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Altered tryptophan catabolite concentrations in major depressive disorder and associated changes in hippocampal subfield volumes

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ABSTRACT

Background: Tryptophan depletion is a well-replicated biological finding in Major Depressive Disorder (MDD). The kynurenine pathway (KP) and its rate-limiting tryptophan degrading enzyme, indolamine 2,3 dioxygenase (IDO), have been implicated in the pathogenesis of depression. IDO expression is driven by inflammatory cytokines, providing a putative link between inflammation and neuropathology. This study examined circulating concentrations of C-reactive protein (CRP), plasma tryptophan, kynurenine (KYN), kynurenic acid (KYNA) and quinolinic acid (QUIN) and whole blood mRNA expression of IDO in patients with major depressive disorder (MDD) compared with healthy controls (HC).

Methods: A diagnosis of major depression was made according to DSM-IV. Depression severity was assessed using the Hamilton depression (HAM-D) rating scale. 74 MDD patients, 39 with a first presentation of MDD (fpMDD) and 35 with chronic or recurrent episodes (rMDD), and 37 HC were recruited to the study. Whole blood and plasma samples were collected. Expression of markers in whole blood were measured by PCR, circulating CRP by ELISA and KP metabolites by LC–MS/MS. Hippocampal cornu ammonis (CA) and subiculum volumes were determined by MRI and calculated using FreeSurfer.

Results: Tryptophan concentrations were significantly reduced in MDD compared to HC. There was a positive correlation between QUIN and both CRP concentrations and whole blood IDO1 in MDD. KYNA concentrations were reduced in MDD patients presenting with a first episode (fpMDD) compared to those presenting with recurrent depression (rMDD) and HC. By contrast QUIN concentrations were elevated in rMDD compared to fpMDD and HC. KYNA/QUIN was reduced in MDD and rMDD but not fpMDD compared to HC. Hippocampal subfield volumes were smaller in MDD patients than HC for CA1 (left only), CA2/3 (left and right) and CA4 (right only). CRP and CA1 volumes were negatively correlated bilaterally in MDD patients. KYNA and subiculum volume were positively correlated bilaterally.

Discussion: This study found evidence of KP metabolism imbalance in MDD patients in addition to tryptophan reduction and mild immune activation. Relationships between CRP and KYNA with some hippocampal subfield volumes in MDD patients suggest that this inflammatory signature may be associated with reduced hippocampal subfield volumes in depression.

Abbreviations: 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; 5-HT, 5-hydroxytryptamine (serotonin); BBB, blood brain barrier; ACMSD, 2-amino-3-carboxymuconate-6-semialdehy dedecarboxylase; CES-D, center for epidemiology scale-depression; CHAID, Chi-square automatic interaction detector; CNS, central nervous system; CRP, C-reactive protein; CTQ, childhood trauma questionnaire; DSM, diagnostic and statistical manual; ELA, early life adversity; ELISA, enzyme linked immunosorbent assay; fpMDD, first presentation major depressive disorder; HAM-D, Hamilton depression rating scale; HPAA, hypothalamic-pituitary-adrenalaxis; HRB, health review board; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; KAT, kynurenine aminotransferases; KP, kynurenine pathway; KYN, kynurenine; KYNA, kynurenic acid; LC–MS, liquid chromatography-mass spectrometry; LC–MS/MS, liquid chromatography tandem mass spectrometry; mRNA, messenger ribonucleic acid; MDD, major depressive disorder; NMDAR, *N*-methyl-D-aspartate receptor; PSQI, Pittsburgh sleep quality index; qPCR, quantitative polymerase chain reaction; QUIN, quinolinic acid; rMDD, recurrent major depressive disorder; RQ, relative quantification; SD, standard deviation; SEM, standard error of the mean; SPSS, statistical package for the social sciences; SSRI, selective serotonin reuptake inhibitor; TDO, tryptophan 2,3-dioxygenase; TNF, tumour necrosis factor; TRYP, tryptophan

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1. Introduction

The kynurenine pathway (KP) is the major metabolic pathway for tryptophan in the body resulting in the production of kynurenine (KYN) and several downstream metabolites (O'Farrell and Harkin et al., 2017; Stone et al., 2013). Induction of the rate limiting enzyme in the KP, indolamine 2,3 dioxygenase (IDO) is driven by inflammatory cytokines which has been proposed as a mechanism by which inflammation can precipitate depressive symptoms via tryptophan depletion. Most particularly activation of the KP and tryptophan depletion has been observed in depression that occurs secondary to exogenous administration of the cytokines IFN-alpha and IL-2 (Raison et al., 2010). The KP involves several enzymes which further catabolize KYN via the kynurenine 3-monooxygenase (KMO) branch into quinolinic acid (QUIN) and through the kynurenine aminotransferase (KAT) arm into kynurenic acid (KYNA). Elucidation of a role for KP activation in MDD has been less clear (Myint et al., 2012; Reus et al., 2015), with some reports of an increase in the tryptophan breakdown index (KYN/tryptophan ratio) and a decrease in concentrations of KYNA in depressed patients relative to healthy controls (Allen et al., 2018; Schwieler et al., 2016). Based on these outcomes Myint and colleagues suggested that KYN was metabolised along the KMO arm of the pathway, although to date, few investigations have reported KP metabolites and expression of the enzymes that drive their production downstream of KMO in depressed patients. KYNA is largely regarded as a neuroprotective compound due to its NMDA receptor antagonist properties whereas QUIN is an excitotoxin (Schwarcz and Stone, 2017). In this regard a suggestion of an imbalance in production of downstream KP metabolites formed the basis of the "neurodegeneration hypothesis of depression" proposed by Myint and Kim (2003). In addition, based on available pre-clinical data demonstrating that KYN itself produces depressive behaviour in an animal model of depression, a role for downstream metabolism of KYN in mediating depressive behaviours has been postulated (O'Connor et al., 2009; O'Farrell and Harkin et al., 2017).

MDD is a recurrent, relapsing and remitting disorder and determining the biological differences between patients presenting with first episode of depression compared to patients who have had multiple episodes is informative with regard to illness progression. fpMDD patients may not present with the same degree of biological dysregulation experienced by recurrently depressed rMDD patients, as recurrent depressives tend to have more severe symptoms and increased co-morbidities (Gili et al., 2011; Roca et al., 2011). While greater inflammation has been reported in patients with rMDD (Valkanova et al., 2013) no studies have been published to date regarding possible differences in KP metabolite measurement between fpMDD and rMDD. Investigating the impact of chronicity of MDD on the KP may provide important insights when implicating the pathway in MDD pathogenesis.

Depression is associated with a low-grade inflammation, detectable as increased expression and circulating concentrations of pro-inflammatory cytokines, chemokines and acute phase proteins. In the case of IL-6, IL-1 and C-reactive protein (CRP) original findings have been supported by meta-analyses (Dowlati et al., 2010; Liu et al., 2012). The immune system is functionally regulated by the hypothalamic pituitary adrenal axis (HPA) where glucocorticoids regulate inflammatory response (Elenkov et al., 1999) and increased inflammation is an established consequence of stress system activation (Miura et al., 2008). Moreover, hepatic tryptophan dioxygenase (TDO) also leads to KP activation. Under normal circumstances TDO activity is relatively stable. Regulation of TDO expression occurs chiefly through glucocorticoid receptor mediated induction. Consequently stress-related changes in the expression of TDO are primarily influenced by activation of the HPA axis through the action of glucocorticoids (for review see O'Farrell and Harkin et al., 2017).

Reductions in hippocampal volume that putatively reflect hippocampal atrophy associated with impaired neurogenesis, reduced neurotrophic function and disturbed glutamatergic transmission are widely reported in MDD (Koo and Duman, 2009; Frodl et al., 2002). Animal models have shown an association between pro-inflammatory cytokine (IL-1) expression, with hippocampal dendritic atrophy, synaptic loss, suppressed neurogenesis and reduced brain derived neurotrophic factor (BDNF) expression in the development of depressive-like behaviours (reviewed by Koo and Duman, 2009). A relationship between inflammation and hippocampal physiology has been proposed and Frodl et al. (2012) show an association between IL-6 and hippocampal volume in depressed patients. Savitz et al. (2015a) reported that the KP ratio KYNA:QUIN may be positively associated with hippocampal volume in unmedicated subjects with MDD raising the possibility that MDD associated changes in KP metabolism may impact the structure of the hippocampus suggesting a pathway through which inflammation may affect hippocampal findings in MDD.

In a recent investigation we reported a negative association between blood IL-1beta expression and morning cortisol reactivity in a cohort of depressed patients indicating a relationship between HPA axis dysregulation and immune system activation (Doolin et al., 2017). In the present investigation we sought to extend our work on this cohort and profile expression of KP enzymes, plasma tryptophan and the circulating tryptophan catabolites KYN, KYNA and QUIN to determine if the KP is activated in these patients and explore possible relationships with hippocampal subfield volumes. A subdivision of the cohort into fpMDD and rMDD was undertaken for comparative purposes to look at how these measures may change over the course of the illness.

2. Materials and methods

2.1. Participant recruitment

In this study, depressed patients (n = 74) were recruited from the Psychiatric Outpatient Department in Tallaght Hospital, Dublin. Recruitment of depressed patients was based on fulfilment of criteria for a Major Depressive Episode (DSM-IV) and a Hamilton depression rating scale (HAM-D) score of > 17 assessed during a clinical interview with a consultant psychiatrist as previously described (Doolin et al., 2017). Patients were excluded from participation in this study if they were known to have any chronic medical conditions or other psychiatric disorders or were on any medication other than antidepressants and the oral contraceptive pill. No participant was undergoing psychological therapy at the time of recruitment.

General participant information was collected upon recruitment including race, marital status, education level (scored on the international standard classification of education, IESCD) including clinical measures such as height, weight (body mass index, BMI), smoking status and medication use were also assessed. Healthy controls (n = 37) were recruited from the local community based on no prior history of mental illness and no chronic medical conditions.

Patients were categorised into groups based on whether or not this was their first presentation with depression (fpMDD) (n = 39) or if they had presented with chronic or recurrent episodes (> 1) of depression (rMDD) (n = 35).

All participants gave fully informed written consent. Ethical approval for this study was granted by the Tallaght Hospital/St. James's Hospital Joint Research Ethics Committee (REC Reference: 2014/12/05/2015-03 List 11).

2.2. Psychiatric rating scales

Patients were asked to complete three self-rating scales to further quantify their depressive symptoms and other factors that might be related to mood. All rating scales were completed under clinical supervision. The Centre for Epidemiological Studies – Depression (CES-D) scale is a 20-item self-report Likert scale. It was completed by the participant and researcher at the time of recruitment to assess the perceived severity of depression symptoms. The possible range of scores