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Proinflammatory Status in Major Depression: Effects of Escitalopram

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Stress-related psychiatric disorders (eg, major depression, bipolar disorder, anxiety disorders, and posttraumatic stress disorder) have been variably associated with pervasive loss of homeostasis in the autonomic nervous system. This loss, often referred to as allostatic load, leads to dysregulation of the autonomic nervous system with sympathetic overdrive and vagal tone diminution. An efferent vagal pathway has been identified, the cholinergic anti-inflammatory pathway, which is believed to exert an anti-inflammatory action. When vagal tone is diminished, inflammation becomes disinhibited and one would expect specific inflammation biomarkers to become elevated in the brain and the periphery. This provides a plausible mechanism for the elevated blood levels of proinflammatory cytokines and chemokines previously reported in depressed patients compared with healthy controls by other groups and ours (Piletz et al, 2009). When proinflammatory cytokines become chronically elevated, endothelial dysfunction eventually ensues, ultimately leading to atherosclerosis and atherothrombosis. Of interest is whether this proinflammatory status of depression can be reversed by antidepressant treatment and/or whether the proinflammatory changes normalize when the depressed mood is alleviated.

Our previous study using venlafaxine-XR (a serotonin-norepinephrine reuptake inhibitor) to treat depression suggested that the elevated plasma proinflammatory cytokines in depression were not normalized after 8 weeks despite mood normalization (Piletz et al, 2009). Other studies have suggested that selective serotonin reuptake inhibitors (SSRIs) might be unique in exerting down-immunoregulatory effects over 6 to 8 weeks of treatment (Lanquillon et al, 2000; Tuglu et al, 2003; Basterzi et al, 2005).

We report here preliminary findings of a follow-up study of six proinflammatory biomarkers (TNFα, MCP1, IL1β, IL6, CRP, and MPO) in the plasma of 14 patients with major depression (MDD) and 8 healthy controls. Seven of the patients were restudied after 12 weeks of treatment with escitalopram (ESC). Prior to treatment, MDD patients had higher concentrations (pg/mL) than controls of TNFα (7.4 ± 0.5 vs 4.0 ± 0.7, $P = 0.001$) and MCP1 (122.3 ± 17 vs 69.6 ± 9, $P = 0.01$) but lower concentrations of IL1β (1.8 ± 0.2 vs 4.3 ± 0.5, $P = 0.001$). Covariate and correlation analyses revealed no biomarker relationships with severity of depression (HAM-D scores). However, the low IL1β finding in depressed patients may have been affected by higher BMIs in our depressed patients relative to controls: BMI was higher in MDD patients ($P = 0.003$), and BMI was negatively correlated with IL1β among the patients ($r = -0.5$, $P = 0.02$). Following 12 weeks of ESC (n = 7), none of the biomarkers normalized even though the severity of depression (HAM-D) and anxiety (HAM-A) significantly normalized in 6 patients. This finding is in line with our prior study of venlafaxine treatment for depression (Piletz et al, 2009).

Thus, our findings confirm previous findings that some proinflammatory biomarkers are high in untreated depressed patients and that successful treatment—in this case with the most selective SSRI—fails to normalize the abnormality. We cannot rule out the possibility that extended treatment beyond 12 weeks may ultimately normalze the proinflammatory status of depression.

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