Random Lead Time of the acute ghrelin response to a psychological stress

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Abstract
Ghrelin is a growth hormone and cortisol secretagogue that plays an important role in appetite and weight regulation. It is not known whether ghrelin is involved in the eating response to stress in humans. In the present study we examined the effects of psychologically induced stress on plasma ghrelin levels in patients with binge-eating disorder (BED) and in healthy subjects of normal or increased body mass index (BMI). Volunteers were subjected to the standardized trier social stress test (TSST). Basal ghrelin levels in patients were at an intermediate level between thin and healthy obese subjects, but this difference did not attain statistical significance. There were no differences in ghrelin levels throughout the test among the groups after correction for BMI, age and gender. A significant difference in the trend time of ghrelin was revealed when the three groups were analyzed according to their cortisol response to stress. Ghrelin levels increased in cortisol responders whereas no change or a decrease in ghrelin levels occurred in cortisol non-responders. We also found optimal time T*, Minimal Repair δ and Random Lead Time g to minimize the ghrelin level.

I. Introduction
Ghrelin is an orexigenic peptide that was originally isolated from the stomach and found to be the endogenous ligand for the growth hormone secretagoge receptor. Counter-intuitively, though, a negative correlation was found to exist between ghrelin levels and body weight, such that at obese subjects have lower plasma ghrelin concentrations than normal and low weight individuals. Ghrelin actions on feeding induction involve the activation of neuropeptide and agouti-related protein (AGRP) neurons in the arcuate nucleus of the hypothalamus [4,6]. Other than the hypothalamus, GHS-Rs have been detected in areas that are not classically involved in the control of feeding, such as the hippocampus and substantia nigra. Furthermore, projections of ghrelin expressing neurons have been detected in areas outside the hypothalamus, including the amygdale and septum. In line with these complex interactions, ghrelin can induce feeding in rats, when directly injected to the ventral tegmental area (VTA), a central part of the mesolimbic reward pathway. Recent reports indicate that both ghrelin and leptin are involved in the modulation of feeding behavior through direct effects on midbrain dopamine neurons. Ghrelin directly activates opaminergic neurons in the VTA and increases synapse formation and dopamine turnover in the nucleus accumbens. Indeed, these effects of ghrelin are mirror effects of leptin injected to the same area, which induces inhibition of dopamine neuron firing and reduces food intake[5,7]. Activation of the mesolimbic dopaminergic system is involved in motivated behavior conducted to obtain rewards like food or addictive drugs. The rewarding nature of palatable food may be a central mechanism that ensures the drive for feeding, and thus, survival and maintenance of the species. The interconnection between the hypothalamus and areas of the limbic system suggests the existence of a neural circuit that facilitates the cross-talk between emotional states and feeding behavior.

II. Methods
Twenty four subjects were recruited from the Obesity Clinic and among personnel at the Tel Aviv-Sourasky Medical Center. Eight subjects were obese (body mass index—BMI 430 kg/m², “obese” group), eight had normal weight (BMI 418 kg/m² and 25 kg/m², “NW” group) and eight were obese and suffered from BED (BMI 340 kg/m², and diagnosis of BED, “BED” group). BED was diagnosed according to criteria from DSM IV-R. Subjects diagnosed with anorexia or bulimia nervosa, and with any psychiatric co-morbidities were excluded from this study. Subjects taking medication affecting the central nervous system such as selective serotonin reuptake inhibitors, tricyclic antidepressants, antiepileptic or antipsychotic drugs were not included in the study. Subjects receiving medication known to interfere with cortisol measurements such as contraceptive
pills, or estrogen replacement therapy were also excluded from the study. Ten patients with hypertension, four with hyperlipidemia, and three with type II diabetes mellitus, three with hypothyroidism and one with osteoporosis were well controlled with appropriate medical treatment. The study was approved by the Institutional Review Board and all subjects signed an informed consent form.

Figure : Ghrelin response during and following the psychological stress test, according to groups and cortisol response. (A) Ghrelin levels according to groups in cortisol non-responders. (B) Ghrelin levels according to groups in cortisol responders. p ¼ 0.038 for the interaction between ghrelin and cortisol response. Time 0 in these graphs represent the mean value of time points _30 and 0. Inset—change in ghrelin according to cortisol response in the three study groups

Notations

\( x_j \) = time between the successive Ghrelin level [ \( j = 1,2, \ldots, n \) ], r.v.
\( y_j \) = amount of damage to the Ghrelin level due to depression[ \( j = 1,2, \ldots, n \) ], r.v.
\( f(y) \) – pdf of time to damage of Ghrelin level
\( g(x) \) = pdf of lead time
\( \delta(y) \) - Repair cost limit function of Ghrelin level
\( T^* \) - optimal time
\( C_1 \) – cost interms of Ghrelin level

Assumption
This model has random leadtime & minimal repair.

- Two types of failure occur
  1. Type-I : with probability \( q(y) \) and is corrected with minimal repair
  2. Type-II : with probability \( p(y) = 1 - q(y) \) and followed by unit replacement.

Mathematical Model
Consider the system with a weibul distribution. The pdf of the weibul distribution with parameters \( \beta \) and \( \theta \) is given by
\[
f(y) = \frac{\beta}{\theta} \left( \frac{y}{\theta} \right)^{\beta-1} \exp\left(-\frac{y}{\theta}\right)^\beta, \quad y > 0, \quad \beta, \theta > 0\]
where \( \beta = 1.487 \); \( \theta = 5.329 \)
The pdf of the random leadtime[2,3] of an order is,
\[
g(x) = \frac{1}{\mu} \exp(-x/\mu), \quad x > 0, \quad \mu > 0\]
Where \( \mu = 4.6375 \)
Suppose the random repair cost is \( \omega \). If \( \omega \leq \delta(y) c_e \) (\( c_e \) = the constant cost ) then there is a minimal repair[1].

If \( \delta(y) \) can be explained as a fraction of the constant cost \( c_e \), at age \( y \) and \( 0 \leq \delta(y) \leq 1 \). Let \( \delta(y) = \delta(\exp(-\lambda y)) \) with \( 0 \leq \delta(y) \leq 1 \) & \( \lambda \geq 0 \).
The optimal time \( T^* \) [8] which minimizes \( C_1(T) \) is,
\[
C_1(T^*) = \lambda C_1 (1-g(x)) e^{-\lambda(1-g(x))T^*}
\]
When \( C_1 = 1.6 \)
\[
\lambda = 0.234
\]
\[
g(x) = 0.2181
\]
\[
T^* = 0.3 \quad \text{then} \quad C_1 (T^*) = 0.0673
\]
III. Conclusion

Considering the high complexity of both the feeding and the stress responses, it is reasonable to assume that additional factors not measured in this study could have been induced by acute psychological stress and may have affected the subjective urge to eat in our subjects. Furthermore, variable sensitivity to the stimulatory effect of ghrelin on feeding may also be playing a part. We have shown that a psychological stress may induce an increase in plasma ghrelin levels in some human subjects, and that the post-stress induced urge for uncontrolled eating is not acutely modulated by stress-related elevations in ghrelin levels. Furthermore, the stress induced increase in plasma ghrelin was associated with an acute response of serum cortisol to stress. Finally, the ghrelin response to the psychological challenge was independent of BMI or the presence of BED, and also found Optimal time $T^*$, Minimal Repair $\delta$ and Random Lead Time $g$ to minimize the ghrelin level.

References