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Variations in circulating cytokine levels during 52 week course of treatment with SSRI for major depressive disorder

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Abstract

Major depressive disorder (MDD) is a psychiatric condition characterized by hypercortisolism and variations in circulatory cytokines. Previously it has been reported that administration of selective serotonin reuptake inhibitors (SSRI) in MDD patients modify cortisol and cytokine levels but these studies only evaluated changes over a short time period. This work reports the long-term effects of administration of SSRI on the cortisol levels and pro-/anti-inflammatory cytokine profile in a group of MDD patients treated for 52 weeks. A total of 31 patients diagnosed with MDD received anti depressant treatment with SSRI. HDRS and BDI were administered over a year, and levels of interleukin IL-1β, IL-10, IL-2, IFN-γ, IL-4, IL-13, and 24-h urine cortisol were determined at weeks (W) 0, 5, 20, 36 and 52 of treatment. Before treatment we found high levels of cortisol, IL-4, IL-13 (Th2) and IL-10 in MDD patients when compared with healthy volunteers. At W20 psychiatric scales indicated a remission of the depressive episode concomitantly with increments in IL-2 and IL-1β but without changes in cortisol. Towards the end of the treatment (W52) we observed a significant reduction ($p<0.01$) in cortisol levels, with an increment in IL-1β and IFN-γ and a decrease in Th2 cytokines. Our results suggest that depressed patients only reach a partial reestablishment of HPA axis function after the long-term administration of SSRI.

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1. Introduction

Several lines of research have documented altered hypothalamic–pituitary–adrenal (HPA) axis function in major depressive disorder (Aihara et al., 2007). Under homeostatic conditions the HPA axis maintains tight regulation of neuro-endocrine-immune interactions (Ader et al., 2001). However in MDD these interactions cause imbalances in neurotransmitter levels, hormones such as cortisol and also in cytokines that contribute to the behavioral and immune disturbances observed in these patients (Axelson et al., 1993; Cleare, 1997; Leonard, 2007; Schiepers et al., 2005).

One of the most consistent clinical features of MDD is hypercortisolism (Holsboer, 2000; Pariante and Miller, 2001) which results from HPA axis hyperactivity. Variations in cortisol levels are directly related to the activation index of the HPA axis (Sapolsky and Plotsky, 1990). High cortisol levels in MDD patients are related to alterations in the nervous (Vythilingam et al., 2004), endocrinal (Axelson et al., 1993) and immunological systems (Zorrilla et al., 2001). Several clinical reports have described alterations in the immune response of MDD patients such as changes in antibody levels and complement deficiencies (Legros et al., 1985), a variation in soluble mediators such as cytokines and numeric alterations in several sub-sets of lymphocytes (Zorrilla et al., 2001), polarization towards a Th2 type circulatory cytokine profile (Elenkov, 2004; Pavon et al., 2006) and an increase in the development of some infectious and tumorous conditions (Cohen et al., 2007) in non-treated patients.

Some studies have demonstrated the existence of a relation between variations in cytokine and cortisol levels in MDD; one of the first findings of the neuromodulatory effects of cytokines was the induction of depressive symptoms with the therapeutic use of IL-2 and IFNs (Kronfol and Remick, 2000) and the reversion of symptoms upon administration of selective serotonin reuptake inhibitors (SSRI) (Loftis and Hausser, 2004). In addition, pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α also elicit adverse behavioral effects (fatigue, soporific effects) and symptoms of anxiety/depression that can be attenuated by chronic antidepressant treatment. With regard to cortisol, it has been demonstrated that MDD patients present with high levels of this hormone in bodily fluids such as saliva, blood, cerebrospinal fluid and urine that diminished after the administration of SSRI (Axelson et al., 1993; Huber et al., 2006; Nikisch et al., 2005b).

SSRI were designed to compensate for altered levels of serotonin, usually this therapy is administered over a one-year period comprising three stages: acute (6–12 weeks), continuation (4–9 months) and maintenance ($\geq$1 year) (Kupfer, 1991). By progressively restoring the balance in CNS neurotransmitter levels in depressed patients, the administration of SSRI may play a role in modifying cortisol levels and circulating cytokine profiles of these patients (Leo et al., 2006; Nikisch et al., 2005b).

Several clinical studies have reported the effects of SSRI on the immune and neuro-endocrine response. One of the main pharmacologic effects induced by SSRI is to increase serotonin (5-HT) levels in the circulation (Blardi et al., 2002). At the endocrine level these drugs cause a decrease in circulating cortisol levels by reestablishing the down-regulated glucocorticoid receptor sensitivity (Okuyama-Tamura et al., 2003). At the immune level the clinical trials that used SSRI can be divided into *in vitro* studies such as those of Maes and Diamond (Diamond et al., 2006; Maes et al., 2005), and those that measured changes in pro-inflammatory cytokine levels in plasma (Leo et al., 2006) and mRNA expression (Tsao et al., 2006). In all previous studies the administration and evaluation of antidepressant therapy was carried out over short periods of time varying from minutes until 16 weeks. The effects that administration of SSRI has on soluble mediators of the immune and neuro-endocrine response in a 52-week follow-up of depressed patients, as presented in this study, have not been previously reported.

Although the major source of cytokines are cells of the immune system, other cell types like endothelial cells, fibroblasts, adipocytes and smooth muscle cells, may contribute to their circulatory levels (Hiscock et al., 2004; Keller et al., 2005; Kern et al., 2001). Cytokines are considered neuromodulatory and immunomodulatory molecules capable of stimulating both immune and nervous (central and peripheral) systems (Ader et al., 2001; Schiepers et al., 2005; Tracey, 2002). Cytokine-releasing cells express functional receptors for neurotransmitters, glucocorticoids and cytokines which include receptors such as the 5-HT_{1A} and 5-HT_2 (Gonzalez et al., 2007; Lima and Urbina, 2002; Sternberg, 2006), the glucocorticoid and mineral corticoid receptors, and the five families of cytokine receptors, which are constitutively expressed (De Kloet et al., 2007; Paul, 2003). By binding to these receptors, soluble mediators like hormones, neurotransmitters and cytokines can modulate the cytokine profile of MDD patients. Previously, our group reported that MDD patients without pharmacological treatment present with predominant Th2 cytokine secretion profile associated with high cortisol levels (Pavon et al., 2006).

Thus, the aim of the present study was to determine changes in cytokine and cortisol levels during a chronic treatment with SSRI for MDD.

2. Materials and methods

2.1. Participants

2.1.1. Patients

The outpatient clinic of the Instituto Nacional de Psiquiatria "Ramón de Fuente" in Mexico City, assessed 216 individuals and recruited a total of 31 Mexican patients that met inclusion criteria from January 2004 to December 2006. Patient recruitment was made following the clinical experimental procedures set out in INPRF-2318 research protocol, approved by the ethics committee of Instituto Nacional de Psiquiatría, México.

The inclusion criteria for this study included participants without medical illnesses, without pharmacological treatments (including psychotropic drugs), without histories of allergies or allergic reactions, and those without mental disorders, including symptoms of dysthymia or chronic depression. Criteria also included a body mass index (BMI) $\leq$25 and low coffee (2 cups/day), alcohol (3 measures/week) or tobacco (7 cigarettes/day) intake. Women who were pregnant were excluded from the study.

All subjects were diagnosed by psychiatrists, who applied the validated Spanish version of the Mini-International Neuropsychiatric Interview (Heinze, 2000), a standardized