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Original article

The role of tryptophan metabolism and food craving in the relationship between obesity and bipolar disorder

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SUMMARY

Background & aims: Individuals with bipolar disorder (BD) have a significantly increased risk of obesity-related conditions. The imbalance between food intake and energy expenditure is assumed to be a major risk factor for obesity in BD. This study analyzed food craving in relation to anthropometric, metabolic, and neurobiological parameters in a well-characterized cohort of euthymic individuals with BD.
Methods: One-hundred-thirty-five patients completed the Food-Craving Inventory assessing four categories of food craving (fat, fast-food, sweets and carbohydrate craving). Additionally, clinical, metabolic and anthropometric parameters were assessed.
Results: Higher levels of fat craving were observed in males, *versus* females, with BD. High levels of carbohydrate craving positively correlated with kynurenine and the kynurenine-to-tryptophan ratio. Higher serum nitrite and neopterin levels were related to fat craving. Parameters of fat metabolism (triglycerides, high-density lipoprotein) were associated with fat and fast-food craving. Anthropometric measures of obesity (e.g. body mass index, waist-to-hip-ratio) were not related to food craving.
Conclusions: Overweight/obese individuals with BD show an increased driving of tryptophan down the kynurenine pathways, as indicated by an increase in the serum kynurenine-to-tryptophan ratio. The driving of tryptophan down the kynurenine pathway is mediated by immune-inflammatory activity and stress. The correlation of increased kynurenine with food craving, especially carbohydrate craving, probably indicates a regulatory deficit in the maintenance of chronic inflammatory processes in obesity and BD. Food craving seems to be of clinical importance in the treatment of metabolic disturbances in BD, although not associated with anthropometric measures of obesity. Rather, food craving correlates with blood metabolic parameters and an increased activation of the kynurenine pathway, both of which are linked to higher affective symptomatology and the development of cardiovascular diseases.

1. Introduction

Bipolar disorder (BD) is a serious psychiatric illness, often with depressive and (hypo-)manic episodes, interspersed with relatively stable euthymic states [1]. Beside affective and psychomotor symptoms, eating dysregulation is very common in BD [2]. BD shows a high co-occurrence of eating disorders, especially binge eating behavior [3], both of which are associated with an earlier age of BD onset and a poorer disease course [4–6]. BD has a considerable increased risk for obesity and metabolic disturbances, contributing to the heightened cardiovascular morbidity and mortality [7–10]. Further medical complications of obesity in BD include neurocognitive impairments [11,12], a more complex illness presentation and poorer treatment outcome [13–15].

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1.1. Obesity in BD

Obesity occurs when energy intake is greater than energy expenditure [16], with a number of factors proposed to underpin this in BD, including: Psychopharmacological medication [17,18], genetic factors [19], serotonergic dysfunction [20], inflammatory mediators [21], and higher levels of oxidative stress [22]. Such factors have all been proposed to contribute to the onset and maintenance of obesity in BD. Likewise, behavioral determinants, such as a sedentary lifestyle and poor eating habits may increase obesity in individuals with BD [23].

The current literature has highlighted a significant role for chronic low-grade inflammation, in interaction with other physiological processes, including oxidative and nitrosative stress, metabolic dysregulation, pro-inflammatory cytokines, and heightened activity of the kynurenine pathway, in mediating the association between obesity and BD [22,24].

1.2. Food craving

Food craving is defined as a profound desire to consume a specific kind of food. It is described as a multidimensional concept, including cognitive (e.g. thoughts about food); emotional (e.g. intense desire to eat); behavioral (e.g. seeking food); and physiological (e.g. salivation) processes [25]. Food craving is the subject of intense interest, underpinning healthy weight maintenance, as well as overweight/obesity [26–29], snacking behavior, binge eating, the consumption of particular types of foods [30–32], cognitive reappraisal strategies [33], reward sensitivity [34], plasma insulin, and hippocampal activation [35]. Environmental factors, including stressors, also contribute to food craving [36]. Carbohydrates craving, in particular, has been associated with serotonergic dysfunction, and thereby to dysphoric mood [37] and depressive symptomatology [38]. A wide body of data shows that food craving is generally more prevalent in women than in men [39,40]. In BD patients, carbohydrate craving can be stimulated by mood stabilizers, including lithium and valproate, as well as some second generation antipsychotics [41].

1.3. Tryptophan metabolism

The α-amino acid, tryptophan (TRP), is the precursor for two crucial biochemical pathways that are related to inflammatory processes in neuropsychiatric, and other medical, disorders: (a) the generation of serotonin and melatonin, and (b) the production of kynurenine (KYN) and KYN derivatives, which ultimately can lead to nicotinamide adenine dinucleotide production. A relative increase of KYN, and therefore the KYN/TRP ratio, has been found in numerous inflammatory and neuropsychiatric diseases. Such increases in the KYN/TRP ratio arise from pro-inflammatory cytokine driven indoleamine-2,3-dioxygenase (IDO) and stress/cortisol driven tryptophan-2,3-dioxygenase (TDO), which drive TRP down the KYN pathway and away from serotonin and melatonin synthesis [24]. Disturbed TRP metabolism also associates with overweight/obesity [42], where increased levels of pro-inflammatory factors are evident. TRP via serotonin and melatonin, are involved in the regulation of satiety and caloric intake [42,43,62]. Serotonin, by regulating carbohydrate and fat intake, can lower caloric intake [44,45], as well as relieving stress [46], and inhibiting neuropeptide Y, which is one of the most potent hypothalamic orexigenic peptides [47]. An increase in the KYN/TRP ratio is associated with a higher likelihood of fatal cardiovascular events, which are more prevalent in individuals with BD [48].

In the etiology and course of BD, alterations in the levels of KYN pathway products, in inverse correlation with changes in the serotonergic and melatonergic pathways, have been proposed to be of clinical relevance in both poles of BD [49].

Neopterin is another marker of immune-inflammatory activity, and correlates with changes of TRP and KYN pathway activation [50]. Neopterin is produced in macrophages following stimulation with the pro-inflammatory cytokine, interferon-γ (IFN-γ), which is considered as sensitive marker for the development, expansion, and persistence of inflammation and the immune response [51]. In BD, raised IFN-γ levels during a manic episode positively correlate with symptom severity, possibly in association with IDO induction [49]. Increased levels of oxidative and nitrosative stress may be intimately linked to higher levels of immune-inflammatory activity, with high serum nitrite levels predictive of metabolic syndrome in females, but not in males, suggesting serum nitrite as a potential biomarker for cardio-metabolic disorders in females [52]. As such, oxidative and nitrosative stress, neopterin, IDO, IFN-γ and changes in relative activity of the KYN, *versus* serotonergic and melatonergic, may be intimately linked, with relevance to the pathophysiology of both BD and obesity.

Given such evidence implicating multiple interacting pathways in the development of overweight/obesity in BD, this study aimed to assess the potential role of food craving in such process. We were especially interested in the relationship between food craving with certain metabolic risk factors (e.g. central obesity, insulin resistance, lipid abnormality), and inflammation related parameters (TRP pathway) in euthymic BD patients. We hypothesized that overweight/obese individuals will have greater food craving that is linked to metabolic risk factors and alterations in TRP metabolism. Moreover, this study aimed to identify sex differences in this context. This is the first study to examine food craving and metabolic risk factors in euthymic BD patients.

2. Materials and methods

2.1. Participants

One-hundred-thirty five individuals with BD, diagnosed according to the Diagnostic and Statistical Manual of mental disorders (DSM-IV) [53], were drawn from a dedicated outpatient center at the Department of Psychiatry of the Medical University of Graz. All patients met the inclusion criteria for euthymia: a score on the *Hamilton Depression Scale* (HAMD) [54] below 11 and a score on the *Young Mania Rating Scale* (YMRS) [55] below 9.

The current investigation was a secondary analysis of data from a cohort study that was originally intended for other purposes, the BIPFAT study, which explored the shared pathophysiological pathways of obesity and altered brain function in BD. The BIPFAT study design comprises clinical and laboratory diagnostics, neuropsychological measures, electroencephalography, and magnet resonance imaging. A detailed description of the study protocol and the study procedure can be found in previous reports by Lackner et al. [8,12] or Reininghaus et al. [20].

2.2. Measurements

All participants completed a German version of the *Food-Craving Inventory* (*FCI*) [32], designed to measure the total amount of food craving on four domains (fat/carbohydrates/sweets/fast-food). The *Structured Clinical Interview* according to DSM-IV (*SCID-I*), containing the *GAF* score (*Global Assessment of Functioning*) [56], the *HAMD*, and the *YMRS* were administered by a trained interviewer. A detailed medical and psychiatric history was taken and participants completed the *Beck Depression Inventory* (*BDI-II*) [57]. A fasting blood sample was collected, allowing the analysis of levels of glucose, hemoglobin A1c (HbA1c) and homocysteine, as well as

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