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Ongoing episode of major depressive disorder is not associated with elevated plasma levels of kynurenine pathway markers

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Summary
Background: It has been suggested that the development of depressive symptoms as a result of cytokine therapy is attributable to cytokine-induced elevated activity of the kynurenine pathway. The few studies of this mechanism in patients with common major depressive disorder (MDD) have yielded inconsistent results. The aim of the present study was to identify markers of the kynurenine pathway in a clinical MDD sample with increased cytokine levels.
Methods: Fifty medication-free MDD patients with a depressive episode and 34 healthy controls were included at baseline; the patients were followed for 12 weeks. Before initiating treatment, the patients were diagnosed and assessed for depressive symptoms and their blood was analyzed for tryptophan and its metabolites in the kynurenine pathway. The clinical assessments and metabolite measurements were repeated after 12 weeks of ''treatment as usual''.

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Results: We did not find significant elevation of kynurenine plasma markers in patients with a depressive episode compared to healthy controls, despite elevated cytokine levels in the patients. Clinical depression scores were significantly reduced after 12 weeks, but no significant change in the plasma kynurenine pathway plasma markers was observed.
Conclusion: The obtained results do not support the hypothesis that MDD depressive episodes are associated with elevated activity in the kynurenine pathway. This suggests that the pathophysiology underlying depressive episodes in common MDD differs from that of interferon induced depression. Our results warrant further study of the interplay between the kynurenine pathway and the cytokine activation patterns in these conditions.

1. Introduction

The etiology of major depressive disorder (MDD) is regarded as multi-causal (Belmaker and Agam, 2008), and the pathophysiology still remains elusive. A connection between depression and alterations in the immune system has been found in numerous studies (Smith, 1991; Maes et al., 1993; Sluzewska et al., 1996; Dantzer and Kelley, 2007; Kim et al., 2007; Leonard and Maes, 2012). The concept that inflammatory factors could cause depression was supported by findings that recombinant human cytokines led to depression in 30—45% of patients in clinical trials of various cancers and viral hepatitis (Miyaoka et al., 1999; Musselman et al., 2001). The causality seems clear in depression induced by cytokine therapy, and experimental studies have revealed detailed information about the interplay between the immune system and the central nervous system (CNS) (Dantzer et al., 2011). In a recent study we showed that plasma concentrations of a range of cytokines, including pro- and anti-inflammatory cytokines, and T-helper (Th)1 and Th2 cytokines, were elevated during an MDD depressive episode, but normalized after recovery (Dahl et al., 2014).

The development of depressive symptoms upon interferon therapy is suggested to be caused by activation of the enzyme indoleamine 2,3-dioxygenase (IDO) (Myint and Kim, 2014), as this enzyme is known to be stimulated by proinflammatory cytokines (Capuron et al., 2003; Wichers et al., 2005). IDO converts the essential amino acid tryptophan (TRP) into kynurenine (KYN), which is then further metabolized along the kynurenine pathway. TRP is also the precursor for serotonin (5-HT), a neurotransmitter regarded as essential for regulation of mood (Hamon and Blier, 2013). Therefore, in states of inflammation, TRP is being catabolized via the kynurenine pathway rather than being used for serotonin production. The degradation of TRP can also be carried out by the enzyme tryptophan 2,3-dioxygenase (TDO), which is stimulated by cortisol. Together IDO and TDO regulate the first step of TRP degradation. KYN is further catabolized to kynurenic acid (KA), or alternatively via a separate branch of the pathway to 3-hydroxy kynurenine (3-OH KYN) and other metabolites, including quinolinic acid (QA), and eventually on to the final product of the pathway, nicotinamide adenine dinucleotide (NAD).

It has been suggested that increasing kynurenine pathway activity may lead to depression in different ways. First, it may decreasethe availability of TRP for serotonin synthesis (Capuron et al., 2003), and reduced activity in the serotonin system may subsequently lead to depressive symptoms (Neumeister et al., 2004). Furthermore, the TRP catabolites (TRYCATs) formed along the KYN pathway are able to cause neurotoxicity and regulate glutamate neurotransmission. The formation of 3-OH KYN leads to the production of reactive oxygen species and initiates neuronal apoptosis (Okuda et al., 1998; Stone et al., 2001). The metabolites QA and KA both bind to the *N*-methyl-D-aspartate (NMDA) receptor; QA is an agonist (Stone, 1993; de Carvalho et al., 1996), while KA is an antagonist (Stone, 1993; Hilmas et al., 2001). Interestingly, it has been shown that ketamine — acting as an NMDA receptor antagonist and thus having the potential to interfere with the KYN pathway activity — is an effective therapy against treatment-resistant depression (Zarate et al., 2006) and suicidality (Price et al., 2009). A recent animal model study confirmed that peripheral inflammation induces KYN pathway activity in the brain, and that the resulting depressive-like effects can be specifically counteracted by ketamine (Walker et al., 2013).

The KYN/TRP ratio reflects the activity of the initial enzymes of the pathway (i.e., IDO and TDO), and is increased by inflammatory cytokines. Measures of other metabolites produced by the kynurenine pathway and their ratios reflect the activity of other subsequent enzymes, as well as the balance in activity between the two main branches of the pathway (Ormstad et al., 2013). TRP has to compete with certain amino acids, the so-called competing amino acids (CAAs), for the transport over the blood—brain barrier (BBB). Thus, the index [(tryptophan titer $\times$ 100)/CAAs titer], the so-called TRP index, can be used as a measure of TRP availability in the brain (Wichers et al., 2005). Moreover, since TRP availability is a limiting factor in the synthesis of 5-HT, the TRP index is also an indicator of 5-HT production in the brain; this could be relevant to the development of depressive symptoms.

It is well established that the kynurenine pathway markers in the blood are increased in cytokine-therapy-induced depression (Capuron et al., 2003; Wichers et al., 2005). Similarly, increased kynurenine pathway activation has been observed in suicidal patients, both in peripheral blood (Sublette et al., 2011) and in the cerebrospinal fluid (CSF) (Erhardt et al., 2013; Bay-Richter et al., 2014). Sublette et al. (2011) found an increased KYN/TRP ratio, which is indicative of an activated pathway, in the peripheral blood of suicide attempters, while Erhardt et al. (2013) and