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Transcutaneous vagal nerve stimulation modulates stress-induced plasma ghrelin levels: A double-blind, randomized, sham-controlled trial

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Abstract

Background: Transcutaneous cervical vagus nerve stimulation (tcVNS) has emerged as a potential treatment strategy for patients with stress-related psychiatric disorders. Ghrelin is a hormone that has been postulated to be a biomarker of stress. While the mechanisms of action of tcVNS are unclear, we hypothesized that tcVNS reduces the levels of ghrelin in response to stress.

Methods: Using a randomized double-blind approach, we studied the effects of tcVNS on ghrelin levels in individuals with a history of exposure to traumatic stress. Participants received

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Statement of interest:

'All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare that J.D.B has research funding support from ElectroCore LLC for the submitted work. Both active and sham stimulation devices used in this study were provided by ElectroCore free of charge. All remaining authors have no competing interests to report

either sham (n = 29) or active tcVNS (n = 26) after exposure to acute personalized traumatic script stress and mental stress challenges (public speech, mental arithmetic) over a three day period.

Results: There were no significant differences in the levels of ghrelin between the tcVNS and sham stimulation groups at either baseline or in the absence of trauma scripts. However, tcVNS in conjunction with personalized traumatic scripts resulted in lower ghrelin levels compared to the sham stimulation group (265.2 ± 143.6 pg/ml vs 478.7 ± 349.2 pg/ml, P=0.01). Additionally, after completing the public speaking and mental arithmetic tests, ghrelin levels were found to be lower in the group receiving tcVNS compared to the sham group (293.3 ± 102.4 pg/ml vs 540.3 ± 203.9 pg/ml, P= 0.009).

Limitations: Timing of ghrelin measurements, and stimulation of only left vagus nerve

Conclusion: tcVNS decreases ghrelin levels in response to various stressful stimuli. These findings are consistent with a growing literature that tcVNS modulates hormonal and autonomic responses to stress.

Keywords

Stress; Transcutaneous cervical vagus nerve stimulation; Ghrelin

Introduction

Stress responses occur when individuals are faced with actual or perceived shifts in the internal or external environment to promote coping and adaptation (Joels and Baram, 2009; McEwen, 1998). These acute stress responses promote adaptive changes that prepare individuals for challenges; however, in patients with post-traumatic stress disorder (PTSD), the repeated and prolonged activation of these responses can cause detrimental effects (Juster et al., 2011; Lederbogen et al., 2011). There is a crucial need to identify novel biomarkers for assessing stress responses in patients with PTSD, which could also serve as therapeutic targets to modulate these responses.

Ghrelin is a peptide synthesized in the stomach and pancreas and is involved in the regulation of appetite, metabolism and food digestion (Lutter et al., 2008). Ghrelin likely mediates the relationship between stress, mood alterations, increased food consumption (especially for high fat diets) and obesity. In addition to the prominent role of ghrelin in eating behaviors and obesity, recent evidence suggests that ghrelin also plays an important role in the stress response (Bremner and Pearce, 2016; Yildiz et al., 2004). Plasma levels of ghrelin transiently increase during both acute and chronic stress exposures (Bali and Jaggi, 2016; Lutter et al., 2008; Zheng et al., 2009) and ghrelin mediates both stress-induced increases in food intake (Chuang et al., 2011), as well as behavioral responses to stress (Yildiz et al., 2004). The candidate mechanism by which therapeutic interventions could modulate stress responses.

Electrical stimulation of the vagus nerve has been shown to modulate vagal afferents through the nucleus tractus solitarus and affect brain areas that regulate stress responses, such as the amygdala, hippocampus and prefrontal cortex. This treatment modality appears to be effective in the treatment of PTSD (Aaronson et al., 2017; Cimpianu et al., 2017; George

et al., 2005). However, widespread adaptation of vagal nerve stimulation (VNS) has been limited by the cost and potential for adverse events associated with implantable devices (Ramsay et al., 1994). Transcutaneous cervical VNS (tcVNS) has emerged as a convenient alternative to implantable devices for stimulation of the cervical portion of the vagus nerve (Adair et al., 2020) that may be particularly useful for stress-related psychiatric disorders due its effects in reducing sympathetic function and inflammation(Bremner et al., 2020b). We have previously shown that tcVNS reduces sympathetic (Gazi et al., 2020b; Gurel et al., 2020a; Gurel et al., 2020b; Gurel et al., 2020d; Gurel et al., 2020f) and Pituitary Adenylate Cyclase Activating Peptide (PACAP) responses to stress (Gurel et al., 2020c), enhances parasympathetic function (Gurel et al., 2020b), modulates brain areas involved in the stress response in traumatized individuals with and without PTSD (Wittbrodt et al., 2020), and reduces inflammatory (interleuken-6 (IL-6) and Interferon-γ (INF-γ)) responses to stress in PTSD (Bremner et al., 2020a).

Herein, we aimed to investigate the role of tcVNS on ghrelin levels in response to stressful stimuli in a group of patients with a history of psychological trauma. We hypothesized that plasma ghrelin levels increase in response to stressful stimuli and that these response are lower in those receiving tcVNS compared to sham controls.

Methods

The present study was approved by the institutional review boards of Emory University, Georgia Institute of Technology, SPAWAR Systems Center Pacific, and the Department of Navy Human Research Protection Program (ClinicalTrials.gov # NCT02992899). All participants provided written informed consent before enrolling in the study. Participants included physically healthy adults between the ages of 18 and 70 with a history of psychological trauma. Patients were excluded if they had a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, bulimia or anorexia, using the Structured Clinical Interview for DSM-5 Disorders. Additional exclusion criteria were current pregnancy, traumatic brain injury, meningitis, active implanted device, evidence or history of serious medical or neurological illness, such as cardiovascular, gastrointestinal, hepatic, renal, or other systemic illness; known carotid atherosclerosis, cervical vagotomy or positive toxicology screen.

Study design

The presents study was a randomized double-blind protocol spanning 3 days (ClinicalTrials.gov NCT02992899), with each subject receiving four administrations—two on the first day and one on each of the following two days—of either “active” tcVNS or “sham” stimulation. These administrations were not accompanied by any other form of stimulus to focus solely on the effects of tcVNS on human physiology.

Each participant provided his/her own traumatic experiences, and personalized voice recordings based on these experiences were presented as traumatic stress as previously described. The outline of the protocol is shown in Supplemental Figure. The first day included six traumatic stress prompts followed by immediate tcVNS or sham stimulation and two stimulation administrations without stress. Each of the second and third days

included one stimulation administration without stress. The neutral scripts included descriptions of pleasant scenery to induce positive feelings to the subject. Stimulation with tcVNS or sham was applied immediately after the traumatic stress recording ended by the researcher from the left side of the neck. Participants also received two stimulation administrations (tcVNS or sham) without any stressor. Blood samples for measurements of ghrelin levels were obtained at baseline, after stimulation administrations without stressors and following the last stimulation was applied after the traumatic stress recording.

During day 2 and 3, participants underwent mental stress testing which included public speech and mental arithmetic tests. First, participants underwent a public speech task for which they were asked to provide a 2-min long defense statement in a scenario where they were accused of theft. After hearing the scenario details, they were given 2 min to prepare their defense and 2 min to present their statement. Stimulation was applied immediately after the public speech task. In the next step, subjects rested for 8 min in silence. Afterwards, participants were given another task for which they were required to answer series of arithmetic questions for 3 min. A researcher provided negative feedback for incorrect answers and delayed response times. A second stimulation was applied immediately after the arithmetic task. After two mental stressors and two stimulation administrations, the subjects were given a 90-min break. Blood samples for ghrelin measurements were taken at baseline and after the 90-min break following mental stress testing on day 2.

Blinding

Randomization into active tcVNS or sham groups was performed with pre-numbered devices by the manufacturer who were not involved in the research. Participants were randomly allocated to one of the two groups based on a statistician-developed computer-generated randomization table that assigned patients (1:1) with block stratification into tcVNS or sham groups. Random allocation was also carried out by personnel who did not take part in data collection or analyses. This was a double-blinded randomized study with both participants and researchers being blinded to the stimulus type. All statistical analyses were carried out by a biostatistician who did not take part in data collection or processing.

Transcutaneous cervical vagal nerve stimulation

Active tcVNS and sham stimuli were both administered using handheld GammaCore devices (ElectroCore, Basking Ridge, New Jersey, Supplemental Figure 2) as previously described (Gazi et al., 2020a; Gurel et al., 2020e). Briefly, stimulation was applied using collar, stainless steel electrodes with a conductive electrode gel that was placed on the left side of the neck over the carotid sheath. Active tcVNS devices produced an alternating current (AC) voltage signal which consisted of five 5 kHz sine bursts (1 ms of five sine waves; pulse width ¼ 40 ms) repeating at a rate of 25 Hz. The frequency of 25 Hz was chosen based on previous studies showing an optimized effect on autonomic function and other measures at this frequency. The sham devices produce an AC biphasic voltage signal consisting of 0.2 Hz square pulses (pulse width ¼ 5 s) eliciting a mild sensation. Both active and sham devices delivered 2 min of stimulation.

Plasma ghrelin

We measured the concentration of ghrelin in EDTA plasma using the MesoScale system (Meso Scale Diagnostics, Rockville, MD) system with a SECTOR Imager 2400. This system uses electrochemiluminescence for high sensitivity and broad dynamic range. Using the U-PLEX Human Ghrelin (total) assay (Catalog number, K1515XK) according to protocol supplied, the intra-assay CV was 4.3%.

Statistical analysis

Continuous variables are presented as means (standard deviation (SD)) and categorical variables as proportions (%). Differences between groups were assessed using the t-test for continuous variables and $\chi 2$ or Fischer exact tests for categorical variables where appropriate. Linear regression analysis was used to determine the bivariate association between ghrelin levels at baseline and after stimulation and baseline demographics. All analyses were conducted using Stata 14 (StataCorp., College Station, Texas). A P-value of < 0.05 was considered statistically significant. Effect sizes were calculated based on Cohen's d for stimulation and post-stimulation intervals of changes in heart rate photoplethysmogram amplitude as described previously (Gurel et al., 2020e).

Results

The study cohort included 55 participants who underwent either tcVNS or sham stimulations. The mean (SD) age of the cohort was 33 (12) years; 55.9% were female, and 30.5% were African American. Table 1 compares the baseline characteristics between those receiving tcVNS compared to sham control group. There were no significant differences between the groups with respect to baseline sociodemographic characteristics (age, sex, race, educational level, marital status) or the prevalence of PTSD (Table 1).

Correlates of Ghrelin Levels

Table 2 describes the bivariate correlates of baseline and post-stress ghrelin levels. There were no significant associations between baseline ghrelin levels and any of the sociodemographic characteristics (Table 2). However, post-stress ghrelin levels were found to be positively associated with older age (B 7.8, 95% CI 0.46, 15.29, P= 0.02). No other significant associations were present between post-stress ghrelin levels and other sociodemographic characteristics.

Modulation of Ghrelin with Vagal versus Sham Stimulation during Stress

Baseline ghrelin levels were not significantly different between the tcVNS and sham stimulation groups at either day 1 (Table 1, and Figure 1) or day 2 (Figure 2). In the absence of trauma scripts, there were no significant differences between the tcVNS and sham groups in the levels of ghrelin measured immediately after the termination of stimulation (Figure 1). However, when exposed to personalized traumatic scripts in conjunction with tcVNS, participants had significantly lower levels of ghrelin compared to the sham group (265.2 ± 143.6 pg/ml vs 478.7 ± 349.2, P=0.01, Figure 1). Similarly, as shown in Figure 2, plasma ghrelin levels measured 90 minutes after completing the public speaking and mental

arithmetic stress tests on day 2 were significantly lower in the group receiving tcVNS compared to the sham group (293.3 ± 102.4 pg/ml vs 540.3 ± 203.9, P= 0.009).

Discussion

The findings from the present study showed for the first time that non-invasive tcVNS reduced the levels of ghrelin after stressful stimuli compared to sham stimulation. These findings were consistent after exposure to either trauma scripts or public and arithmetic stress tests. Of note, plasma levels of ghrelin were not significantly affected by vagal stimulation following exposure to neutral (non-traumatic) scripts. These findings suggest that ghrelin may have a role in the protective effects of tcVNS against stressful stimuli.

Neuromodulation represents novel treatment modalities for stress-related psychiatric disorders (Adair et al., 2020). Among these strategies, vagal nerve stimulation with implantable devices has shown to be effective in the treatment of depression and epilepsy (Kraus et al., 2013; Nemeroff et al., 2006). However, FDA-approved vagal stimulation for these diseases have historically involved surgical implantation to provide direct electrical stimulation of the vagus nerve (Aaronson et al., 2017; Bremner and Rapaport, 2017). The emergence of non-invasive devices for stimulation of the vagal nerve provides an attractive alternative as it reduces cost and the inconvenience associated with implanted devices (Bremner and Rapaport, 2017). However, the mechanisms of action of these devices and their efficacy have not been extensively studied. In the present study, we showed that ghrelin levels were lower in those undergoing tcVNS compared to sham controls in response to mental stress stimuli.

Ghrelin was discovered in 1999 as a hormone produced and secreted mostly by the stomach and was thought to act as a pro-hunger hormone as levels increased with starvation (Cummings et al., 2002). Further research, however, has revealed that ghrelin's response to acute or chronic hunger states does not necessarily reflect a role of ghrelin in hunger, but rather a more prominent role as a stress response. This proposal has been further supported by observations that ghrelin levels are chronically higher in those with psychiatric illnesses such as major depressive disorder or bipolar disorder (Kurt et al., 2007; Ozsoy et al., 2015; Tuncel et al., 2016). More significantly, it has been shown that ghrelin could be a marker of treatment response in psychiatric disorders. Previous studies have demonstrated that a decrease in ghrelin levels were associated with treatment responses (Kurt et al., 2007; Lopez-Alarcon et al., 2020; Ozsoy et al., 2014; Ricken et al., 2017). These findings are consistent with the results of our study showing the association between lower ghrelin levels and responses to vagal stimulation during mental stress.

Previous studies have shown that ghrelin is transiently elevated by acute stress exposure (Raspopow et al., 2010; Rouach et al., 2007; Sinha et al., 2019), by short-term interpersonal stress (Jaremka et al., 2014), or in anticipation of laboratory stress (Raspopow et al., 2014). Similarly, exposure to chronic stress has shown to be associated with higher ghrelin levels in both humans and animal models with levels remaining elevated for extended periods of time even after the cessation of the stressful stimuli (Lutter et al., 2008; Yousufzai et al., 2018). In our study, we did not observe higher ghrelin levels after stressful stimuli with either

trauma scripts or mental stress challenges (speaking and arithmetic). This lack of increase in ghrelin levels in response to stress could be attributed to the fact that we measured blood samples around 90 minutes after stressful stimuli. Ghrelin has a short half-life of between 10 and 31 minutes (Akamizu et al., 2004; Nagaya et al., 2001). Results from a recent meta-analysis indicate that ghrelin reaches its highest levels in the first 5 minutes following the stress intervention, and levels return to baseline after 45 minutes post-stress exposure (Bouillon-Minois et al., 2021).

Our study has a number of limitations. Blood samples for ghrelin measurements were collected 90 minutes after stressors and it is possible that the magnitude of the ghrelin response to tcVNS would vary at different time points post-stress exposure. Our study is also limited by the fact that only the left vagus nerve was stimulated per the study design. It is unclear if right sided vagal stimulation could also be associated with similar changes in ghrelin levels in response to mental stressors. We also did not evaluate the effects of blinding in either the tcVNS or sham groups. Psychometric measures were also not adopted in this study. Patients were also allowed to take their prescribed medications during the study period. While these medications could potentially confound the results of our study, we have previously shown that empirical evidence for relevant medications having a confounding effect on task performance remains sparse (Lanius et al., 2010). Therefore, future studies are needed to further confirm the results of our study.

In summary, we found that tcVNS modulates ghrelin levels in response to various stressful stimuli. Future work is needed to understand the longitudinal outcomes of tcVNS and whether ghrelin measurements could be utilized as a biomarker for assessment of response to neuromodulation treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Ghrelin levels were similar between the tcVNS and sham groups at baseline
- tcVNS and traumatic scripts resulted in lower ghrelin levels compared to sham group
- With stress, ghrelin levels were lower in the tcVNS group than the sham group

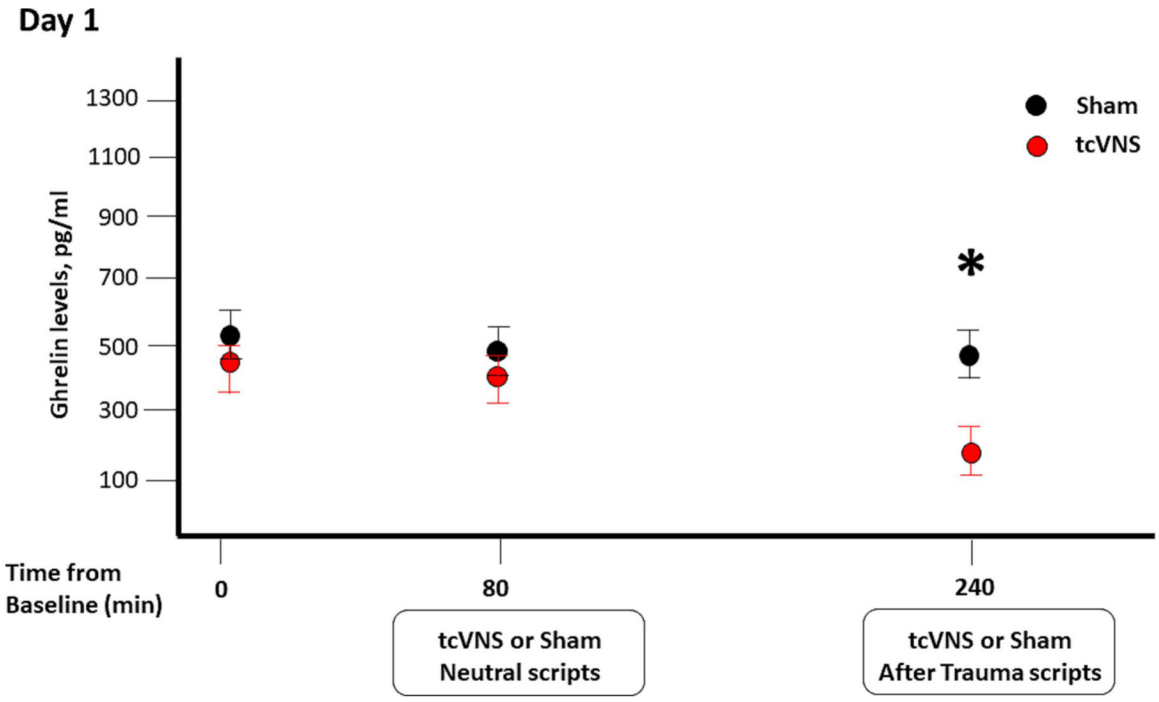

Figure 1.

Effects of sham (black) or tcVNS (red) on ghrelin levels. Blood samples were collected at baseline, after stimulation following neutral scripts and after stimulation following trauma scripts.

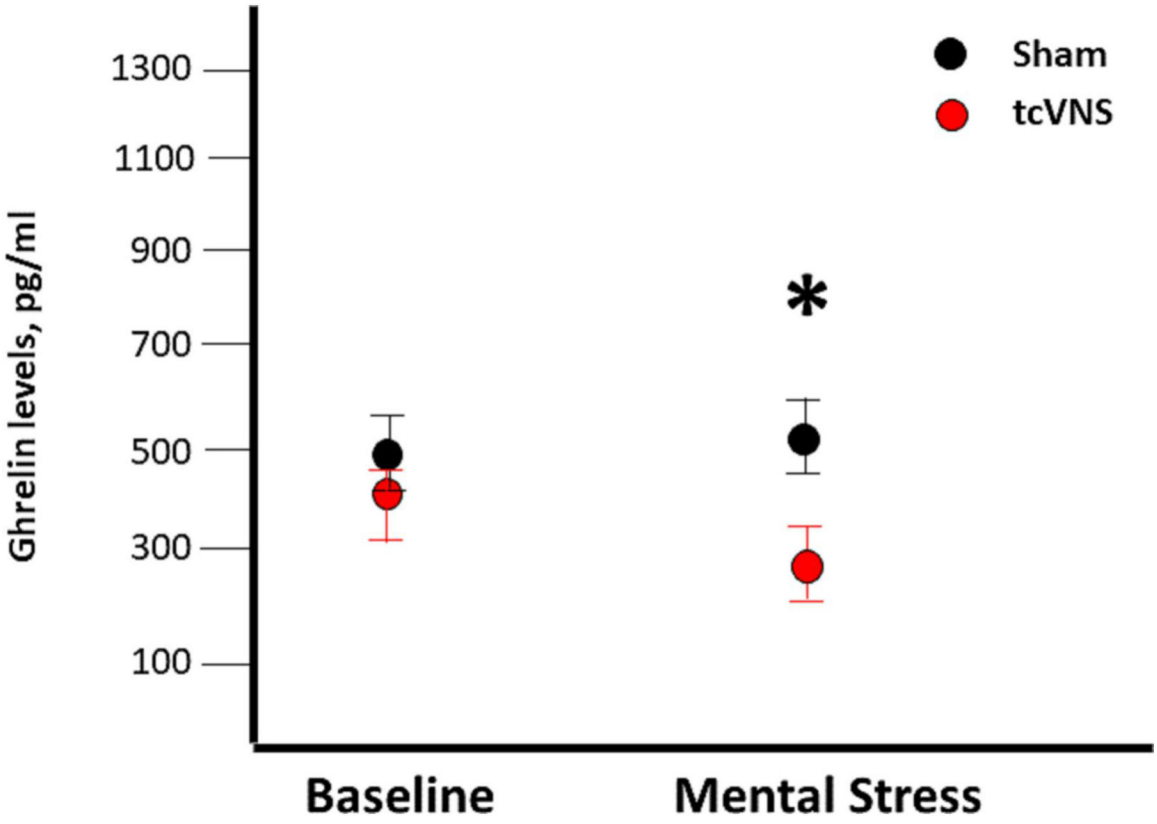

Figure 2.
Effects of sham (black) or tcVNS (red) on ghrelin levels. Blood samples were collected at baseline, after the completion of public speaking and arithmetic mental stress.

Table 1.

Baseline characteristics of the study cohort stratified by treatment group (Sham vs tcVNS)

Variable	Sham (N= 29)	VNS (N= 26)	P-value
Age, Mean (SD)	34 (12)	31 (10)	0.23
Female, N (%)	16 (55.2)	16 (61.5)	0.62
Black race, N (%)	8 (28.6)	10 (38.5)	0.44
BMI, Mean (SD)	28.8 (5.3)	27.0 (6.5)	0.28
Educational level, N (%)			
College graduate	18 (56.7)	15 (57.3)	0.71
Marital Status, N (%)			0.72
Never married	16 (59.3)	17 (65.4)	
Married	4 (14.8)	5 (19.2)	
Divorced/separated	7 (25.9)	4 (15.3)	
PTSD, N (%)	13 (44.8)	14 (53.8)	0.48
Baseline ghrelin (pg/ml), Mean (SD)	530.8 (336.2)	432.3 (298.1)	0.21

BMI= body mass index, PTSD= Post traumatic stress disorder

Table 2.

Bivariate analysis investigating the correlates of baseline and post-stress ghrelin

	Baseline Ghrelin	Post-stress Ghrelin
	B (95% CI)	
Age	6.9 (−1.3, 15.9)	**7.8 (0.4, 15.2)**
Female sex	183.3 (−14.2, 381.2)	82.3 (−113.2, 278.5)
Black race	−148.2 (−356.2, 61.3)	−128.2 (−340.7, 84.1)
BMI	−9.8 (−27.0, 7.4)	−2.27 (−19.7, 15.1)
Educational level	55.2 (−41.3, 152.0)	40.8 (−51.2, 132.9)
Marital Status	101.0 (−11.3, 213.4)	105.2 (−0.67, 211.9)
PTSD	32.2 (−175.2, 240.6)	62.3 (−134.5, 259.8)

BMI= body mass index, PTSD= Post traumatic stress disorder