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Invited Review

Anti-inflammatory signaling in schizophrenia

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ABSTRACT

A great deal of interest has been centered upon activated inflammatory processes in schizophrenia and their contribution to disease-relevant brain and behavioral impairment. In contrast, the role of anti-inflammatory signaling has attracted somewhat less attention in this context. The present article focuses on the emerging role of anti-inflammatory signaling in schizophrenia and discusses the potential influence of altered anti-inflammatory activity on progressive inflammatory processes, physical and metabolic functions, and treatment effects related to the use of conventional antipsychotic drugs and immunomodulatory agents in the pharmacotherapy of schizophrenia. By reviewing existing evidence, it appears that enhanced anti-inflammatory activity has many faces in schizophrenia: On the one hand, it may effectively limit potentially harmful inflammatory processes and may contribute to the improvement of psychopathological symptoms, especially when the anti-inflammatory system is boosted at early stages of the disease. On the other hand, enhanced anti-inflammatory activity may render affected individuals more susceptible to distinct physiological abnormalities such as cardiovascular disease, and may further impede the resistance to specific infectious agents. Therefore, an enhancement of anti-inflammatory signaling in schizophrenia might not simply be said to be either advantageous or disadvantageous, but rather should be interpreted and dealt with in a context-dependent manner. Increased awareness of the multiple roles of anti-inflammatory signaling may readily help to reduce additional health burdens in schizophrenia, and at the same time, may provide opportunities to further explore the benefits associated with anti-inflammatory strategies in the symptomatological and/or preventive treatment of this disorder.

1. Introduction

Schizophrenia is a chronic form of psychotic illness that affects approximately 1% of the population worldwide (Tandon et al., 2008). The onset of full-blown schizophrenic disease is typically in late adolescence or early adulthood, and includes distinct (but often co-existing) symptom classes which are commonly referred to as positive, negative and cognitive symptoms (Tandon et al., 2008, 2009). Positive symptoms are features that are normally not present in healthy individuals but appear as a result of the disease. These include visual and/or auditory hallucinations, delusions, paranoia and major thought disorders. Negative symptoms refer to features that are normally present, but are reduced or absent as a result of the disease process, including social withdrawal, apathy, anhedonia, alogia, and behavioral perseveration. Cognitive symptoms of schizophrenia typically involve disturbances in executive functions, working memory impairment, and inability to sustain attention.

Besides the multiple neurochemical and neuropathological changes pertinent to the disorder (Abi-Dargham et al., 1997; Coyle et al., 2003; Lewis et al., 2005; Howes and Kapur, 2009), schizophrenia has been linked to numerous alterations in basic physiological and metabolic functions, including cardiovascular disease, type-2 diabetes and obesity (Marder et al., 2004). An appreciable body of evidence further implicates a spectrum of immunological dysfunctions in this disorder (Müller et al., 2000; Müller and Schwarz, 2010; Drexhage et al., 2010). Indeed, the idea that immune abnormalities may play an important role in schizophrenia has a long history (Stevens, 1982; Müller et al., 1991; Smith, 1991). Renewed awareness of the immunological aspects of this disorder has further been boosted by several lines of recent research, including clinical trials with anti-inflammatory drugs for the symptomatic treatment of schizophrenia (Miyaoka, 2008; Müller and Schwarz, 2008; Berthold-Losleben et al., 2009) and genome wide association studies (GWAS) consistently implicating immune-related genes as genetic risk factors of this disorder (Shi et al., 2009; Stefansson et al., 2009).

In the past two decades, a great deal of interest has been centered upon activated inflammatory processes in schizophrenia and their contribution to disease-relevant brain and behavioral impairment (Fan et al., 2007; Potvin et al., 2008; Drexhage et al., 2010). In contrast to the numerous discussions surrounding the

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potential importance of altered pro-inflammatory activity, the role of anti-inflammatory signaling has attracted somewhat less attention in this context. This seems surprising in view of the inherent linkage and cross-regulation of the pro- and anti-inflammatory arms of the immune system (Gallin et al., 1999). Against this background, the present article focuses on the emerging role of anti-inflammatory signaling in schizophrenia. After providing an up-to-date summary of altered pro-inflammatory activity and its neuronal and behavioral consequences pertinent to schizophrenia, existing evidence for altered anti-inflammatory activity in affected individuals is reviewed. Furthermore, the article discusses the potential influence of anti-inflammatory signaling on progressive inflammatory processes, physical and metabolic functions, and treatment effects related to the use of conventional antipsychotic drugs (APDs) and immunomodulatory agents in schizophrenia.

2. The pro-inflammatory system

2.1. Peripheral systems

Signs of an activated inflammatory response system in schizophrenia have been noted since decades, and several recent articles have discussed these issues in detail (Fan et al., 2007; Potvin et al., 2008; Müller and Schwarz, 2010; Monji et al., 2009; Drexhage et al., 2010). Peripheral inflammatory responses in affected individuals have most often been evidenced by the presence of elevated serum/plasma levels or in vitro production of specific pro-inflammatory factors, including prostaglandin E_2 (PGE_2), C-reactive protein (CRP), and pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α (Table 1). Members of the pro-inflammatory cytokine family are essential to the inflammatory response by contributing to febrile reactions, activating phagocytotic cells such as macrophages, facilitating vascular permeability, and promoting the release of plasma-derived inflammatory mediators such as bradykinin and components of the complement system (Curfs et al., 1997; Gallin et al., 1999). In the periphery, pro-inflammatory cytokines are produced and released to a great extent by activated endothelial cells and cells of the mononuclear phagocyte system (monocytes, macrophages and monocyte-derived dendritic cells). Given this, it is not surprising that peripheral inflammatory responses in schizophrenia have also been linked to aberrations in circulating monocytes (reviewed in Drexhage et al., 2010).

In addition, activated T helper 1 (T_H1) lymphoyctes are also capable of secreting appreciable amounts of pro-inflammatory cytokines (Curfs et al., 1997; Gallin et al., 1999), and recently, functional changes in T_H1-mediated pro-inflammatory activity have been found in schizophrenic patients (Drexhage et al., in press). However, the nature and/or severity of altered T cell responses in schizophrenia remains equivocal, with some studies reporting diminished T cell proliferation and functions (e.g., Craddock et al., 2007; Maino et al., 2007; Steiner et al., 2010), whereas others find increased relative T cell counts and/or functions (e.g., Henneberg et al., 1990; Sperner-Unterweger et al., 1999) or no differences between schizophrenic patients and healthy controls (e.g., Rudolf et al., 2004). As recently discussed elsewhere (Steiner et al., 2010), at least part of this inconsistency may be explained by differences in the methodology used to assess T cell numbers and functions, as well as by different clinical sub-populations studied. In addition, several confounding factory may complicate a reliable analysis of T functions in schizophrenia, including smoking and APD treatment (Steiner et al., 2010).

It has also been widely recognized that APDs can markedly influence cytokine networks (see Section 5). However, pro-inflammatory cytokine abnormalities, including up-regulation of peripheral IL-1β, IL-6, and TNF-α levels, have also been described in medication-naïve first-episode and/or medication-free patients (e.g., Akiyama, 1999; van Kammen et al., 1999; Theodoropoulou et al., 2001; Sirota et al., 2005; Na and Kim, 2007; Kim et al., 2009; Song et al., 2009). Hence, the reported pro-inflammatory changes in peripheral tissues and organs of schizophrenic patients is unlikely to stem solely from medication effects. It also seems unlikely that the reported alterations in pro-inflammatory cytokines (and anti-inflammatory cytokines, see Section 4.1) may primarily stem from ongoing infectious processes at the time of cytokine assessment. This is because most studies exclude cases with signs of ongoing infection for the purpose of in vivo or post-mortem investigations of inflammatory markers (see e.g., Maes et al., 2002; Arion et al., 2007). Taken together, even though the precise cellular sources remain to be further explored, it appears that the alterations in pro-inflammatory markers in schizophrenia cannot solely be accounted for by possible confounding factors such as medication effects or ongoing infection, but rather, they seem to represent a genuine immunological phenotype of this disorder.

2.2. Central nervous system

Owing to their multiple roles in mediating and modulating inflammatory processes in the CNS (Block et al., 2007; Ransohoff and Perry, 2009), a great deal of interest has been centered upon

Table 1
Pro-inflammatory factors implicated in schizophrenia. The table summarizes the major cellular sources and biological activities of selected pro-inflammatory factors described to be altered in schizophrenic patients.

Factor	Main cellular source	Main biological activities
IL-1β	Activated monocytes/macrophages; endothelia cells; microglia	Promotion of fever (endogenous pyrogen), stimulation of other pro-inflammatory cytokines and hematopoietic growth factors; induction of acute-phase proteins; stimulation of HPA axis; activation of T-, B- and endothelial cells
IL-2	T_H1 cells	Activation, growth, and differentiation of T cells; promotion of antigen-specific immune responses; stimulation of pro-inflammatory cytokine production by polymorphonuclear neutrophils and natural killer cells
IL-6	Activated monocytes/macrophages; T cells (T_H2 and T_H17 cells), hepatocytes; osteoclasts; fibroblasts; astrocytes	Promotion of fever (endogenous pyrogen), induction of acute-phase proteins; stimulation of immunoglobulin-G production; activation of T cells; stimulation of HPA axis
sIL-6R	Activated monocytes/macrophages; hepatocytes; osteoclasts	Augmentation of IL-6 responses by acting as an IL-6 agonist
IL-8	Activated monocytes/macrophages; endothelia cells; fibroblasts	Activation of neutrophils; chemotactic for neutrophils, T cells and basophils
TNF-α	Activated monocytes/macrophages; T cells (T_H1 cells), natural killer cells; endothelia cells; microglia	Promotion of fever (endogenous pyrogen) and sepsis; direct cytotoxic effects by inducing apoptosis; activation of monocytes, lymphocytes, and endothelial cells
PGE_2	All nucleated cells expressing arachidonic acid	Central mediator of fever and pain; promotion of vasodilation and vascular permeability
CRP	Hepatocytes in response to pro-inflammatory signals (especially IL-6)	Activation of the complement system; enhancement of phagocytosis by macrophages (opsonin-mediated phagocytosis)