Immunology of Schizophrenia

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Abstract
Increased proinflammatory markers like cytokines have been described in the blood and cerebrospinal fluid of patients suffering from schizophrenia. Animal models have shown that a hit in early life to the immune system might trigger a lifelong increased immune reactivity. Many epidemiological and clinical studies show the role of various infectious agents as risk factors for schizophrenia with overlap to other psychoses. The first large-scale epidemiological study in psychiatry from Denmark clearly demonstrates severe infections and autoimmune disorders during lifetime to be risk factors for schizophrenia. Genetic studies have shown the strongest signal for schizophrenia on chromosome 6p22.1, in a region related to the major histocompatibility complex and other immune functions. The vulnerability-stress-inflammation model is important as stress may increase proinflammatory cytokines and even contribute to a lasting proinflammatory state. The immune system itself is considered an important further piece in the puzzle, as in autoimmune disorders in general, which are always linked to three factors: genes, the environment and the immune system. Alterations of dopaminergic, serotonergic, noradrenergic and glutamatergic neurotransmission have been shown with low-level neuroinflammation and may directly be involved in the generation of schizophrenic symptoms. Loss of central nervous system volume and microglial activation has been demonstrated in schizophrenia in neuroimaging studies, which supports the assumption of a low-level neuroinflammatory process. Further support comes from the therapeutic benefit of anti-inflammatory medications in specific studies and the anti-inflammatory and immunomodulatory intrinsic effects of antipsychotics.

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Introduction

We humans are constantly being assaulted by infectious agents, noxious chemicals and physical trauma. Fortunately, we have evolved a complex process – the inflammatory response – to help fight and clear infection, remove damaging chemicals and repair damaged tissue [1]. The mechanisms underlying inflammation are of major interest because, as noted by Hunter in 1794 [100], 'when inflammation cannot accomplish that salutary purpose, it does mischief'. The harmful effects of inflammation can be observed in many infectious or autoinflammatory diseases. The interactions between environmental factors and genetically encoded components of the inflammatory response determine whether the result will be health or disease.

As in other sites of the body, inflammation in the central nervous system (CNS) has a dual role: it may be neuroprotective or neurotoxic [2]. While acute inflammation in the CNS (e.g. acute encephalitis) leads to life-threatening states within hours or days, chronic inflammation in the CNS might be associated with impairment over months, years or a lifetime.

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As an example, multiple sclerosis (MS) is an inflammatory disease of the CNS that shows a relapsing-remitting course and, in a certain percentage of patients, also a chronic, progressive course. Parallels between MS and schizophrenia – both often show a chronic course – have repeatedly been highlighted as arguments for similar pathogenetic mechanisms in these disorders [3].

The concept of 'smoldering inflammation' has been postulated for MS. It implies that CNS inflammation drives the disease process in both the chronic and acute stages [4]. While there is a close interaction between the peripheral immune system and the CNS during acute inflammation, with invasion of macrophages, B and T cells into the latter, in chronic processes the immune response is thought to be increasingly secluded from the peripheral immune system ('compartmentalization' of the inflammatory process) [5, 6]. Chronic MS, for example, is primarily characterized by disseminated activation of microglial cells.

There are numerous descriptions of an association between chronic inflammation of the CNS and schizophrenia [7]. For example, symptoms of schizophrenia have been described in the encephalitic form of MS [8], in viral CNS infection with herpes simplex virus types 1 [9] and 2 [10], and measles [11], and also in autoimmune processes such as poststreptococcal disorders [12–15], lupus erythematodes and scleroderma [16–19].

Inflammatory Mechanisms in the CNS

Inflammation in the CNS is mediated by proinflammatory cytokines, microglial cells (resident macrophages in the brain), astrocytes and invading immune cells such as monocytes, macrophages and T or B lymphocytes. Although a well-regulated inflammatory process is essential for tissue homeostasis and proper function, an excessive inflammatory response can be the source of additional injury to host cells. Uncontrolled inflammation may be the result of either infectious agents (e.g. bacteria, viruses) or a secondary reaction to neuronal lesions from trauma, a genetic effect or environmental toxins.

Microglia as an Important Cellular Basis of Inflammation in the CNS
Microglia comprise approximately 15% of the total CNS cells and are the primary component of the intrinsic immune system in the CNS, where they provide the first line of defense after injury or disease and are the principal component of neuroinflammation.

Microglia can be activated in different ways. One example is when a systemic inflammatory challenge triggers microglia activation, resulting in the release of proinflammatory cytokines in the CNS, which can mediate 'sickness behavior' [20] and other mental states. Microglia play a role in the synthesis of these central cytokines [18]. Cytokine release can be sustained in the absence of the triggering signal for a period of about 10 months, and thus contribute to a chronic inflammatory state. Alternatively, microglia are 'sensitized' or 'primed' [21] by different stimuli, including neurodegeneration [22], ageing [23] and stress [24]. This process of sensitization or priming results in the elicitation of an exaggerated immune response to a low stimulus. After priming, a second stimulus, e.g. low systemic inflammation or stress, may lead to microglia proliferation and increased production of proinflammatory cytokines by microglia [25]. This exaggerated cytokine response may result in acute changes in behavior by exacerbating or re-exacerbating an inflammatory pathology in the CNS.

Kindling and Sensitization of the Immune Response: Basis for the Stress-Induced Inflammatory Response in Psychiatric Disorders
The immune response and the release of cytokines can become more sensitized for activating stimuli by a kindling process: the initial immune response, i.e. the release of cytokines and other mediators of immune activation, is initiated as a result of exposure to a certain stimulus; thereafter, re-exposure to the same stimulus, e.g. stress or infection, is associated with an increased release of cytokines or a weaker stimulus is necessary for the same activation process. This 'sensitization' or 'kindling' may be due to the memory function of the acquired immune system [24, 26]. Stress-associated release of interleukin (IL)-6 was shown to reactivate (prenatal) conditioned processes [27]. In healthy individuals, a second stimulus (e.g. systemic inflammation, stress) led to immune activation associated with cellular proliferation, and increased production and release of proinflammatory cytokines [25]. This is a key mechanism for triggering an immune activation and inflammation, e.g. the stress-induced immune activation leading to psychopathological symptoms. A sensitization process in the immune system is in accordance with the view that after an infection during early childhood, re-infection or another stimulation of the immune system in later stages of life might be associated with a boosted release of sensitized cytokines resulting in neurotransmitter disturbances.

Sensitization phenomena play a role in stress-related, cytokine-induced, neurotransmitter-mediated behavioral abnormalities, i.e. the cytokine response to a stimulus increases while the intensity of the stimulus decreases [24]. In animal experiments, however, cytokines promote greater neurotransmitter responses when the animals are re-exposed to the cytokine [28], for example TNF-α [29]. In the CNS, the stress-induced activation and proliferation of microglia may mediate these cytokine effects [30].

The Vulnerability-Stress-Inflammation Model of Schizophrenia

The vulnerability-stress model of psychiatric disorders, first postulated for schizophrenia more than 30 years ago [31], focuses on the role of physical and mental stress in triggering a psychotic episode. In schizophrenia an increased vulnerability of the offspring was shown – in addition to genetic vulnerability – if an inflammatory response was induced in the mother during the second trimester of pregnancy or in the offspring during later stages of CNS development.

The underlying mechanisms of the co-occurrence of stress and inflammation were studied in animal experiments and stress was repeatedly shown to be associated with an increase in proinflammatory cytokines [24]. The genetic risk contribution in the context of pathogen-host-defense is evident [32].

The specific influence of the inflammatory mechanisms described in schizophrenia on neurotransmitter systems will be discussed below. Moreover, the modulation of glutamatergic neurotransmission will be highlighted – glutamate is the most abundant neurotransmitter in the CNS and is differentially involved via cytokine-directed tryptophan/kynurenine metabolism in schizophrenia, presumably but not exclusively mediated by N-methyl-D-asparate (NMDA) receptors. Beside others, genetic factors of the kynurenine metabolites play a role [33].

Inflammatory Markers in Schizophrenia

Signs of inflammatory degradation products have been described in schizophrenic brain tissue [34] – but not in control tissue – and in the cerebrospinal fluid (CSF) of about 50% of schizophrenic patients [35]. Regarding the cytokine pattern in schizophrenia, a blunted type 1 and (compensatory) increased type 2 cytokine pattern has been repeatedly observed in unmedicated schizophrenic patients [36]. Overviews on the imbalance of the type 1 and type 2, and the pro- and anti-inflammatory immune systems, as well as the innate immunity, including the monocytic system, in schizophrenia have recently been published, revealing that an inflammatory process plays an important role in the pathophysiology of at least a subgroup of schizophrenic patients [37, 38].

The Impact of Inflammation on Neurotransmitters in Schizophrenia

Over the last 5 decades, research on the neurobiology of schizophrenia has focused overwhelmingly on disturbances of dopaminergic neurotransmission [39]. There is no doubt that a dysfunction of the dopamine system is involved in the pathogenesis of schizophrenia, although the mechanism is not clear and antipsychotic antidopaminergic drugs still show unsatisfactory therapeutic effects.

IL-1β, which can induce the conversion of rat mesencephalic progenitor cells into a dopaminergic phenotype [40–42], and IL-6, which is highly effective in decreasing the survival of fetal brain serotonergic neurons [43], seem to have an important influence on the development of the neurotransmitter systems involved in schizophrenia, although the specificity of these cytokines is a matter for discussion. Maternal immune stimulation during pregnancy was shown to increase the number of mesencephalic dopaminergic neurons in the fetal brain; the increase was probably associated with a dopaminergic excess in the midbrain [44]. Persistent pathogens might be key factors that drive imbalances of the immune reaction [19]. Nevertheless, many questions about immunity and immune pathology in virus infections remain unanswered [45].

Much evidence seems to indicate that a lack of glutamatergic neurotransmission, mediated via NMDA antagonism, is a key mechanism in the pathophysiology of schizophrenia [46]. The only NMDA receptor antagonist known to occur naturally in the human CNS is kynurenic acid [47]. Kynurenic acid is one of at least three neuroactive intermediate products of the kynurenine pathway. A predominant type 2 immune response inhibits the enzyme indoleamine 2,3-dioxygenase, resulting in an increased production of kynurenic acid in schizophrenia and in NMDA receptor antagonism [46, 48]. The recent findings of NMDA receptor antibodies in about 10% of acute diseased schizophrenia patients (unmedicated) is especially interesting in this regard [49, 50].

Regarding the kynurenic acid in schizophrenia, however, discrepancies in the findings have to be discussed. Elevated kynurenic acid has mainly been described in the

CSF [51, 52] and brains of schizophrenic patients [53, 54], or in animal models of schizophrenia [55]. In the peripheral blood of first-episode schizophrenia [56] and other samples of schizophrenic patients, no increased kynurenic acid levels were observed [57]. Antipsychotic medication, however, influences kynurenine metabolites and has to be regarded as an interfering variable [56–58].

The Possible Role of Infection in Schizophrenia

Animal models of schizophrenia show that stimulation of the maternal immune system by viral agents leads to typical symptoms in the offspring [59, 60]. Evidence for pre- or perinatal exposure to infections as a risk factor for schizophrenia has not only been obtained from animal models [61, 62], studies in humans have also been performed on several viruses [63–65]. Increased risk for schizophrenia in the offspring was also observed after respiratory infections [66, 67] or genital or reproductive tract infections [67, 68]. Infection of mothers with *Toxoplasma gondii* was also described to be a risk factor [69].

Infections before birth increase the risk for later schizophrenia [70–73] as well as infections – in particular CNS infections – during later stages of brain development. Nevertheless, antibody titers against viruses have been examined in the sera of schizophrenic patients for many years [74]. The results, however, have been inconsistent, for example because interfering factors were not controlled for. Antibody levels are associated with the medication state, a finding which partly explains earlier controversial results [75]. In one of our own studies, higher titers of different pathogens were found in schizophrenic patients than in controls, a phenomenon that we called the 'infectious index' [76].

Prenatal immune activation – infection-triggered or not – is an important risk factor for schizophrenia [60]. In humans, increased maternal levels of the proinflammatory cytokine IL-8 during pregnancy were shown to be associated with an increased risk for schizophrenia in the offspring, regardless of the reason for the increase in IL-8 [77]. Moreover, increased maternal IL-8 levels in pregnancy were also significantly related to decreased brain volume in the schizophrenic offspring, i.e. lower volumes of the right posterior cingulum and the left entorhinal cortex, and higher volumes of the ventricles [78].

However, a recent study, the first large-scale epidemiological study in psychiatry, showed that severe infections and autoimmune disorders during lifetime in-crease additively the risk of schizophrenia and schizophrenia spectrum disorders [79], whereas infections of the parents, including intrauterine infections, in this large-scale scenario were not confirmed as definite risk factors [79, 80]. As the study sensitivity was evaluated as being not very high despite its large scale, only the 'tip of an iceberg' of risk factors may have been clearly identified [80].

CNS Volume Loss in Imaging Studies – A Consequence of an Inflammatory Process?

Gross inflammatory changes have not been found in neuroimaging or neuropathological studies of schizophrenia. However, there is no doubt that a decreased CNS volume can already be observed during the first episode and a progressive loss in CNS volume occurs during the further course of the disease [81–84]. Moreover, a relationship has been described between the volume loss and an increased genetic risk for a higher production of the immune marker IL-1β [85], whilst the relationship between maternal IL-8 levels and CNS volume has been mentioned before [78].

The PK11195 ligand is used in positron emission tomography, PET, to estimate microglial activation [86]. In schizophrenia, the increased expression of PK11195 was shown to be a marker of an inflammatory process in the CNS [87, 88]. Moreover, a positive correlation between schizophrenic-positive symptoms and expression of the PET-activation marker DAA1106, and of duration of disease and expression of the microglial activation marker DAA1106 was observed as well [89].

Cyclo-Oxygenase-2 Inhibition as an Anti-Inflammatory Therapeutic Approach in Schizophrenia

Modern anti-inflammatory agents have been explored in schizophrenia. The cyclo-oxygenase-2 (COX-2) inhibitor celecoxib was studied in a prospective, randomized, double-blind study of acute exacerbation of schizophrenia. There was a statistically significant better outcome in the patients receiving celecoxib. The clinical effects of COX-2 inhibition in schizophrenia were especially pronounced in cognition [90]. The efficacy of therapy with a COX-2 inhibitor seems most pronounced in the first years of the schizophrenic disease process [91, 92]. A recent study also demonstrated a beneficial effect of acetyl-

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salicylic acid in schizophrenic spectrum disorders [93]. A meta-analysis of the clinical effects of nonsteroidal anti-inflammatory drugs in schizophrenia revealed significant effects on schizophrenic total, positive and negative symptoms [94], while another meta-analysis found a significant benefit only in schizophrenic patients with a short duration of disease or in first manifestation schizophrenia [95].

Regarding the role of microglia activation in inflammation, minocycline, an inhibitor of microglia activation, is an interesting substance for the treatment of schizophrenia. The improvement of cognition by minocycline has been described in animal models of schizophrenia [96], as well as in two double-blind, placebo-controlled add-on therapy trials in schizophrenia [97, 98]. In clinical studies, positive effects on schizophrenic-negative symptoms were noted as well [98]. Case reports have documented positive effects of minocycline on the whole symptom spectrum in schizophrenia [99].

Conclusion

The possible influence of an immunological process for the pathogenesis of schizophrenia resulting in inflammation has long been neglected. Increasing evidence for a role of proinflammatory cytokines in schizophrenia, the strong influence of pro- and anti-inflammatory cytokines on the tryptophan/kynurenine metabolism and, related to that mechanism, the influence of cytokines on the glutamatergic neurotransmission, the results of imaging studies, genetic findings and, last but not least, the therapeutic effect of anti-inflammatory drugs support the view that psychoneuroimmunology and inflammation have rightly come more into the focus of schizophrenia research. On the other hand, it has to be regarded that immunological research is susceptible to artefacts, interfering variables such as medication, smoking, stress, sleep and others play an important role and cannot always be controlled. This can be shown with the example of stress, which, according to the 'vulnerability-stress model', is not only a condition sine qua non in schizophrenia, but is also a confounding factor for research of the immune system and inflammatory processes. Similarly for neuroimaging studies, volume loss might be the result of different pathological processes and factors other than inflammatory causes may play a role. Nevertheless, the results of these studies are encouraging and further studies should focus on the relationship between inflammatory markers in the blood, CSF and volume loss of the CNS. Moreover, the influence of different stages in schizophrenia might have been neglected, too. It is discussed that schizophrenia is a syndrome with different underlying pathological processes. Inflammation, however, also includes different stages and processes ranging from an acute to a chronic inflammation, including an autoimmune process.

These considerations show that a lot of further research is necessary to clarify the role of the immune system in schizophrenia. However, recent results, including therapeutic progress, encourage further emphasis in this fascinating field.

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