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The effect of minocycline on amelioration of cognitive deficits and pro-inflammatory cytokines levels in patients with schizophrenia

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ABSTRACT

Background: Cognitive deficits of schizophrenia are predictors of poor function, but antipsychotic medication has limited efficacy for cognitive deficits. These deficits in learning and memory may result from activity of pro-inflammatory cytokines, which microglia produce. The microglia inhibitor minocycline might arrest this cytokine damage to the hippocampus and reverse the cognitive deficits of schizophrenia.
Methods: A double-blind, placebo-controlled study involved 75 patients with schizophrenia who randomly received low dose (100 mg/day) or high dose minocycline (200 mg/day) or placebo added to risperidone. MATRICS Consensus Cognitive Battery (MCCB) was used to assess the cognitive functioning, and serum levels of Interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor−α (TNF-α) were assessed.
Results: $\text{Minocycline}_{\text{high dose}}$ group was significantly superior to $\text{minocycline}_{\text{low dose}}$ or placebo group not only for the improvements in cognitive tests' scores as well ($P < 0.05$), but for IL-1β and IL-6 serum levels reduction ($P < 0.01$). The amelioration of cognitive deficits with minocycline correlated not only with the remission of negative symptoms, but also with the reduction in serum levels of IL-1β and IL-6.
Conclusions: Minocycline adjunctive treatment was effective in improving cognitive deficits of patients with schizophrenia. The beneficial effect of minocycline may be related to reducing pro-inflammatory cytokines through microglia inhibition.

1. Background

Schizophrenia is a severe mental disorder marked by delusions, hallucinations, negative symptoms, cognitive impairments, and can potentially become a lifetime burden for many patients (Zhang and Zhao, 2014). Currently, there is ineffective treatment for the all symptoms of schizophrenia, especially for cognitive deficits. Understanding the cause of schizophrenia helps us with effective treatments for specific biological subtypes of schizophrenia. Previous studies have proposed a “microglia hypothesis of schizophrenia” in which microglia release of pro-inflammatory cytokines mediates neuro-inflammation and brain damage in schizophrenia (Horvath and Mirnics, 2014; Fan et al., 2007; Zhao and Zhang, 2015; Monji et al., 2009; Monji et al., 2013). Immune-related disturbances and neuro-inflammation may lead to cognitive deficits in schizophrenia (Tay et al., 2017; Blank and Prinz, 2013; Fillman et al., 2013; Racki et al., 2016). Thus, finding potential neuroinflammatory biomarkers of schizophrenia has been challenging and new treatment targets is needed.

Minocycline, a second-generation tetracycline, is known to have anti-inflammatory effects and is able to inhibit microglial activation (Plane et al., 2010). Animal models of schizophrenia have reported that minocycline could alleviate behavioral changes, such as hyperlocomotion, social interaction and pre-pulse inhibition deficits (Zhang et al., 2007; Mizoguchi et al., 2008; Zhu et al., 2014a, 2014b). Some clinical trials have also shown that minocycline treatment can improve cognitive functioning in schizophrenia patients (Levkovitz et al., 2010; Liu et al., 2014; Kelly et al., 2015). Therefore, we have hypothesized that minocycline may ameliorate cognitive

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deficits in schizophrenia through alleviating neuro-inflammation. To test this hypothesis we completed this double-blind, placebo-controlled study to assess the efficacy of minocycline for cognitive deficits of schizophrenia patients and to detect the serum levels of pro-inflammatory cytokines.

2. Methods

2.1. Participants

Patients aged 18 to 45 years with a diagnosis of schizophrenia (the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnosis, SCID) were recruited from Guangzhou Baiyun Psychiatric Hospital between June 2013 and September 2014. Subjects with a higher negative subscale score than positive subscale score on the Positive and Negative Syndrome Scale (PANSS) were included, and the PANSS negative score of subjects on baseline was greater than 20 with at least one moderate negative symptom (Potkin et al., 2002; Rabany et al., 2011). The disease duration of patients was limited to 2 to 10 years. All patients had not taken antipsychotics for at least half a month before study entry. Exclusion criteria were significant inflammatory or immune conditions, minocycline allergy and pregnancy. Patients with anti-inflammatory drugs, hormones or immunosuppressant agents in the last half year were also cause for exclusion.

2.2. Procedures

The study was a 3-month, randomized double-blind placebo controlled comparison of adjunctive minocycline or placebo added to risperidone. The protocol was approved by the ethics committee of Guangzhou Baiyun Psychiatric Hospital.

After the screening meeting including SCID assessment, patients who signed the informed consent form were randomized to receive low dose minocycline (100 mg/day) or high dose minocycline (200 mg/day) or placebo. The dose of risperidone was able to be adjusted between 3 mg and 6 mg/day. The combined use of lorazepam and trihexyphenidyl hydrochloride was allowed to respectively treat insomnia or extrapyramidal symptoms.

2.3. Outcome measures

The primary outcome was the change of cognitive functioning after treatment. Cognitive evaluation was performed using eight tests from the MATRICS Consensus Cognitive Battery (MCCB) covering six cognition domains (Green and Nuechterlein, 2004): Trail Making Test (TMT), Symbol Coding Test, Verbal Fluency, the Continuous Performance Test-Identical Pairs (CPT-IP), Spatial Span, Hopkins Verbal Learning Test-Revised (HVLT-R), Brief Visuospatial Memory Test- Revised (BVMT-R) and Mazes. Investigators completed the consistency training for these scales (Kappa = 0.85).

We made follow-up visits at month 3 after starting treatment. Each enrolled patient was underwent a series of assessments both at baseline and month 3 including the Treatment Emergent Symptom Scale (TESS), physical examinations including weight, routine laboratory tests and concomitant medication. PANSS was assessed at baseline and month 1, 2, 3, while MCCB was assessed at baseline and month 3 to avoid the practice effect of cognitive function tests. The date and reason of dropping-out from the study were recorded.

Interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor−α (TNF-α) serum levels were analyzed by quantitative enzyme-linked immunosorbent assay (ELISA) at baseline and month 3. The fasting forearm venous blood samples were collected in schizophrenia patients and 30 healthy volunteers.

2.4. Data analysis

Statistical analysis was performed using SPSS version 22.0. Since we collected MCCB and pro-inflammatory cytokine measurements at baseline and month 3, we used the data from all randomized patients (per-protocol analysis). Continuous variables were described using summary statistics such as means and standard deviations. Categorical variables were described using frequencies and percentages. We performed baseline between-group comparisons using the analysis of variance (ANOVA) for continuous variables and Chi-square analysis for categorical variables.

The main strategy involved univariate analysis of variance for the changes of each MCCB score and pro-inflammatory cytokine serum level after treatment, using a between-group factor of drug (placebo, 100 mg and 200 mg minocycline), with baseline value as a covariate. We used the Bonferroni post hoc test to compare the specific treatments between groups. The within-dosage group comparisons were performed using the paired *t*-test for continuous variables, and the Fisher exact test for categorical variables. The relationship between the changes in cytokine serum levels and cognitive functioning was analyzed using Pearson correlation coefficients. We investigated potential response predictors associated with changes in cognitive functioning using multiple linear regression. For all analyses, a *P* value less than 0.05 (2-tailed) was used for statistical significance.

3. Results

3.1. Demographic and basic descriptive data

We randomized 75 of the 110 patients screened to $\text{minocycline}_{\text{high dose}}$, $\text{minocycline}_{\text{low dose}}$ or placebo group (25 patients on each group). 57 patients completed the whole 3-month trial (Fig. 1), and there was no difference in completion rates between groups ($\text{minocycline}_{\text{high dose}}$ group: $n = 18$, $\text{minocycline}_{\text{low dose}}$ group: $n = 20$, placebo group: $n = 19$). The reasons for dropout in the per-protocol population did not appear related to side effects of the medication and did not differ from the placebo dropouts. There were no statistical differences in demographic or clinical characteristics between the three groups at baseline (Table 1). The average daily dose of risperidone was not statistically different between the 3 treatment groups (Table 1).

3.2. Change in cognitive functioning

All cognitive tests' scores of the three treatment groups both at baseline and at month 3 were obviously worse than those of healthy volunteers ($P < 0.01$). However, patient scores improved obviously after 3-month treatment ($P < 0.01$) (Table 2).

By using ANCOVA, we found a significant difference in the improvement of the following 6 MCCB test scores between baseline and month 3: TMT ($df_1 = 2$, $df_2 = 54$, $F = 21.885$, $P = 0.000$, ES = 0.448, 95%CI: 0.234–0.579), BACS SC ($df_1 = 2$, $df_2 = 54$, $F = 4.530$, $P = 0.015$, ES = 0.144, 95%CI: 0.005–0.297), Verbal Fluency ($df_1 = 2$, $df_2 = 54$, $F = 15.434$, $P = 0.000$, ES = 0.364, 95%CI: 0.152–0.509), HVLT-R ($df_1 = 2$, $df_2 = 54$, $F = 4.543$, $P = 0.015$, ES = 0.144, 95%CI: 0.006–0.298), BVMT-R ($df_1 = 2$, $df_2 = 54$, $F = 7.340$, $P = 0.002$, ES = 0.214, 95%CI: 0.039–0.371), Maze ($df_1 = 2$, $df_2 = 54$, $F = 3.566$, $P = 0.035$, ES = 0.117, 95%CI: 0.000–0.266) (Table 3). After the Bonferroni post hoc test, the improvement of TMT and Verbal Fluency score on $\text{minocycline}_{\text{high dose}}$ were both significantly greater than on $\text{minocycline}_{\text{low dose}}$ and placebo (both $P < 0.05/3 = 0.017$) (Table 3). The improvement of HVLT-R and BVMT-R score on $\text{minocycline}_{\text{high dose}}$ were obviously greater than on $\text{minocycline}_{\text{low dose}}$ ($P = 0.017$, $P = 0.002$ respectively) (Table 3). But the changes in MCCB tests' scores on $\text{minocycline}_{\text{low dose}}$ were not obviously different with the changes on placebo.