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Soluble interleukin-2 receptor levels correlated with positive symptoms during quetiapine treatment in schizophrenia-spectrum disorders

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ABSTRACT

Background: Some but not all antipsychotics have been shown to modulate plasma cytokine levels in schizophrenia patients. Thus far, the most consistent finding has been the increase in plasma levels of soluble interleukin (IL)-2 receptor (sIL-2R) associated with clozapine treatment. Quetiapine is a second-generation antipsychotic with a pharmacological profile similar to that of clozapine, but its immunomodulatory effects have not been investigated in schizophrenia yet. The purpose of this exploratory study was to examine the changes in plasma levels of sIL-2R in schizophrenia during quetiapine treatment and association with psychopathology.

Methods: Participants were 29 schizophrenia-spectrum disorder patients (DSM-IV criteria), and 28 healthy controls. Patients had a comorbid substance use disorder (cannabis>alcohol>cocaine), since quetiapine is increasingly used in this population of dual diagnosis. No participant suffered from infection or overt inflammatory diseases. On baseline, patients taking mostly second-generation antipsychotics were switched to quetiapine for a 12-week open-label trial. Five patients were drop-outs. Mean dose of quetiapine for trial completers ($n=24$) was 466.6 mg ± 227.3. Psychiatric variables were evaluated with the Positive and Negative Syndrome Scale and the Calgary Depression Scale for Schizophrenia. Plasma sIL-2R levels were assessed at baseline, weeks 6 and 12 in patients, and in healthy controls, using sandwich immunoassay. Plasma IL-6 and IL-1 receptor antagonist (IL-1RA) were measured for comparison purposes.

Results: On baseline, plasma sIL-2R, IL-6 and IL-1RA levels were higher in dual-diagnosis patients, compared to controls. Plasma sIL-2R further increased after quetiapine treatment ($p=0.037$), while plasma IL-6 and IL-1RA did not change. Clinical improvements were observed in positive, negative and depressive symptoms, and substance abuse severity (all $p<0.01$). Interestingly, changes in sIL-2R levels during treatment were inversely correlated with changes in positive symptoms ($r=-0.524$; $p=0.009$). That is, increases in sIL-2R levels were associated with reductions in positive symptoms.

Conclusion: These data show that quetiapine elevates, like clozapine, sIL-2R levels in schizophrenia. Furthermore, the results suggest that sIL-2R alterations in schizophrenia rely on complex interplays between antipsychotics and the positive symptoms of the disorder. Future randomized controlled trials involving larger samples of schizophrenia patients are warranted to determine whether changes in plasma sIL-2R are quetiapine-related.

1. Introduction

In a recent meta-analysis, we showed that schizophrenia is associated with an inflammatory syndrome, as illustrated by elevated circulating levels of three cytokines: interleukin (IL)-6 (IL-6), IL-1 receptor antagonist (IL-1RA) and soluble IL-2 receptor (sIL-2R) (Potvin et al., 2008a). Such cytokine alterations could be related to: (i) the physiopathology or etiology of schizophrenia; (ii) phenotypic

Abbreviations: ANOVA, analyses of variance; DD, dual diagnosis; ELISA, enzyme-linked immunosorbent assay; IL-1RA, IL-1 receptor antagonist; sIL-2R, soluble IL-2 receptor; PANSS, positive and negative syndrome scale; SUDs, substance use disorders.

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traits yet to be characterized; (iii) uncontrolled confounding factors (e.g. stress, smoking, or weight gain); and/or (iv) psychiatric medication (Hinze-Selch and Pollmächer, 2001; Potvin et al., 2008a). Some sub-analyses did substantiate the importance of antipsychotics (Potvin et al., 2008a). Indeed, the increase in circulating sIL-2R levels was only true for schizophrenia patients treated with antipsychotics. Apart from cross-sectional studies, prospective pharmacological trials also examined the effects of antipsychotics on plasma/serum cytokine levels in schizophrenia. So far, the most consistent finding has been the increase in sIL-2R associated with clozapine treatment, a finding that has been replicated with olanzapine and risperidone treatment (Drzyzga et al., 2006; Kluge et al., 2009; Maes et al., 1994). Clozapine was repeatedly shown to induce a strong increase in plasma IL-6, which, however normalized within few weeks (Kluge et al., 2009; Maes et al., 1997; Pollmächer et al., 1996). Olanzapine (Kluge et al., 2009) and risperidone (Kim et al., 2001) reportedly had no significant effect on plasma IL-6. As for IL-1RA, limited data are available about the effects of antipsychotics on this cytokine receptor antagonist (Drzyzga et al., 2006). Nonetheless, the effects of second-generation antipsychotics on cytokine profiles, and the relationship between altered cytokine levels and psychopathology are gaining increasing interest. For example, risperidone has been shown recently to reduce abnormally elevated serum IL-2 levels in schizophrenia patients, and these reductions were correlated with the reductions in the Positive and Negative Syndrome Scale (PANSS) total score (Zhang et al., 2009).

Quetiapine is a second-generation antipsychotic with broad range of efficacy across symptoms of schizophrenia, and it has a pharmacological profile similar to that of clozapine (loose dopamine-D_2 receptor binding, moderate 5-HT_{2A} antagonism and 5-HT_{1A} partial agonism) (Cheer and Wagstaff, 2004). Recently, in vitro studies have shown that quetiapine inhibit TNF-alpha release from activated mouse microglial cells, suggesting the ability of this antipsychotic to modulate cytokine production (Bian et al., 2008). To our knowledge, the immunomodulatory effects of quetiapine have not been investigated in schizophrenia yet. The objective of the current study was to examine the changes in plasma levels of sIL-2R in schizophrenia during quetiapine treatment, taking advantage of a clinical trial investigating the efficacy of quetiapine in dual diagnosis (DD) of schizophrenia and substance use disorders (SUDs). This patients' population was chosen because the lifetime prevalence of SUDs in schizophrenia is close to 50% (Kavannagh et al., 2002; Regier et al., 1990), and SUDs negatively interfere with the course and the treatment of the disease (Mueser et al., 1998; Negrete, 2003).

2. Methods

2.1. Participants

Patients were diagnosed with a schizophrenia-spectrum disorder and a comorbid SUD (abuse or dependence), using the Structured Clinical Interview for DSM-IV. Healthy controls consisted of 28 volunteers without any known history of any DSM-IV Axis-I psychiatric disorder, including schizophrenia or SUD, and none of them was taking any centrally-acting medication. Patients and controls were similar in terms of age (patients: 30.2 ± 10.1 years; controls: 28.2 ± 6.3; $t = 0.880$; $p = 0.383$), sex (patients: 25 M/4 F; controls: 22 M/6 F; $\chi^2 = 0.574$; $p = 0.449$). The body mass index (BMI) of patients was 13% higher than that of controls (patients: BMI = 26.0 ± 5.2; controls: 23.0 ± 3.8), but the difference did not reach statistical significance ($t = 1.944$; $p = 0.059$). All participants signed a detailed informed consent form. The study was approved by the local scientific and ethics committee.

Exclusion criteria were the following: (i) patients already on quetiapine or clozapine; (ii) patients hospitalized or acutely ill; (iii) patients with total score lower than 65 on the PANSS (Kay et al., 1987); (iv) pregnant patients and controls; (v) female patients of childbearing potential without adequate contraception; (vii) patients with abnormal liver function; (viii) patients and controls with any clinically meaningful unstable renal, hepatic, cardiovascular, respiratory, cerebrovascular disease; and (ix) patients and controls with infection or inflammatory diseases.

On baseline, 29 patients were switched to quetiapine for a 12-week open-label trial. 5 patients were drop-outs, for the following reasons: lost-to-follow-up (n = 2), dissociative experience (n = 1), hostility (n = 1) and tachycardia (n = 1). 23 patients completed the whole trial while one patient completed 9 weeks. Before being switched to quetiapine, study completers (n = 24) were treated with one or more of the following antipsychotics: olanzapine (n = 15); risperidone (n = 5); ziprasidone (n = 1); and first-generation antipsychotics (n = 7). Mean taken dose (pill count) of quetiapine for trial completers was 466.6 mg ± 227.3 (dose range: between 200 and 800 mg). Concomitant drugs were allowed and were kept stable throughout the study.

The 29 patients assessed on baseline suffered from schizophrenia (n = 16), schizoaffective disorder (n = 11) and schizophreniform disorder (n = 2). The mean duration of illness of patients was 90.9 months ± 99.0. On baseline, patients had moderated levels of psychiatric symptoms (Mean PANSS total score = 79.8 ± 10.1). Patients responded to one or more of the following SUD: cannabis (n = 18); alcohol (n = 13); cocaine (n = 7); amphetamine (n = 1); hallucinogen (n = 1) and phencyclidine (n = 1).

2.2. Clinical assessments

Psychiatric variables were evaluated with the PANSS and the Calgary Depression Scale for Schizophrenia (Addington et al., 1992). SUD outcomes – including tobacco smoking – were evaluated with the Alcohol and Drug Use Scales (Drake et al., 1990), the Time Line Follow Back procedure (Sobell and Sobell, 1992), a DSM-IV adapted scale, and the Fagerström Tobacco Questionnaire (Fagerström and Schneider, 1989) (for more information, see Potvin et al., 2006).

2.3. Assessment of cytokines

Plasma cytokines were assessed at baseline, weeks 6 and 12 after quetiapine treatment, and in healthy controls. To this end, blood samples were withdrawn between 13:00 and 16:00 pm. They were centrifuged within an hour, and plasma samples were collected and stored at −80 °C until analysis. Plasma sIL-2R was first measured in a multiplex assay together with IL-6 and IL-1RA by sandwich immunoassay with beads coated with biotinylated anti-cytokine antibodies and the presence of the target cytokine was revealed with streptavidin-RPE (BioSource, Camarillo, CA, USA). The reading was analyzed with a Luminex LX100 instrument (Luminex, Austin, TX, USA), using StarStation 2.0 software (Applied Cytometry, Sacremento, CA, USA). Plasma levels of sIL-2R were readily quantified by the Luminex assay, while those of IL-1RA and IL-6 were mostly below the detection limit. For this reason, plasma IL-6 and IL-1RA were further measured in monoplex assays by high sensitivity sandwich ELISA (R&D systems). Minimum detectable limits were 0.039 pg/ml, 6.26 pg/ml, and 30 pg/ml for IL-6, IL-1RA and sIL-2R, respectively, according to manufacturer's instructions.

2.4. Statistical analyses

Between-group differences in plasma cytokine levels were assessed using analyses of variance (ANOVAs). Changes in psychiatric symptoms and cytokine levels were analyzed using repeated-measures ANOVAs. Relationships between baseline cytokine levels and baseline clinical variables, as well as relationships between changes in cytokine levels and changes in clinical variables were