Ghrelin and Eating Disturbances in Psychiatric Disorders

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Key Words

Ghrelin • Depression • Schizophrenia • Three-Factor Eating Questionnaire • Weight gain • Psychiatric disorders

Abstract

Introduction: Appetite and eating behavior are frequently altered in psychiatric patients. The newly discovered gut-derived neuropeptide ghrelin stimulates hunger and weight gain. Therefore, it might be involved in appetite regulation during psychiatric disorders. **Methods:** In 83 depressed, 42 schizophrenic patients and 46 healthy controls plasma ghrelin levels were measured, and the psychometric scores on the Three-Factor Eating Questionnaire (TFEQ) were assessed. **Results:** Neither ghrelin levels nor TFEQ scores differed between both patient groups and healthy subjects. However, TFEQ subscale 2 (disinhibition) was predicted by BMI-corrected ghrelin levels, while age, sex, smoking, and medication did not show any influence. **Discussion:** Ghrelin correlates with factors of eating behavior, specifically with subscale 2 on the TFEQ. Ghrelin might be involved in appetite-regulating pathways during psychiatric disorders. However, its influence is not likely to be displayed as a difference between diagnostic groups. Rather, ghrelin is associated with eating behavior in psychiatric patients meaning susceptibility to eating problems.

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Introduction

Appetite and eating behavior are frequently altered in psychiatric patients suffering from major depression or schizophrenia [1]. The first author describing weight loss as a typical symptom of depression was Emil Kraepelin in the year 1901 [2]. Early studies in the middle of the 20th century found weight loss in about 80% of the depressed patients [3, 4]. In contrast, there are also studies reporting weight gain in 40% of depressed patients compared to 30% who lost weight [5]. With regard to schizophrenia a newer study found normal or slightly higher body mass indices (BMI) in patients compared to controls [6]. The results were confirmed by another group suggesting an increased prevalence of obesity among young patients with schizophrenia (nontreated) and especially among patients chronically treated with atypical antipsychotics [7].

Reasons for this variability, among others, were the varying influences of medication, comorbidity and culture. The phenomenon of eating and appetite disturbances during major depression or schizophrenia itself is only little characterized. This is partly due to lacking psychometric instruments.

Moreover, only little is known about the neuroendocrinological mechanisms of weight and appetite regula-

tion in psychiatric disorders. Leptin, an important long-term regulating peptide of body weight, seems to play a major role in the regulation of appetite and weight in patients suffering from depression or schizophrenia [8]. The recently discovered gut-derived growth hormone secretagogue ghrelin, a 28-amino-acid-containing peptide, seems to exert the opposite effects in the regulation of body weight, namely, increasing hunger and food intake [9]. It is synthesized in the human stomach as an endogenous ligand for the growth hormone secretagogue receptor [10] and provides a peripheral signal to the hypothalamus to stimulate food intake and adiposity via the neuropeptide Y and Agouti-related peptide system [11, 12]. Circulating ghrelin is increased under conditions of negative energy balance such as starvation and anorexia nervosa, while it is decreased during states of positive energy balance such as feeding and obesity [13].

Some data are available showing the influence of plasma ghrelin levels on psychiatric disorders. One study exists demonstrating higher ghrelin levels in patients medicated with olanzapine or risperidone [14]. Moreover, there is also a study including 52 patients receiving psychopharmacological treatments. In this study, no significant differences in plasma ghrelin levels were found between different medication groups [15]. Other studies did not find significant differences either in serum ghrelin levels between different groups of medication with olanzapine or risperidone [16], or with clozapine or risperidone [17] in the course of treatment. In contrast to ghrelin levels which did not change in the time course of 10 weeks, BMI and leptin levels changed significantly in the group of patients treated with clozapine [18]. These results do not support a causal involvement of ghrelin in weight gain under clozapine as an antipsychotic. Weight gain is considered to be an early side effect in antipsychotic treatment, even before ghrelin levels rise. Therefore, this weight gain does not seem to be a consequence of altered ghrelin levels but it may be caused by other metabolic changes.

It would be interesting to know whether the psychiatric disorder per se influences the appetite-regulating system represented by ghrelin. Furthermore, the question arises whether differences in eating behaviors are co-varying with the plasma levels of the 'hunger hormone' ghrelin. They might differ between healthy subjects and patients suffering from depression or schizophrenia and they might correlate with scores of a psychometric instrument measuring different factors of appetite and eating behavior.

Subjects and Methods

One hundred and twenty-five psychiatric patients suffering from depression or schizophrenia and 46 healthy controls were consecutively included in a pilot study, the patients from the first day of hospitalization.

Inclusion of patients depended on fulfilling the criteria of a major depressive episode or a schizophrenic/schizoaffective disorder according to ICD-10 [19] and DSM-IV [20]. The patients gave written informed consent to participate in the study that was approved by the local ethics committee. All participants were carefully screened to rule out the existence of inflammatory, cardiac, endocrine, renal and hepatic disease by means of a structured medical history, a physical examination and routine laboratory testing. They were excluded if there was comorbidity of alcohol or substance dependence.

We also collected information on each patient such as weight in kilograms, height, age, sex, and smoking habits. To characterize appetite and eating behavior the Three-Factor Eating Questionnaire (TFEQ) [21] was used in the validated German version called FEV (*Fragebogen zum Essverhalten* [22]). The BMI was calculated by dividing weight in kilograms by height in meters squared. For assessment of the ghrelin plasma levels, venous blood samples were collected in the morning between 7:30 and 9:00 a.m. following an overnight fast. Patients were examined on the first day of hospitalization. Plasma ghrelin levels and routine laboratory parameters were assessed. Blood was stabilized with Na-EDTA and frozen to -60°C after immediate centrifugation in order to guarantee the stability of the analyte [23]. Ghrelin levels were determined using Phoenix Total Ghrelin RIA Kit. The detection limit was 0.010 ng/ml. The intra-assay coefficient was below 10% and the interassay coefficient was 12% by own testing [24]. The software SPSS 11.0 was used for statistical analysis. By means of the Kolmogorov-Smirnov test we proved the assumption of normal distribution. Data were log-transformed or nonparametric tests were used, if data were not normally distributed. General linear models were applied for calculating the predictions of TFEQ score by ghrelin plasma levels, which were corrected for BMI. As covariates in this analysis age and sex, smoking habits, diagnosis and medication group were entered. We subdivided the patients according to their medication during the last 4 weeks: atypical neuroleptics with known weight gain (olanzapine, clozapine or quetiapine), atypical neuroleptics or antidepressants without known weight gain as side effect (ziprasidone, risperidone), selective serotonin reuptake inhibitor, dual serotonergic antidepressant (mirtazapine) and no medication. Only 34 patients (21 depressed and 13 schizophrenic patients) reported changes in weight during their medication: 13 depressed patients gained and 8 lost weight; in the group of schizophrenic patients, 5 reported weight loss and 8 weight gain. This information refers to the last 4 weeks. Additionally, receiver operating characteristic curves with the corresponding 95% confidence interval of the area under the curve were calculated for TFEQ subscales (as shown in the general linear model), where the BMI-corrected ghrelin level was identified as a significant factor.

Fig. 1. General linear models were applied for calculating the predictions of TFEQ score by ghrelin plasma levels, which were corrected for BMI.

Results

All variables were normally distributed except for TFEQ scales 1 and 3. Neither ghrelin levels nor TFEQ scores differed between patients suffering from depression or schizophrenia and healthy subjects, while age, smoking habits, weight, BMI and fat mass were significantly different in the three diagnostic groups (table 1). When comparing only two groups (patients vs. controls, depression vs. schizophrenia) no significant differences could be detected either (data not shown). According to a general linear model, in the total group TFEQ subscale 2 (disinhibition) is predicted by BMI-corrected ghrelin levels ($F = 5.72$, $p = 0.018$), while the covariates age, sex, smoking habits, diagnostic group, and medication group did not show any influence. In both groups (depressed patients and psychotic patients) we did not find any predictive effect of BMI-corrected ghrelin levels on TFEQ subscales. As significant interaction terms, sex and diagnostic group ($F = 6.24$, $p = 0.014$), and diagnostic and medication group ($F = 3.08$, $p = 0.019$) were used. Furthermore, to demonstrate the predictive power of the BMI-corrected ghrelin levels for the TFEQ subscale 2 in

Table 1. Subject characteristics

	Patients		Controls	
	major depression	schizophrenia		
Number of subjects	83	42	46	
Male/female	44/39	25/17	24/22	
Age, years	40.42 (SD 13.98)	33.60 (SD 11.50)	35.70 (SD 12.93)**	
Smoking habits (smokers/nonsmokers)	35/48	26/16	13/33*	
Weight, kg	77.89 (SD 18.98)	85.23 (SD 20.73)	70.98 (SD 14.37)*	
BMI	26.01 (SD 5.55)	27.28 (SD 5.80)	23.51 (SD 4.05)*	
Fat mass/kg	22.38 (SD 11.10)	25.61 (SD 14.28)	18.11 (SD 7.58)*	
Ghrelin, pg/ml	79.05 (SD 37.24)	73.41 (SD 43.02)	76.28 (SD 37.00)	n.s.
BMI-corrected ghrelin	3.27 (SD 1.96)	2.84 (SD 1.82)	3.38 (SD 1.77)	n.s.
TFEQ				
Subscale 1	6.25 (SD 5.25)	7.17 (SD 4.67)	5.37 (SD 3.93)	n.s.
Subscale 2	5.75 (SD 3.84)	5.52 (SD 3.29)	5.39 (SD 2.93)	n.s.
Subscale 3	5.01 (SD 3.89)	5.12 (SD 2.99)	5.24 (SD 3.03)	n.s.
Medication during last 4 weeks	SSRI (n = 15) mirtazapine (n = 10) quetiapine (n = 1) risperidone (n = 1) no medication (n = 56)	SSRI (n = 1) risperidone (n = 5) ziprasidone (n = 4) quetiapine (n = 6) olanzapine (n = 2) clozapine (n = 1) no medication (n = 23)		

* $p < 0.05$, ** $p < 0.001$ vs. both patient groups by the general linear model. SSRI = Selective serotonin reuptake inhibitor.

the total group, a receiver operating characteristic analysis was performed (fig. 1). The area under the curve was 0.69 (95% CI: 0.61–0.77; $p < 0.001$).

Discussion

The appetite-stimulating hormone ghrelin seems to be associated with traits of eating behavior in the context of psychiatric disorders. Ghrelin is known as a hunger hormone that is increased in starvation and decreased in states of obesity [9]. Unexpectedly, patients suffering from depression, normally complaining about loss of appetite and weight [2], did not show higher scores of perceived hunger on the TFEQ (factor 3) compared to healthy controls. In fact, this result does not seem in line with former examinations of characteristic eating behavior during major depressive episodes [5, 25]. Remarkably, none of the other studies found an association with perceived hunger on the eating scale. Rather, the disinhibition factor of the TFEQ significantly correlated with weight changes during depression and differentiated weight gain from weight loss patients at a high level of statistical significance. Therefore, the changes of eating behavior during an episode of major depression or schizophrenia seem to be more precisely characterized by TFEQ factor 2 than by factors 1 (cognitive restraint) or 3 (perceived hunger sensations).

Disinhibition means to be incapable of cognitive restraint in situations of seduction with favorite foods. It is tempting to speculate that a kind of 'reward system' lacks during depression that would normally inhibit 'cognitive restraint'. The eating behavior depicted in the TFEQ not really describes the feeling of hunger itself but rather a kind of characteristic trait of the personality.

During typical depression, cognitive restraint outweighs experience of desire. In contrast, in atypical depression, where patients complain of increased hunger and weight gain, disinhibition has gained control. Similar effects might appear in recovering from typical depression. Yet, direct effects of ghrelin on the dopaminergic reward system have not been observed. Rather, it was found that ghrelin did not modify dopamine or norepinephrine release but inhibited serotonin release [26]. Thus, it might be hypothesized that the appetite-stimulating activity of ghrelin is mediated by inhibiting serotonin release.

Interestingly, BMI-corrected ghrelin levels did not differ between depressed or schizophrenic patients and healthy controls and could not be detected as a predictive

factor for eating behavior in depressed or schizophrenic patients. This contrasts with the finding that the neuropeptidergic satiety factor leptin is both negatively correlated to ghrelin [27] and seems to differ between depressed or schizophrenic patients and healthy controls [16]. However, in neuroendocrinological systems mechanisms of regulation are often more complex than represented by simple baseline differences.

Eating behavior was not different between both patient groups. Moreover, we did not find an influence of the medication on eating behavior or weight changes. However, the role of pharmacological treatment has not been investigated sufficiently enough up to now. Our results indicate that ghrelin is not a direct cause for changes in eating behavior during pharmacological treatment and therefore it is not used as a predictive factor for these changes.

A limitation of this work is that we have only determined total plasma levels of ghrelin and not the fraction of biologically active ghrelin [28]. Nevertheless, both studies available measuring ghrelin during psychopharmacological treatment in psychiatric patients did not find essential differences between plasma levels of total and biologically active ghrelin [29, 30].

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