Inflammation and Immunity in Schizophrenia

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14.1 Introduction

Well-regulated inflammation is an essential protective mechanism, for example, to eliminate bacterial and viral infections; however, excessive inflammatory processes can cause harm, as in autoinflammatory diseases such as multiple sclerosis. In the central nervous system (CNS), inflammation can also be either neuroprotective or neurotoxic [1]. The outcome of inflammation depends on interactions between environmental factors and the inflammatory response; genetics; and whether the inflammation is acute or chronic [2]. For example, acute inflammation in the CNS, such as encephalitis, can be fatal within a few hours or days, but a chronic, harmful inflammatory state can also continue over months or even years, such as in multiple sclerosis. In acute CNS inflammation, macrophages and B- and T-cells from the peripheral immune system are assumed to cross the blood-brain barrier. In contrast, chronic CNS inflammation is hypothesized to be related to the activity of the CNS-based immune system. In multiple sclerosis, for example, this local immune activity in the CNS is seen as disseminated activation of microglia [3]. Researchers have referred to these differences between THE involvement of the peripheral and central immune systems as "compartmentalization" [2, 4].

The pathogenetic mechanisms of multiple sclerosis and schizophrenia may show similarities because both affect the CNS, can be chronic, and are characterized by phases of active disease interspersed with phases of remission [5]. However, the inflammatory mechanisms in these two diseases differ. For example, a general neuroinflammatory state is typical for schizophrenia [6], whereas multiple sclerosis shows focal areas of neuroinflammation [3]. This chapter will review possible inflammatory mechanisms of schizophrenia and potential immune-based treatments.

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14.2 CNS Inflammation

Various components of the immune system are involved in inflammation in the CNS, including microglia, astrocytes, cytokines, and cells of the peripheral immune system, such as monocytes, macrophages, and T- and B-lymphocytes. These different parts of the immune system can be affected by a range of factors, including not only environmental toxins and pathogens but also genetics and secondary reactions to neuronal lesions resulting from trauma.

14.2.1 Microglia

Microglia make up 15% of cells in the CNS and are the most important component of the local immune defense system. They are activated in case of neuroinflammation, for example, resulting from injury or infection in the CNS [7]. Systemic infection also activates microglia, which contribute to the synthesis of proinflammatory cytokines in the CNS that cause so-called sickness behavior and other illness-related mental states [8, 9]. Although initially produced in response to an acute signal, proinflammatory cytokines may then continue to be released for up to 10 months; this finding led to the hypothesis that microglia may be involved in chronic inflammation [7]. In schizophrenia, in addition to activated microglia some studies found higher levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines (see below). As a caveat, one must note that the subdivision of cytokines into pro- and anti-inflammatory is an oversimplification because certain cytokines can show both properties; the respective activity of such cytokines depends on several factors, including the activating signal, timing, and type of target cell [10]. However, this topic is beyond the scope of this chapter.

14.2.2 Sensitization of the Immune System and the Effects of Stress

Microglia can also be "sensitized" or "primed" by various low-level stimuli [11], including ageing-related processes [12], neurodegeneration [13], and stress [14]. After sensitization, the response of microglia to a low-level stimulus such as minor infection is exaggerated and they show greater pro-inflammatory reactivity [15], perhaps leading to an exacerbation or re-exacerbation of a CNS immune response and affecting behavior. This process of sensitization is also seen in the peripheral immune system. As with microglia, an initial immune response to a stimulus, e.g., stress, strengthens the subsequent immune response or lowers the threshold for a response upon re-exposure to the same stimulus [16]. On the basis of earlier studies, researchers hypothesized that this process is related to a memory function in the acquired immune system [14, 17]. For example, later re-exposure to a stimulus that caused an early childhood infection can result in increased cytokine release and associated neurotransmitter disturbances [18]. Furthermore, in rats stress-related

release of the cytokine interleukin-6 (IL-6) reactivated (prenatally) conditioned processes [19].

In addition to infections and trauma, stressful events can evoke a pro-inflammatory immune response [20]. Stress increases the levels of corticosterone, which activates the *N*-methyl-D-aspartate (NMDA) receptor, and this receptor activation causes microglia to proliferate [21]. The increased cytokine levels associated with this response can present as psychopathological symptoms and behavioral changes [22]. After an acute stressful event, the immune response is normally downregulated; however, studies have shown that chronic stress or repeated stressful events can lower the threshold for the physiological reactions to stress, including the immune system response or neurotransmitter changes [23]. Furthermore, the brains of aged animals were found to be in a proinflammatory state that sensitized them to peripheral infection and stress, so that they showed a greater cytokine response to these stimuli than younger animals [14]. In other animal studies, neurotransmitter responses to a cytokine, for example, tumor necrosis factor-alpha (TNF-α), were greater upon re-exposure [24, 25].

14.3 The Vulnerability-Stress-Inflammation Model of Schizophrenia

The vulnerability-stress model of schizophrenia was first proposed by Zubin and Spring over four decades ago [26]. The authors hypothesized that physical or mental stress can cause a psychotic episode. Because stress is known to be a cause of inflammation, and inflammation is known to be involved in schizophrenia, the model was further developed into the so-called vulnerability-stress-inflammation model. Evidence for the validity of this model is provided by animal studies, which show that offspring are more vulnerable to developing schizophrenia if an inflammatory response of the mother is stimulated in the second trimester or in the young offspring soon after birth [27]. Besides sensitization (see above), vulnerability to stress is also influenced by genetic factors, as proposed in the pathogen host defense hypothesis of depression [28]. Inflammatory markers and the effects of inflammation on neurotransmitter systems in schizophrenia are further elucidated.

14.3.1 Inflammatory Markers

An inflammatory process is hypothesized to be involved in the pathophysiology of at least a subgroup of patients with schizophrenia [29, 30], a theory that is supported by a range of findings. First, postmortem studies in schizophrenia have found degradation products of fibrin (a protein involved in coagulation and inflammation) in the brain [31] and cerebrospinal fluid (CSF) [32]. Furthermore, untreated patients with schizophrenia have a blunted type 1 cytokine response and an increased type 2 cytokine response [33]. Meta-analyses of studies in schizophrenia found higher levels of pro-inflammatory cytokines in the peripheral blood in patients with a first

episode of the disease and those who had relapsed [34], including the inflammation-marker C-reactive protein [35]; in contrast, levels of some anti-inflammatory cytokines were lower than in healthy controls [34]. The results of a meta-analysis of studies on cytokines in the CSF were similar [36]. When examining these findings, however, one must consider the potential effects of confounding factors such as smoking, body mass index, sex, sleep, and medication. Moreover, blood levels of cytokines may not appropriately reflect their function because several cytokines have a primarily paracrine effect. Lastly, the brain is protected from peripheral inflammation by the blood-brain barrier, and an immune activation with increased pro-inflammatory cytokines in the blood does not necessarily reflect the situation in the brain [37].

14.3.2 Inflammation and Neurotransmitters

For a long time, research on the neurobiology of schizophrenia has focused mainly on disturbances in dopaminergic neurotransmission. Studies have clearly shown that the dopamine system is altered in schizophrenia [38], but the exact relationship remains unclear and results of studies on antidopaminergic drugs have been disappointing. At least two cytokines may be involved in the changes in neurotransmitter systems seen in schizophrenia: IL-1ß, which has been shown to cause rat mesencephalic progenitor cells to be converted into a dopaminergic phenotype [39–41], and IL-6, which shortens the survival of serotonergic neurons in the fetal brain [42].

The interaction between cytokines and neurotransmitters in certain brain regions and in particular during brain development has been shown to contribute to the pathophysiology of schizophrenia. In a mouse model, Winter et al. [43] found a significant increase in the dopamine levels in fetal brains after eliciting an immune response in the pregnant dams with a viral mimetic (poly I:C). The authors suggested that the poly I:C-induced immune response caused an excess of dopamine in the midbrain, a structure that is affected in patients with schizophrenia [43]. However, chronic administration of the cytokine interferon-alpha in animals was associated with a reduction in striatal dopamine release and with anhedonia [44]. Anhedonia is a characteristic negative symptom of schizophrenia, and negative symptoms are often found in chronic schizophrenia [45]. Other authors have proposed that latent persistent infections may result in imbalanced immune reactions [46]. Thus, inflammation may have diverse effects on dopaminergic neurotransmission and may be involved in the chronification of schizophrenia.

Another key neurotransmitter in the pathophysiology of schizophrenia is glutamate, the most abundant neurotransmitter in the CNS, which is involved in cytokine-directed tryptophan/kynurenine metabolism. Kynurenic acid, one of three or more intermediate neuroactive products in the kynurenine pathway, is the only known naturally occurring NMDA receptor antagonist in the human CNS [47]. In schizophrenia, a predominant type 2 immune response is proposed to inhibit indoleamine

2,3-dioxygenase (IDO), resulting in increased kynurenic acid production; kynurenic acid acts as an antagonist at NMDA receptors, which in turn decreases glutamate neurotransmission [48, 49]. Support for this hypothesis is provided by studies that found NMDA receptor antibodies in about 10% of untreated patients with acute schizophrenia [50, 51]. Some studies found higher kynurenic acid levels in the CSF [52, 53] and brains of patients with schizophrenia [54, 55] and in animal models of schizophrenia [56], and others found no changes in levels in the peripheral blood of patients with first-episode schizophrenia [57] or in other groups of schizophrenia patients [58]. Antipsychotic medication affects kynurenine metabolites and thus may be a confounder in studies [57–59].

14.4 Infection and Schizophrenia

Studies in animal models have shown that pre- and perinatal infections increase the likelihood of schizophrenia in offspring [60, 61]. For example, after prenatal exposure to viral agents animal offspring show symptoms typical of schizophrenia, including cognitive deficits and abnormalities in the startle reflex [62, 63]. The relationship between exposure to infections and a higher risk for schizophrenia appears to hold true in humans, too, and has been shown for prenatal or childhood viral exposure [64–67], respiratory infections [68], genital or reproductive tract infections [68, 69], *Toxoplasma gondii* infection [70], and other infections [71–74]. Findings on virus antibody titers in patients with schizophrenia are inconsistent [75], although this may be because the studies did not control for potential confounders, such as medication [76]. In an earlier study, we found higher titers of antibodies to various pathogens in patients with schizophrenia than in healthy controls, a phenomenon we named the “infectious index” [77]. Another study showed that the mothers of people with schizophrenia spectrum disorders had higher second-trimester levels of the pro-inflammatory cytokine IL-8 than controls [78].

Possible mechanisms of the association between early life infection and schizophrenia are of interest because schizophrenia is a disease of late adolescence/early adulthood. Many studies in animal models have shown that early infection or immune activation influences several neurodevelopmental processes, including dopaminergic and glutamatergic neurotransmission [40, 79]. In humans, studies on some infections [80] and a cohort study of bacterial infection are examples that support this explanation [68]. Furthermore, increased levels of cytokines or CRP in childhood predict an increased risk for schizophrenia [81].

Infection in adulthood also increases the risk of developing schizophrenia. A large epidemiological register study in Denmark found a higher risk for schizophrenia and schizophrenia spectrum disorders in people hospitalized for autoimmune disorders or severe infections, particularly in patients with both diseases [82]. However, the study found no evidence that early exposure to infections, including prenatal exposure, increased the risk for schizophrenia [82, 83].

14.5 Inflammation and CNS Volume Loss

Neuroimaging studies have not shown marked inflammation-related changes in schizophrenia, although they have found CNS volume reductions in first-episode schizophrenia and progressive volume loss in the further disease course [84–87]. People with schizophrenia showed decreased brain volume, i.e., lower volumes of the right posterior cingulum and left entorhinal cortex and higher volumes of the ventricles, after prenatal exposure to higher maternal IL-8 levels (measured in assays from archived prenatal sera) [88], and volume loss in schizophrenia was found to be associated with an increased genetic risk for greater production of the immune marker IL-1β [89].

The peripheral benzodiazepine receptor is expressed on microglia and is upregulated in inflammation [90]. Positron emission tomography (PET) studies therefore used radiolabeled PK11195, a ligand for the receptor, to estimate microglial activation in the CNS and found that binding of PK11195 is higher in schizophrenia, indicating neuroinflammation [91–93]. Another PET study used DAA1106, another marker of microglial activation, to investigate the brains of people with chronic schizophrenia and found a correlation between binding of the marker and positive symptoms, as well as the duration of the disease [94].

14.6 Anti-Inflammatory Treatment in Schizophrenia

Treatment with anti-inflammatory drugs, such as celecoxib (a cyclooxygenase-2 [COX-2] inhibitor) and acetyl salicylic acid, has positive effects in schizophrenia and schizophrenia spectrum disorders [95, 96], providing support for an involvement of inflammation in the disease. In a 6-week prospective, double-blind, randomized controlled trial in patients receiving risperidone for an acute schizophrenic episode, outcome was significantly better in the add-on celecoxib group ($n = 25$) than in the add-on placebo group ($n = 25$) [97]. Cognition also improved significantly more in the celecoxib group [98]. A pooled analysis ($n = 90$) of the data from this and another 6-week study of celecoxib add-on to risperidone found that the duration of illness influenced the effects of celecoxib; i.e., the drug was beneficial in patients with a duration of illness <2 years but not superior to placebo in case of a longer illness duration [99] (see Fig. 14.1).

Other studies also provided support for the hypothesis that duration of illness is an important factor in the efficacy of anti-inflammatory treatment in schizophrenia. In a 6-week study of celecoxib add-on treatment in patients with first-manifestation schizophrenia being treated with amisulpride, the Positive and Negative Syndrome Scale (PANSS) positive, negative, total, and general psychopathology scores improved more in the celecoxib add-on group than in the placebo add-on group [102]. However, an 8-week double-blind study comparing celecoxib and placebo augmentation in continuously ill outpatients with schizophrenia receiving stable antipsychotic treatment found no benefit of celecoxib [103]. In addition,

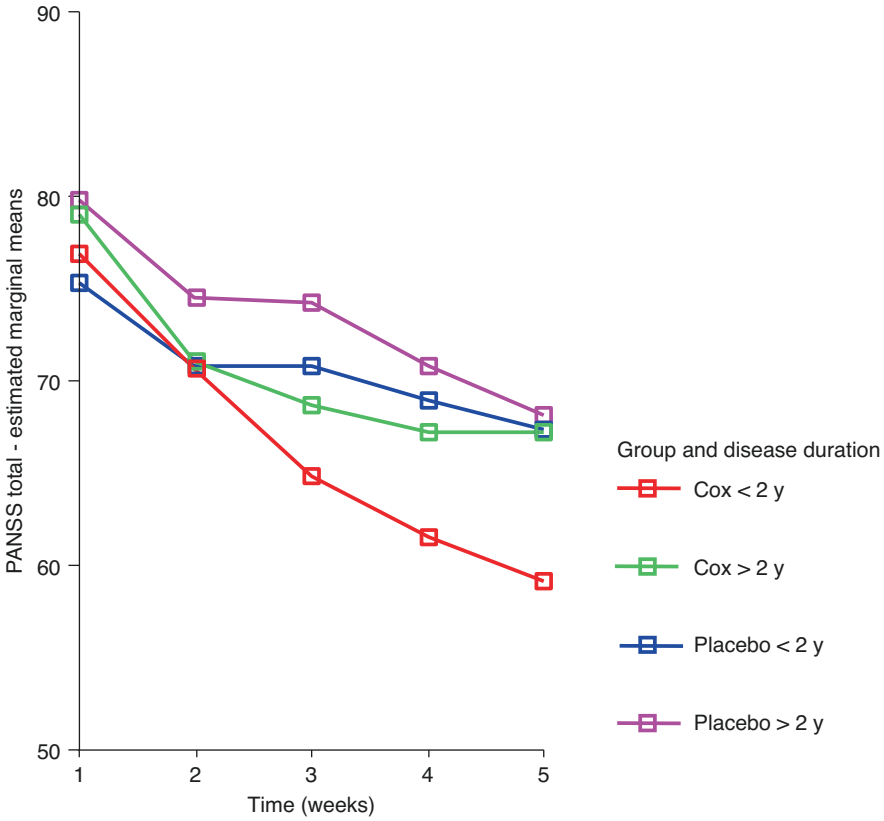

Fig. 14.1 Comparison of disease duration on the effects of celecoxib add-on therapy to risperidone. Patients with a disease duration <2 years and celecoxib treatment had a better outcome than patients with a disease duration >2 years and placebo and both groups of patients with a disease duration of more than 2 years (results not statistically significant). Reprinted from [100] by permission of Oxford University Press and [101] Copyright © 2017 Karger Publishers, Basel, Switzerland. *Cox* celecoxib, *PANSS* Positive and negative syndrome scale

a meta-analysis of eight studies (six of celecoxib and two of acetylsalicylic acid) found significant effects in first-episode but not chronic schizophrenia [104].

A possible explanation for the importance of the duration of illness for the efficacy of anti-inflammatory agents may be neuroprogression (Müller 2017). We know from studies of first- and second-generation antipsychotics that the efficacy of these treatments is worse in chronic schizophrenia than in acute schizophrenia. However, so far anti-inflammatory treatment in schizophrenia has been studied for a maximum of 8 weeks (see above). Furthermore, short-term anti-inflammatory treatment also has poor efficacy in chronic inflammatory diseases. Therefore, longer studies are needed to evaluate anti-inflammatory treatment in chronic schizophrenia [105].

Studies are also needed to investigate potential predictors of treatment response to anti-inflammatory treatment. Earlier studies found that a higher amount of inflammation is associated with worse response to antipsychotics [106–109]. The question remains open whether higher levels of inflammation predict a better outcome to anti-inflammatory treatment, as was shown for anti-TNF treatment and celecoxib in major depression [28, 110]. So far, no immune-related predictive markers for anti-inflammatory treatment have been identified.

14.7 Other Potential Inflammation-Related Treatments in Schizophrenia

As mentioned earlier, microglia play a role in CNS inflammation, and CNS inflammation is hypothesized to be involved in schizophrenia. Thus, studies have examined whether agents that can cross the blood-brain barrier and inhibit microglia activation may be useful in schizophrenia. One such drug is the antibiotic minocycline. Minocycline was studied in animal models of schizophrenia, where it was shown to have positive effects on cognition [111]. In a double-blind, placebo-controlled study, add-on minocycline improved negative symptoms of schizophrenia [112, 113]. In addition, case reports described positive effects on the overall symptom spectrum [114].

Studies have also found some positive effects of other anti-inflammatory substances, such as acetylcysteine and omega-3 fatty acids [115] and interferon-gamma, a cytokine that stimulates the monocytic type 1 immune response [116]. Interferon-gamma may not be a viable treatment option, though, because it can have adverse effects on the immune system and is thus probably a "double-edged sword" in psychiatric diseases, as it is in cancer [117].

Monoclonal antibodies to pro-inflammatory cytokines have also been proposed as a potential treatment for schizophrenia, and treatment appears to be feasible and potentially efficacious, warranting further research [118].

14.8 Conclusion

In the context of research on the immune system and inflammation, it is important to note that drug treatment, smoking, stress levels, sleep patterns, etc., can affect results. Nevertheless, research appears to support a role of immunological and inflammatory processes in the pathogenesis of schizophrenia. Data have been obtained from a range of approaches, including studies on the role of proinflammatory cytokines in the disease; the effects of cytokines on tryptophan/kynurenine metabolism and glutamatergic neurotransmission; the binding of markers of inflammation in imaging studies; genetics; and the effects of anti-inflammatory drugs. Further research is required, particularly into a potential association of inflammation with volume loss in the CNS and the importance of the duration of illness for treatment outcome. However, findings so far, in particular on the positive effects of anti-inflammatory treatment in schizophrenia, are encouraging.

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Conflict of Interest None to declare.

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