Cytokine Changes and Tryptophan Metabolites in Medication-Naive and Medication-Free Schizophrenic Patients

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Cytokine • Inflammatory response • Tryptophan • Tryptophan breakdown • Schizophrenia

Abstract
Cytokine imbalances especially between CD4+ helper type (Th) 1 and Th2 and tryptophan breakdown were reported to be involved in the pathophysiology of schizophrenia. The hyperactive inflammatory response system could induce enhanced tryptophan breakdown. This study aimed to investigate the relationship between cytokine changes, tryptophan breakdown parameter changes and clinical parameters in patients with schizophrenia in comparison with normal controls. In the plasma of schizophrenic patients, Th1-specific interferon-γ was significantly higher (F = 7.485, p = 0.007) and Th2-specific interleukin (IL)-4 was significantly lower (F = 126.327, p < 0.0001). The Th1-related cytokine IL-2 was lower (F = 5.409, p = 0.021) but tumor necrosis factor-α (TNF-α) and Th2-related IL-6 were higher (F = 95.004, p < 0.0001 and F = 108.77, p < 0.0001, respectively) in the plasma of schizophrenic patients. After 6 weeks of treatment, IL-6 and TNF-α were significantly reduced (t = −3.762, p < 0.0001 and t = −2.668, p = 0.008). At the time of admission, plasma tryptophan concentrations were lower (F = 6.339, p = 0.012) in schizophrenic patients and were negatively correlated with the total positive symptoms score (r² = −0.343, p = 0.004). After 6 weeks of medication, both plasma tryptophan and kynurenine concentrations were increased (t = −2.937, p = 0.005 and t = −3.214, p = 0.002, respectively). The findings of this study indicate a hyperactive pro-inflammatory response inducing a change in tryptophan metabolism that might be related to the development of positive symptoms in schizophrenia.

Introduction
The importance of the tryptophan-serotonin interaction in the pathophysiology of major psychiatric disorders has been well documented [1–9]. Serotonin is synthesized from the essential amino acid tryptophan by tryptophan hydroxylase. Tryptophan, instead of being synthesized into 5-hydroxytryptophan and serotonin, can also be metabolized into kynurenine. This could result in tryptophan depletion which in turn induces serotonin depletion. An increased catabolism of tryptophan is the result of the enhanced activity of kynurenines 3,4-dioxygenase (TDI) in the liver [10] or indoleamine 2,3-dioxygenase...