Ghrelin and Eating Disturbances in Psychiatric Disorders

A. Schanzea U. Reulbacha M. Scheuchenzuber a M. Gröschlb J. Kornhubera T. Kraus a

Departments of Psychiatry and Psychotherapy, and Pediatrics, University Hospital, Erlangen, Germany

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

Introduction

Appetite and eating behavior are frequently altered in psychiatric patients. The newly discovered gut-derived neuropeptide ghrelin simulates 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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Thomas Kraus, MD
Frankenalbklinik
DE–91238 Engelschl (Germany)
Tel. +49 9158 925 111, Fax +49 9158 925 225, E-Mail mail@thomaskraus.de

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

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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 pa-
patients suffering from depression or schizophrenia [8].
The recently discovered gut-derived growth hormone
secretagogue ghrelin, a 28-amino-acid-containing pep-
tide, seems to exert the opposite effects in the regulation
of body weight, namely, increasing hunger and food in-
take [9]. It is synthesized in the human stomach as an
endogenous ligand for the growth hormone secreta-
gogue receptor [10] and provides a peripheral signal to
the hypothalamus to stimulate food intake and adiposity
via the neuropeptide Y and Agouti-related peptide sys-
tem [11, 12]. Circulating ghrelin is increased under con-
ditions 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 plas-
ma ghrelin levels on psychiatric disorders. One study ex-
distsributes higher ghrelin levels in patients med-
icated with olanzapine or risperidone [14]. Moreover,
there is also a study including 52 patients receiving psy-
chopharmacological treatments. In this study, no signifi-
cant differences in plasma ghrelin levels were found be-
tween different medication groups [15]. Other studies did
not find significant differences either in serum ghrelin
levels between different groups of medication with olan-
zapine or risperidone [16], or with clozapine or risperi-
done [17] in the course of treatment. In contrast to ghre-
lin 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 re-

dults 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 antipsy-
chotic treatment, even before ghrelin levels rise. There-
fore, 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 psychiat-
ric disorder per se influences the appetite-regulating sys-
tem 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 in-

strument measuring different factors of appetite and eat-
ing 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 dis-
order 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, car-
diac, endocrine, renal and hepatic disease by means of a struc-
tured medical history, a physical examination and routine labora-
tory testing. They were excluded if there was comorbidity of alco-
hol or substance dependence.

We also collected information on each patient such as weight
in kilograms, height, age, sex, and smoking habits. To character-
ize appetite and eating behavior the Three-Factor Eating Ques-
tionnaire (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 analy-
sis. 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 dis-
stributed. 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 (zipra-
sidone, 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 de-
pressed patients gained and 8 lost weight; in the group of schizo-
phrenic patients, 5 reported weight loss and 8 weight gain. This
information refers to the last 4 weeks. Additionally, receiver op-
erating characteristic curves with the corresponding 95% confi-
dence 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.
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

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>major depression</td>
<td>schizophrenia</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>83</td>
<td>42</td>
</tr>
<tr>
<td>Male/female</td>
<td>44/39</td>
<td>25/17</td>
</tr>
<tr>
<td>Age, years</td>
<td>40.42 (SD 13.98)</td>
<td>33.60 (SD 11.50)</td>
</tr>
<tr>
<td>Smoking habits (smokers/nonsmokers)</td>
<td>35/48</td>
<td>26/16</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.89 (SD 18.98)</td>
<td>85.23 (SD 20.73)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.01 (SD 5.55)</td>
<td>27.28 (SD 5.80)</td>
</tr>
<tr>
<td>Fat mass/kg</td>
<td>22.38 (SD 11.10)</td>
<td>25.61 (SD 14.28)</td>
</tr>
<tr>
<td>Ghrelin, pg/ml</td>
<td>79.05 (SD 37.24)</td>
<td>73.41 (SD 43.02)</td>
</tr>
<tr>
<td>BMI-corrected ghrelin</td>
<td>3.27 (SD 1.96)</td>
<td>2.84 (SD 1.82)</td>
</tr>
<tr>
<td>TFEQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subscale 1</td>
<td>6.25 (SD 5.25)</td>
<td>7.17 (SD 4.67)</td>
</tr>
<tr>
<td>Subscale 2</td>
<td>5.75 (SD 3.84)</td>
<td>5.52 (SD 3.29)</td>
</tr>
<tr>
<td>Subscale 3</td>
<td>5.01 (SD 3.89)</td>
<td>5.12 (SD 2.99)</td>
</tr>
<tr>
<td>Medication during last 4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SSRI (n = 15)</td>
<td>SSRI (n = 1)</td>
</tr>
<tr>
<td></td>
<td>mirtazapine (n = 10)</td>
<td>risperidone (n = 5)</td>
</tr>
<tr>
<td></td>
<td>quetiapine (n = 1)</td>
<td>ziprasidone (n = 4)</td>
</tr>
<tr>
<td></td>
<td>risperidone (n = 1)</td>
<td>quetiapine (n = 6)</td>
</tr>
<tr>
<td></td>
<td>no medication (n = 56)</td>
<td>olanzapine (n = 2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clozapine (n = 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no medication (n = 23)</td>
</tr>
</tbody>
</table>

* $p < 0.05$, ** $p < 0.001$ vs. both patient groups by the general linear model. SSRI = Selective serotonin reuptake inhibitor.
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 disinhibit ‘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 out-weighs 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].

Acknowledgement

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