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Antipsychotics can modulate the cytokine profile in schizophrenia: Attenuation of the type-2 inflammatory response

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ABSTRACT

Objective: We recently reported that the type-2 cytokine response is increased in schizophrenia. The aim of this study was to analyse the effects of antipsychotic drugs on the serum levels of type-1 (TNF-α, IFN-γ), type-2 (IL-4, IL-10), type-17 (IL-17) and regulatory cytokines (TGF-β, IL-27 and IL-6).
Methods: Cytokine measurements in the patients were performed on day 0 and day 30 of the treatment using standard ELISA assays. Three groups of subjects were studied: patients that were unmedicated with First Episode Psychosis (FEP; n = 88), patients that were treated with antipsychotics with Schizophrenia in relapse (SC in relapse; n = 45) and healthy controls (n = 36).
Results: TGF-β levels were increased in both patient groups and were further enhanced after treatment in the FEP group ($p = 0.014$) but not in the SC relapse group. Antipsychotic treatment was correlated with lower levels of IL-4, IL-6 and IL-27 ($p < 0.005$) in the FEP group. Finally, the serum levels of IL-17 were not significantly altered between the two measurements but were significantly lower in the FEP group ($p < 0.001$) when compared with healthy controls. After therapy, patients with SC who were in relapse had decreased serum levels of IL-4 ($p = 0.006$) and IL-6 ($p = 0.007$). We also observed a weak negative correlation between the IFN-γ/TGF-β ratio and the total PANSS score and between the IL-17/TGF-β ratio and the negative and general psychopathology subscales.
Conclusion: The increased type-2 cytokine serum levels in schizophrenia appear to be downregulated by antipsychotic treatment.

1. Introduction

Schizophrenia is most likely a heterogeneous disorder when clinical symptoms, course, treatment response and etiology are considered (Carpenter, 2011). Immunological studies in schizophrenia have shown variable results (Yolken and Torrey, 1995; Müller et al., 2000b; Cazzullo et al., 2003). Immune alterations in schizophrenia had been demonstrated before antipsychotics were introduced into clinical practice (Yolken and Torrey, 1995).

The first antipsychotic drug used to treat schizophrenia was chlorpromazine. Interestingly, chlorpromazine was tested as an antihistamine in subjects with schizophrenia and its antipsychotic effects were discovered incidentally (Shen, 1999). All currently available antipsychotic drugs decrease dopaminergic neurotransmission (Freedman, 2003). Atypical antipsychotics, similar to typical antipsychotics, are D2 dopamine-receptor antagonists but are less tightly bound to the D2 receptor. Therefore, D2-receptor antagonism is not the sole mechanism of therapeutic action (Yilmaz et al., 2012).

Some recent reports have suggested that atypical antipsychotics could produce neurotrophic, neurogenetic, or neuroprotective effects (Monji et al., 2009) when cultured brain cells were used as a model (Kato et al., 2008; Zheng et al., 2008). It has been suggested that the relative capacity of antipsychotics to normalise pro-inflammatory immune changes may be an important factor that contributes to clinical efficacy in the treatment of psychotic symptoms (Meyer, 2011). Previous studies have presented dissimilar or conflicting results regarding the effects that atypical antipsychotic may have on cytokine levels (Zhang et al., 2005; Reale et al., 2011).

After the administration of typical antipsychotics, the serum levels of IL-6 and IL-6R were reported to be decreased (Maes et al., 1995; Müller et al., 1997). Additionally, chlorpromazine reduces the secretion of IL-1β and IL-2 in mixed cultures of rat glial and microglial cells (Labuzek et al., 2005). Haloperidol increases the serum levels of the IL-1R antagonist and decreases secretion of IFN-γ and IL-4 in humans (Leykin et al., 1997; Song et al., 2000).

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