**Effects of SSRIs on Peripheral Inflammatory Cytokines in Patients with Generalised Anxiety Disorder**

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**Short title:** Effects of SSRIs on Inflammatory Cytokines in Generalised Anxiety Disorder

**ABSTRACT**

**Background:** Extensive research into psychoneuroimmunology has led to substantial advances in our understanding of the reciprocal interactions between the central nervous system and the immune system in neuropsychiatric disorders. To date, inflammation has been implicated in the pathogenesis of depression and anxiety. The immunomodulating effects of antidepressants on depression have been reported, however, there is no evidence of the similar effects of antidepressants on anxiety. The aim of the study was to investigate the effects of selective serotonin reuptake inhibitors (SSRIs) on peripheral inflammatory cytokines in patients with first episode generalized anxiety disorder (GAD). **Methods:** A prospective cohort design was employed: 42 patients with first episode GAD were treated with either escitalopram or sertraline for 12 weeks. Anxiety was measured by the Generalized Anxiety Disorder Scale and the State Trait Anxiety Inventory, serum pro-inflammatory cytokine levels were measured by the enzyme-linked immunosorbent assay (ELISA), and CRP determined by an immunoturbidimetric method before and after SSRIs treatment. **Results:** Baseline levels of anxiety and pro-inflammatory cytokines including IL-1α, IL-6, IL-8, IL-12, IFN-γ, and CRP were significantly reduced after treatment of SSRIs (p<0.05 in all cases). In addition, the change of anxiety measures co-vary with the change of peripheral cytokine levels (p<0.05 in all cases). The regression model revealed that log transformed baseline levels of CRP and IL-6 predicted treatment response (p<0.05 in both cases). **Conclusions:** This study is the first to investigate the effects of SSRIs on pro-inflammatory cytokines in patients with first episode GAD. The findings indicate moderate acute anti-inflammatory effects of SSRIs in GAD, and suggest that these anti-inflammatory effects may underlie anxiolytic effects of SSRIs. The study also indicates that serum levels of CRP and IL-6 may predict treatment response. However, data from randomized controlled trials is warranted to confirm these findings.

**Keywords:** Generalised Anxiety Disorder; SSRIs; inflammation; cytokine

**Text**

**1. INTRODUCTION**

Anxiety disorders are among the most prevalent and disabling mental disorders (Buist-Bouwman et al., 2006; Kessler et al., 2005). By 2026 the total number of people with anxiety disorders is projected to rise to 2.56 million, and the projected service costs will be £2 billion with a total cost at £14.2 billion in England (McCrone et al., 2008). Generalised anxiety disorder (GAD) is one of the most common impairing anxiety disorders, having an estimated twelve-month prevalence of 1.7-3.4% (Wittchen et al., 2011). Since signs of immune disturbances in depression were first reported in early 1990s (Maes et al., 1990; Maes et al., 1991; Maes et al., 1992a; Maes et al., 1992b), the presence of inflammatory responses and the role of cytokines in major depression have been extensively studied. The high comorbidity of anxiety disorders and major depression and similar effects of antidepressants suggest common neurobiological substrates; while an integrated specificity model emphasizes specific patterns of biological responses to specific psychological states (Kemeny, 2003; Moons et al., 2010). Since psychological stress-induced anxiety was first reported to be associated with inflammatory responses (Maes et al. 1998), the pronounced response of central and peripheral cytokines to stress has prompted further interest in the role of cytokines in the pathogenesis of anxiety disorders (Hou and Baldwin 2013). Evidence of the anxiety-specific effect on inflammatory activity in clinically anxious individuals suggests a specific anxiety inflammatory phenotype independent of depression (O’Donovan et al., 2010; Hou et al. 2017a). Research evidence from our recent work demonstrates an increased pro-inflammatory response and decreased anti-inflammatory response and an altered cytokine balance in GAD (Hou et al., 2017a; Tang et al., 2018).

Biological mechanisms underlying how this cytokine imbalance may contribute to the development of anxiety are not entirely clear, but current evidence suggests that this could be via the following potential mechanisms: 1) cytokine imbalance can alter the metabolisms of neurotransmitters via influencing the activity of enzymes controlling tryptophan which has preferential metabolism either to 5HT or Kynurenine (KYN). Low 5HT level and tryptophan depletion in anxiety disorders maybe mediated by a Th1 predominant response; and 2) cytokine imbalance can also alter the function of hypothalamic–pituitary–adrenal axis (HPA) via stimulant effects on the expression and release of corticotropin-releasing hormone, adrenocorticotropic hormone and cortisol (Pariante and Miller, 2001; Raison et al., 2010). The release of inflammatory cytokines, such as IL-1 (Koo and Duman, 2008), IL-6 (Bierhaus et al., 2003) and TNF-α (Olszewski et al., 2007) has been found to be triggered by stress. The elevated cytokine levels stimulate para-ventricular nuclei in hypothalamus which release corticotropin-releasing hormone (CRH); CRH then stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH) which affects adrenal gland releasing cortisol that inhibits the cytokine release to keep the cytokine balance. However, chronic fear and anxiety keep the immune cells continually releasing cytokines (Pongratz and Straub, 2014) which lead to a disrupted cytokine balance. Extensive evidence supports the dysregulated HPA in anxiety disorders (Leonard and Myint, 2009) as well as the effects of SSRI treatment on HPA activity (Lenze et al. 2011). Therefore, potential mechanisms of action of antidepressants when exerting anxiolytic effects may also be via these two pathways. In addition, cytokines may also affect neurogenesis and neurocircuitry involved in regulating anxiety behaviour (Ben Menachem-Zidon et al., 2008; Miller, 2009).

Our research group recently conducted a systematic review and meta-analysis examining effects of selective serotonin reuptake inhibitors (SSRIs) on inflammatory cytokines in 22 studies including 827 major depression patients, indicating anti-inflammatory effects of SSRI treatment (Hou et al., 2017b; Wang et al., 2019). While extensive work has been conducted in depression, so far, there is no evidence of the immunomodulating effects of SSRIs when exerting anxiolytic effects, leading to several interesting questions: Does SSRIs treatment affect inflammatory cytokines in GAD? Do cytokine changes co-vary with changes in anxiety? Can baseline cytokine levels predict treatment response? To answer these questions, we conducted a prospective study in patients with first episode GAD. The primary aims of our study were to (1) examine whether SSRIs treatment affect inflammatory cytokine levels in patients with GAD in comparison to healthy controls; (2) determine whether cytokine changes co-vary with changes in anxiety; (3) identify baseline cytokine predictors for treatment response. There is a pressing need for research in these areas as a better understanding could help us to identify biomarkers for treatment response and reveal novel targets for treatment.

**2. METHODS**

*2.1 Participants*

*GAD patient group*: Following referrals from consultant psychiatrists in the outpatient clinic at Suzhou Psychiatric Hospital, 73 patients, aged 18-60 years, with a BMI between 18-30, with 6 or more years of education, and a primary diagnosis of first episode GAD based on the International Classification of Diseases 10th Revision (ICD-10), were initially approached by researchers. 67 patients completed a pre-test screening interview comprising a structured diagnostic Mini International Neuropsychiatric Interview - MINI (Sheehan et al. 1998) and the 7-item Generalised Anxiety Disorder Questionnaire (GAD-7) with a threshold score of 10 points (Spitzer et al. 2006). All GAD patients were medication naive and had no history of any antidepressant or anxiolytic intake. Participants were excluded if they reported any inflammatory events or had any intake of any medication with known immune-modulating effects, such as glucocorticoids, within 4 weeks prior to their testing session. Other exclusion criteria included pregnancy, acute or chronic infectious, autoimmune, allergic, neoplastic, or endocrine diseases and other acute physical diseases, including surgery or infarction of the heart or brain within the last 3 months. After giving their written informed consent, 48 GAD patients were recruited. 12 weeks after treatment, 6 GAD patients dropped out due to adverse events (n=3), request for CBT (n=1) and inflammatory events (n=2), so data from a total of 42 patients were entered into final analysis (see recruitment flow chart in Figure 1).

The study was approved by the Clinical Research Ethics Committee in Suzhou Psychiatric Hospital.

*2.2. Drug treatment*

No participants took any medication 2 weeks before taking part in the study. 48 Participants took SSRI treatment (either escitalopram 5-20mg/d or sertraline 50-200mg/d) for a period of 12 weeks. 6 Participants dropped out after 12 weeks including 2 on escitalopram and 4 on sertraline. Therefore, 28 participants who took escitalopram 5-20mg/d and 14 participants who took sertraline 50-200mg/d completed the study.

*2.3 Measures*

2.3.1. Measure of inflammatory cytokines

A sample of 10ml venous blood was taken before treatment from all participants at approximately the same time of day (9:00-10:00AM) and centrifuged for 15 min at 2500rpm. The cell free-serum was pipetted and aliquoted in 2 ml standard freezer vials which were then stored within 2 hours at -80° C until further analysis. The following inflammatory cytokines were measured by enzyme linked-immuno-sorbent assay (ELISA) including IL-1β, IL-6, IL-8, IL-12p70, and IFN-γ. The ELISA kits were manufactured by Wuhan Boshide Biotechnology Limited Company. The concentration of C-reactive protein (CRP) was measured by immunological transmission turbidity and the kits were produced by Shenzhen Mindray Bio-Medical Electronics Limited Company. Selection of cytokines was based on a recent review of inflammation and anxiety (Hou et al., 2013). Test-retest variability of each kit was under 10%. The same measure was taken after 12 weeks treatment. Processing of blood samples and measurement of cytokine levels was based on recommendations provided by the manufacturer. Samples were tested in duplicate and the mean of the two measures was used for analysis.

2.3.2. Questionnaire measures of anxiety

Generalized Anxiety Disorder Scale (GAD-7)(Spitzer et al., 2006).

The GAD-7 is a self-report questionnaire for screening and severity measuring of GAD. The seven items assess severity of key symptoms of GAD according to reported response categories with assigned points. The sensitivity of the Chinese version was 86.2% and the specificity was 95.5% with a Kappa value 0.825 which indicates its good reliability and validity (He et al., 2010).

State Trait Anxiety Inventory (STAI)(Spielberger et al., 1983).

The STAI is a well-established self-report instrument that clearly differentiates between the temporary condition of state anxiety and the longstanding quality of trait anxiety. The scale includes State Anxiety Inventory (SAI) and Trait Anxiety Inventory (TAI), which assess the severity of state anxiety and trait anxiety respectively. For the Chinese version of STAI, the Cronbach's alpha of SAI is 0.90 and the Cronbach's alpha of TAI is 0.73, and their correlation coefficient *r* was 0.59～0.75. The test-retest reliability c2oefficients of SAI and TAI were 0.88 and 0.90 respectively(Wang et al., 2000).

*2.4 Study design and procedure*

A prospective cohort design was employed. All eligible participants provided written informed consent before taking part in the study. Participants were invited to attend the laboratory testing on two occasions including baseline testing before treatment and follow-up testing 12 weeks after treatment at the clinical research facility in Suzhou Psychiatric Hospital. During each visit, they were asked to rest for 5 minutes before their testing session. After blood samples were taken, participants were instructed to complete a questionnaire booklet.

*2.5 Data analysis*

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS version 24). All variables were tested for normality, and transformation to symmetry using normal scores was undertaken when necessary. Repeated measures of analysis were used to compare pre- and post- measures of anxiety and inflammatory cytokine levels, and paired samples t-test was used for parametric data and Wilcoxon signed ranks test was used for non-parametric data. Pearson and Spearmen correlational analyses were used as appropriate based on the distribution of the data to assess associations between measures of anxiety and serum levels of pro-inflammatory cytokines. Logistic regression analysis was conducted to examine the predictive power of log transformed baseline inflammatory markers.

**3 RESULTS**

*3.1* *Effects of SSRIs on measures of anxiety and peripheral inflammatory markers*

Pre- and post- treatment measures of anxiety including GAD, SAI and TAI, and peripheral inflammatory markers including CRP, IL-1β, IL-6, IL-8, IL-12p70, and IFN-γ are presented in Table 1. As measures of anxiety and concentration levels of CRP, IL-6, IL-1α and IL-8 were normally distributed, paired samples t-test was used; whereas levels of IL-12 and IFN-γ were non-parametric, Wilcoxon signed ranks test was conducted. There were significant differences between pre- and post-measures of anxiety and inflammatory markers (p<0.05 in all cases).

*3.2 Correlation analysis of change of anxiety and changes of peripheral inflammatory markers*

After controlling for BMI, smoking, and alcohol consumption, Pearson correlation analysis was conducted to examine how the change of anxiety (measured by GAD-7) co-vary with the changes of peripheral levels of CRP, IL-6, IL-1α and IL-8; whereas Spearman correlation analysis was conducted for examining the change of anxiety and levels of IL-12 and IFN-γ. Correlation analysis demonstrated significant positive correlations between change in anxiety and change of peripheral inflammatory markers (p<0.05 across all cases, see Table 2), indicating that patients who had greater reduction in anxiety, also had greater decrease in cytokine levels.

*3.3 Logistic regression analysis of baseline inflammatory markers for treatment response to SSRIs*

To find out the predictive power of baseline inflammatory markers, logistic regression analysis was conducted. Treatment response was defined as a reduction of GAD-7 score after SSRIs ≥50%; whereas lack of treatment response was defined as SSRIs <50%. Log transformed CRP and inflammatory cytokines were entered into the logistic regression model, with treatment response being dependent variable, labelled as ‘0’ for no treatment response and ‘1’ for treatment responsive, and CRP and cytokines being independent variables. After controlling for BMI, smoking, and alcohol consumption, the regression model revealed that log transformed baseline concentration levels of CRP and IL-6 had significant predict value for treatment response (p<0.05 in both cases, see Table 3), indicating patients who had higher levels of CRP and IL-6 responded to treatment better.

**4 DISCUSSION**

To our knowledge, this study is the first to investigate the effects of SSRIs on peripheral inflammatory markers in patients with first episode GAD. The finding of the current study revealed moderate acute anti-inflammatory effects of SSRIs in GAD and these effects were also positively associated with anxiolytic effect of SSRIs, suggesting patients who had greater reduction in anxiety, also had greater decrease in cytokine levels. In addition, baseline CRP and IL-6 levels were found to predict treatment response to SSRIs.

Our recent work in GAD has shown an immune activation during the acute stage of the disease, which indicates anxiety symptoms associated with increased inflammation (Hou et al., 2017; Tang et al., 2018)). Therefore, we hypothesized that levels of inflammation would reduce with resolution of anxiety symptoms in GAD after treatment, and anti-inflammatory effects of SSRIs may underlie their anxiolytic effects. Short term trials of antidepressant medication in patients with major depression have produced inconsistent findings with regards to systemic markers of inflammation (Dawood et al., 2007; O'Brien et al., 2006; Tousoulis et al., 2009). It is worth noting that that noradrenaline has pro-inflammatory effects on innate immune cells and thus potentiate cytokine production (Elenkov and Chrousos, 2002; Thayer and Sternberg, 2010). Norepinephrine reuptake inhibitors (SNRIs), tricyclic or tetracyclic antidepressants (TCAs and TeCAs) have a combined serotonergic/noradrenergic effect, whereas SSRIs act purely serotonergic, which may explain difference effects of antidepressants on inflammatory cytokines.

Antidepressants might affect glucocorticoid receptors and the hypothalamic pituitary adrenal axis, which lead to both anti- and pro-inflammatory effects (Pace and Miller, 2009; Pariante, 2009). As these mechanisms are also involved in stress response and anxiety, the underestimated anti-inflammatory effect may be one of the mechanisms underlying the mode of action of SSRIs when exerting anxiolytic effects (Galecki et al., 2009; Leonard et al., 2001). One hypothesis of this mechanism is via the kynurenine pathway (Dantzer, 2017; Maes et al., 2011) where immune imbalance influences the activity of enzymes controlling tryptophan which has preferential metabolism either to 5HT or Kynurenine (KYN) metabolism. Elevated inflammation can cause excessive activation of indoleamine-2,3dioxygenase (IDO) - an enzyme present in microglia, astrocytes and neurons. This enzyme catabolises tryptophan, the source of serotonin, into kynurenine, and reduce the production of serotonin (Anderson et al., 2016). A recent meta-analysis revealed robust improvement in depressive symptoms after anti-inflammatory treatment (monoclonal antibody or cytokine inhibitor)(Kappelmann et al., 2018),while the current study indicates significant associations between immunemodulating effects and anxiolytic effects of SSRIs in GAD, which seems to support a potentially causal role for cytokines in clinical anxiety and that cytokine modulators may be beneficial for chronically inflamed anxiety patients.

Although several pharmacological and psychological treatment options are available for anxiety disorders, the average response rate to usual care from the current evidence was only 26% (Hunot et al., 2007; Kapczinski et al., 2003). Therefore, there is an urgent need for research to identify biomarkers which could help clinicians to stratify medications for patients and improve clinical outcome. The prospective design of the current study has allowed us to examine how inflammatory changes co-vary with change in anxiety after SSRIs treatment in patients with GAD. To our knowledge, this is the first study to demonstrate a positive association between the two, which suggests that patients who had greater decrease in cytokine levels, also had greater reduction in anxiety. This supports the potential inflammatory pathway underlying the anxiolytic effects of SSRIs and has also led us to further investigate the predictive value of baseline inflammatory markers for treatment response which can have important clinical implications.

The current study revealed higher baseline CRP and IL-6 level predicting better treatment response to SSRIs. This is in line with the study conducted by Lindqvist et al (Lindqvist et al., 2017) who found that IL-6 decreased significantly in responders during the course of 8 week SSRIs treatment in MDD. This is also in line with the study conducted by Yoshimura (Yoshimura et al., 2013) who found baseline level of IL-6 was higher in the responder group than in the non-responder group to SNRIs in MDD. Sertraline has also been previously reported to decrease IL-1β mRNA expression and TNF-α expression after repeated doses (Sitges et al., 2014). The predictive value of CRP is in contrary to what has been found in a recent study conducted by Chamberlain et al (Chamberlain et al., 2019). They found elevated CRP in treatment-resistant MDD patients in comparison to treatment-responsive patients and healthy volunteers. There are two possible explanations for this: one could be that Chamberlain et al. examined treatment resistance to all anti-depressants instead of SSRIs with anti-inflammatory effects; the other might be a specific neuroinflammatory pathway underlying anxiety which is independent from depression (Hou et al., 2017; Moons et al., 2010; O'Donovan et al., 2010). Using a stratified subgroup analysis in a meta-analysis, Hannestad and colleagues found that SSRIs treatment may decrease levels of IL-1β, IL-6 and possibly TNF-α (Hannestad et al., 2011). A recent meta-analysis of 22 studies by our group also found significant anti-inflammatory effects of SSRIs on IL-1β and, IL-6, and TNF-α (Hou et al., 2017). Data from the current study are in line with the anti-inflammatory effects of SSRIs in depression. In addition to the most commonly reported cytokines and CRP, we also found a low grade anti-inflammatory effects across a series of other pro-inflammatory cytokines including IL-8, IL-12p70, and IFN-γ. These findings further support the role of immune disturbance in the pathogenesis of anxiety. Undoubtedly, further studies must be conducted in order to replicate these immune responses in SSRI-treated GAD patients. If the predictive value of baseline CRP and IL-6 can be replicated in further research, it can have important clinical implication. It can help us to stratify GAD patients based on pro-inflammatory biomarkers, such as treating patients with elevated CRP or IL-6 with antidepressants which have anti-inflammatory property or augmentation with anti-inflammatory drugs, leading to better treatment response and improved clinical outcome, with the goal of achieving a more personalized approach to treat patients with GAD.

The findings of the study must be interpreted in light of several limitations. First, the study did not employ a randomized controlled study design; Second, the study recruited a relatively small number of patients who may have heterogeneous clinical phenotypes; Third, psychological stress should be measured and controlled as they may affect inflammatory status; Fourth, the study only examined two SSRIs (escitalopram or sertraline) and the dosages were not fixed. Therefore, data from larger randomized controlled trials assessing anti-inflammatory effects of SSRIs as well as other antidepressants in GAD is warranted. Further studies are also required to identify the cellular source of the pro-inflammatory cytokines and the underlying mechanisms that drive these changes.

In conclusion, data from the current study provide new evidence of moderate anti-inflammatory effects of SSRIs in GAD, and suggest that these anti-inflammatory effects may underlie anxiolytic effects of SSRIs. The study also indicates that serum levels of CRP and IL-6 may predict treatment response, which suggests that the key to treatment resistance is likely to be not just the dysregulation of neurotransmitters but also the dysregulated immune system. Targeting a subgroup of anxiety patients with higher baseline inflammatory markers using anti-inflammatory agents may improve clinical outcome. The advance in psychoneuroimmunology has enabled prediction of response and understanding of treatment resistance. Targeting the immune system can have therapeutic benefit in psychiatry, psychoneuroimmunology has transformed to an established mainstream research and translational area (Pariante, 2016, 2017). While more research is needed in anxiety disorders, research so far has shown tremendous promise.

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**Figure:** 1

**Table:** 3

**Number of supplementary material:** zero