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Peptide YY and ghrelin predict craving and risk for relapse in abstinent smokers

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Abstract

Appetite hormones are directly involved in regulating satiety, energy expenditure, and food intake, and accumulating evidence suggests their involvement in regulating reward and craving for drugs. This study investigated the ability of peptide YY (PYY) and ghrelin during the initial 24–48 hours of a smoking cessation attempt to predict smoking relapse at 4 weeks. Multiple regression analysis indicated that increased PYY was associated with decreased reported craving and increased positive affect. Cox proportional hazard models showed that higher ghrelin levels predicted increased risk of smoking relapse (Hazard Ratio=2.06, 95% CI=1.30 – 3.27). These results indicate that circulating PYY may have buffering effects during the early stages of cessation while ghrelin may confer increased risk of smoking relapse. Further investigation of the links between these hormones and nicotine dependence is warranted.

Keywords

Peptide YY; Ghrelin; Craving; Withdrawal; Nicotine Dependence; Relapse

1. Introduction

The first 24–48 hours of abstinence from smoking are critical to the ultimate success of the smoker’s ability to maintain abstinence. Craving cigarettes, particularly cue-induced cravings, is a strong motivation for relapse (Ferguson and Shiffman 2009). Appetite

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Contributors

Mustafa al’Absi designed the study, wrote the protocol, and the manuscript. Andrine Lemieux assisted with reviewing the literature and with the writing and interpretation of the results. Motohiro Nakajima helped with data management and analyses. All authors contributed to and have approved the final manuscript.

Conflict of Interest

The authors have no conflicts of interest to report.

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hormones have been implicated in craving, relapse, and the reward properties of addictive drugs (Lee, Joe et al. 2006; Leggio, Ferrulli et al. 2012; Aguiar-Nemer, Toffolo et al. 2013). While leptin has been extensively studied and linked to the rewarding effects of nicotine (Aguiar-Nemer, Toffolo et al. 2013) other appetite hormones have received relatively less attention. Ghrelin and PYY are additional appetite hormones that may be involved in regulating the rewarding effects of drug use (Hillemacher, 2011; Malik, McGlone, Bedrossian, & Dagher, 2008; Schloegl, Percik, Horstmann, Villringer, & Stumvoll, 2011). Ghrelin, an orexigenic hormone released primarily by the stomach, is involved in eating initiation and termination (Challis et al., 2004; Challis et al., 2003; Date et al., 2000; Sakata et al., 2002; Wren & Bloom, 2007). Ghrelin is expressed centrally in several areas of the brain, including the arcuate nucleus (ARC), paraventricular nucleus, and ventromedial nucleus, as well as the lateral hypothalamic area, perifornical area, and ventral tegmental area (Valassi, Scacchi, & Cavagnini, 2008; Xu, Elmquist, & Fukuda, 2011). The interaction of appetite hormones with other neuropeptides within these regions of the brain suggests their involvement in the rewarding effects of drug use (Kenny, 2011; Menzies, Skibicka, Dickson, & Leng, 2012; Volkow, Wang, Fowler, Tomasi, & Baler, 2012).

Specific to smoking, ghrelin declines rapidly in response to acute cigarette smoking for naïve smokers but not habitual smokers (Kokkinos, Tentolouris et al. 2007). Ghrelin also declines following two months of successful abstinence from nicotine (Lee, Joe et al. 2006) but some have shown that ghrelin is not associated nicotine craving and withdrawal symptoms (Mutschler et al., 2012). In addition, ghrelin interacts with the nicotinic acetylcholine receptor to stimulate dopamine release in the brain, particularly in areas related to drug reward and emotional functioning (Jerlhag, Janson, Waters, & Engel, 2012; Palotai et al., 2013a, 2013b). An early genetic study has identified ghrelin genes and personality trait relationships that may have implications for trait differences between alcoholics and non-alcoholics (Landgren et al., 2011). The evidence that ghrelin and nicotine have an additive effect on dopamine release in areas linked to drug reward makes ghrelin a prime appetite hormone for the study of nicotine and withdrawal.

While the literature on nicotine addiction and ghrelin is small but growing, it is nonexistent in relation to PYY. PYY, an anorexic hormone, is produced in the gut in response to eating and acts to inhibit food intake (Valassi, Scacchi, & Cavagnini, 2008). Although PYY has not been, to our knowledge, examined in smokers, there is reason to believe that PYY may be implicated in smoking. Both ghrelin and PYY share with nicotine the ability to modulate the reward circuits of the mesoaccumbens dopamine pathway. Like drugs of abuse, ghrelin and PYY stimulate neurons within the mesoaccumbens dopaminergic pathways (Abizaid et al., 2006; Jerlhag et al., 2006; Jerlhag et al., 2007; Nakazato et al., 2001) and interact with other neuropeptides in multiple brain regions linked to the rewarding effects of both food and drugs (Volkow, Wang et al. 2012). PYY is known to inhibit NPY neurons and activates pro-opiomelanocortin (POMC) neurons within the hypothalamic ARC, and may therefore impact affective and reward related processes (Batterham et al., 2002; Challis et al., 2003). This was demonstrated in a study in which knockout mice lacking PYY production exhibited enhanced anxiety and depression-like behaviors (Painsipp, Herzog, & Holzer, 2010).

To our knowledge, no study has investigated PYY or ghrelin in smokers during the critical first 24–48 hours of cessation. This paper reports novel findings on circulating PYY and ghrelin during this early withdrawal from nicotine. Our goal was to determine the feasibility of utilizing these hormones in conjunction with measures of withdrawal symptoms early in withdrawal process to predict relapse at a 4-week follow-up period. We predicted a priori that total ghrelin would be associated with increased levels of craving and later risk for smoking relapse. Given its novelty, no prediction was made for PYY.

2. Methods

2.1. Participants

Sixty-six female and 86 male dependent cigarette smokers were recruited into two different studies (al'Absi, Hatsukami et al. 2005, al'Absi, et al. 2013). They were 34.27 years old on average (SD=12.40). Participants were free from major physical illness or psychiatric disorders, weighed within $\pm 30\%$ of Metropolitan Life Insurance norms, and reported a high level of motivation to quit. The motivation to quit was assessed using a 7 point scale (1 = not at all; 7 = very strong). Subject report of ≥ 6 (strong desire or higher) was defined as a high level of motivation to quit. Subjects also were excluded if they reported using alcohol 2 or more times per day. All participants signed a written consent form approved by the Institutional Review Board of the University of Minnesota. Participants received monetary compensation for their time (approximately \$15/hour).

2.2. Measures

Plasma PYY was measured using commercial ELISA assay (Millipore, Billerica, MA; minimum detection 1.4 pg/mL). The average intra- and inter-assay coefficients of variation were $<8\%$ and $<7\%$. Plasma total ghrelin was determined using commercial ELISA assay (Millipore, Billerica, MA; minimum detection 100 pg/mL). The average intra- and inter-assay coefficients of variation were 5.3% and 4.3%. Since the samples were collected to assess stress hormones for a larger project, procedures for collecting and preparing of samples for acetylated active ghrelin were not justified. Furthermore, the literature indicates that total ghrelin data yield useful information (Pilhatsch, Scheuing et al. 2014). Cotinine concentrations in saliva were assayed using enzyme immunoassay (EIA; DRG Diagnostics, Marburg, Germany) with inter- and intra-assay variations below 12%. Measurement of expired CO was performed using MicroCO™ monitors (Micro Direct Inc., Auburn, Maine).

The assessment of withdrawal symptoms utilized the Subjective State Scale which includes the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes & Hatsukami 1986; Hughes & Hatsukami 1998), positive affect and distress subscales. The abbreviated Questionnaire of Smoking Urges (QSU-brief; Tiffany & Drobes 1991; Cox, Tiffany et al. 2001) was used to assess craving motivations such as the appetitive desire to smoke (F1) and the desire to avoid the aversive experience of withdrawal (F2). Demographic information, smoking history, and nicotine dependence (the Fagerstrom test for nicotine dependence levels; FTND; Heatherton et al. 1991) were also assessed.

2.3. Procedures

All participants attended their first laboratory session after their initial 24 hour (study 1, n=36) to 48 hour (study 2, n=86) abstinence period. Participants were instructed to have a light lunch at least two hours prior to the session. Interviews were used to review participant's consumption prior to the lab session and confirm compliance. A blood sample and self-report measures were collected in the first hour of the lab session and were used in the analyses reported here. Blood samples were centrifuged and stored at -70°C until analysis. Participants also attended four weekly follow-up sessions for social support and assessment of abstinence. No pharmacological aids were provided to participants. Expired carbon monoxide (CO) and saliva samples for cotinine assays were collected after the 24–48 hour abstinence and during each of the follow-up sessions to verify smoking abstinence.

2.4. Data Analysis

Appetite hormones were examined for outliers and influential points. Ghrelin and craving scores were square root transformed to normalize. Relapse was defined as smoking 1 or more cigarettes after a quit attempt. One way analysis of variance (ANOVA) was used to examine sex differences in basic demographics, sleep, and smoking characteristics. Paired T-tests were used to measure change in cotinine and carbon monoxide pre- and post-abstinence. Hierarchical multiple regression models were conducted using each hormone separately as a predictor of craving and withdrawal. Age, BMI, and data source (study 1 or study 2) were entered first as covariates followed by gender and each hormone. The regression models were examined and overall R^2 and standardized betas are reported. Cox proportional hazard models were conducted similarly to test the extent to which ghrelin and PYY predicted days until smoking relapse. Data analysis was conducted by SPSS v20 (Chicago, IL).

3. Results

3.1. Subject Characteristics

On average the subjects were 34 years old (standard deviation: ± 12.4), had at least a high school education (14.06 ± 2.62) and had a body mass index of 25 (25.30 ± 4.28). Men had greater body mass index than women (26.18 ± 4.30 versus 24.13 ± 3.98 respectively, $p < .01$). They had smoked an average of 18.62 (± 6.86) cigarettes per day for an average of 11.39 years (± 9.97). Their nicotine dependence score on the FTND was 5.46 (± 2.04) and they had attempted to quit an average of 5 times in the past (± 7.96). Men and women were of similar age, education, average hours of sleep, number of cigarettes per day, duration of smoking, number of previous quit attempts, or motivation to quit (see Table 1).

Carbon monoxide levels declined with 24–48 hour abstinence (pre-abstinence 24.22 ± 11.23 versus post-abstinence 4.33 ± 2.91 ; $p < .001$) and did not exceed 8 (study 2) to 10 (study 1) ppm at 24–48 hours post. Reduced cotinine supported self-reported abstinence (pre-abstinence 156.98 ± 140.13 versus post-abstinence 55.36 ± 71.78 ; $p < .0001$). Cotinine and carbon monoxide levels did not differ between abstainers and relapsers or genders ($p > .10$).

3.2. Appetite Hormones and Craving

PYY was not correlated with ghrelin either as a bivariate correlation or when partialled by gender ($p > .10$). According to the multiple regression models (see Table 2), higher PYY predicted more positive affect ($R^2=.14$, $p<.01$; Std. Beta= 0.21 , $p<.05$). PYY did not predict QSU-B F1 urge to smoke ($p > .10$), but higher PYY predicted lower QSU-B F2 desire to avoid withdrawal symptoms ($R^2=.15$, $p<.01$; Std. Beta= $-.24$, $p<.01$). The PYY prediction of MNWS was marginal ($R^2=.08$, $p=.09$; Std. Beta= $-.17$, $p=.06$) as was the prediction of distress ($R^2=.04$, $p=.09$; Std. Beta= $-.17$, $p=.06$). Ghrelin did not predict any withdrawal or craving symptoms despite significant overall models for positive affect ($R^2=.14$, $p<.01$; Std. Beta= $.06$, $p > .10$) and QSU-B F2 desire to avoid withdrawal symptoms ($R^2=.10$, $p<.05$; Std. Beta= $-.05$, $p > .10$). In these models the covariates for age had a large effect on both positive affect and QSU-B F2 (Model 1 $R^2=.13$, $p<.01$ and $R^2=.10$, $p<.01$ respectively). No significant gender or BMI effects were found in any of these models. Length of abstinence (study 1=24 hours, study 2=48 hours) predicted positive affect scores in the ghrelin model (Beta= $.29$, $p<.01$) and PYY model (Beta= $.26$, $p<.01$), as well as distress in the PYY model (Beta= $.18$, $p<.05$) and QSU-B F2 in the ghrelin (B= $.21$, $p<.05$) and PYY models (Beta= $.23$, $p<.01$).

The Cox proportional hazard models of relapse was predicted by ghrelin (hazard ratio (HR)= 2.06 , $p<0.01$). The relative effects of high versus low ghrelin are depicted as a median split. From this we see that the individuals with ghrelin above the median have a two-fold increased risk of relapse. Despite the fact that men have lower ghrelin than women (413 ± 227.62 pg/ml versus 579.65 ± 342.36 pg/ml respectively, $p<0.01$), gender was not a significant predictor of relapse in the Cox model ($p > .10$). PYY was not a significant predictor of relapse using cox regression. While males had higher PYY than women (92.45 ± 43.90 pg/ml versus 82.64 ± 34.02 pg/ml respectively, $p<.01$), neither gender nor any other factors were significant in this model.

4. Discussion

This study demonstrated for the first time that PYY was associated withdrawal and craving symptoms but it did not appear to predict relapse. Elevated PYY was associated with greater positive affect and lower desire to avoid withdrawal symptoms (QSU-B F2). While ghrelin did not predict withdrawal or craving, it was a significant predictor of relapse. Higher ghrelin increased the risk of relapse above and beyond age, BMI, gender, and time of blood sample (24 versus 48 hours). The current study provides promising results supporting the utility of these appetite hormones as biomarkers of withdrawals symptoms and risk for smoking relapse.

The finding that elevated PYY was associated with positive affect and reduced motivation to avoid withdrawal symptoms suggests the possibility that this hormone may have buffering effects during this critical early stage of cessation. One mechanism for this effect may include mood-related changes and/or PYY's noted antidepressant-like effects (Painsipp, Herzog et al. 2011).

Our ghrelin results support previous preclinical evidence that ghrelin is relevant to the rewarding effects of drugs including nicotine (Jerlhag and Engel 2011), but there are critical distinctions between our results and those of others. While ghrelin correlates positively with craving for alcohol (Koopmann, von der Goltz et al. 2012, Leggio, Ferrulli et al. 2012), ghrelin was not related to craving or withdrawal symptoms here. This is consistent with other reports comparing smokers after 24 hours of abstinence (Mutschler et al., 2012). The increased risk of relapse shown here would be inconsistent with ghrelin's recent preclinical evidence of an anti-depressive effect (Lutter, Sakata et al. 2008). While there are inconsistencies, our demonstration that higher ghrelin predicts tobacco relapse was consistent with the alcohol relapse findings by Leggio and colleagues (2012). The trend towards a negative association with distress during withdrawal but strong positive association with relapse risk for higher ghrelin might be reconciled by considering cue sensitivity. For example, environmental cues are sufficient to trigger a release of ghrelin (Abizaid 2009); thus our results may reflect an increased sensitivity to relapse cues in those most likely to relapse. Here it is important to consider the fact that our plasma samples were taken at the 24–48 hour post quitting time point and not at the time of relapse. It may be that sampling in closer proximity to the relapse event would be more informative. It should be noted that the association of ghrelin with craving may vary between active and total ghrelin. For example, a study by Koopmann and colleagues (2012) demonstrated that biologically active, acetylated ghrelin was associated with craving during alcohol withdrawal, but this association was not found with total ghrelin.

Notwithstanding the novelty of the results presented here, we should note that the short follow-up period and the reliance on self-report of dietary behaviors prior to assessment may limit our conclusions. The study was limited by the by the exclusion of individuals with active psychiatric treatment and those greater than 30% beyond normal weight range. As such, our results cannot be extended to those smokers who are obese or suffering from active psychopathology. In addition, our smokers were heavy smokers and thus these results may not apply to those with infrequent or lighter tobacco use. Future studies may also be strengthened by linking these hormones with appetite and weight changes among smokers after cessation and over a longer period of time. Although we assessed total ghrelin instead of acetylated, active ghrelin, we note that total ghrelin has been related to craving with acute nicotine dosing (Pilhatsch, Scheuing et al. 2014). Finally, additional experimental control over food intake prior to blood sampling should be considered.

5. Conclusion

In conclusion, our results suggest that PYY and ghrelin may be useful markers of withdrawal symptoms during the early abstinence period and later relapse. These results suggest there is value in continued study of the role of PYY and ghrelin in smoking cessation, though much work needs to be done. For example, a great deal of progress has been made with experimental animals in the study of ghrelin gene polymorphisms and central versus peripheral signaling in alcohol reward and intake. A review of this work is beyond the scope of this paper, but the reader may find the following original works and reviews helpful (Dickson et al., 2011; Landgren et al., 2011; Suchankova et al., 2013). Further understanding of the relationship between appetite hormones and craving for

nicotine could be greatly enhanced by replicating the recent study of intravenous exogenous ghrelin administration on alcohol cue-induced craving in heavy drinkers (Leggio et al., in press). Extending this to PYY is also feasible as intravenous PYY has been used safely in human obesity research for over a decade (Zac-Varghese, De Silva, & Bloom, 2011). These results should stimulate work to examine actual changes in appetite and weight after cessation and determine the extent to which these hormones contribute to post-cessation changes in appetite and weight among smokers.

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Highlights

- Appetite hormones are directly involved in regulating satiety, and evidence of their involvement in regulating craving for drugs is growing.
- Here, increased peptide YY was associated with decreased craving and increased positive affect.
- Higher ghrelin levels predicted increased risk of smoking relapse
- Circulating peptide YY and ghrelin are promising biomarkers for craving and smoking relapse.

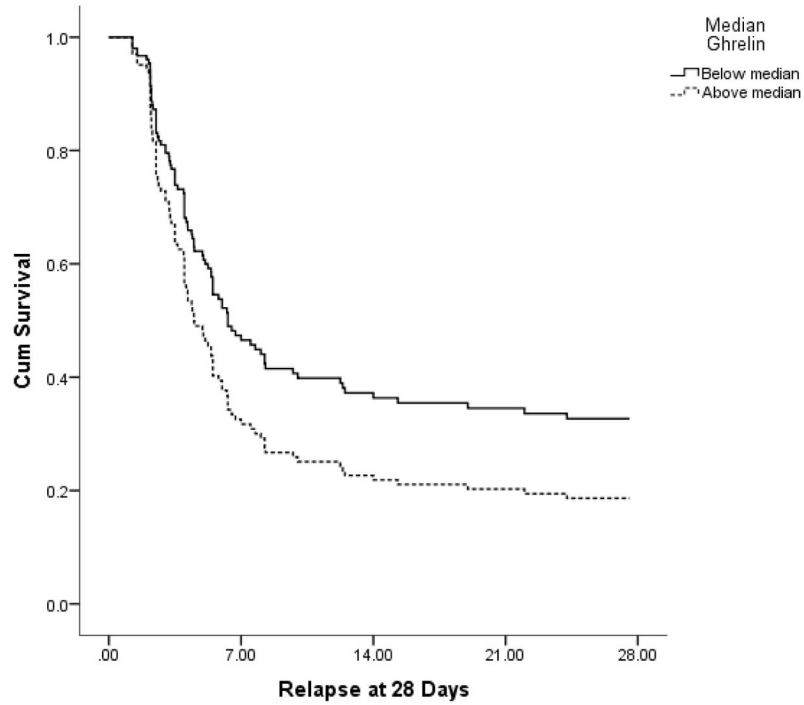


Figure 1. The survival plot between ghrelin and days to relapse from a censored normalized Cox regression model.

Table 1

Demographic variables for the entire group and each gender.

	N	Total Mean (SD)	N	Female Mean (SD)	N	Male Mean (SD)
Age	152	34.27 (12.40)	66	34.47 (12.81)	86	34.12 (12.15)
Body Mass Index	149	25.30 (4.28)	64	24.13 (3.98)	85	26.18 (4.30)**
Education	145	14.06 (2.62)	62	14.35 (2.37)	83	13.85 (2.78)
Average Sleep	137	7.08 (1.18)	59	7.11 (1.31)	78	7.06 (1.09)
Cigarettes per day	151	18.62 (6.86)	65	18.65 (8.03)	86	18.60 (5.86)
Nicotine dependence	152	5.46 (2.04)	66	5.28 (2.21)	86	5.59 (1.90)
Duration (yrs)	149	11.39 (9.97)	64	9.96 (8.62)	85	12.47 (10.80)
Past quit attempts	141	5.38 (7.96)	63	6.08 (10.64)	78	4.82 (4.82)

Note: SD = standard deviation.

** p < .01 Gender effect

Table 2

Regression results with hormone and other covariates as the predictors of withdrawal and craving.

	Withdrawal & Craving Symptoms ^d				
	MNWS	Positive Affect	DISTRESS	QSU-B F1	QSU-B F2
Ghrelin					
Model 1 ^b	.04	.13***	.05	.06 [#]	.10**
Data source	.13	.29**	.14	.07	.21*
Age ^c	-.14	.18 [#]	-.11	-.22*	-.17 [#]
BMI ^c	-.01	-.13	.04	.00	-.08
Model 2 ^b	.05	.14**	.07 [#]	.06	.10*
Gender ^c	-.05	.12	-.04	-.03	.02
Hormone ^c	.07	.06	-.18 [#]	-.03	-.05
PYY					
Model 1 ^b	.04	.10**	.02	.05 [#]	.10**
Data source ^c	.15 [#]	.26**	.18*	.08	.23**
Age ^c	-.14	.21*	-.16 [#]	-.21*	-.20**
BMI ^c	-.01	-.17 [#]	.08	-.03	-.04
Model 2 ^b	.08 [#]	.14***	.04 [#]	.06	.15**
Gender ^c	.11	.10	.02	.03	.06
Hormone ^c	-.17 [#]	.21*	-.17 [#]	-.11	-.24**

^aRegression results predicting withdrawal (MNWS, positive affect & distress) and craving (QSU-B F1 & F2) with each appetite hormones separately.

^bThe data represents R² and significance for Model 1 (covariates) and 2 (gender & hormone).

^cThe data for each predictor (covariates in Model 1; gender and hormone in Model 2) are represented by standardized beta values and significance.

[#] p<.10;

* p<.05;

** p<.01;

*** p<.001