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Research paper

The association between the hypothalamic pituitary adrenal axis and tryptophan metabolism in persons with recurrent major depressive disorder and healthy controls

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ABSTRACT

Objectives: Persistent changes in serotonergic and hypothalamic pituitary adrenal (HPA) axis functioning are implicated in recurrent types of major depressive disorder (MDD). Systemic tryptophan levels, which influence the rate of serotonin synthesis, are regulated by glucocorticoids produced along the HPA axis. We investigated tryptophan metabolism and its association with HPA axis functioning in single episode MDD, recurrent MDD and non-depressed individuals.

Methods: We included depressed individuals (n = 1320) and controls (n = 406) from the Netherlands Study of Depression and Anxiety (NESDA). The kynurenine to tryptophan ratio (kyn/trp ratio) was established using serum kynurenine and tryptophan levels. Several HPA axis parameters were calculated using salivary cortisol samples. We adjusted the regression analyses for a wide range of potential confounders and differentiated between single episode MDD, recurrent MDD and control.

Results: Tryptophan, kynurenine and the kyn/trp ratio did not differ between controls and depressed individuals. Increased evening cortisol levels were associated with a decreased kyn/trp ratio in the total sample (Crude: $\beta = -.102$, $p < .001$; Adjusted: $\beta = -.083$, $p < .001$). This association was found to be restricted to recurrently depressed individuals (Crude: $\beta = -.196$, $p < .001$; Adjusted: $\beta = -.145$, $p = .001$). Antidepressant treatment did not affect this association.

Conclusions: Our results suggest that an imbalance between HPA axis function and tryptophan metabolism could be involved in recurrent depression.

1. Introduction

Major depressive disorder (MDD) is predicted to be the leading cause of disease burden worldwide by the year of 2030 (World Health Organization, 2008). This is largely attributed to the chronic and recurrent nature of the disease. Persistent neurobiological changes in (i) the regulation of cortisol secretion through the hypothalamic pituitary adrenal axis (HPA axis) and (ii) serotonergic functioning have been suggested to be involved (Bhagwagar and Cowen, 2008; Cowen, 2010; Pariante and Lightman, 2008). Tryptophan metabolism, being regulated by cortisol and being crucial in serotonin synthesis, might bridge the gap between these features (Cowen, 2002).

Disturbances of the HPA axis are a common finding in MDD. Several meta-analyses indicated that patients suffering from MDD show increased levels of cortisol throughout the day when compared to healthy controls (Belvederi Murri Martino et al., 2014; Burke et al., 2005; Knorr

Abbreviations: AUCg, Area under the curve with respect to the ground; BMI, Body mass index; CAR, Cortisol awakening response; CIDI, Composite international diagnostic interview; DSM-IV, Diagnostic and statistical manual of mental disorders, fourth edition; DST, Dexamethasone suppression test; HPA axis, Hypothalamic pituitary adrenal axis; hsCRP, High-sensitivity C-reactive protein; IDO, Indoleamine 2,3-dioxygenase; IDS, Inventory of depressive symptoms; IFN-y, Interferon gamma; IL-6, Interleukin-6; Kyn/trp ratio, Kynurenine to tryptophan ratio; MDD, Major depressive disorder; NESDA, Netherlands study of depression and anxiety; SNRI, Serotonin-norepinephrine reuptake inhibitors; SSRI, Selective serotonin reuptake inhibitor; TCA, Tricyclic antidepressant; TDO, Tryptophan 2,3-dioxygenase; TeCA, Tetracyclic antidepressant; TNF-alpha, Tumour necrosis factor alpha; XLC-MS/MS, Extraction-liquid chromatographic-tandem mass spectrometric

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et al., 2010; Lopez-Duran et al., 2009; Stetler and Miller, 2011). These findings were reproduced in patients in remission of recurrent MDD (Bhagwagar et al., 2003; Lok et al., 2012). Others showed these disturbances to be independent of remission status (Vreeburg et al., 2009). Focusing on recurrence, reports showed that both decreased and increased morning cortisol levels predict the recurrence of depression (Bockting et al., 2012; Hardeveld et al., 2010; Vreeburg et al., 2013; Vrshek-Schallhorn et al., 2012). These inconsistent findings are explained by methodological differences. Nonetheless, all these findings support the believe that disturbances of the HPA axis resemble a trait marker for depression rather than a state-dependent effect of the disease. In recurrent MDD, this trait-dependency suggests biological scarring due to previous episodes of depression.

Serotonergic dysfunction is a central concept in both the pathophysiology and the treatment of MDD (Belmaker and Agam, 2008; Kaufman et al., 2016). Studies indirectly linked serotonergic dysfunction to MDD by showing that acute tryptophan depletion induced depressive symptoms in both remitted MDD patients and non-depressed individuals with a family history of depression (Ruhé et al., 2007). Using neuroimaging technologies, several studies showed increased serotonin 1A receptor binding throughout the brain of currently depressed patients and remitted, unmedicated MDD patients (Miller, et al., 2009b, 2013; Parsey et al., 2010). These results suggest that central serotonergic dysfunction could persist in recurrent types of depression, regardless of the depressive state.

In the central nervous system, serotonin is synthesized de novo from the essential amino acid tryptophan. In order to cross the blood-brain barrier, tryptophan competes with other large neutral amino acids (Fernstrom, 2013). A meta-analysis showed that serum tryptophan levels were decreased in depressed individuals compared to healthy controls (Ogawa et al., 2014). Tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) are the two inducible enzymes that oxidize tryptophan to form kynurenine. The kynurenine to tryptophan (kyn/trp) ratio is often used as an indicator of tryptophan degradation through the kynurenine pathway (Corm et al., 2009; de Jong et al., 2011; Quak et al., 2014; Suzuki et al., 2010). Beside reduced availability of tryptophan for serotonin synthesis, activation of these pathways has been implicated in depression as it results in formation of downstream kynurenine metabolites with neuroactive properties (Schwarcz et al., 2012). Both in vitro and in vivo models showed that glucocorticoids, both endogenous and synthetic, induced expression and activity of TDO resulting in reduced levels of tryptophan (Danesch et al., 1983; Maes et al., 1990b; Young, 1981). IDO activity is induced by inflammatory cytokines including interferon gamma (INF-y), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) (Campbell et al., 2014). Patients with depression have been found to display increased levels of these cytokines (Miller et al., 2009a). A previous study within the same cohort as the current study, showed that increased levels of high-sensitivity C-reactive protein (hsCRP) and IL-6 were associated with an increased kyn/trp ratio (Quak et al., 2014).

We hypothesize that in patients suffering from recurrent episodes of depression, chronic cortisol hypersecretion causes depletion of tryptophan through activation of tryptophan degrading enzymes including TDO. We believe that the resulting disturbances of serotonergic functioning and central levels of kynurenine metabolites could play a role in the recurrent course of the disease. We first compared tryptophan metabolism and HPA axis functioning across a large cohort of non-depressed, single episode depressed and recurrently depressed individuals. We next assessed the association between HPA axis functioning and the kynurenine to tryptophan ratio while taking into account a wide range of confounding variables including inflammatory parameters and antidepressant treatment. Finally, we investigated whether this association differed between non-recurrent (single episode MDD) and recurrent types of depression.

2. Material and methods

2.1. Subjects

Data were obtained from the longitudinal cohort of the Netherlands Study of Depression and Anxiety (NESDA). Detailed rationale, objectives and methods are described elsewhere (Penninx et al., 2008). In brief, the cohort (n = 2981) consists of subjects (aged 18–65) recruited from the general population, general healthcare institutes and specialized mental healthcare institutes. Besides healthy controls, individuals with a depressive disorder and a prior history of a depressive disorder were included. Patients were excluded when they suffered from a primary clinical diagnosis other than a depressive or anxiety disorder (psychotic disorder, obsessive compulsive disorder, bipolar disorder or severe addiction disorder). Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnoses (American Psychiatric Association, 2000) for anxiety disorders and depressive disorders were assigned on the basis of responses to the Composite International Diagnostic Interview (CIDI) 2.1 lifetime version (Wittchen, 1994) that was administered by trained interviewers. In addition, severity of depression was established in all participants using the 28-item self-report Inventory of Depressive Symptoms (IDS) (Rush et al., 1996). The study protocol was approved by the Ethical Review Board of the VU University Medical Center Amsterdam and subsequently by the local review boards of each participating institute. All subjects provided informed consent.

From the total NESDA sample, we excluded subjects with missing or failed tryptophan and/or kynurenine measurements (n = 32) (see 'Tryptophan, kynurenine and kynurenine to tryptophan ratio'). Next, we excluded individuals who did not return any salivary sample (n = 834) and from which no marker of HPA axis functioning could be obtained (n = 71) (see 'Section 2.3'). We then selected two groups based on the recurrence status of the depression: persons who suffered from a single episode of depression (n = 625) and persons with recurrent depressions (n = 695). Recurrence was defined as a either a history of a single MDD episode ('Single episode MDD') or a history of more than one episodes of depression ('Recurrent MDD'). Recency of MDD diagnosis was defined as either an ongoing MDD episode at the time of data gathering ('Current MDD') or no MDD episode at the time of data gathering but with a lifetime history of MDD ('Remitted MDD'). Both the groups 'Single episode MDD' and 'Recurrent MDD' consisted of currently depressed individuals and individuals in remission of depression. Individuals included in the 'Control' group had no lifetime depression or anxiety disorder (assessed using CIDI) and an IDS score below 15 (n = 406). None of the included participants used corticosteroid derivates. Our final sample thus consisted of 1726 individuals. A flowchart showing sample size and exclusion is provided (Fig. S1A).

2.2. Tryptophan, kynurenine and kynurenine to tryptophan ratio

At baseline, fasting blood samples were drawn and stored at −70 °C. Serum kynurenine and tryptophan concentrations were measured at the department of Laboratory Medicine of the University Medical Center Groningen using a validated automated online solid-phase extraction-liquid chromatographic-tandem mass spectrometric (XLC-MS/MS) method with deuterated internal standards (de Jong et al., 2009). The reliable detection range was established for both tryptophan (range, 30–110 nmol/l) and kynurenine (range, 1–50 nmol/l) (Salter et al., 1995). Values outside these thresholds were assigned missing (n = 20). A kyn/trp ratio was constructed for all included participants by dividing the level of kynurenine by the level of tryptophan and multiplying this value by 1*10^3.

2.3. Salivary cortisol

HPA axis function is reflected by cortisol production. Cortisol output