Psychoneuroendocrinology 94 (2018) 25–30

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Changes in the tryptophan-kynurenine axis in association to therapeutic response in clinically depressed patients undergoing psychiatric rehabilitation

B. Reininghaus[a,b], K. Riedrich[a,b], N. Dalkner[a,b,*], S.A. Bengesser[b], A. Birner[b], M. Platzer[b], C. Hamm[b], J.M. Gostner[c], D. Fuchs[c,d], E.Z. Reininghaus[b]

[a] Therapie Zentrum-Justuspark Bad Hall, Austria
[b] Department of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz, Auenbruggerplatz 31, 8036, Graz, Austria
[c] Division of Medical Biochemistry, Biocenter, Medical University of Innsbruck, Innsbruck, Austria
[d] Division of Biological Chemistry, Biocenter, Medical University of Innsbruck, Innsbruck, Austria,

ARTICLE INFO

Keywords:
Tryptophan
Kynurenine
Psychiatric disorder
Unipolar depression
Treatment response
Psychiatric rehabilitation

ABSTRACT

Introduction: In recent decades a number of studies have shown an association between the Tryptophan (Trp)-Kynurenine (Kyn) axis and neuropsychiatric disorders. However, the role of the Trp-Kyn pathway on the affective status in a general psychiatric cohort requires clarification. This study aimed to measure peripheral changes in Trp, Kyn and the Kyn/Trp-ratio as well as in the inflammatory markers high sensitive C-reactive protein (hsCRP) and interleukine-6 (IL-6) in individuals undergoing a six-week course of intensive treatment program comparing subgroups of treatment responders and non-responders.

Methods: In this investigation 87 currently depressed individuals with a life-time history of depressive disorders were divided into treatment responders (n = 48) and non-responders (n = 39). The individuals were selected for an extreme group comparison out of 598 patients undergoing a 6-week psychiatric rehabilitation program in Austria. Responders were defined according to great changes in Becks Depression Inventory (BDI-II) between time of admission and discharge (BDI-II > 29 to BDI-II < 14), while non-responders had no or minimal changes (BDI > 20, max. 4 points change over time). Differences in the levels of Trp, Kyn, and the Kyn/Trp ratio as well as levels of hsCRP and IL-6, were compared between groups. Differences were analyzed at the time of admission as well as at discharge.

Results: A significant group x time interaction was found for Kyn [$F(1.82) = 5.79$; $p = 0.018$] and the Kyn/Trp ratio [$F(1.85) = 4.01$, $p = 0.048$]. Importantly, Kyn increased significantly in the non-responder group, while the Kyn/Trp ratio decreased significantly in the responder group over time. Furthermore, changes in Kyn as well as hsCRP levels correlated significantly with changes in the body mass index over time (Kyn: $r = 0.24$, $p = 0.030$; hsCRP: $r = 0.25$, $p = 0.021$). No significant interactions were found for Trp and hsCRP, although they increased significantly over time.

Discussion: Given the limitations of the study, we could show that the therapeutic response to a multimodal treatment in clinically depressed patients not receiving cytokine treatment is associated with changes in Kyn levels and the Kyn/Trp ratio as well as with hsCRP. However, it is too early to draw any causal conclusion. Future research should clarify relevant clinical and neurobiological parameters associated with changes in Kyn levels and Kyn/Trp ratio, especially in regard to clinical response.

1. Objective

Numerous studies have indicated the association of unipolar and bipolar affective disorders with systemic inflammation (reviewed in Krishnadas and Harrison, 2016). Inflammation is intimately associated with monoamine regulation, with increased levels of the pro-inflammatory cytokines interleukin (IL)-1B, IL-6, IL-18, tumor necrosis factor-alpha (TNF-a) and especially interferon-gamma (IFNg) inducing indoleamine 2,3-dioxygenase-1 (IDO), thereby driving tryptophan (Trp) down the kynurenine (Kyn) pathway and away from serotonin and melatonin synthesis. The role of such processes has been shown in the emergence of depression in IFN-treated hepatitis C patients (Bonaccorso

* Corresponding author at: Department of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz, Auenbruggerplatz 31, 8036, Graz, Austria.
E-mail address: nina.dalkner@medunigraz.at (N. Dalkner).

https://doi.org/10.1016/j.psyneuen.2018.04.029
Received 30 March 2018; Received in revised form 25 April 2018; Accepted 26 April 2018

et al., 2002a; Bonaccorso et al., 2002b; Capuron and Dantzer, 2003; Capuron et al., 2003). Decreased levels of central serotonin, which have classically been associated with mood disorders, may therefore be driven by systemic inflammatory processes (Dantzer et al., 2011; Widner et al., 2002). However, the conversion of Trp into Kyn and Kyn pathway products, such as the excitotoxic quinolinic acid, are important. Such data suggest that it is not only the loss of serotonin, that is important, but also the production of neuroregulatory Kyn pathway products and the relative ratios of these products (Dantzer et al., 2011). Significant alterations in such neuroregulatory products will drive changes in glial-neuronal networks, which may render the brain more susceptible to depression (Won and Kim, 2016). The Kyn/Trp ratio reflects the levels of Trp breakdown and serves as a proxy measure of IDO activity (Fuchs et al., 1990). Evidence of a role for IDO in cytokine-induced depression comes from a number of studies, that have demonstrated correlations between cytokine- induced depression with lower Trp levels coupled to raised levels of Kyn and an increase in the Kyn/Trp-ratio (Capuron et al., 2002; Capuron et al., 2003).

Despite the large number of studies investigating the Trp-Kyn pathways in individuals undergoing cytokine treatment and its association with neuropsychiatric symptoms, there is no general consensus how Trp-Kyn changes interact with the therapeutic response in general psychiatric cohorts without cytokine treatment. Psychiatric rehabilitation settings in Austria commonly offer an intensive, multidisciplinary 6-week program for individuals with serious mental illness, most typically suffering from affective disorders. In this setting, current symptomatology of patients is not serious enough to require acute care in a psychiatric hospital, with most patients receive rehabilitative treatment following acute psychiatric care. The rehabilitation program in Austria is a structured and targeted, including medical, psychiatric, psychological and psychotherapeutic treatments, as well as occupational therapy, physiotherapy and diet counseling. The principal goals of such a setting include long-term symptom management, social skills improvement, active participation in everyday life, strengthening of cognitive functioning and decreasing the rates of hospitalization and retirement on the grounds of disability (Hinterhuber and Meise, 2007). However, not all patients exhibit minor symptomatology at the beginning and some do not show improvements during the course of treatment.

As the psychiatric rehabilitation program is a very structured treatment with a predefined treatment plan that applies the same therapy levels to all patients, different patient groups can be easily compared in regard to their treatment outcome. Alterations in the neurobiological parameters in major depressive disorder patients that compare non-Responders (Non-RESP) and responders (RESP) may be of particular interest, given its potential to highlight clinically meaningful biomarkers.

Utilizing the “inflammatory hypothesis of depression”, the current study aimed to evaluate changes of inflammatory processes (Trp, Kyn the Kyn/Trp ratio, high sensitive C-reactive protein (hsCRP), IL-6) over the course of a 6-week rehabilitation program in individuals with life-time major depressive disorder and current depressive symptomatology, divided into RESP *versus* Non-RESP. For this purpose Trp, Kyn, the Kyn/Trp ratio as well as hsCRP and IL-6 were analyzed at the time of treatment admission (t1) and discharge (t2). The study design included the comprehensive evaluation of depressive symptoms.

2. Material and methods

The present investigation comprised 87 individuals with a life-time history of depressive disorders and current moderate to severe depressive symptoms. To measure severity of depressive symptomatology, we used clinical evaluation according to ICD-10 by specialists in psychiatry. In addition, the Becks Depression Inventory (BDI-II, Hautzinger et al., 2006) was administered to the participants at admission (t1) and discharge (t2). The BDI-II is a self-rating scale including 21 items measuring common depressive symptoms, each answer being scored on a scale value of 0–3, higher total scores indicating a higher depression severity. The standardized cutoffs according to the literature are: 0–13 points: minimal depression; 14–19 points: mild depression; 20–28 points: moderate depression; 29–63 points: severe depression.

The participants were selected for an extreme group comparison out of 598 patients with mood disorders during lifetime undergoing a 6-week psychiatric rehabilitation program in Austria (mean age 52.8 years; mean BDI score: 19.4).

The first criteria for extreme group selection were: (1) history of mood disorder (uni- or bipolar depressive disorder), (2) currently moderate to severe depressive episode based on clinical evaluation, (3) currently moderate to severe depressive symptoms based on the BDI-II cut off scores (see below).

In a second step the following criteria were applied for the selected 304 patients to filter out extreme groups of RESP and Non-RESP: according to the changes in BDI-II score, the participants were assigned as RESP (n = 48) and Non-RESP (n = 39). Patients with changes from severe to non/minimal during the rehabilitation program (BDI-II > 29 to BDI-II < 14) were defined as RESP. Patients, who had at the time of admission as well as discharge a BDI-II of at least 20 and less than a 4-point difference from t1 to t2 were classed as Non-RESP. Data of the

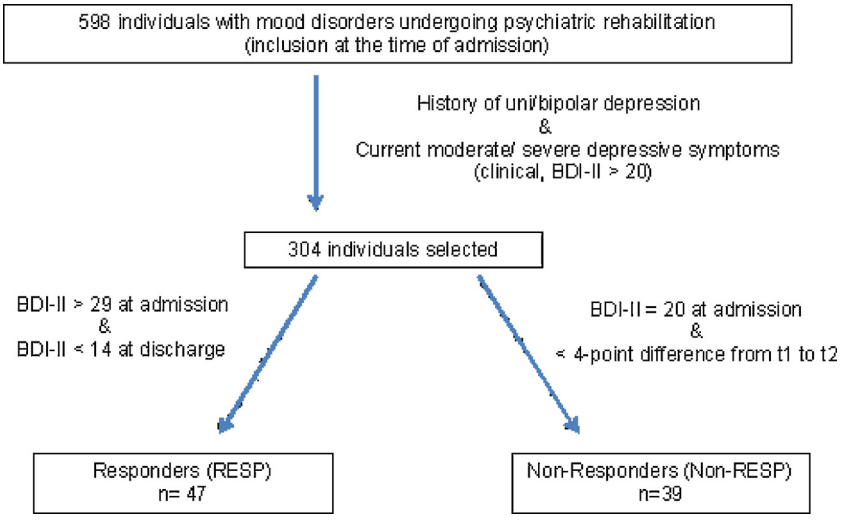

Fig. 1. Detailed description of extreme group selection.