symptoms, cognitive impairment, functional decline, and, in most cases, a chronic course. It occurs, on average, in ~1% of the population worldwide, with variability around this mean in different countries and cultures. Despite 100 years of research, much about schizophrenia remains unknown, including its etiology and the extent of its heterogeneity. An emerging consensus is that schizophrenia is best conceptualized as a category, like dementia, epilepsy, cancer, or anemia, with multiple causes and types. It is now generally accepted that schizophrenia is not a single disease state.

While there have been many attempts to characterize schizophrenia's heterogeneity (e.g., based on level of premorbid functioning, types of symptoms, etc.), few have led to advances in treatment, and improvements in this endeavor are still needed (Corvin et al., 2013). At the same time, the validity of the classic subtypes has been challenged (Braff et al., 2013). Recent data on inflammatory processes in schizophrenia, and the role of maternal and/or patient infection as etiological factors, may aid in the effort to characterize heterogeneity by identifying specific subtypes of patients with one or more infectious/inflammatory processes, and perhaps by identifying subgroups with an absence of inflammation (i.e., other etiological factors) (Allan et al., 2009). It has recently been proposed to include a distinct sub-group of schizophrenia to be classified according to the presence of mild encephalitis (Bechter, 2013). Moreover, it is now clear that data on inflammatory and infectious processes can be integrated with evidence on neurotransmitter (e.g., glutamate) and receptor (e.g., *N*-methyl-D-aspartic acid receptor, or NMDA-R) abnormalities (Muller and Schwarz, 2006), developmental history (e.g., links between child abuse and inflammatory processes) (Dennison et al., 2012), and the biological bases of specific symptoms and cognitive impairments (Meyer et al., 2011).

Therefore, the purpose of this review is to examine current data on infectious and inflammatory processes, with a particular focus on different developmental stages and their relevance for schizophrenia. We then try to fit the pieces together regarding the implications for understanding heterogeneity in research and clinical domains, including diagnosis, prevention, and treatment. In discussing developmental stages, we also emphasize the "two-hit" theory of schizophrenia, suggesting that inflammatory processes may represent the sequelae of the first hit, and therefore serve to increase overall risk in the event of a second adverse event.

2. Background

2.1. Two-hit hypothesis

The two-hit hypothesis of schizophrenia suggests that a combination of genetic susceptibility coupled with a distinct developmental insult can prime an individual for a later event that ultimately leads to onset of the full clinical syndrome (Bayer et al., 1999). In the case of schizophrenia, multiple genetic liabilities have been suggested to interact with environmental factors, ultimately affecting the development of the central nervous system in a way that creates an abnormal signaling network (van Os et al., 2008). This network, however, may not become abnormal until later in life: schizophrenia tends to first occur in the early and late 20s in males and females, respectively, suggesting that an event in adolescence or post-adolescence may be highly influential in the development of the disorder (this is explored below). A number of structural abnormalities in schizophrenia are associated with symptom development: gray and white matter alterations, cerebral asymmetries, and ventricular enlargement, accompanied by abnormal neuronal density, size, shape, and migration (for review, see Hoistad et al., 2009; Walterfang et al., 2011; Rapoport et al., 2012; Shepherd et al., 2012). A multifactorial conceptualization of psychiatric disease is emerging in which multiple biologically significant events (or "hits") are temporally distributed across early periods of the overall lifespan, and result in the development of schizophrenia-like diseases (Giovanoli et al., 2013). Until now, genetic abnormalities were viewed as the likely 'first hit,' however, as we suggest below, infection and inflammatory processes may also serve this function.

2.2. Inflammation/immune system

There is ample evidence that cytokines and the immune system can influence and shape the development of the CNS and behavior (Bauer et al., 2007; Deverman and Patterson, 2009; Yirmiya and Goshen, 2011; Bilbo and Schwarz, 2012). The importance of this information as a factor in the etiology of schizophrenia has been strongly emphasized by different laboratories investigating