Antipsychotics Modulates Cytokines in FEP-patients

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Cytokines have a major impact on the neurotransmitter networks that are involved in schizophrenia pathophysiology. First Episode Psychosis (FEP) patients exhibit abnormalities in cytokines levels prior to the start of treatment. Previous studies showed that antipsychotic treatment modulates cytokines levels.

Keywords: schizophrenia ; cytokines ; first episode psychosis ; immune activation ; psychiatry

1. Introduction

Immune system dysfunction is a well-established factor in schizophrenia pathogenesis. Influenza, infection with Toxoplasma gondii, and Herpes Simplex Virus Type-2 during pregnancy are known risk factors that contribute to later development of schizophrenia in the offspring [1][2][3]. Animal and human studies confirmed that lymphocyte T cells transmigrating to the central nervous system (CNS) are responsible for cytokines release, neurogenesis modulation, and cognitive deficits, as well as altered behavior [4][5]. The lymphocyte T helper cells (Th cells), also known as CD4+ cells, are a type of T cells that have an important function in the immune system, mainly through the release of cytokines. Cytokines and their receptors are a group of regulatory proteins with critical impact on processes related to immunomodulation and inflammation, which influences the central nervous system (CNS) [6]. Proinflammatory cytokines-interleukin 2 (IL-2), IL-12, interferon (IFN)-γ and tumor necrosis factor (TNF)-α take part in the immune response type 1—cellular immunity for which Th1 cells are responsible [6]. On the other hand, proinflammatory IL-6 and anti-inflammatory IL-4, IL-10, and IL-13 take part in humoral immunity (immune response type 2) modulated by Th2 cells [6]. Additionally, a third subtype of CD4+ T cells is distinguished-Th17. It produces a proinflammatory IL-17 cytokine [6]. Studies showed that it plays an important role in neuroinflammation and exhibits neurotoxic properties [7]. Additionally, another process in which IL-1β, IL-6, and TNF-α are released in CNS is microglia activation. It contributes to apoptosis, inhibition of neurogenesis, and white matter abnormalities in the brain of patients with onset and relapse stages of schizophrenia [8][9][10].

It was proved that cytokines have a major impact on neurotransmitter networks that are involved in schizophrenia pathophysiology. IL-6 decreases the survival rate of serotoninergic neurons in the brain of rat's fetus [11]. Potter et al. showed that IL-1β induces rat mesencephalic progenitor cells to convert into a dopaminergic phenotype [12]. A relationship between chronic administration of IFN-α and decreased release of dopamine, resulting in anhedonia, was observed in animals' striatum [13]. It was also shown that cytokines influence tryptophan metabolism in the kynurenine pathway [14]. Proinflammatory cytokines, such as IL-6, IFN-γ, TNF-α, IL-1β, IL-2, and IL-18 are known inductors of indoleamine 2,3-dioxygenase (IDO)-1 expression. This enzyme takes part in tryptophan transformation into kynurenine, which is converted in astrocytes into a N-methyl-D-aspartate (NMDA) receptor antagonist-kynurenic acid (KYNA). NMDA hypofunction is also involved schizophrenia pathophysiology [14]. Elevated KYNA levels and increased IDO activity were observed in schizophrenia subjects.

Abnormalities in cytokine levels are present in patients diagnosed with schizophrenia, their first-degree relatives and first episode psychosis (FEP) individuals [15][16]. There are several operational definitions of FEP, which might be misleading and cause inconsistencies in conducted studies. It may be discussed in three categories: as first treatment contact, by duration of psychosis, or duration of antipsychotic treatment [17]. For the scope of this review we assumed that FEP is a distinct episode of psychotic symptoms with early onset that has occurred for the first time in an antipsychotic-naïve subject.

A meta-analysis carried out by Miller et al. showed that in comparison with healthy controls (HC) FEP subjects exhibited elevated levels of the following markers: IL-1β, IL-6, IL-12, IFN-γ, TNF-α, transforming growth factor (TGF)-β and the soluble interleukin-2 receptor (sIL-2R). No differences in IL-2 concentrations were observed [16]. Increased levels of IL-6, IFN-γ, TNF-α, and TGF-β were also noted in acute relapsed schizophrenia inpatients (AR). AR patients exhibited higher concentrations of IL-8 and IL-1RA and lower of IL-10 [16]. Results of a meta-analysis performed by Goldsmith et al. largely confirmed the findings of Miller et al. [18]. Both studies showed that FEP patients have higher levels of IL-1β, IL-6, IL-12,

IFN-γ, TNF-α, TGF-β, sIL-2R, and no difference in concentration of IL-2 in comparison with HC [16][18]. Additionally, the Goldsmith et al. study showed that FEP subjects exhibit elevated levels of the interleukin-1 receptor antagonist (IL-1RA) and IL-10, lowered IL-4 and no difference in IL-17 and IL-18 in comparison with control groups. Differences in cytokine levels were similar in AR patients' group, whereas only IL-10 levels were lower when compared to the control group, which is similar to Miller et al. [16][18]. A recent meta-analysis performed on 59 studies, comprising of 3002 FEP subjects confirmed increased levels of IL-6 and TNF-α when compared to HC. What is more, the authors failed to establish any relationship between higher levels of these proinflammatory cytokines and mean age, sex, diagnosis, BMI, tobacco/cannabis/other substance use or abuse, exclusion of medical comorbidity, or exclusion of anti-inflammatory treatment [19]. These findings further imply a relation between IL-6, TNFα and psychosis occurrence.

As studies discussed above show, FEP patients exhibit abnormalities in cytokines levels prior to the start of treatment. Feigenson et al. suggested that it may constitute a biochemical endophenotype in certain schizophrenia populations [20]. The importance of immune dysfunctions as a clinical marker was confirmed by the OPTiMiSE study—a largescale trial of antipsychotic response in FEP subjects [21]. Researchers identified a subtype of FEP individuals who exhibited the most severe symptoms and were at the highest risk of being non-responders when treated with amisulpride. Prior to antipsychotic treatment this subgroup had elevated serum levels of several pro-inflammatory cytokines and inflammation-associated biomarkers when compared to other patients [21].

Meta-analyses of studies, evaluating the influence of antipsychotic drugs on cytokines and their receptors, show antipsychotic treatment-induced changes in levels of inflammation markers. However, the scope of affected biomarkers, and their influence on pathogenesis and the clinical state of schizophrenia, are still a subject of research [16][18][22][23]. Evaluating the impact of antipsychotic treatment on inflammation markers in FEP individuals is of particularly high value, as it enables us to exclude the influence of a chronic psychotic process, as well as prolonged antipsychotic treatment and its side effects. Capuzzi et al. and Romeo et al. presented meta-analyses of studies measuring levels of cytokines prior to, and after, antipsychotic treatment in the specific population of FEP subjects. These analyses were conducted on a relatively low number of studies—7 [22] and 8 [24]. Their results were not fully convergent. Both Capuzzi et al. and Romeo et al. showed a significant impact of antipsychotic treatment on the decrease in pro-inflammatory cytokines IL-1β and IL-6. There was no effect on concentrations of TNF-α, IFN-γ. Results of these meta-analyses vary with regard to impact on IL-2, IL-4, and IL-17 [22][24]. The aim of this review and meta-analysis is to synthetize up-to-date findings and further investigate the influence of antipsychotics on the cytokine levels in FEP individuals. This meta-analysis was conducted in accordance with the PRISMA 2020 guidelines [25].

2. the Influence of Antipsychotics on Cytokines Levels in First Episode Psychosis

Our results demonstrate that, in FEP patients, antipsychotic treatment is related to decreased concentration of pro-inflammatory IL-1β, IL-6, IFN-γ, and TNF-α and anti-inflammatory IL-4, IL-10 cytokines. On the other hand, levels of pro-inflammatory IL-2 and IL-17 remain unaffected. The exclusion of studies including subjects with history of prior treatment with antipsychotic medications had no significant impact on IL-1β, IL-6, and IFN-γ results, while rendering decreased TNF-α levels statistically insignificant. We also showed that baseline levels of IL-1β, IL-4 and TNF-α in FEP subjects were considerably higher in comparison to HC. After treatment, the levels of these cytokines were similar to those in HC. However, IL-6 and IFN-γ concentrations in FEP subjects were notably higher than in HC both before and after antipsychotics administration. Despite a decrease in the concentration of these pro-inflammatory cytokines, their levels remained elevated. The results that we obtained confirm earlier reports indicating elevated concentrations of IL-1β, IL-6, IFN-γ, and TNF-α in FEP subjects [16][18][19]. Significantly elevated levels of macrophage-derived cytokines IL-1β, IL-6, and TNF-α, as well as the Th1-derived cytokine IFN-γ support the macrophage-T-lymphocyte theory of schizophrenia pathophysiology.

Meta-analyses, evaluating the influence of antipsychotic treatment, on levels of cytokines, and their receptors, in subjects diagnosed with schizophrenia confirm anti-inflammatory effects of neuroleptic drugs to a varying degree. In Miller et al., meta-analysis the impact of neuroleptics was assessed based on 40 studies involving FEP and AR patients, and it showed an increase in sIL-2R and IL-12 and a decrease in IL-1β, IL-6, and TGF-β. Antipsychotic treatment had no effect on IFN-γ and TNF-α. These cytokines, along with sIL-2R, were described as "trait markers" which stems from the fact that they were elevated both before and after treatment [16]. On the other hand, IL-1β, IL-6, and TGF-β were identified as state markers, because their concentration significantly lowered after antipsychotic treatment [16]. The Toujrman et al. meta-analysis indicated increased levels of IL-12 and sIL-2R and a decrease in IL-1β and IFN-γ. No change in concentration of other measured markers (IL-2, IL-4, IL-6, IL-10, IL-1RA, sIL-6R, TGF-β, TNF-α) was observed [23]. Goldsmith et al. showed that antipsychotic treatment leads to a decrease in IL-1β, IL-6, IL-4, an increase in sIL-2R, IL-12, and no influence

on IFN-γ, TNF-α, IL-2, as well as TGF-β [18]. The Romeo et al. meta-analysis, consisting of 47 studies, 7 of which involved FEP subjects, showed that antipsychotic treatment decreases pro-inflammatory IL-1β and IFN-γ and increases anti-inflammatory sTNF-R2 and sIL-2R. Additionally, a decreasing tendency in IL-6, TNF-α, and IL-4 was reported [22]. The results of aforementioned meta-analyses are not consistent, although all of them indicate a decrease in IL-1β and an increase in sIL-2R, which is coherent with the suggested anti-inflammatory impact of antipsychotic drugs. Studies involving FEP subjects partially confirm these results. A meta-analysis of 7 FEP studies showed that after antipsychotic treatment, IL-1β, IL-6, IL-4 (but not IFN-γ and TNF-α) diminished, which is in contrast to observations from AR studies [22]. Results obtained by Capuzzi et al. are to some extent coherent with prior meta-analyses. After 4 weeks of antipsychotic treatment a decrease in concentration of IL-1β, IL-6 and IL-2 was observed. These 3 interleukines were described as state markers. Similarly, Romeo et al. observed no difference in concentration of TNF-α i IFN-γ in FEP patients [16][18][22]. These markers along with IL-17 were identified as trait markers [22].

In all mentioned meta-analyses, a decrease in IL-1β was reported after antipsychotic treatment. When considering FEP subjects only, both Romeo et al. and Capuzzi et al. observed a significant impact of neuroleptic treatment on decrease in IL-1β and IL-6 levels and no impact on TNF-α and IFN-γ concentrations [22][24].

When compared with meta-analyses of studies involving FEP individuals, and the results we obtained are consistent with Capuzzi et al. and Romeo et al. (decrease in IL-1β and IL-6 levels), with Romeo et al. (decrease in IL-4) and with Capuzzi et al. regarding no impact on IL-17 [22][24]. On the other hand, our results were different on changes of TNF-α and IFN-γ levels. We concluded that after treatment levels of these markers were significantly lower, while both Capuzzi et al., and Romero et al. didn't observe notable changes in their concentrations. Comparing outcomes of our study with meta-analyses, involving the general population of schizophrenic subjects, our results are consistent when it comes to decrease in IL-1β [16][18][22][23]], IL-6 [16][18][22], IL-4 [18][22], TNF-α and IFN-γ [22], and no difference in IL-2 [18][23]. Our study is the only one which indicates a decrease in anti-inflammatory IL-10 in FEP patients after antipsychotic treatment.

The main difference from previous meta-analyses on the same topic in FEP subjects is the number of studies included (12 vs. 8 and 7 respectively). Inclusion of new studies enabled us to facilitate new comparisons for cytokines' levels. We decided for our inclusion criteria to be less strict than those applied by Capuzzi et al. [24]. The analyzed studies included mostly, but not only, drug-naïve subjects. As stated in the sensitivity analysis, elimination of previously medicated patients only influenced the significance of TNF-α decrease without effects on the results of IL-1β, IL-6, and IFN-γ. Furthermore, some of the studies involved FEP patients both in the course of schizophrenia as well as in a wide spectrum of psychotic disorders. It is notable that assessing whether a FEP patient is schizophrenic or not may be subject to diagnostic error. We decided to include them, as these disorders can have similar genetic and psychopathological backgrounds [26]. Although providing significant implications for further research, our decisions on liberal criteria resulted in high heterogeneity scores.

Overall, our results indicate a major anti-inflammatory effect of antipsychotic treatment due to decreased concentrations of proinflammatory IL-1β, IL-6, IFN-γ, and TNF-α. We also established a significant decrease in anti-inflammatory cytokines IL-4 and IL-10. It may be a consequence of general amelioration of inflammatory activity. Lower levels of anti-inflammatory markers stemming from antipsychotic treatment may also be a result of its side effects. Tek et al. observed that all antipsychotic drugs, apart from ziprasidone, caused increased body weight in FEP subjects [27]. Moreover, metabolic syndrome and obesity are related to increased pro-inflammatory and decreased anti-inflammatory cytokines' levels, including IL-4 and IL-10 [28][29]. Russel et al. suggest that patients who have higher levels of inflammation in the early stages of schizophrenia may be at greater risk of developing short-term metabolic abnormalities, dyslipidemia in particular [30]. Our results, as well as previous studies, indicate elevated concentration of pro-inflammatory cytokines IL-1β, IL-6, IFN-γ, and TNF-α in FEP subjects [16][18][19]. Independently of proven anti-inflammatory effects, treatment with several antipsychotic drugs including olanzapine, quetiapine and clozapine is also associated with adverse cardio-metabolic side effects, including weight gain, dyslipidemia, and increased risk of diabetes [31]. These metabolic effects of antipsychotic drugs are associated with increased peripheral inflammation, with elevated levels of IL-6, and macrophage infiltration into adipose tissue [31].

Anti-inflammatory effects of antipsychotic drugs may be explained in two ways. Firstly, as a direct drug action exhibited on the immunological system through a decrease in pro-inflammatory/increase in anti-inflammatory cytokines' levels or an inhibition of microglial activation [32]. Secondly, this effect can occur indirectly, through amelioration of acute psychological stress. This could lead to decrease in pro-inflammatory factors such as IL-6, IL-1β, and TNF-α [33]. Occurrence of a psychotic episode may act as a major stress factor and contribute to increase in inflammatory markers which subsequently normalize while symptoms ease as a result of administered antipsychotic drugs [22]. Karanikas et al. discovered higher levels of both pro-inflammatory (TNF-α, IL-2, IL-12, IFN-γ) and anti-inflammatory (IL-10) cytokines in

the FEP group compared with the Ultra High Risk for psychosis (UHR) matched controls group [34]. It indicates an increased mobilization of both the pro- and anti-inflammatory cytokine networks when positive symptoms intensify, reaching psychosis threshold [35]. In the Borovcanin et al. study, IL-6 levels in FEP patients were found to be significantly higher than in AR subjects. It was explained by duration of illness and possible habituation to psychotic symptoms in individuals that were ill for a longer period. Researchers suggested that psychotic symptoms exacerbation may be a lesser stress factor for AR than FEP patients [36]. These results confirm that cytokines' abnormalities could be a stress-related marker and positive symptoms a potential stressor that activates inflammation.

Kato et al. suggested that antipsychotics may have neurotrophic, neuroprotective, and therapeutic effects on patients with schizophrenia by reducing microglial inflammation and oxidative stress and cellular reactions that follow [32]. Microglia are known to have various receptors of neurotransmitters, including dopamine D2/3 receptors. Through their inhibition, antipsychotics may directly affect microglia activity [32]. This effect may also be caused indirectly. The blockade of D2 receptors increases the turnover of dopamine in the acute and subacute phase, which is associated with the formation of cytotoxic free radicals and oxidative damage [31]. Dopamine signaling regulates some aspects of microglial function in response to immune stimulation with lipopolysaccharide [37]. The microglial hypothesis assumes an elevation in proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, which is consistent with our results at baseline in FEP subjects. Kato et al. showed that risperidone significantly inhibits IFN-γ induced microglial activation in vitro [38]. MacDowell et al. confirmed the risperidone effect on microglial function by demonstrating that acute exposure attenuates the inflammatory response induced by systemic administration of lipopolysaccharide in rats [39]. IFN-γ induced microglial activation can also be inhibited by aripiprazole through the suppression of intracellular Ca^{2+} concentrations' increase in microglia [10]. The Ca^{2+} signaling dysfunction was proposed as a central unifying molecular pathology in schizophrenia [32]. The inhibitory effects of antipsychotics on microglial activation could be caused by modulation of the intracellular cascades, such as mitogen-activated protein kinase (MAPK), protein kinase C (PKC) pathways, and also calcium signaling and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) cascades [32].

Researches showed that the impact of antipsychotic drugs on particular cytokines is substantially related to the therapeutic effect and clinical state in schizophrenia. Romero et al. also confirmed a correlation between differences of IL-6 levels, and positive schizophrenia symptoms' scores, after antipsychotic treatment [22]. Simsek et al. demonstrated that the concentration of anti-inflammatory interleukin IL-4 and IL-10 was inversely correlated with the intensity of negative symptoms in first schizophrenic episode [35]. The influence of IL-10 levels on increase in negative symptoms was also confirmed by Noto et al. [40]. They demonstrated an inverse correlation between decrease in IL-10, after risperidone treatment, and PANSS negative score, which suggests that IL-10 may be protective against negative symptoms. It was proposed earlier that IL-10 has neuroprotective effects. Arimoto et al. showed that IL-10 protects dopaminergic neurons in the substantia nigra against inflammation-mediated degeneration [41]. Pathophysiology of inflammatory responses may be of crucial importance in the development and treatment of negative and cognitive symptoms. Goldsmith et al.'s findings suggest that the deficit schizophrenia subtype is associated with increased inflammation. TNF-α and IL-6 were associated with the deficit syndrome, and TNF-α predicted blunted affect, alogia, and total negative symptoms in schizophrenia patients [42]. Goldsmith et al. also reported that TNF-α and IL-6 may predict development of negative symptoms (TNF-α irrespective of baseline depressive symptoms) in individuals at clinically high-risk of psychosis [43]. Moreover, chronic peripheral inflammation may be associated with cognitive impairment in schizophrenia. The Multicentric FACE-SZ Dataset demonstrated that abnormal CRP levels in schizophrenic individuals were associated with a decline in cognitive functions, such as working and semantic memory, learning abilities, mental flexibility, visual attention, and speed of processing [44].

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