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Reduction in total plasma ghrelin levels following catecholamine depletion: Relation to bulimic and depressive symptoms

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Summary There is increasing preclinical and clinical evidence of the important role played by the gastric peptide hormone ghrelin in the pathogenesis of symptoms of depression and eating disorders. To investigate the role of ghrelin and its considered counterpart, peptide tyrosine tyrosine (PYY), in the development of bulimic and depressive symptoms induced by catecholamine depletion, we administered the tyrosine hydroxylase inhibitor alpha-methyl-paratyrosine (AMPT) in a randomized, double-blind, placebo-controlled crossover, single-site experimental trial to 29 healthy controls and 20 subjects with fully recovered bulimia nervosa (rBN). We found a decrease between peprandial and postprandial plasma ghrelin levels ($p < 0.0001$) and a postprandial rise in plasma PYY levels ($p < 0.0001$) in both conditions in the entire study population. Plasma ghrelin levels decreased in the entire study population after treatment with AMPT compared to placebo ($p < 0.006$). AMPT-induced changes in plasma ghrelin levels were negatively correlated with AMPT-induced depressive symptoms ($p < 0.004$). Plasma ghrelin and plasma PYY levels were also negatively correlated ($p < 0.05$). We did not observe a difference in ghrelin or PYY response to catecholamine depletion between rBN subjects and healthy controls, and there was no correlation between plasma ghrelin and PYY levels and bulimic symptoms induced by catecholamine depletion. These findings suggest a relationship between catecholamines and ghrelin with depressive symptoms.

Introduction

There is increasing evidence suggesting an association between ghrelin and mood. It has been shown in preclinical experiments that ghrelin might be part of the defense against stress-induced depression and anxiety (Lutter et al., 2008).

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Specifically, ghrelin levels were increased in a chronic social defeat stress model of depression, and ghrelin receptor knockout mice showed an increase in depression-like behaviors such as social avoidance (Lutter et al., 2008). In addition, ghrelin involvement is reported in the dopaminergic mesolimbic circuitry, a system that communicates hedonic and reinforcing aspects of natural rewards. High concentrations of ghrelin receptor have been reported in the ventral tegmental area (VTA) (Guan et al., 1997; Zigman et al., 2006), which supports a role for ghrelin in VTA-mediated reward signaling, which is typically impaired in patients suffering from anhedonia (Nestler and Carlezon, 2006; Sullivan and Dufresne, 2006). Additional evidence for ghrelin involvement in the regulation of mood is that ghrelin infusion into the lateral ventricle in rats produced an anxiolytic-like effect (Isogawa et al., 2005) and inhibition of ghrelin induced an increase in depression-like and anxiety-like behaviors (Kanehisa et al., 2006). In clinical studies, patients suffering from major depression (MDD) had lower plasma ghrelin levels (Barim et al., 2009) and antidepressant effects were reported following ghrelin administration (Kluge et al., 2011). Together, these findings suggest that ghrelin plays a role in the pathogenesis of depressive symptoms.

The eating disorder bulimia nervosa (BN) is frequently associated with depressive symptoms. In BN, patients may eat large amounts of food (binge eating) and feel a lack of control over the eating. The binge eating is then followed by a compensatory behavior, such as purging (*e.g.*, vomiting, use of laxatives, excessive exercise). In line with the increased food intake in BN, patients with the disorder have been reported to have elevated ghrelin concentrations at baseline (Kojima et al., 2005; Prince et al., 2009; Tanaka et al., 2002, 2003). However, some studies are in disagreement with these findings, showing normal (Devlin et al., 2012; Monteleone et al., 2005, 2008; Troisi et al., 2005) or decreased (Monteleone et al., 2003) ghrelin levels in BN.

Although the pathways underlying plasma ghrelin level changes in the pathogenesis of depressive symptoms are still largely unknown, it has been hypothesized that they are mediated by activation of the sympathetic nervous system and catecholamine release (Mundinger et al., 2006; Zhao et al., 2010). In fact, there is increasing *in vitro* and *in vivo* evidence for a stimulatory effect of catecholamines on ghrelin (Gagnon and Anini, 2012; Iwakura et al., 2011; Schulpis et al., 2004; Zhao et al., 2010). An instructive paradigm to further evaluate the influence of catecholamines on ghrelin is to transiently deplete catecholamine stores by oral administration of alpha-methyl-paratyrosine (AMPT) (Berman et al., 1999; Hasler et al., 2008). AMPT is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis (Nagatsu et al., 1964). Transient decreases in catecholamine transmission by depletion of central dopamine and norepinephrine stores are evidenced by reduced plasma, urine, and cerebrospinal fluid concentrations of catecholamines and their metabolites (Stine et al., 1997) and by decreased occupancy of striatal dopamine receptors (Verhoeff et al., 2003). As catecholamine depletion is also a reliable way to induce transient depressive symptoms (Berman et al., 1999), the association of mood and ghrelin can also be evaluated by catecholamine depletion. Thus, the aim of the current study was to test the role of catecholaminergic ghrelin secretion in humans. In addition, we assessed the effects of catecholamine depletion on peptide tyrosine tyrosine (PYY) plasma levels, because by modulating satiety, PYY has been considered a counterpart of ghrelin (Batterham et al., 2006; Karra and Batterham, 2010; Murphy and Bloom, 2006). We hypothesized that plasma ghrelin levels would decrease upon catecholamine depletion, and that alterations in ghrelin levels would be negatively correlated to catecholamine-induced depressive symptoms (Carlini et al., 2012). As altered ghrelin and PYY levels have previously been reported in bulimia nervosa (Kojima et al., 2005), an additional hypothesis was that catecholamine depletion would be associated with different alterations in hormone secretion in subjects with remitted bulimia nervosa (rBN) compared to healthy controls, which is why we included a patient-group with rBN and a healthy control group. We chose remitted patients because AMPT effects in symptomatic patients were shown to be considerably smaller than AMPT effects in fully remitted subjects, possibly due to a ceiling effect (Miller et al., 1996).

Methods and materials

Participants

We used the data from the study sample described in (Grob et al., 2012) and recruited females aged 19—39 years who had previously met DSM-IV criteria for BN and had been in remission from BN for at least six months (index subjects; $n = 23$) or who had no history of any psychiatric disorder and no major psychiatric condition in first-degree relatives (control subjects; $n = 30$). The screening visit included a diagnostic Structured Clinical Interview for DSM-IV with a psychiatrist and a physical examination. In order to obtain comparable samples, participants for both study groups were recruited by advertisements in local newspapers and announcements at the University of Zurich and the Swiss Federal Institute of Technology Zurich (ETH). Exclusion criteria included current Axis I psychiatric disorders, a lifetime diagnosis of psychosis, major medical or neurological illness, psychoactive medication exposure within six months, pregnancy, lifetime history of substance dependence, and suicidal ideation or a history of suicide attempts. All subjects gave written, informed consent before participation. The study protocol was approved by the ethics committee of the Canton Zurich (Kantonale Ethikkommission Zürich).

Experimental design

This was a randomized, double-blind, placebo-controlled, crossover study during which all subjects underwent two identical sessions separated by at least seven days wherein they received either AMPT or placebo. Each session included a two-day stay at the Department of Psychiatry and Psychotherapy of the University Hospital of Zurich. One-bed rooms with a separate lavatory were available on a separated floor for all participants, and they had no contact with other hospitalized subjects. None of the rBN subjects had been previously hospitalized at this Department of Psychiatry and Psychotherapy. Participants received regular standardized meals during the hospital sessions. Each subject was contacted daily by telephone for three subsequent days after