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Does escitalopram reduce neurotoxicity in major depression?

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ABSTRACT

A pro-inflammatory state and a dysregulation in the tryptophan/kynurenine pathway have been documented in depression. This study examined whether treatment with the SSRI, escitalopram (ESC), could suppress inflammation and favorably shift metabolites of the kynurenine pathway in patients with major depressive disorder (MDD) within the utilized treatment period. Twenty seven healthy control subjects were included for comparison. Thirty patients were enrolled after completing baseline assessments. They received a 12-week ESC monotherapy. Twenty subjects were completers. Clinical assessments were carried out at each visit using the HAM-D, HAM-A, CGI and BDI rating scales. Blood samples were collected at each assessment and stored until analyzed. Cytokines were analyzed with Randox multiplex assay and tryptophan and kynurenine metabolites were analyzed using HPLC/GCMS. Baseline plasma concentrations of *hs*CRP, TNFα, IL6 and MCP-1 were significantly higher in patients compared to healthy controls. IL10 trended toward an increase. Baseline plasma IL1β correlated significantly with IL1α, and IL4. Patients showed significant improvement in all outcome measures with a high remission rate. Significant correlations were obtained between specific symptoms and certain biomarkers at baseline but these correlations must be viewed as very preliminary. During ESC treatment concentrations of inflammatory biomarkers did not change except for TNFα that trended lower. Metabolites and ratios of the tryptophan/kynurenine pathway showed reductions of the neurotoxic metabolites, 3-hydroxykynurenine and quinolinic acid, 3-hydroxykynurenine/kynurenine, quinolinic acid/tryptophan, kynurenic acid/quinolinic acid and quinolinic acid/3-hydroxykynurenine. The results indicate that ESC may exert its antidepressant effect in part through inhibition of synthesis of certain neurotoxic kynurenine metabolites and possibly also through reduction of the inflammatory response, although there was no concordance in the time course of changes between antidepressant efficacy and reversal of the pro-inflammatory status.

1. Introduction

The link between major depressive disorder (MDD) and serotonergic function is well established. Additionally, depression has been consistently associated with changes in peripheral biomarkers indicative of a chronic, albeit subthreshold, pro-inflammatory state. Increases in pro-inflammatory cytokines and an imbalance between pro- and anti-inflammatory cytokines in depression have been well documented in the literature (Anisman et al., 1999; Connor and Leonard, 1998; Kaestner et al., 2005; Kim et al., 2002; Lanquillon et al., 2000; Mikova et al., 2001; Thomas et al., 2005; Myint et al., 2005; Piletz et al., 2009). Treatment with pro-

Abbreviations: MDD, Major depressive disorder; ESC, Escitalopram; HAM-D, Hamilton depression scale; HAM-A, Hamilton anxiety scale; CRP, C-reactive protein; IL, Interleukin; TNF, Tumor necrosis factor; MCP, Monocyte chemoattractant protein; TRP, Tryptophan; KYN, Kynurenine; KYNA, Kynurenic acid; 3HK, 3-hydroxy-kynurenic acid; QUIN, Quinolinic acid.

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inflammatory cytokines, such as interferon-α for melanoma or hepatitis C, can induce severe depression in a significant percentage of patients receiving such treatments.

Since the late 1960's a reduction in tryptophan (TRP) availability for serotonin synthesis due to a metabolic shunt toward the kynurenine (KYN) pathway has been considered to be a likely pathophysiological mechanism in depression. This has been known as the 'kynurenine shunt" and the "kynurenine theory of depression" (Lapin and Oxenkrug, 1969). With the demonstration that the enzyme, indoleamine 2,3-dioxygenase (IDO), is activated by pro-inflammatory cytokines, such as interferon-γ, interferon-α, interferon-β and interleukin-2 (Carlin et al., 1987, 1985; Hu et al., 1995; Taylor and Feng, 1991; Yasui et al., 1986), the connection between pro-inflammatory changes and TRP depletion in depression has gained interest in psychiatric research. Many studies have confirmed the presence of a pro-inflammatory state in depression, and have addressed the involvement of IDO activity and its association with TRP depletion, or TRP diversion to KYN. In addition, KYN metabolites from the downstream metabolism of TRP have been shown to be neuroactive. Specifically, 3-hydroxy-kynurenine (3HK) and quinolinic acid (QUIN), the N-methyl-D-aspartate (NMDA) receptor agonist, have been demonstrated to exert neurotoxic effects (Bender and McCreanor, 1985; Chiarugi et al., 2001). By contrast, kynurenic acid (KYNA), the NMDA receptor antagonist, exerts a neuroprotective effect (Perkins and Stone, 1982). Taken together, these intriguing findings have led Myint and Kim (2003) to postulate an imbalance in KYN metabolism as a possible pathophysiological mechanism in depression (Fig. 1). In a later study Myint et al. (2007) assessed the profile of TRP, the competing large amino acids and the KYN metabolites, in drug naïve and drug-free depressed patients before and after 6-weeks of SSRI treatment. They reported that the plasma KYNA and the KYNA/KYN ratio were significantly reduced in patients compared to healthy control (HC) subjects. The 6-week SSRI treatment significantly increased KYNA/KYN ratios in those drug naïve patients with first episode of depression.

The present study had two major goals: a) to confirm the presence of a pro-inflammatory state in depression and compare a panel of biomarkers of inflammation and metabolites of the tryptophan/kynurenine pathway in MDD subjects at pretreatment and a carefully selected cohort of healthy control subjects, and b) to investigate the longitudinal profile of key inflammation biomarkers related to TRP metabolism and TRP/KYN pathway metabolites in the same MDD patients treated with escitalopram (ESC) for 12 weeks. An ancillary goal was to seek possible associations between specific symptoms of depression and the biomarkers analyzed. We chose ESC because it exhibits a highly selective, dose-dependent inhibitory effect on the serotonin transporter (SERT) and inhibition of serotonin reuptake into the presynaptic terminal enhances serotonergic activity postsynaptically. Numerous controlled trials have shown the advantage of ESC over citalopram in terms of remission rates and reduction of clinical symptoms (Lalit et al., 2004; Moore et al., 2005; Yevtushenko et al., 2007; Ou et al., 2011). A meta-analysis comparing ESC and citalopram supported the results of the controlled studies (Montgomery et al., 2011). In addition, ESC has a more favorable side effect profile compared to other SSRIs or SNRIs (Kennedy et al., 2009). It is generally well tolerated as maintenance treatment and, compared to other SSRIs and SNRIs, ESC has the highest matched acceptability and efficacy rate (Kirino, 2012), although weight gain and sexual dysfunction can be limiting side effects with this agent as well. Regarding a possible anti-inflammatory effect of ESC, some reports have demonstrated anti-inflammatory effects in measures of soluble interleukin-2 receptor (sIL2R) (Eller et al., 2008), or C-reactive protein (CRP) (Chavda et al., 2011). However, another study found no anti-inflammatory effect of ESC (Haastrup et al., 2012). These discrepancies could be due to the fact that those studies did not assess a wider range of pro- and anti-inflammatory molecules thereby rendering the results inconclusive. Additionally, the length of treatment with an antidepressant is likely to be critical in assessing the possible anti-inflammatory action of these agents (Piletz et al., 2009).

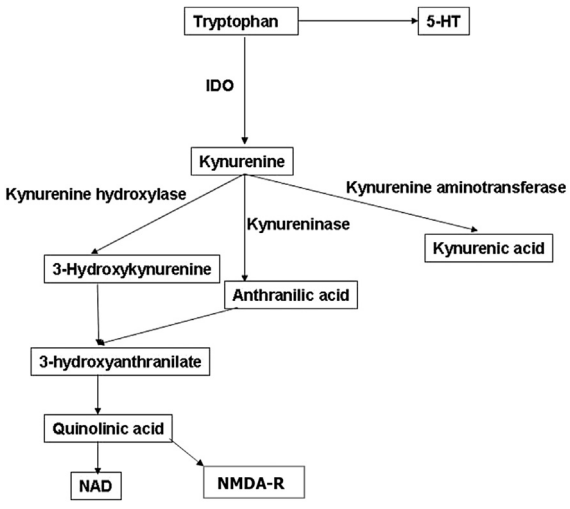

Fig. 1. Tryptophan degradation pathway.

2. Methods

2.1. Study population

The study was approved by the Institutional Review Board of Loyola University Medical Center and was conducted according to the principles expressed in the Declaration of Helsinki. Potential candidates were screened to determine eligibility for the study by meeting inclusion criteria and by being capable of understanding the nature of the study and giving informed consent. Males and females between 20 and 65 years of age who met DSM-IV criteria for major depressive disorder (MDD), first episode or recurrent type, and were otherwise physically healthy were considered. The index episode had to be of at least 2 weeks' duration and the patient could not have received pharmacological treatment in the preceding four weeks. A minimum score of 18 on the 17-item Hamilton Depression Scale (HAM-D 17) was required for admission into the study. The exclusion criteria stipulated that the subject had to be free of heart disease, active inflammation including gum disease, hypertension, dyslipidemia, diabetes mellitus, history of smoking or substance abuse in the preceding 6 months. Female subjects could not be pregnant or lactating or be on oral contraceptives. Sexually active females had to use reliable contraception for the duration of the study. The presence of active suicidality and any other Axis I diagnosis were exclusion criteria. A total of 30 patients met the above screening criteria and were eligible to be enrolled in the study. They underwent all baseline assessments as stipulated in the protocol and were started on ESC on an open label basis with dose titration at the discretion of the psychiatrist. During the ensuing 8 weeks of treatment 10 subjects were lost to attrition (1 became actively suicidal, 4 dropped out due to side effects and 5 dropped out for reasons unrelated to the study). Twenty patients completed the minimum 8 weeks of treatment to be considered completers. One subject was withdrawn after the 8th week due to non-response and the observations at week 8 were carried forward for statistical analyses. A total of 19 patients completed 12 weeks.