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Antipsychotics' effects on blood levels of cytokines in schizophrenia: A meta-analysis

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ABSTRACT

Objectives: Evidence-based medicine suggests that schizophrenia is associated with an inflammatory syndrome, but the extent to which this syndrome is normalized by antipsychotic treatment has yet to be determined.
Methods: A systematic quantitative review of the effects of antipsychotics on peripheral cytokine levels in schizophrenia was performed, using follow-up studies providing in vivo cytokine assessments before and after treatment.
Results: We retrieved 23 studies (total of 762 subjects) which showed that antipsychotic treatment significantly increases plasma levels of soluble interleukin-2 receptor and reduces the plasma levels of interleukin-1β and interferon-γ.
Conclusions: These results show that antipsychotics produce anti-inflammatory effects in schizophrenia.

1. Introduction

The incidence rates of schizophrenia are on the order of 12 to 15 per 100,000 person-years (McGrath et al., 2008). This mental disorder is associated with poor outcome, and significant and persistent impairment (Newman et al., 2012). Schizophrenia is a heterogeneous disorder and its etiology remains incompletely elucidated. Among possible causes, immunological factors have been increasingly implicated in its pathogenesis and course (Benros et al., 2012). The inflammatory system may trigger or modulate the course of schizophrenia through complex mechanisms influencing neuroplasticity and neurotransmission (Benros et al., 2012). Alterations in cytokine levels in schizophrenia have been repeatedly described (Potvin et al., 2008; Miller et al., 2011). The effect of antipsychotics on cytokine levels remains, as yet, incompletely explored. A few groups have recently published reviews which concluded that antipsychotics have anti-inflammatory effects in schizophrenia that may be related to antipsychotic response, and in some cases, pro-inflammatory effects that may be related to important side effects, such as weight gain (Drzyzga et al., 2006; Tourjman et al., 2012). In order to further clarify the extent of these effects, we conducted a meta-analysis of antipsychotic-induced cytokine changes in schizophrenia.

2. Methods

2.1. Selection procedures

2.1.1. Search strategies

A systematic search was performed in the electronic databases PubMed and EMBASE using the keywords "antipsychotic" and "inflammation" or "cytokine" or "interleukin" or "inflammatory markers" or "IFN" or "TGF" or "TNF". This search identified studies before January 1st, 2013. Additionally, studies were identified by cross-referencing.

2.1.2. Selection criteria

Studies were included if they met the following criteria: (a) had involved subjects with DSM/ICD schizophrenia-spectrum disorder; (b) had employed a pre–post design which involved the administration of antipsychotics (typical, atypical, mixed); and (c) had measured in vivo the level of at least one cytokine before and after the treatment

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in plasma or serum. When several articles dealt with the same population, we selected the article with the largest sample. Studies were excluded if: 1) the study design was cross-sectional; 2) the sample of patients comprised patients with DSM Axis-I disorders other than schizophrenia-spectrum disorders; 3) cytokine levels were measured using cerebrospinal fluid; and 4) cytokine levels were measured using supernatants of leucocytes stimulated in vitro, which vary widely in the conditions of in vitro incubation. We excluded from the meta-analysis outcome measures reported in less than 2 studies.

2.1.3. Recorded variables

The variables for each article included in the meta-analysis were: sample sizes, year of publication, gender (proportion of females), participants' mean age, follow-up length, duration of illness, antipsychotic type, and type of cytokine assessed. To achieve a high standard of reporting, we have adopted 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines (Moher et al., 2009).

2.2. Statistical analysis

Data were entered into an electronic database and analyzed with a quantitative meta-analytical approach using Comprehensive Meta-Analysis software version 2 (Biostat, Inc., Englewood, NJ, USA). CMA software employs the same computational algorithms used by the Cochrane collaborators to weight studies by the inverse variance method (Borenstein et al., 2005). The primary effect size measure was the difference in plasmatic cytokines after antipsychotic treatment (follow-up vs baseline). The effect size was estimated by calculating Hedges' unbiased g, with negative values reflecting decreased levels of plasmatic cytokines at follow-up as compared to baseline. Hedges' g is obtained with the difference between the means of the baseline and follow-up groups, divided by the SD and weighted for sample size, in order to correct for bias from small sample sizes (Hedges and Holkin, 1985).

To determine whether categorical factors modified the cytokine changes, subgroup analyses were performed (Paulson and Bazemore, 2010). The influence of continuous moderator variables was tested using meta-regression analyses. To limit risk of false positive (type I) errors arising from multiple comparisons we adjusted $p<0.05$ by dividing α with the number of meta-regressions. Heterogeneity among study point estimates was assessed with the Q statistics (Paulson and Bazemore, 2010) with magnitude of heterogeneity being evaluated with the I^2 index (Lipsey and Wilson, 2000). As the database was characterized by high heterogeneity, we employed random effect models which are more conservative than fixed-effect models, and appear to better address heterogeneity between studies and study populations (Cooper et al., 2009). The possibility of publication bias in the present study was examined by applying the regression intercept of Egger (Egger et al., 1997). In case of publication bias, we adopted the 'trim and fill' method, which aims to both identify and correct for funnel, plot asymmetry arising from publication bias (Duval and Tweedie, 2000). To assess the robustness of the results, we performed sensitivity analyses by sequentially removing each study and rerunning the analysis.

3. Results

3.1. Database

This literature search uncovered 71 potential articles. After initial assessment, 48 articles were excluded for the following reasons: in vitro studies, add-on treatment with drugs other than antipsychotics supposed to affect the immune system, incomplete data or non-parametric statistics, and the measure of other immune markers. The final database included 23 studies for a total of 762 subjects (mean age ± SD: 35 ± 6.8 years; mean % of female: 45; n = 21 studies) (Akiyama, 1999; Baptista et al., 2007; Crespo-Facorro et al., 2008; Hinze-Selch et al., 2000; Hori et al., 2007; Igue et al., 2011; Kim et al., 2000, 2001, 2004, 2009; Lin et al., 2011; Maes et al., 1995, 1997, 2000, 2002; Monteleone et al., 1997; Müller et al., 1997; Pae et al., 2006; Pollmächer et al., 1995; Sarandol et al., 2007; Sirota et al., 2005; Song et al., 2009; Zhang et al., 2009). The follow-up assessment of the cytokine levels was performed on average after 8 weeks. The PRISMA flow chart for inclusion in the meta-analysis and the details of the retrieved studies are described in Supplementary Fig. 1 and Supplementary Table 1.

3.2. Heterogeneity

The overall database was characterized for moderate level of between-studies heterogeneity ($Q = 47.679$, $I^2 = 53.9\%$, $p < 0.001$) which justified the use of random effect models in the analysis.

3.3. Publication bias

The visual inspection of funnel plot did not reveal any clear asymmetry, and Egger's regression test ($p = 0.65$) indicated no publication bias.

3.4. Antipsychotic effects on cytokine levels

3.4.1. Antipsychotic effects on specific cytokines

Antipsychotic treatment increased the plasmatic levels of IL-12 and sIL-2R and reduced the plasmatic levels of IL-1β and IFN-γ (Fig. 1A, B). No effects were observed on IL-2, IL-4, IL-6, IL-10, IL-1RA, sIL-6R, TGF-β1 and TNF-α (Fig. 1A, B). In the case of cytokines measured in less than 2 studies, preliminary evidence suggests that antipsychotic treatment increased the plasmatic levels of soluble TNF receptors (sTNF-R) and reduced plasmatic levels of IL-13. No clear evidence of antipsychotic effect on IL-8 has been reported.

3.5. Sensitivity analysis

Sensitivity analysis confirmed that the results were robust as no study affected the meta-analytic estimate by more than 6%.

3.6. Moderators

Meta-regression analysis revealed that treatment duration had no effect on the meta-analytical estimates ($\beta = -0.005$; CI95%: -0.028 to 0.016; $p = 0.595$). There was a significant effect for publication year on meta-analytical estimates ($\beta = -0.018$; CI95%: -0.033 to -0.004; $p = 0.012$), with older studies estimating larger effect sizes than the most recent ones. Publication year was able to explain a very little part of the observed heterogeneity ($Q = 6.32$; $p = 0.012$). Gender and age revealed no significant effect ($\beta = -0.001$; CI95%: -0.005 to 0.003; $p = 0.604$; $\beta = 0.001$; CI95%: -0.011 to 0.013; $p = 0.876$; respectively; $n = 21$ studies).

4. Discussion

This meta-analysis confirms that antipsychotic treatment increases peripheral sIL-2R levels in schizophrenia, as previously observed by others (Drzyzga et al., 2006; Miller et al., 2011). Despite significant heterogeneity across studies, the data cumulated here also demonstrates in a quantitative manner that antipsychotic treatment leads to decreases in IL-1β and IFN-γ levels in schizophrenia-spectrum disorders, and possibly to increases in IL-12. Although treatment with clozapine seems to be associated with increased IL-6 levels (Maes et al., 1997), this pro-inflammatory cytokine is generally unaffected by antipsychotic treatment. Also unchanged are IL-2, IL-4, IL-10, IL-1RA, sIL-6R, TGF-β1 and TNF-α.

Most of the observations are consistent with an anti-inflammatory effect. Activated T-cells shed sIL-2R, and the presence of this receptor competes with its membrane counterpart, thus attenuating the activity of IL-2. Hence, the presence of sIL-2R is a reliable indicator of