European Neuropsychopharmacology (2016) 26, 1286–1296

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Increased plasma levels of competing amino acids, rather than lowered plasma tryptophan levels, are associated with a non-response to treatment in major depression

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Received 4 February 2016; received in revised form 12 April 2016; accepted 8 May 2016

KEYWORDS
Depression;
Inflammation;
Serotonin;
Tryptophan;
Kynurenine;
Indoleamine 2,3-dioxygenase

Abstract
Lowered plasma tryptophan (TRP) and TRP/competing amino acid (CAA) ratio may be involved in the pathophysiology of major depression (MDD). Increased cortisol and immune-inflammatory mediators in MDD may affect the availability of TRP to the brain.
We investigated whether baseline or post-treatment TRP, CAAs and TRP/CAA ratio are associated with a treatment response in MDD and whether these effects may be mediated by cortisol or immune biomarkers.
We included 50 medication-free MDD patients with a depressive episode (DSM diagnosis) and assessed symptom severity with the Inventory of Depressive Symptomatology (IDS) before and after treatment as usual for 12 weeks (endpoint). Plasma levels of TRP, CAAs, the ratio, cortisol, CRP and 6 selected cytokines were assayed. The primary outcome was a 50% reduction in the IDS, while the secondary was a remission of the depressive episode.

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http://dx.doi.org/10.1016/j.euroneuro.2016.05.005

In IDS non-responders, CAAs increased and the TRP/CAA ratio decreased, while in IDS responders CAAs decreased and the TRP/CAA ratio increased from baseline to endpoint. In patients who were still depressed at endpoint TRP and CAAs levels had increased from baseline, while in remitted patients no such effects were found. Increases in CAAs were inversely correlated with changes in interleukin-1 receptor antagonist levels.
The results show that increased CAA levels from baseline to endpoint are associated with a non-response to treatment in MDD patients. This suggests that the mechanism underpinning the CAA-related treatment resistance may be related to changes in immune pathways. CAA levels and amino acid metabolism may be new drug targets in depression.

1. Introduction

Although estimates of lifetime prevalence and course vary considerably across countries, the World Health Organization (WHO) has ranked major depression disorder (MDD) the 4th leading cause of disability worldwide and estimates that by 2020, it will be the second leading cause (Kessler and Bromet, 2013). An estimated lifetime prevalence of 16% has been reported (Andrade et al., 2003; Kessler and Ustun, 2004; Kessler et al., 2010). Treatment includes psychotherapy and pharmacological agents, mainly antidepressants (AD). The tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were discovered in the late 1950s and early 1960s. Today, practical guidelines recommend treating moderate to severe depressive episode with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (Bauer et al., 2007; National Institute for Health and Clinical Excellence, 2009; Ramasubbu et al., 2012). The response to treatment is, however, slow and difficult to predict, and a substantial part of patients will not respond to treatment at all.

The serotonin hypothesis of depression was introduced by Coppen in 1967, and has been a major hypothesis in the pathophysiology in MDD (Coppen, 1967). Tryptophan (TRP), the precursor of serotonin, is an essential amino acid, which is metabolized under constricted control. The availability of plasma TRP to the brain determines the rate of serotonin synthesis in the brain (Moir and Eccleston, 1968). Other amino acids, notably tyrosine (TYR), valine (VAL), phenylalanine (PHE), leucine (LEU) and isoleucine (ILE), compete with TRP for transport across the blood brain barrier (BBB) (referred to as competing amino acids, CAAs) and therefore modulate the availability of TRP to the brain (Fernstrom, 1983). A decreased TRP availability due to increased levels of CAAs may reduce the biosynthesis of serotonin (Fernstrom et al., 1975). TRP homeostasis is generally maintained via the oxidative pathway in which TRP is degraded to several neuroactive compounds in an enzymatic cascade known as the kynurenine (KYN) or the TRP catabolite (TRYCAT) pathway. Quantitatively, this pathway is the major metabolic pathway of TRP; the main exception is the brain, in which almost half of the TRP is used for serotonin synthesis.

In a recent meta-analysis, Ogawa and co-workers concluded that there is convincing evidence for lowered plasma TRP in patients with MDD (Ogawa et al., 2014). These findings support the serotonin hypothesis of MDD (Cowen et al., 1989). While most studies reported significantly lower TRP and TRP/CAA ratio in MDD patients, some studies also found negative results (Myint et al., 2007; Pinto et al., 2012). In our recent study of involvement of the KYN pathway in MDD (Dahl et al., 2015), the levels of TRP and TRP/CAA ratio were not significantly different between depressed MDD patients and controls. Some data has indicated that a lowered TRP/CAA ratio is associated with treatment resistance in MDD (Maes et al., 1997).

Growing evidence has suggested that the lowered availability of TRP to the brain in MDD may be a consequence of increased cortisol production and activated immune-inflammatory pathways (Maes et al., 1991a, 1991b, 1993a., 1994). There is now evidence that activation of immune, e.g. Thelper (Th)-1 and inflammatory pathways (M1) with increased production of interferon-(IFN)γ and increased cortisol production are important in the pathophysiology of MDD (Greden et al., 1980; Maes et al., 1993b; Leonard and Maes, 2012). IDO is activated principally via Th1 responses via IFNγ. The first papers in depression indicating that tryptophan is connected with immune activation and increased IFNγ production were published in 1993b and 1994 (Maes et al., 1994). Previously, relationships between IFNγ and tryptophan catabolism were detected in vivo and in vitro (Yoshida et al., 1981; Werner-Felmayer et al., 1989; Brown et al., 1991).

Th1 cytokines such as IFNγ and hypercortisolemia may activate indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), thereby inducing the production of TRYCATs and lowering plasma TRP (Pemberton et al., 1997; Fujigaki et al., 2001). In MDD inverse associations are detected between lowered availability of plasma TRP to the brain and activated immune-inflammatory pathways and increased glucocorticoid activity (Maes et al., 1991a, 1991b, 1993a, 1994). This is indicative of a close relationship between immune system activity, glucocorticoid activity and the IDO/TDO-induced TRYCAT pathway (Leonard and Maes, 2012). We have recently reported a broader activation of the cytokine network in MDD (Dahl et al., 2014). Most importantly, recovery from depression was associated with normalized cytokines levels. Normalization of the cortisol axis may predict clinical recovery in MDD patients (Greden et al., 1980).

The aim of the present study was to delineate whether baseline or post-treatment TRP, CAAs and TRP/CAA ratio are associated with the response to treatment of acute depressive episode in MDD and whether these putative associations are modulated via changes in glucocorticoid activity or the cytokine network.