Inflammatory processes in schizophrenia: A promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond

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ABSTRACT

Emerging evidence indicates that schizophrenia is associated with activated peripheral and central inflammatory responses. Such inflammatory processes seem to be influenced by a number of environmental and genetic predisposition factors, and they may critically depend on and contribute to the progressive nature of schizophrenic disease. There is also appreciable evidence to suggest that activated inflammatory responses can undermine disease-relevant affective, emotional, social, and cognitive functions, so that inflammatory processes may be particularly relevant for the precipitation of negative and cognitive symptoms of schizophrenia. Recent clinical trials of anti-inflammatory pharmacotherapy in this disorder provide promising results by showing superior beneficial treatment effects when standard antipsychotic drugs are co-administered with anti-inflammatory compounds, as compared with treatment outcomes using antipsychotic drugs alone. Given the limited efficacy of currently available antipsychotic drugs to ameliorate negative and cognitive symptoms, the further exploration of inflammatory mechanisms and anti-inflammatory strategies may open fruitful new avenues for improved treatment of symptoms undermining affective, emotional, social and cognitive functions pertinent to schizophrenic disease.

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1. Introduction

Schizophrenia is a chronic form of psychotic illness that affects approximately 1% of the population worldwide (Tandon et al., 2008; van Os & Kapur, 2009). The onset of full-blown schizophrenic disease is typically in late adolescence or early adulthood. The disorder includes distinct but often co-existing symptom classes which are commonly referred to as positive, negative and cognitive symptoms (Tandon et al., 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. Taken together, schizophrenia is characterized by a wide spectrum of behavioral and cognitive dysfunctions that can readily undermine basic human processes of perception and judgment.

There is increasing recognition of the importance of negative and cognitive symptoms in schizophrenia, partly because currently available antipsychotic drugs (APDs) show a limited clinical efficacy in improving these dysfunctions (Bowie & Harvey, 2006; Insel, 2010; Tandon et al., 2010). Negative symptoms are typically classified as primary or secondary, with primary negative symptoms representing a core feature intrinsic to the disorder, whilst secondary negative symptoms are temporary and often attributable to effects imposed by acute psychotic episodes and/or APD treatment (Möller, 2007). Similar to the primary negative symptoms, cognitive symptoms of schizophrenia appear to be a core feature of the disorder and represent a major contributor to functional disability (Elvevåg & Goldberg, 2000; Bowie & Harvey, 2006). Both primary negative as well as cognitive symptoms often precede the onset of full-blown psychotic episodes and persist subsequent to the pharmacologically controlled resolution of acute psychotic phases (Reichenberg, 2005; Möller, 2007).

The pathophysiology of schizophrenia likely involves neurochemical imbalances in various neurotransmitter systems. Alterations in the central dopamine (DA) system have been discussed for decades, originally based on evidence that the therapeutically effective APDs act, at least in part, by blocking DA receptors, especially the DA D2 receptor subclass; and that DA-stimulating drugs can induce psychosis-like behavior in non-psychotic human subjects and exacerbate (positive) symptoms in schizophrenic patients (Carlsson et al., 2001; Howes & Kapur, 2009). Subsequently, the putative impact of a hypofunctioning cortical DA system has been incorporated into the theories of altered DA functions in schizophrenia (Carlsson et al., 2001; Howes & Kapur, 2009). In addition to these cortical–subcortical DA imbalances, functional changes in serotonergic and glutamatergic transmission seem highly relevant for the disorder (Abi-Dargham et al., 1997; Carlsson et al., 2001; Coyle et al., 2003; Javitt, 2007). The current consensus is that alterations of these neurotransmitter systems either lead to a functional imbalance of DA transmission via interaction with the DA system, and/or contribute pathophysiologically to schizophrenia by direct non-dopaminergic actions. Finally, alterations in the central γ-aminobutyric acid (GABA) (Benes & Berretta, 2001; Lewis et al., 2005) and cholinergic (Martin & Freedman, 2007) systems have also been in the focus of attention by virtue of their modulatory functions at the relevant synapses and their impact on cognitive functions known to be impaired in schizophrenia.

Besides these neurochemical and neuropathological changes, schizophrenia has also been linked to numerous alterations in basic physiological and metabolic functions, including cardiovascular disease, type-2 diabetes, and obesity (Marder et al., 2004). A large body of evidence further implicates a spectrum of immunological abnormalities in this disorder. Indeed, the idea that altered immune functions may play an important role in schizophrenia has a long history (Delisi & Wyatt, 1982; Müller et al., 1991; Smith, 1991; Müller et al., 2000). However, it is not unusual that attempts to explain some of the underlying pathophysiological mechanisms by immune abnormalities are met with skepticism (Delisi, 1996). One has often raised the issue as to whether the presence of immunological alterations may provide a genuine contribution to schizophrenia pathogenesis, or whether such immune alterations should be considered a pathophysiologically irrelevant epiphenomenon. There is now appreciable evidence to assume that the former may indeed be the case, and several lines of recent research have readily boosted renewed awareness of the immunological facets of schizophrenia (Müller & Schwarz, 2010).

One emerging aspect of immune changes in schizophrenia relates to activated inflammatory processes (Fan et al., 2007a; Potvin et al., 2008; Drexhage et al., 2010). In this article, we discuss that activated inflammatory responses in schizophrenia may provide a promising neuroimmunological target for the treatment of multiple psychopathological symptoms, including those pertinent to the negative and cognitive symptoms of schizophrenia. First, the basic principles and components of inflammation are outlined, followed by an up-to-date summary of inflammatory signs in schizophrenia and their potential origins. We then discuss behavioral and neuronal effects of inflammation, with a special emphasis on those effects that seem closely linked to the negative and cognitive symptoms of schizophrenia. Finally, we highlight the immunomodulatory effects of conventional APDs and discuss recent progress in treating schizophrenic disease by adjunctive anti-inflammatory pharmacotherapy.

2. Main components of the inflammatory response system

Inflammation is one of the first defense mechanisms of the innate immune system to infection and other physiological insults such as tissue damage or stress (Gallin et al., 1999). Typically, it is characterized by redness and swelling of infected/wounded tissue and is promoted by a number of secreted pro-inflammatory factors, including prostanoids, leukotrienes, pro-inflammatory cytokines and chemokines. Prostaglandins are import mediators of the febrile response and of blood vessel dilation, whereas leukotrienes together with chemokines are critical for attracting leukocytes to sites of infection and/or tissue damage (Gallin et al., 1999). Cytokines have wide-ranging roles in the innate and adaptive immune systems, where they help regulate the recruitment and activation of lymphocytes as well as immune cell differentiation and homeostasis (Curs et al., 1997). In addition, some cytokines possess direct effector mechanisms, including induction of cell apoptosis and inhibition of protein synthesis (Curs et al., 1997). Members of the pro-inflammatory cytokine family, including interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α, are essential to the inflammatory response by contributing to febrile reactions, activating phagocytic cells such as macrophages or dendritic cells, facilitating vascular permeability, and promoting the release of plasma-derived inflammatory mediators such as bradykinin and components of the complement system. 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 macrocyte-derived dendritic cells). The synthesis of pro-inflammatory molecules is strongly stimulated upon activation of the innate immune system. This most often occurs upon binding of microbe-specific components by a special class of receptors known as pathogen recognition receptors, or when damaged or infected cells send out alarm signals, many of which are recognized by the same receptors as those that recognize pathogens (Janeway & Medzhitov, 2002; Mogensen, 2009).

Under normal conditions, inflammation is controlled by various homeostatic processes that limit or counteract inflammation once it has been induced by a pro-inflammatory stimulus such as infection (Serhan & Savill, 2005). Such control mechanisms ensure that inflammatory processes efficiently remove invading pathogens and contribute to tissue repair and wound healing without inducing collateral damage to non-infected, healthy and unwounded tissue. Dysfunction of such surveillance mechanisms may lead to persistent inflammation, known from numerous pathological conditions such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, and Crohn’s disease (Serhan & Savill, 2005; Briand & Muller, 2010).

In the central nervous system (CNS), microglia and astrocytes are the major immunocompetent cells regulating both the induction as well as limitation of inflammatory processes (Seth & Koul, 2008; Ransohoff & Perry, 2009). This is achieved through the synthesis of cytokines, up- or down-regulation of various cell surface receptors such as pathogen
recognition receptors, cytokine receptors, and numerous receptors crucial for antigen presentation. Acting as the first and main form of active immune defense in the brain, microglia are considered to be the resident macrophages of the CNS, which constantly scavenge the CNS for damaged neurons, plaques, and infectious agents (Ransohoff & Perry, 2009). Microglia appear to play crucial roles in both neuronal protection and pathology, and are often referred to as a “double-edged sword” (Block et al., 2007). On the one hand, they secrete neurotrophic factors pivotal for cellular repair, and recruit immune cells into the brain for clearance of infection or cellular debris. On the other hand, chronic or exaggerated microglial activation is linked to excessive secretion of pro-inflammatory factors and has been linked to (progressive) neurodegenerative processes (Block et al., 2007). With regards to astrocytes, it has been considered for long that the main roles of these glial cells are related to neuronal support functions. However, accumulating evidence suggests that astrocytes exert a much wider spectrum of functions, including regulation of neuronal differentiation, axonal guidance, synapse formation, and brain plasticity (Seth & Koul, 2008). Of note, astrocytes have also become the focus of attention due to their modulatory effects on microglia cells: They seem to have noticeable inhibitory as well as stimulatory influences on microglia functions depending on the precise immune milieu in which astrocyte–microglia interactions take place (Wang, 2010; Bianchi et al., 2011; Zhang et al., 2011).

3. Inflammatory signs in schizophrenia

3.1. Peripheral inflammation

Signs of peripheral inflammatory responses in schizophrenia have typically been evidenced by the presence of elevated serum/plasma levels or in-vitro production of specific pro-inflammatory factors, including prostaglandin E2 (PGE₂), C-reactive protein (CRP), and numerous pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α (for recent reviews, see Fan et al., 2007a; Potvin et al., 2008; Drexhage et al., 2010). Table 1 provides a summary of inflammatory markers that have been repeatedly described to be altered in schizophrenic patients. Peripheral inflammatory responses in schizophrenia further seem to involve aberrations in circulating monocytes (Drexhage et al., 2010), which notably are one of the main sources of pro-inflammatory molecule production and secretion (Curfs et al., 1997; Gallin et al., 1999). Indeed, several studies have reported significant increases in the absolute and/or relative counts of monocytes and total white blood cells in schizophrenic patients (Zorrilla et al., 1996; Rothermundt et al., 1998; Fan et al., 2010). In addition, activated T helper 1 (Th1) lymphocytes are also capable of secreting appreciable amounts of pro-inflammatory cytokines (Curfs et al., 1997; Gallin et al., 1999), and functional changes in Th1-mediated pro-inflammatory activity have been found in schizophrenic patients (Drexhage et al., 2011).

Emerging evidence suggests that in schizophrenia, increased pro-inflammatory activity concurs with enhanced anti-inflammatory peripheral responses. Among the most consistent findings in this context are elevated peripheral levels and/or in-vitro production of soluble IL-1 receptor antagonist (sIL-1RA) and soluble IL-2 receptor (sIL-2R) (Maes et al., 1994, 1996; Akiyama, 1999; Breeze & Rapaport, 2009). sIL-1RA binds to IL-1 receptors in competition with IL-1α/β, but in contrast to the latter, it fails to actuate intracellular signaling cascades (Gabay et al., 2010). Likewise, sIL-2R is shed from the cellular surface of activated immune cells and efficiently blocks the biological activity of IL-2 by preventing its binding to the membrane-anchored and signal-transducing IL-2 receptor complex (Nelson & Willerford, 1998). sIL-1RA and sIL-2R can thus both efficiently block pro-inflammatory effects typically associated with IL-1 and IL-2 signaling, respectively. Changes in the anti-inflammatory response systems of schizophrenic patients may further involve peripheral elevations in soluble TNF receptor (sTNFR), IL-10, and transforming growth factor (TGF)-β (Maes et al., 2002; Kim et al., 2004; Coelho et al., 2008; Hope et al., 2009; Kunz et al., 2011), all of which are known to exert potent anti-inflammatory and/or immunosuppressive functions (Murray, 2006; Bradley, 2008; Yoshimura et al., 2010). However, conflicting reports exist with regards to these markers in schizophrenia (e.g., Naudin et al., 1997; Haack et al., 1999), so that the nature and/or direction of their changes in schizophrenic patients still awaits further validation.

In support of the notion that schizophrenia is associated with both enhanced pro-inflammatory and anti-inflammatory activity, several studies assessing within-subjects cytokine changes report concomitant up-regulation of pro- and anti-inflammatory cytokines in affected individuals (e.g., Maes et al., 2002; Kim et al., 2004). A recent study by Drexhage et al. (2011) further indicates that this concurrent enhancement of pro- and anti-inflammatory activity can be readily extended to the level of peripheral immune cells. More specially, it has been noted that schizophrenic patients not only show higher percentages of pro-inflammatory monocytes, activated CD3+CD25+ T cells and pro-inflammatory Th17 cells, but they also display higher amounts of anti-inflammatory CD4+CD25highFoxP3+ regulatory T cells and IL-4+ lymphocytes (Drexhage et al., 2011).

The concomitant up-regulation of pro- and anti-inflammatory markers in schizophrenia may not be unprecedented in view of the inherent linkage and cross-regulation of the pro- and anti-inflammatory arms of the immune system (Gallin et al., 1999; Serhan & Savill, 2005). The relative potency of schizophrenic patients to mount enhanced anti-inflammatory actions in response to the presence of pro-inflammatory stimuli may readily be favorable in as much as this would provide an efficient way to counteract and restrict on-going pro-inflammatory processes, thereby preventing the development of progressive and potentially detrimental effects of chronic inflammation. Indeed, it is important to recognize that despite the signs of enhanced pro-inflammatory responses, the severity of such responses in schizophrenia seems relatively modest compared to pathologies that are characterized by marked chronic inflammation such as rheumatoid arthritis or atherosclerosis (Serhan & Savill, 2005). The inflammatory response in schizophrenia is therefore often referred to as “low-grade inflammation” (Fan et al., 2007a; Drexhage et al., 2010; Meyer et al., 2011).

It needs to be pointed out that reports of peripheral cytokine alterations in schizophrenia have not always been consistent between individual studies. Several confounding factors have often been discussed to contribute to discrepant outcomes, including smoking, weight gain, and age (Hinze-Selch & Pollmächer, 2001; Maes et al., 2002). In addition, it has been widely recognized that APDs can markedly influence cytokine levels, especially with regards to their serum/plasma concentrations (Drzyzga et al., 2006). Even though differences in the precise medication status may readily complicate the interpretation of individual findings, the immunomodulatory effects of APDs appear to have considerable beneficial effects in the treatment of schizophrenic disease. This issue is discussed in detail below (see Section 6.1). It is also important to point out that inflammatory cytokine abnormalities, including up-regulation of peripheral IL-1β, sIL-1RA, sIL-2R, IL-6, IL-8, and TNF-α levels, have been described in medication-naive or minimally medicated first-episode schizophrenic patients (e.g., Akiyama, 1999; van Kammen et al., 1999; Theodoropoulou et al., 2001; Zhang et al., 2002; Sirota et al., 2005; Na & Kim, 2007; Kim et al., 2009; Song et al., 2009). It is therefore unlikely that inflammatory cytokine changes in peripheral tissues and organs of schizophrenic patients may stem solely from medication effects, but rather, they seem to represent a genuine immunological phenotype of this disorder.

3.2. Central inflammation

Owing to their multiple roles in mediating and modulating inflammatory processes in the CNS (Block et al., 2007; Ransohoff &
Table 1

Secreted immunological factors implicated in the inflammatory response in schizophrenia. The table summarizes the major cellular sources and biological activities of pro- and anti-inflammatory molecules, and the various effects described in peripheral (serum/plasma) and central (CNS) systems of patients with schizophrenia. Symbols (+) and (-) denote significant increases and decreases, respectively; symbol (↔) signifies no significant changes.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Main cellular source</th>
<th>Main biological activities</th>
<th>Effect in schizophrenia</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>Activated monocytes/macrophages; endothelia cells; microglia.</td>
<td>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.</td>
<td>↑ (Serum/plasma)</td>
<td>Theodoropoulou et al., 2001; Song et al., 2009.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>↑/↓ (CSF)</td>
<td>Barak et al., 1995; Söderlund et al., 2009.</td>
</tr>
<tr>
<td>sIL-1RA</td>
<td>Activated monocytes/macrophages; endothelia cells; fibroblasts, astrocytes.</td>
<td>Inhibition of IL-1 activity; homeostatic control of inflammation through anti-inflammatory actions.</td>
<td>↑ (Serum/plasma)</td>
<td>Maes et al., 1996; Akiyama, 1999; Sirota et al., 2005.</td>
</tr>
<tr>
<td>IL-2</td>
<td>T_H1 cells</td>
<td>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.</td>
<td>↓ (CSF)</td>
<td>Barak et al., 1995; McAllister et al., 1995; Kim et al., 2000; Zhang et al., 2002.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑/→ (CNS)</td>
<td>Licinio et al., 1993; Barak et al., 1995; McAllister et al., 1995; Rapaport et al., 1997.</td>
</tr>
<tr>
<td>sIL-2RA</td>
<td>Activated T cells.</td>
<td>Inhibition of IL-2 activity; homeostatic control of T cell activation.</td>
<td>↑ (Serum/plasma)</td>
<td>Maes et al., 1994; Breeze and Rapaport, 2009; Akiyama, 1999.</td>
</tr>
<tr>
<td>IL-6</td>
<td>Activated monocytes/macrophages; T cells (T_H2 and T_H17 cells); hepatocytes; osteoclasts; fibroblasts; astrocytes.</td>
<td>Promotion of fever (endogenous pyrogen); induction of acute-phase proteins; stimulation of immunoglobulin-G production; activation of T cells; stimulation of HPA axis.</td>
<td>↓ (CSF)</td>
<td>Maes et al., 1994; Akiyama, 1999; van Kammen et al., 1999; Zhang et al., 2002; Na and Kim, 2007; Kim et al., 2009.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑/→ (CNS)</td>
<td>van Kammen et al., 1999; Garver et al., 2003.</td>
</tr>
<tr>
<td>sIL-6R</td>
<td>Activated monocytes/macrophages; hepatocytes; osteoclasts.</td>
<td>Augmentation of IL-6 responses by acting as an IL-6 agonist.</td>
<td>↓ (Serum/plasma)</td>
<td>Maes et al., 1994; Müller et al., 1997a.</td>
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<td></td>
<td></td>
<td></td>
<td>↑ (CNS)</td>
<td>Müller et al., 1997a.</td>
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<td></td>
<td>↑ (Serum/plasma)</td>
<td>Maes et al., 2002; Zhang et al., 2002.</td>
</tr>
<tr>
<td>IL-10</td>
<td>Activated monocytes/macrophages; T cells (T_H2 cells); B cells.</td>
<td>Inhibition of pro-inflammatory cytokine synthesis; inhibition of sepsis; promotion of humoral immune responses involving antibody secretion.</td>
<td>↑ (Serum/plasma)</td>
<td>Maes et al., 2002; Kunz et al., 2011.</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Activated monocytes/macrophages; hepatocytes; osteoclasts.</td>
<td>Promotion of fever (endogenous pyrogen) and sepsis; direct cytotoxic effects by inducing apoptosis; activation of monocytes, lymphocytes, and endothelial cells.</td>
<td>↑ (Serum/plasma)</td>
<td>Theodoropoulou et al., 2001; Na and Kim, 2007; Kim et al., 2009; Song et al., 2009.</td>
</tr>
<tr>
<td></td>
<td>T cells (T_H1 cells); natural killer cells; endothelia cells; microglia.</td>
<td>Activation of neutrophils; chemoattract for neutrophils, T cells and basophils.</td>
<td>↑ (Serum/plasma)</td>
<td>Maes et al., 2002; Zhang et al., 2002.</td>
</tr>
<tr>
<td>sTNFR</td>
<td>Virtually all nucleated cells.</td>
<td>Inhibition of TNF activity; homeostatic control of inflammation through anti-inflammatory actions.</td>
<td>↑ (Serum/plasma)</td>
<td>Coelho et al., 2008; Hope et al., 2009.</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Megakaryocytes; T cells (T_H3 cells).</td>
<td>Inhibition of pro-inflammatory cytokine synthesis; inhibition of natural killer cell activity and growth of T- and B-cells; in the presence of IL-6 stimulation of T_H17 cells.</td>
<td>↑ (Serum/plasma)</td>
<td>Kim et al., 2004.</td>
</tr>
<tr>
<td>PGE_2</td>
<td>All nucleated cells expressing arachidonic acid.</td>
<td>Central mediator of fever and pain; promotion of vasodilation and vascular permeability.</td>
<td>↑ (Serum/plasma)</td>
<td>Kawai et al., 1989.</td>
</tr>
<tr>
<td>CRP</td>
<td>Hepatocytes in response to pro-inflammatory signals (especially IL-6).</td>
<td>Activation of the complement system; enhancement of phagocytosis by macrophages (opsonin-mediated phagocytosis).</td>
<td>↑ (Serum/plasma)</td>
<td>Dickerson et al., 2007; Fan et al., 2007b.</td>
</tr>
</tbody>
</table>

Perry, 2009), a great deal of interest has been centered upon the role of microglia in schizophrenia (Bernstein et al., 2009; Monji et al., 2009). Initial post-mortem immunohistochemical investigations have provided equivocal results with regards to microglia abnormalities in this disorder: Whereas some studies report enhanced microglial cell densities in the brains of schizophrenic patients (Bayer et al., 1999; Radewicz et al., 2000; Carey, 2010), others do not find significant microglia changes in affected individuals using post-mortem immunohistochemical techniques (e.g., Steiner et al., 2006,2008). More recent approaches have used positron emission tomography (PET) to study the role of microglia in schizophrenia. These studies have confirmed enhanced microglial activation especially in temporolimbic gray matter of schizophrenic patients (van Berckel et al., 2008; Doorduin et al., 2009), suggesting that the disorder may indeed be associated with significant microglia over-activation. However, there is an ongoing debate as to whether such microglia abnormalities may be attributable to medication effects rather than genuine neuroinflammatory processes inherent to schizophrenic disease (Bernstein et al., 2009). This issue awaits further validation by investigations of possible microglia abnormalities in drug-naïve (or minimally medicated) first-episode patient with schizophrenia.

There is an appreciable body of evidence suggesting that the neuroinflammatory pathology in schizophrenia involves abnormal astrocyte functions. Indeed, one well-established finding in this context is the increase in serum and/or cerebrospinal fluid (CSF) levels of S100B, a protein of the S-100 protein family that is involved in variety of neuronal and glial signaling mechanisms (Rothermundt et al., 2009). In the CNS, S100B is primarily produced by activated astrocytes, so that elevated central levels of this protein likely reflect astrocyte over-activation (Rothermundt et al., 2009). Interestingly, S100B exerts a direct functional impact on microglia cells (Bianchi et al., 2011; Zhang et al., 2011), so that this protein may provide an important molecular link between abnormal astrocyte functions and the presumed microglia activation in schizophrenic disease. It is also important to note that in schizophrenic patients, S100B over-expression takes place in the absence of astrogliosis (Bernstein et al., 2009; Rothermundt et al., 2009). This suggests that the nature of such over-expression is related to altered astrocyte activity rather than density. The lack of overt astrogliosis is in line with the neurodevelopmental hypothesis of schizophrenia, suggesting that the majority of the histological and neuroanatomical changes is unlikely to be the result of marked neurodegeneration, but rather may reflect (progressive) changes in...
neurodevelopmental processes (Weinberger, 1987; Fatemi & Folsom, 2009).

Increased CSF levels of pro-inflammatory cytokines such as IL-1β and IL-6 (Garver et al., 2003; Söderlund et al., 2009) as well as up-regulated cyclooxygenase (COX) expression (Das & Khan, 1998) have also been noted in schizophrenic patients, providing additional support for the hypothesis of activated central inflammatory responses in affected individuals. Some reports further suggest that schizophrenia is associated with reduced potency to mount anti-inflammatory and immuno-suppressive responses in the CNS, as supported by findings of reduced gene and/or protein expression of sIL-1RA and TGF-β receptor (Vawter et al., 1997; Toyoooka et al., 2003). Consistent with this impression, Müller et al. (1997a) demonstrated that the levels of the soluble IL-6 receptor (sIL-6R) are increased in the CSF of schizophrenic patients. In contrast to other soluble cytokine receptors such as sIL-1RA or sIL-2R, sIL-6R does not inhibit IL-6 signaling, but instead enhances IL-6 functions by acting as an agonist in combination with IL-6 (Knüpfer & Preiss, 2008). Taken together, there seems to be a relative shift towards enhanced pro-inflammatory and blunted anti-inflammatory activity with regards to secreted inflammatory factors in the CNS of schizophrenic patients. This pattern readily contrasts the immunological profile described in the periphery, where enhanced pro-inflammatory activity appears to concur with increased release of anti-inflammatory and/or immuno-suppressive factors. However, it remains a matter of debate as to whether distinct brain regions may be differentially affected by inflammatory processes in schizophrenia, and current immunological research in schizophrenia has not yet been able to provide any conclusive data that would support this possibility. Additional research is thus clearly warranted to explore this issue directly.

4. Sources of activated inflammatory responses in schizophrenia

4.1. Genetic predisposition

It has long been recognized that schizophrenia is a heritable disorder that probably involves multiple genetic abnormalities with relatively modest effects across large populations (Sullivan, 2005). There have been tremendous efforts to identify potential schizophrenia susceptibility genes using single nucleotide polymorphisms (SNPs) approaches, and such investigations have put forward a number of genes that may be relevant for the genetic etiology of this disorder, including neuregulin-1 (NRG-1), catheol-O-methyltransferase (COMT), and disrupted in schizophrenia-1 (DISC-1) (Harrison & Weinberger, 2005; Gogos & Gerber, 2006). However, many of these genes have been identified and portrayed in relatively small populations, and recent research suggests that several of the presumed candidate genetic factors do not reach significance in association studies conducted in larger populations (Sanders et al., 2008; Nieratschker et al., 2010).

More recently, genome-wide association studies (GWAS) have been initiated with the aim of indentifying genetic variants which increase susceptibility to schizophrenia in large populations (O’Donovan et al., 2009). Interestingly, schizophrenia GWAS have consistently implicated genetic variants in the major histocompatibility complex (MHC) on chromosome 6 as common susceptibility factor for the disorder (Pericell et al., 2009; Shi et al., 2009; Stefansson et al., 2009). In humans, this MHC region contains 140 genes, most of which have known immune functions (Kumánovics et al., 2003). Several other studies confirm the importance of variants in immune-related genes in schizophrenia. For example, recent schizophrenia GWAS pathway analyses show that numerous signaling pathways involved in inflammation are consistently associated with schizophrenia in large genetic data sets (Jia et al., 2010). Moreover, a genome-wide microarray study demonstrates that an appreciable number of genes found to be down-regulated in the superior temporal cortex of schizophrenic patients are closely associated with immune functions (Schmitt et al., 2011). These recent findings may be indicative of the possibility that at least part of the reported immune abnormalities in this disorder may have a genetic etiology.

This impression is also supported by the numerous reports of genetic variations in specific cytokine genes and/or cytokine gene promoter polymorphisms in individuals with schizophrenia. Schizophrenic patients have repeatedly been shown to display allelic variants in IL-1 and IL-1RA (Katila et al., 1999; Zanardini et al., 2003; Papiol et al., 2005; Xu & He; 2010), IL-6 (Sun et al., 2008; Paul-Samojedy et al., 2010), IL-10 (Bocchio Chiavetto et al., 2002; Yu et al., 2004; He et al., 2006), and TNF-α (Boin et al., 2001; Schwab et al., 2003; Saviouk et al., 2005) genes and/or promoters. It is likely that such genetic variants exert a functional impact on cytokine protein networks in affected subjects because many of the cytokine gene promoter polymorphisms are known to directly influence protein synthesis. For example, schizophrenic patients display those IL-10 promoter variants more frequently which facilitate IL-10 gene transcription and protein synthesis (Bocchio Chiavetto et al., 2002). This specific association thus fits well the report of enhanced baseline peripheral IL-10 levels in schizophrenia (Maes et al., 2002). Taken together, there is appreciable evidence to assume that cytokine protein and/or gene expression abnormalities pertinent to the inflammatory response in schizophrenia may be accounted for, at least in part, by the presence of allelic variants in immune-related genes.

It is also of note that genetic variants in immune-related genes may significantly impact on the clinical efficacy of APD treatment. For example, there is a remarkable pharmacogenetic relationship between IL-1RA gene polymorphism and clinical improvement of negative symptoms during antipsychotic treatment in patients with a first non-affective psychotic episode (Mata et al., 2006). The clinical efficacy of APDs has also been found to be modulated by polymorphisms in the TNF-α gene (Zai et al., 2006) and other immune-related genes, including human leukocyte antigens (HLA) (Lahdelma et al., 2001).

4.2. Early-life immune priming

A plethora of epidemiological studies in humans and experimental work in animals emphasizes the critical impact of the early-life environment in shaping postnatal physiological, emotional and behavioral functions. Stimulated by the seminal work of David Barker conducted in the context of coronary heart disease (Dover, 2009), the concept of “early-life programming of adult disease” is now well accepted. This concept refers to the phenomenon whereby specific environmental factors acting during sensitive prenatal or early postnatal developmental periods can induce persistent changes in physiological, emotional and behavioral functions throughout life (Bale et al., 2009; Dover, 2009; Meyer et al., 2011). Accumulating evidence suggests that such early-life programming also exists for the functional development of the immune system (Merlot et al., 2008; Bilbo & Schwarz, 2009).

Perinatal exposure to infection and/or immune activation is one of the prominent environmental factors with known impact on postnatal immune functions (Bilbo & Schwarz, 2009). For example, prenatal maternal exposure to the bacterial endotoxin lipopolysaccharide (LPS) or the pro-inflammatory cytokine IL-6 in rats leads to enhanced microglial densities and elevation of peripheral and central pro-inflammatory cytokine levels in the offspring (Borrell et al., 2002; Samuelsson et al., 2006; Romero et al., 2010). Such inflammatory changes can persist even until adulthood (Borrell et al., 2002; Samuelsson et al., 2006; Romero et al., 2010), suggesting that immune challenge early in life can permanently alter postnatal immune functions. Further to the precipitation of overt immune dysfunctions, which may be evident even under basal conditions, early-life exposure to infection and/or immune activation may also induce sensitizing or preconditioning effects. In this scenario, immunological exposure in early (prenatal or neonatal) life can cause the organism to mount exacerbated reactions to subsequent immunological or non-immunological challenges in later life (Bilbo & Schwarz, 2009; Meyer et al., 2011).
Notably, early-life infection and/or immune activation not only shapes the functional development of the immune system, but it also elevates the risk of developing schizophrenia and related psychotic disorders in later life (Bale et al., 2009; Brown & Derkits, 2010). One prevalent hypothesis suggests that infection/inflammation-induced disruption of fetal neurodevelopmental processes may predispose the organisms to long-lasting changes in subsequent brain and behavioral development, thereby increasing the risk of psychotic disturbances in early adulthood (Gilmore & Jarskog, 1997; Meyer et al., 2009). This hypothesis has been substantiated by numerous investigations in experimental rodent models demonstrating the emergence of altered fetal brain development (Meyer et al., 2008a; Vuillermot et al., 2010) and multiple long-term brain and behavioral abnormalities relevant to schizophrenia following prenatal exposure to infection and/or immune activation (Meyer & Feldon, 2010). Recent molecular studies further underscore the essential role of prenatal cytokine-associated inflammatory processes in mediating the effects of maternal infection on the offspring: Blocking the actions of the pro-inflammatory cytokine IL-6 in the pregnant maternal host by genetic or pharmacological interventions, or genetically enforced over-expression of the anti-inflammatory cytokine IL-10, prevents the long-term brain and behavioral consequences of prenatal viral-like immune activation in mice (Smith et al., 2007; Meyer et al., 2008b). In addition to the suggested role of cytokine alterations, several other immune factors such as complement and MHC I or II proteins may be critical in mediating the effects of (prenatal) inflammation in altering neurodevelopmental trajectories: These molecules are essential for normal brain development by regulating various neurodevelopmental processes (Huh et al., 2000; Boulanger & Shatz, 2004; Boulanger, 2009; Shatz, 2009), and their expression is strongly regulated by inflammatory stimuli such as cytokines (Boulanger et al., 2001). Hence, abnormal expression of immune factors such as complement and MHC proteins may be an essential molecular pathway by which prenatal inflammation can induce changes in brain and behavioral development.

In view of its concomitant impact on schizophrenia risk and immune system development, it is intriguing to speculate that early-life immune exposure may provide a developmental source of altered immune functions in schizophrenia. Hence, inflammatory processes targeting the fetal and/or neonatal brain may not only interfere with normal brain development, but may further induce long-term changes in postnatal immune functions. A similar conclusion has been drawn from a recent microarray study suggesting that at least a subset of schizophrenic patients may carry altered immune/chaaperone gene signatures in the prefrontal cortex that reflect long-term consequences of early-life exposure to infection and/or immune challenge (Arion et al., 2007).

4.3. Impaired neuroendocrine feedback inhibition

Immunological functions are inherently linked to and modulated by neuroendocrine systems, especially the hypothalamic–pituitary–adrenal (HPA) axis (Rivest, 2010). Activation of the (innate) immune system increases the activity of the HPA axis, a process that can be mediated directly or indirectly through pro-inflammatory cytokines (Dantzer et al., 2008; Rivest, 2010). Release of glucocorticoids (cortisol in humans and primates, corticosterone in rodents) by the adrenal cortex is the major hormonal output of the HPA axis. In addition to their wide-ranging metabolic functions, glucocorticoids are an essential part of the homeostatic control of the immune system, where they potently suppress various immune functions in general, and inflammatory responses in particular (Rhen & Cidlowski, 2005). With regards to the latter, glucocorticoids have potent anti-inflammatory properties by suppressing the production and/or secretion of pro-inflammatory molecules such as pro-inflammatory cytokines, prosta-glandins, leukotrienes and COX-1/COX-2 (Rhen & Cidlowski, 2005). Blunted neuroendocrine feedback inhibition of immune functions can thus readily facilitate the persistence of inflammation once inflammatory processes have been initiated (Raison & Miller, 2003).

Given this, impairments in the neuroendocrine regulation of inflammation may provide another source of the abnormally enhanced inflammatory responses in schizophrenia (Fig. 1). Indeed, there is an appreciable body of evidence implicating insufficient glucocorticoid signaling and/or glucocorticoid resistance in this disorder. Using the dexamethasone suppression test, a test that is commonly used to assesses glucocorticoid responsiveness, several studies report higher rates of non-suppression in schizophrenia (Yeragani, 1990), indicating that at least a sub-group of patients display impaired responsiveness to glucocorticoids. It is of interest to note that such glucocorticoid unresponsiveness is more prevalent in those schizophrenic patients who show marked negative symptoms as compared to those patients with modest negative symptomatology (Altamura et al., 1989; McGauley et al., 1989). One implication is that impaired neuroendocrine regulation of immune functions may contribute to abnormal inflammatory responses especially in those patients showing severe forms of negative symptomatology.

5. Relevance of inflammatory processes to distinct symptom classes of schizophrenia

In the context of neuropsychiatry, activated inflammatory processes are by no means specific to schizophrenia, but have also been implicated in other mental illnesses, especially major depression (Anisman et al., 2002; Müller & Schwarz, 2007; Dantzer et al., 2008; Müller et al., 2009) and bipolar disorder (Drexhage et al., 2010). This may not be unprecedented, nor does it undermine the relevance of inflammatory processes to schizophrenia, because the clinical features of schizophrenia, especially those that are included in the category of negative/cognitive symptoms, overlap significantly with affective, social and cognitive dysfunctions typically implicated in depressive and bipolar disease (Möller, 2007). Indeed, the clinical similarities between negative and depressive symptoms on the one hand, and between negative and cognitive symptoms on the other hand, may readily be appreciated in view of their shared manifestations (Möller, 2007). For example, apathy, anhedonia, and psychomotor retardation are common to negative symptoms and depression, whereas reduced attention and poor communication seem common to the negative/cognitive symptoms of schizophrenia and major depression (Segrin, 2000; Eizenman et al., 2003; Bell & Mishara, 2006; Harvey et al., 2006; Günter et al., 2011). It is beyond the scope of this article to provide a discussion of the role of activated inflammatory response systems in major depression and bipolar disorder, so we would like to refer to those articles that have discussed this issue in detail (Anisman et al., 2002; Müller & Schwarz, 2007; Dantzer et al., 2008; Müller et al., 2009).

In what follows, we go on to draw attention to the intriguing possibility that activated inflammatory responses in schizophrenia may be relevant especially for the pathogenesis and treatment of the negative and cognitive symptoms. To this end, we integrate experimental and clinical findings of the behavioral, cognitive and neuronal effects of activated inflammatory systems, and we discuss the recent progress in treating schizophrenia disease by anti-inflammatory pharmacotherapy.

5.1. Negative symptoms

Pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α, have long been recognized to play an essential role in the modulation of various brain functions (Larson & Dunn, 2001; Anisman et al., 2002). One well-established finding is that enhanced peripheral and/or central pro-inflammatory cytokine signaling markedly impairs affective, emotional and social functions (Dantzer et al., 2008). For example, peripheral and/or central administration of pro-inflammatory cytokine releasing agents robustly induces anhedonic behavior and social impairments.
Genetic source for altered immune responses in schizophrenia; and prenatal immune priming induced by in-utero exposure to infection may provide a developmental source of long-term inflammation. Abnormal expression of inflammatory genes in monocytes/macrophages (M/M) facilitates the development of peripheral low-grade inflammation in patients with schizophrenia (represented by solid orange and green lines) as compared to healthy subjects (represented by dashed orange and blue lines). Such peripheral low-grade inflammation seems to be characterized by fluctuations in abnormal pro- and anti-inflammatory activity, whereby enhanced pro-inflammatory activity (orange lines) typically precedes the onset of increased anti-inflammatory activity (green lines). In schizophrenia, inflammatory responses may follow processes of sensitization and thus may react more vigorously to the presence of specific environmental factors such as physical or psychological stress, or pathogen contact. Stress and/or pathogen exposure in psychosis-prone subjects may lead to an over-activation of microglia (MG) cells, which in turn promote functional activation of astrocytes (AST). Abnormally enhanced astrocyte activity is accompanied by up-regulated ST100B expression. In addition, activated astrocytes release a set of cytokines (primarily IL-6, IL-10, and TGF-β) that stimulate the production of kynurenic acid (KYN) by facilitating the enzymatic activity of tryptophan 2,3-dioxigenase (TDO) in astrocytes. KYN blocks signaling at the NMDA receptor (NMDA-R) and α7 nicotinic acetylcholine receptor (α7nAChR). On the other hand, activated MG secrete a set of pro-inflammatory cytokines (primarily IL-1β, IL-12, and TNF-α) that stimulate the enzymatic activity of indoleamine 2,3-dioxigenase (IDO), which in turn weakens the biosynthesis of serotonin (5-HT) and promotes the production of quinolinic acid (QUIN) and 3-hydroxykynurenine (3-OH-KY). QUIN and 3-OH-KY are neurotoxic and may therefore contribute to inflammation-mediated neurotoxicity. Note that there is a mutual inhibitory effect of IDO and TDO, so that their enzymatic activities are critically determined by the prevailing cytokine milieu. Abnormal HPA axis functions may further contribute to the development of low-grade inflammation and sensitized inflammatory responses in schizophrenia. Under normal conditions, corticotropin-releasing hormone (CRH) released by the paraventricular nucleus of the hypothalamus (PVN) stimulates secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland (PG), which in turn promotes the release of cortisol (CORT) from the adrenal cortex (AC). CORT normally exerts fast feedback inhibition of HPA axis functions and suppresses pro-inflammatory activity by immune cells. These inhibitory mechanisms are disrupted in patients with schizophrenia, so that impaired neuroendocrine regulation of immune functions may further facilitate the development of abnormally enhanced pro-inflammatory responses in this disorder. Genetic variants in several immune-related genes and/or gene promoter regions (MHC, IL-1, IL-6, IL-10, and TNF) may provide a genetic source for altered immune responses in schizophrenia; and prenatal immune priming induced by in-utero exposure to infection may provide a developmental source of long-term immune abnormalities pertinent to schizophrenia.

(Anisman et al., 2002; Dantzer et al., 2008), both of which have been consistently linked to the negative symptoms of schizophrenia (Müller, 2007; Tandon et al., 2009). Furthermore, peripheral inflammation involving enhanced release of IL-6 has been associated with two other hallmark features of negative symptoms, namely deficiency in sustained attention (Holden et al., 2008) and psychomotor retardation (Brydon et al., 2008).

One of the emerging neuroimmunological mechanisms linking enhanced pro-inflammatory activity with the induction of affective, emotional and social impairment involves alterations in the central tryptophan metabolism (Müller & Schwarz, 2007). Tryptophan is an essential amino acid needed for the biosynthesis of serotonin. As discussed in detail elsewhere (Müller & Schwarz, 2007), enhanced pro-inflammatory actions in the CNS lead to increased tryptophan degradation into kynurenine by indoleamine 2,3-dioxigenase (IDO), thereby reducing the bioavailability of tryptophan for serotonin synthesis (Fig. 1). Hence, increased pro-inflammatory activities in the CNS can critically contribute to central serotonin deficiency. Besides its involvement in depressive illness (Müller & Schwarz, 2007), serotonin insufficiency has been suggested to play an important role in the pathogenesis of negative symptoms of schizophrenia (Abi-Dargham et al., 1997; Silver, 2004).

In view of the aforementioned behavioral and neuronal effects of activated inflammatory responses, one would expect a positive correlation between signs of peripheral and/or central inflammation in schizophrenia and clinical measures of negative symptoms. Several findings readily fulfill this expiation: First, there is an established association between elevated ST100B levels and persistent negative symptoms as well as poor therapeutic response in patients with schizophrenia (Rothermundt et al., 2004, 2005). Furthermore, concentrations of plasma IL-6 and IL-8 (Kim et al., 2000; Zhang et al., 2002) as well as soluble markers indicative of blood brain barrier disruption (Müller & Ackenheil, 1995) have been reported to positively correlate with the severity of negative (but not positive) symptoms. These findings have further been complemented by a study showing that serum CRP levels positively correlate with the negative (but not positive) symptoms in a subset of schizophrenic patients displaying marked increases of this inflammatory marker in the periphery (Fan et al., 2007b). However, it appears that this specific correlation cannot be generalized to a broader sample of schizophrenic patients covering a wider spectrum of peripheral CRP levels (Dickerson et al., 2007), suggesting that the specific association between high CRP levels and severe forms of negative symptoms is limited to those patients with markedly high levels of this marker.

5.2. Cognitive symptoms

The impact of activated inflammatory response systems in schizophrenia may well be extended to disease-relevant cognitive impairments. Indeed, there is a growing body of evidence highlighting a positive correlation between the severity of cognitive deficits and enhanced levels of inflammatory markers in schizophrenic patients, including IL-1β, IL-6, TNF-α, CRP, and ST100B (Dickerson et al., 2007; Pedersen et al., 2008; Liu et al., 2010). The specificity of the cognitive effects induced by inflammatory processes in schizophrenia remains to be further elucidated. However, experimental studies in animals and correlative investigations in non-schizophrenic individuals suggest that the spectrum of inflammation-mediated cognitive impairments may primarily affect domains of executive functions, sustained attention and working memory (Marsland et al., 2006; Holden et al., 2008; Cohen et al., 2011), all of which have been implicated in schizophrenia (Elevaag & Goldberg, 2000; Bowie & Harvey, 2006; Tandon et al., 2009). Molecular investigations in experimental
rodent models have also confirmed that pro-inflammatory cytokines can exert appreciable influences on various forms of synaptic plasticity, which is recognized to provide an important neuronal substrate for multiple aspects of learning and memory (Bauer et al., 2007). It is therefore feasible that altered pro-inflammatory activity may exert its cognitive effects by modulating synaptic architecture and functions (McAfoose & Baune, 2009). Indeed, pro-inflammatory cytokines have been described to exert a direct functional interaction with specific neurotransmitter systems and/or or receptors (Schneider et al., 1998; Curran & O’Connor, 2001; Balschun et al., 2004). Of particular interest in this context is the recently described interaction between the IL-1β signaling system and the N-methyl-D-aspartate (NMDA) receptor complex (Gardoni et al., 2011), the latter of which is critically involved in numerous cognitive processes (Lynch, 2004; Neill et al., 2010).

An alternative (but not mutually exclusive) neuronal mechanism by which enhanced pro-inflammatory activity could affect cognitive functions may again be related to changes in the central kynurenine pathway (Fig. 1). More specifically, imbalances in the (local) astrocyte/microglia cytokine milieu together with enhanced astrocyte functions can result in altered expression and/or activation of catalytic enzymes involved in this pathway, eventually resulting in enhanced production of kynurenic acid (KYNA) (Müller et al., 2009; Müller & Schwarz, 2010; Wonodi & Schwarz, 2010). KYNA is a potent endogenous NMDA receptor antagonist acting at the glycine site of the receptor (Wonodi and Schwarz, 2010). Impaired glutamatergic signaling at NMDA receptors has frequently been associated with schizophrenia in general (Carlsson et al., 2001; Coyle et al., 2003; Javitt, 2007), and with the emergence of disease-relevant cognitive symptoms in particular (Morgan et al., 2004; Lewis & Moghaddam, 2006; Yang & Svensson, 2008). Moreover, enhanced production of KYNA (Nilsson et al., 2005; Linderholm et al., in press) and associated changes in the central kynurenine pathway (Condray et al., 2011; Sathysaikumar et al., in press) have been consistently documented in schizophrenic patients. Experimental work in animals further shows that enhancement of KYNA disrupts a variety of schizophrenia-relevant cognitive functions in general, and on peripheral cytokine networks in particular. This issue has been thoroughly discussed elsewhere (Pollmächer et al., 2000; Drzyzga et al., 2006). For the present purpose, we would like to draw attention to the anti-inflammatory effects of APDs: A large body of evidence indicates that (long-term) treatment with APDs potently enhance anti-inflammatory activity as indexed by the augmentation of peripheral production of sIL-1RA, sIL-2R and sIL-10 (Maes et al., 1996, 1997; Müller et al., 1997b; Song et al., 2000; Cazzullo et al., 2002; Sirota et al., 2005; Sugino et al., 2009), and by the concomitant reduction of pro-inflammatory markers such as sIL-1β, sIL-6, and TNF-α (Müller et al., 1997b; Kim et al., 2009; Song et al., 2009; Sugino et al., 2009). Interestingly, it seems that the class of atypical (second-generation) APDs such as clozapine may have more pronounced effects on enhancing anti-inflammatory cytokine signaling compared to the class of typical (first-generation) APDs (reviewed in Pollmächer et al., 2000; Drzyzga et al., 2006). It has been further suggested that the relative capacity of APDs to normalize pro-inflammatory immune changes may be an important contributing factor determining the clinical efficacy of APDs in the symptomatological treatment of schizophrenia disease (Müller & Schwarz, 2008, 2010). Consistent with this hypothesis, it has been show that those schizophrenic patients who are resistant to APD-induced behavioral improvement display persistently high IL-6 levels, and that such immune abnormalities in treatment-resistant schizophrenic patients cannot be restored by APDs either (Lin et al., 1998; Zhang et al., 2005).

6. Anti-inflammatory treatment strategies

In view of the apparent involvement of inflammatory processes, the use of compounds with primary anti-inflammatory properties has received increasing attention in the pharmacotherapy of schizophrenia. Importantly, recent clinical trials of anti-inflammatory add-on therapy in schizophrenia provide promising results by showing superior beneficial treatment effects when standard APDs are co-administered with anti-inflammatory compounds, as compared with treatment outcomes using APDs alone. As summarized in Table 2, two main classes of anti-inflammatory drugs have been tested as adjutive medication in schizophrenia, namely the tetracycline antibiotic minocycline (Miyako et al., 2008; Levkovitz et al., 2010) and non-steroidal anti-inflammatory drugs (NSAIDs), including the mixed COX-1/2 inhibitor acetylsalicylic acid (Laan et al., 2010) and the selective COX-2 inhibitor celecoxib (Müller et al., 2002, 2005; Rapaport et al., 2005; Akhoundzadeh et al., 2007; Müller et al., 2010). It is also worth emphasizing that in addition to the use of primary anti-inflammatory agents, compounds with potent...
placebo-controlled clinical trial using the COX-2 inhibitor celecoxib. Potential benefits against negative/cognitive symptoms of schizophrenia have recently been discussed elsewhere (Do et al., 2009; Bitanihirwe & Woo, 2011). The rationale and biological basis of anti-oxidant therapies in schizophrenia have recently been discussed elsewhere (Do et al., 2009; Bitanihirwe & Woo, 2011).

6.3. Efficacy of anti-inflammatory treatment against negative/cognitive symptoms

The clinical data thus far available highlight that in addition to their potential beneficial influence on positive symptoms (Akhondzadeh et al., 2007; Laan et al., 2010), anti-inflammatory add-on therapies in schizophrenia are readily effective in the treatment of negative and cognitive symptoms. Indeed, in a recent double-blind, randomized, placebo-controlled study in the early-phase of schizophrenia, minocycline administration in conjunction with standard atypical APDs has been shown to significantly improve negative and cognitive symptoms (Levkovitz et al., 2010). The pro-cognitive effects of minocycline treatment were primarily seen in improvements of executive dysfunctions (Levkovitz et al., 2010). Importantly, combined minocycline and APD treatment was well tolerated and showed superior treatment effects relative to treatment outcomes using APDs alone. However, it needs to be emphasized that this clinical trial using minocycline add-on therapy did not specifically address potential beneficial effects against positive symptoms (Levkovitz et al., 2010), so that this anti-inflammatory approach still awaits further validation with regards to its specificity against distinct symptom classes of schizophrenia.

Add-on therapies using COX-2 inhibitors in schizophrenia have also provided clear evidence for a therapeutic efficiency of this anti-inflammatory agent in the treatment of schizophrenic symptoms, including negative and cognitive symptoms (Table 2). In the first clinical trial conducted in patients with acute exacerbation of schizophrenic psychosis, the COX-2 inhibitor celecoxib given in conjunction with the atypical APD risperidone has been shown to be superior to risperidone treatment alone in improving total Positive and Negative Syndrome Scale (PANSS) scores (Müller et al., 2002). Such COX-2 inhibitor add-on therapy has subsequently been reported to exert appreciable beneficial effects on cognitive symptoms (Müller et al., 2003). Even more compelling are the findings of a recent randomized, double-blind, placebo-controlled clinical trial using the COX-2 inhibitor celecoxib given in conjunction with standard atypical APD in the early-phase of schizophrenia, demonstrating that such anti-inflammatory add-on therapy has selective effects in improving negative symptoms (Müller et al., 2010). Together, these findings suggest that anti-inflammatory adjunctive therapies, at least those which use COX-2 inhibitors or the broad-spectrum antibiotic minocycline, may have potent beneficial effects on negative/cognitive symptoms of schizophrenia.

6.4. Anti-inflammatory treatment and disease progression

Recent data obtained from clinical trials using COX-2 inhibitor treatment in schizophrenia indicate that the efficacy of such anti-inflammatory pharmacotherapy to improve schizophrenic symptoms may be critically influenced by factors pertinent to the disease progression. In randomized, double-blind, placebo-controlled clinical trials using celecoxib given in conjunction with atypical APDs, superior beneficial treatment effects are obtained especially when such anti-inflammatory add-on therapy is initiated in the early-phase of schizophrenia as opposed to later chronic stages (Müller et al., 2010; Müller & Schwarz, 2010). In fact, such anti-inflammatory pharmacotherapy may exert no superior effects in the symptomatological treatment of schizophrenia when implemented in patients with a long duration of disease (Rapaport et al., 2005).

These findings raise the possibility that the nature and/or severity of activated inflammatory responses in schizophrenia may critically change as a function of disease progression, so that primary anti-inflammatory strategies may be particularly efficient when targeting those immune abnormalities that are characteristic of the early stage of schizophrenia. There is no doubt that our understanding of the precise immune signature in the early-phase of schizophrenia is far from complete. However, from the findings obtained in clinical trials of COX-2 inhibitor adjuvant therapy (Müller et al., 2010; Müller & Schwarz, 2010), one may speculate on a model in which enhanced pro-inflammatory activity may be particularly prominent in the early-phase of schizophrenic disease (Fig. 2). This impression would be compatible with the (limited amount of) data indicating that enhanced pro-inflammatory activity precedes altered anti-inflammatory activity in schizophrenia, so that the former is readily noticeable in drug-naive first-episode schizophrenic patients (O’Donnell et al., 1996; Theodoropoulou et al., 2001; Song et al., 2009; Reale et al., 2011). It is of note that patients with schizophrenia frequently report phases of stress in the proximity of or during the transition to full-
b a
Pro-inflammatory activity Anti-inflammatory activity

Fig. 2. Inflammatory responses and disease progression in schizophrenia. The figure provides a hypothetical model illustrating potential relationships between temporal changes in inflammatory responses and disease progression in schizophrenia. (a) Increased pro-inflammatory activity (represented by solid orange lines) may be particularly prominent in the early stage of schizophrenic disease, including the (initial) prodromal phase and onset of full-blown psychotic episodes. The subsequent enhancement in anti-inflammatory activity (represented by straight green lines) may provide a compensatory response to the initial pro-inflammatory stimulus and may contribute to the resolution of psychotic episodes and abnormally enhanced pro-inflammatory activity. The enhancement of anti-inflammatory activity may partly be driven by endogenous response mechanisms, and partly by the anti-inflammatory effects of antipsychotic drug treatment (not shown).

(b) Pharmacologically induced enhancement of anti-inflammatory activity by administration of primary anti-inflammatory agents during the early phase of schizophrenic disease may attenuate gradual increases in pro-inflammatory activity and progression into full-blown psychotic disease. (c) Reduced potency to mount anti-inflammatory responses (during the early phase of schizophrenic disease) may facilitate the gradual elevation of pro-inflammatory activity and may increase symptom severity and duration.

blown psychosis (Phillips et al., 2006), and exposure to physical or psychological stressors is well known to enhance the production and release of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α (Garcia-Bueno et al., 2008). Psychosocial and/or physical stress in the early-phase of schizophrenic disease may therefore readily contribute to the enhancement of pro-inflammatory activity as reported by several studies (O’Donnell et al., 1996; Theodoropoulou et al., 2001; Song et al., 2009; Reale et al., 2011). Whatever the precise source of enhanced pro-inflammatory activity, the presence of such immune imbalances in the early-phase of schizophrenia may explain as to why anti-inflammatory strategies (at least those which are based on COX-2 inhibition) may be particularly efficient in improving schizophrenic symptoms when implemented at early stages of the disease (Fig. 2).

6.5. Should anti-inflammatory agents be used for preventive reasons?

There is increasing interest in prospectively identifying psychosis-prone subjects when they are in the prodromal phase of the disorder. The (initial) prodromal phase of schizophrenia refers to a muted form of psychosis-related behavior that precedes the onset of full-blown schizophrenic disorder (Klosterkötter et al., 2001). Prodromal symptoms appear to involve numerous but relative subtle emotional, social, and cognitive abnormalities, and may further involve attenuated forms of positive symptoms (Larson et al., 2010). It has been suggested that early pharmacological treatment during the prodromal phase may prevent or delay the subsequent emergence of a full-blown psychotic episode by attenuating or even halting the progression of the underlying pathology (McGlashan, 1996; Yung & McGorry, 1996). The underlying rationale is based on the hypothesis that the longer a psychotic state is left untreated, the more severe the long-term psychopathological outcome is likely to be (Perkins et al., 2005). For this reason, chronic administration of APDs to peri-adolescent and/or adolescent subjects with prodromal symptoms has recently been introduced as preventive treatment of schizophrenia (McGlashan et al., 2003; Woods et al., 2003; McGlashan et al., 2006).

In view of the beneficial clinical effects of anti-inflammatory treatment in the early-phase of schizophrenia (Müller et al., 2010), it is interesting to ask whether administration of compounds with primary anti-inflammatory properties could exert preventive effects against the development of full-blown schizophrenic disease. An answer to this question would be far from conclusive and, as a matter of fact, would primarily be based on speculations. However, it is at least theoretically feasible that in the event of enhanced pro-inflammatory activity, early anti-inflammatory interventions in psychosis-prone subjects may indeed be coupled with favorable long-term outcomes. As described in Section 3.2, schizophrenia seems associated with reduced potency to mount anti-inflammatory and immunosuppressive responses in the CNS. Functional deficiency in anti-inflammatory/immunosuppressive homeostatic control systems in the brain may have detrimental long-term consequences on brain and behavioral functions: If initially induced, inflammatory stimuli may not be sufficiently counteracted by appropriate anti-inflammatory reactions, and this may in turn facilitate the development of persistent and presumably detrimental effects of neuroinflammation on psychopathological and neuropsychological symptoms (Fig. 2).

Recent advances in brain imaging techniques have emphasized the importance of progressive brain changes that occur during and subsequent to the onset of full-blown psychosis (Hulshoff Pol & Kahn, 2008; Wood et al., 2008). The data thus far available suggest that such progressive brain changes involve a marked loss of gray matter volume especially during the adolescent stage of life and resemble an exaggeration of gray matter reduction occurring as a result of normal adult development (Hulshoff Pol & Kahn, 2008; Wood et al., 2008). Even though the underlying molecular and cellular mechanisms remain to be identified, it has been suggested that enhanced pro-inflammatory activity in general, and microglia over-activation in particular, may play a role in precipitating such progressive brain changes in schizophrenia (van Berckel et al., 2008; Meyer et al., 2011).

Besides numerous other effects (Block et al., 2007), sustained neuroinflammation readily facilitates the enzymatic activity of IDO, and enzyme involved in the central kynurenine pathway (Müller et al., 2009; Müller & Schwarz, 2010; Wonodi & Schwarz, 2010). Enhanced IDO activity leads to elevated production of quinolinic acid (QUIN) and 3-hydroxykynurenine (3-OHKY), both of which have potent neurotoxic properties. Interestingly, a recent study by Condray et al. (2011) has confirmed enhanced levels of 3-OHKY in drug-naïve first-episode schizophrenic patients. The authors went on to show that following APD treatment, the levels of 3-OHKY predicted clinical improvement in as much as the lowest concentrations of 3-OHKY were associated with the greatest improvement in symptoms (Condray et al., 2011). In view of the neurotoxic effects of 3-OHKY, it will be highly relevant to further explore whether increased levels of 3-OHKY and other inflammation-associated factors may contribute to volumetric gray matter loss occurring during and subsequent to the onset of full-blown psychosis.
If so, early anti-inflammatory interventions may indeed hold promise for attenuating unfavorable neuropathological and psychopathological outcomes in the disease progression of schizophrenia.

7. Conclusions

A large number of serologic and genetic studies support the presence of activated peripheral and central inflammatory responses in schizophrenia. Such inflammatory processes seem to be influenced by a number of environmental and genetic predisposition factors, and they may critically depend on and contribute to the progressive nature of schizophrenia. There is also appreciable evidence to suggest that activated inflammatory processes can undermine disease-relevant affective, emotional, social, and cognitive functions, so that inflammatory processes may be particularly relevant for the precipitation of negative and cognitive symptoms of schizophrenia. Against this background, anti-inflammatory therapies in schizophrenia appear to be a promising approach to improve such dysfunctions, and the extension of anti-inflammatory therapies to the early stages of schizophrenia seems feasible.

The available neuroimnunological and clinical data leave many questions unanswered, especially with regards to the precise cellular and molecular mechanisms underlying the beneficial therapeutic effects of anti-inflammatory drugs in schizophrenia. However, these data readily provide testable hypotheses, given the fact that the cellular and molecular effects of most currently available anti-inflammatory drugs are relatively well described. Animal models of schizophrenia, particularly those which recapitulate inflammatory components of the disorder, may further help to identify the relevant neuroimmunological mechanisms pertinent to the beneficial clinical effects of anti-inflammatory therapies in schizophrenia. Given the limited efficacy of currently available APDs to ameliorate negative and cognitive symptoms, the further exploration of inflammatory mechanisms and anti-inflammatory strategies may open fruitful avenues for a better treatment of symptoms undermining affective, emotional, social and cognitive functions relevant for schizophrenic disease.

Disclosure

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