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REVIEW

INFLAMMATION IN SCHIZOPHRENIA

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Abstract

Schizophrenia is a chronic and debilitating mental disorder that affects approximately 1% of the world population. Inflammation is a complex response of a living body to pathological agent. This normal response plays the role to eliminate the pathogens by starting the immune response. The pro-inflammatory cytokines are divided into predominantly pro-inflammatory and predominantly anti-inflammatory types. Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are secreted by monocytes and macrophages and activate other cellular components of the inflammatory response. Anti-inflammatory cytokines with properties, such as interleukin-4 (IL-4), help to down-regulate the inflammatory immune response.

Key words: schizophrenia, inflammation, cytokines, treatment, antipsychotics.

Résumé

L'inflammation dans la schizophrénie

La schizophrénie est une maladie mentale chronique et débilitante qui touche environ 1% de la population mondiale. L'inflammation est une réponse complexe d'un organisme vivant à un agent pathologique. Cette réponse normale joue le rôle d'éliminer les agents pathogènes en commençant la réponse immunitaire. Les cytokines pro-inflammatoires sont divisées en prédominantes pro-inflammatoires et principalement anti-inflammatoires. Les cytokines pro-inflammatoires, telles que l'interleukine-6 (IL-6) et le facteur de nécrose tumorale alpha (TNF-a), sont sécrétées par des monocytes et des macrophages et activent d'autres composants cellulaires de la réponse inflammatoire. Les cytokines anti-inflammatoires, telles que l'interleukine-4 (IL-4), contribuent à la réduction de la réponse immunitaire inflammatoire.

Mots clés: schizophrénie, inflammation, cytokines, traitement, antipsychotiques.

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Introduction

Schizophrenia is a chronic and debilitating mental disorder that affects approximately 1% of the world population. Inflammation is a complex response of a living body to pathological agent[1]. This normal response plays the role to eliminate the pathogens by starting the immune response. The pro-inflammatory cytokines are divided into predominantly pro-inflammatory and predominantly anti-inflammatory types[2]. Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are secreted by monocytes and macrophages and activate other cellular components of the inflammatory response. Anti-inflammatory cytokines, such as interleukin-4 (IL-4), help to down-regulate the inflammatory immune response.

Schizophrenia-like symptoms have been described in the encephalitic form of MS (multiple sclerosis)[3], in viral CNS infection with herpes simplex virus type 1[4], HSV-2[5], and measles[6]. In the same time, psychotic symptoms were found also in autoimmune processes such as lupus erythematosus, and scleroderma[7].

Cytokines

The most known hypothesis postulates that chronically activated macrophages produce cytokines, such as interleukin-1 (IL-1), interleukin-2 (IL-2), tumor necrosis factors, interferon-alpha and interferon-gamma[8]. Cytokines IL-1β and IL-β have a strong implication in neurotransmitter systems which are involved in schizophrenia. In an experimental model, IL-16 induced a dopaminergic phenotype in rat mesencephalic progenitor cells[9]. The specificity is not clear and it is possible that IL-1 and IL-6, released from monocytes indicated only an immune activation status. The changes in IL-10 levels in patients treated with antipsychotics were significantly correlated with the improvements in symptoms.

Cytokines level is affected in women by the use of oral contraceptives, menopausal status, and hormone replacement therapy[10].

There are reports regarding differences between Afro-Americans and Hispanics, who might have higher levels of inflammatory markers than the whites[11]. Another factor is the socioeconomic status (SES) frequently associated with inflammatory state and many patients with schizophrenia have lower SES[12].

The impact of sex on cytokine levels was examined. In a previous study, the results show raised level of cytokines in female patients with schizophrenia[13]. The same author reported that pro-inflammatory cytokines and body mass index (BMI) were higher in female patients compared to male patients and controls.

These findings led to the idea that visceral fat and altered adipocyte function could mechanistically explain elevated levels of pro-inflammatory cytokines in schizophrenia[14].

Infection

Infections during the prenatal or perinatal period are a risk factor for schizophrenia[15]. Respiratory infections, genital infections, and reproductive tract infections[16] have been linked to increased risk for schizophrenia in offspring. More recently, infection with the protozoan *Toxoplasma gondii* in pregnant women has been studied as a potential risk factor for schizophrenia and bipolar disorder[17]. Raised or disrupted dopamine levels have been reported in both rodent and human *T. gondii* infection and within human patients with schizophrenia, obsessive compulsive disorder (OCD) and bipolar disorder. The stimulation of the maternal immune system in animal models of schizophrenia during pregnancy by viral or bacterial agents leads to schizophrenia-like symptoms in the offspring[18,19].

In humans studies, the risk factors for schizophrenia have been found in several viral disorders[20-22], such as respiratory infections[23,24] and genital infections[25].

Antibody titers against viruses have been examined in schizophrenia patients, but the results have been inconsistent due to interfering factors. In one study, higher titers of different pathogens were found in schizophrenia patients than in the controls, a phenomenon called by authors as „infectious index"[26].

Another study showed that increased maternal levels of the proinflammatory cytokine interleukin-8 (IL-8) during pregnancy were associated with an increased risk of schizophrenia in the offspring. This phenomenon was independent by the cause of inflammation[21]. Increased maternal IL-8 levels in pregnancy were also significantly related to decreased brain volume. The most important studies show lower volumes of the right posterior cingulum and left entorhinal cortex and higher volumes of the ventricles in the schizophrenic offspring[27].

Neurotransmitters and inflammation in schizophrenia

Research on the neurobiology of schizophrenia has focused mainly on dopaminergic neurotransmission in the last five decades[28]. Despite the fact that the dysfunction of the dopamine system plays an important role in the pathogenesis of schizophrenia,

antipsychotic drugs targeting D2 receptors still show unsatisfactory therapeutic effects. Winter and colleagues showed that maternal immune stimulation during pregnancy increased the number of mesencephalic dopaminergic neurons in the fetal brain[29]. These authors concluded that the increase was caused by the dopaminergic excess in the midbrain. One of the recent studies found NMDA receptor antibodies in about 10% of acute schizophrenia patients[30].

With focus on this topic was the role of kynurenic acid in schizophrenia[31], because high level of kynurenic acid has been described in the CSF of the brains of patients with schizophrenia[32]. On the other hand, increased kynurenic acid levels were not observed in the peripheral blood of first-episode schizophrenia patients or other groups of schizophrenia patients[33]. The studies were inconclusive, because antipsychotic medication influences kynurenine metabolites and has to be regarded as an interfering variable[34].

Evidence in schizophrenia

Despite the lack of RCTs (randomized clinical trials), we found a meta-analysis of 40 studies investigating cytokines in schizophrenia. The authors of this meta-analysis reported that cytokines with proinflammatory effect were significantly elevated in patients with schizophrenia. This meta-analysis is important, because it differentiated between drug-naive first-episode psychosis, acute exacerbation and patients with TRS (treatment resistant schizophrenia). The levels of IL-6, IFN-γ, and TNF-α were higher in patients with a first-episode and acute relapse. The group treated with antipsychotics showed significant lower levels of IL-6, I1-1β, and IFN-γ, and higher level of IL12 and soluble IL-2 receptor. The results were not clear and the authors did not conclude if the effect was a consequence of antipsychotic treatment, chronicity, or both[35].

A study from Denmark investigated the relationship between inflammation and schizophrenia, in a nationwide study. The results indicated an association between schizophrenia and rare conditions, such as Guillain-Barré syndrome, multiple sclerosis, autoimmune hepatitis, biliary cirrhosis, and pernicious anemia. The authors reported also a lower incidence than expected of schizophrenia among patients with autoimmune diseases such as ankylosing spondylitis, rheumatoid arthritis, autoimmune thyroiditis and rheumatic polymyalgia. The interfering factors[36] must be considered and include:

- weight gain,
- body mass index,
- smoking,
- age,
- age of onset,
- duration of disease,
- severity of the disorder,
- symptoms,
- cancer.

Genetics

A recent review of genetics in schizophrenia reported consistent results about the genome-wide association of schizophrenia with major histocompatibility complex locus located on chromosome 6p21.3 (MHC) or human leukocyte antigen (HLA) system[37]. Significant MHC single-nucleotide polymorphisms were associated with major psychiatric diseases, such as schizophrenia and bipolar disorder[38]. Immune-mediated brain anomalies seem to be transmitted to subsequent generations[39].

Potential benefit of anti-inflammatory treatment

The inflammatory theory in schizophrenia leads to adjunctive therapy trials, especially with non-steroid anti-inflammatory drugs (NSAIDs) that directly targets COX-2 (cyclooxygenase-2) inhibitors for potential benefit. There is a study with risperidone (a second generation antipsychotic) and celecoxib (COX-2 inhibitor) in patients with acute exacerbations of schizophrenia[40]. The 2-arms double blind randomized study showed a better outcome of patients treated with risperidone-celecoxib combination than those treated with risperidone monotherapy[40]. Moreover, on cognitive scales, the patients treated with COX-2 inhibitor obtained higher scores[41]. In another study, the results were significant only for patients with the onset of schizophrenia less than 2 years, confirming another study that did not find a benefit of COX-2 inhibition in chronic schizophrenia. In another add-on study, celecoxib was used with amisulpride, a SGA (second generation antipsychotic), in first-episode schizophrenia. The results were encouraging for the Positive and Negative Syndrome Scale (PANSS) total score, but also on the positive symptoms, negative symptoms, and general psychopathology scores[42,43].

One of the most used NSAIDs agents is acetylsalicylic acid (aspirin), a mixed COX-l/COX-2 inhibitor. Added to antipsychotics, it showed to have a beneficial effect, especially in the early stages of schizophrenia[44].

Minocycline, an antibiotic and inhibitor of microglia activation, was studied as a potential treatment of schizophrenia. In animal model, treatment with minocycline has improved cognition[45], as well as in two double-blind, placebo-controlled add-on clinical trials in schizophrenia[46,47]. Moreover, the authors

reported effects on both positive and negative symptoms.

Acetylcysteine (ACC) and other substances, including omega-3 fatty acids with anti-inflammatory effects, also provide some benefit to schizophrenia patients[48].

A study with cytokine interferon gamma (IFN-γ), which stimulates the monocytic type 1 immune response, reported encouraging (but preliminary) results in schizophrenia[49]. In all these studies, the researchers reported immune side effects.

The limitations of the anti-inflammatory add-on studies are the short time of administration, in most cases a few weeks. It is well-known that schizophrenia becoming chronic has a negative impact on treatment response and outcome and the response to treatment is better at the first or second episodes. Further studies with longer anti-inflammatory treatment might show different effects in chronic schizophrenia[50].

Conclusion

There is growing evidence underlying the role of the inflammatory process in the pathogenesis of schizophrenia. In the last decade, several studies proposed treatment with anti-inflammatory agents as an adjunctive therapy in schizophrenia, based on inflammatory theory. The association between schizophrenia and inflammation lacks specificity, mainly due to similar correlations reported in major depression and bipolar disorder. COX-2 inhibitors show beneficial effects in the early stages of schizophrenia. Further research is necessary in order to clarify whether an immune-related therapy is beneficial in schizophrenia and a possible pipeline for drugs with antipsychotic properties.

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