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Changes in circulating leptin levels during the initial stage of cessation are associated with smoking relapse

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Abstract

Rationale—Leptin has been linked to tobacco craving and withdrawal related symptoms. Very few studies have examined leptin prospectively in both male and female nonsmokers and smokers.

Objectives—We examine leptin concentrations prospectively in both male and female nonsmokers and smokers to assess the associations of leptin with psychological symptoms and smoking relapse during ad libitum smoking, the first 48 hours post quit, and four weeks post-cessation.

Methods—Self-report psychological, anthropomorphic and biological measures (cotinine, carbon monoxide and plasma leptin) were collected before and after 48 hours of smoking abstinence. Smokers were stratified at 28 days post quit as abstinent or relapsed if they had smoked daily for 7 consecutive days at any point in the 28 days.

Results—Leptin concentration (square root transformed ng/ml) increased over the 48-hour abstinence, but only in female abstainers. In contrast, leptin was very stable across time for nonsmokers, relapsers and males. Cox regression supported that increased leptin was associated with decreased risk of relapse. Leptin was correlated negatively with withdrawal symptoms for abstainers only. Females produce more leptin than males and this level increases from ad libitum smoking to 48-hours post quit.

Conclusions—The current analysis indicates that a leptin increase early in cessation predicts abstinence. The increase in women, but not men, in response to abstinence provides further evidence of important gender differences. The negative correlation between leptin and withdrawal symptoms indicate a possible protective effect of leptin. Further research is ongoing to elucidate the psychological and biological determinants of this effect.

Keywords

smoking; tobacco; withdrawal; leptin; relapse; prospective; gender; nicotine

Introduction

The hormone leptin contributes to the modulation of multiple appetitive behaviors beyond food intake. Although research has demonstrated its role in food intake and energy regulation (Sobrinho Crespo et al. 2014), there is increasing evidence that leptin is related to the consumption of psychoactive substances such as alcohol and nicotine (Addolorato et al. 2009; Aguiar-Nemer et al. 2013; al'Absi et al. 2011; Ersche et al. 2013). Leptin in peripheral circulation correlates positively with craving cigarettes in smokers who are actively smoking (von der Goltz et al. 2010). Increased baseline circulating leptin also predicts higher self-reported cravings for cigarettes during smoking cessation, higher withdrawal symptoms, lower positive mood, higher distress and higher physical symptoms in smokers who have been abstinent for 24 hours (al'Absi et al. 2011). Baseline leptin, however, has not been linked to relapse or abstinence following four weeks of smoking cessation (al'Absi et al. 2011; Stadler et al. 2014). While baseline leptin (during ad libitum smoking or smoking abstinence) may not be helpful in predicting relapse, the extent to which dynamic changes in leptin concentrations during the initial phase of a quit attempt relative to ad libitum are associated with subsequent cessation outcomes is not clear. Two longitudinal studies of successful quitters showed that leptin did not change from ad libitum smoking to 4 weeks (Won et al. 2014) or 3 months post quit date (Stadler et al. 2014; Won et al. 2014). While intriguing, these studies did not assess relapsed smokers nor was the immediate post-cessation leptin change relative to ad libitum smoking reported. Thus the potential predictive value of changes in leptin in the early cessation period in both relapsed and abstinent smokers remains untested and unclear.

In addition, little is known about leptin relative to gender and smoking cessation. Past studies of smoking cessation have used all males (Won et al. 2014) or have failed to report gender in their results (Stadler et al. 2014). This is unfortunate given that female smokers have been shown to have higher leptin than their male counterparts (al'Absi et al. 2011). While previous studies have shown that successful abstinence is not related to leptin across three months of cessation, no study has directly examined leptin levels relative to smokers who eventually relapsed and those who maintained abstinence either in smokers as a whole or as a comparison of male and female smokers. The purpose of this study was to examine associations of leptin concentrations prior to and immediately following smoking cessation with early smoking relapse. In addition, this study will examine the relative predictive value of dynamic leptin changes across the first 48 hours of abstinence and gender in predicting risk of relapse.

Methods

Participants

A total of 38 nonsmokers (50% women) and 116 smokers (45% women) were recruited for the parent study. Nonsmokers were recruited to provide clarity on the potential for systematic leptin variability across the two sessions and to determine whether there are important group differences based on chronic exposure to nicotine (smokers vs. nonsmokers). Due to the secondary nature of this study, plasma samples were available for

leptin analysis for 34 nonsmokers and 72 smokers bringing the total to 106 participants for this analysis. They were recruited through advertisements in newspapers, on Craigslist and on posters in Duluth and Minneapolis, MN. Participants contacted the laboratory and were invited to an on-site screening session. Exclusion criteria included recent or acute major illness, chronic medical conditions, current psychiatric disorder, and prescription medication (with the exception of contraception), alcohol abuse or illegal substance use. Furthermore, all participants were required to be within 30% of the Metropolitan Life Insurance normal weight range and reporting two or less alcoholic beverage consumption per day. The smokers were heavy smokers who smoked on average 10 or more cigarettes per day and all reported at least a moderate level of desire to quit smoking (see Results). The current data was based on a larger study reported elsewhere (al'Absi et al. 2015). As reported elsewhere (al'Absi et al. 2015), a total of 48% of the women (16/33) in this study were tested in the follicular phase of the menstrual cycle (days 0–14) while the remaining were tested during the luteal phase (days 15–28). Relapse status (abstained versus relapsed) was not associated with menstrual phase (al'Absi et al. 2015).

Psychological & smoking measures

Smoking history variables were collected during the initial screening interview and included average cigarettes/day, years at this level, hours since last cigarette and age at smoking onset. Severity of nicotine addiction was estimated using the Fagerström Test of Nicotine Dependence (Heatherton et al. 1991). Withdrawal symptoms were assessed using the Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami 1986). The craving item was analyzed separately from the MNWS as it has been reported to be independent of withdrawal-related symptoms (MNWS; Hughes and Hatsukami 1986). Craving was also measured using subscales specific to appetitive urges (F1) and aversive urges (F2) from the abbreviated Questionnaire of Smoking Urges (QSU-B Cox et al. 2001; Tiffany and Drobes 1991). Positive affect, physical complaints and distress were tracked across time in a manner similar to past stress and smoking studies using a subjective state adjective checklist scale (al'Absi et al. 2013). Adjectives representing these constructs were rated on a 7-point scale ranging from “not at all” to “very strong.”

Biological measures

Blood samples were collected at the beginning of each session using 8-ml EDTA Vacutainer tubes. Samples were centrifuged and stored at –80°C until assayed. Plasma leptin was assayed using a direct sandwich ELISA (Linco, Missouri) with Inter- and intra-assay coefficients of variance for these assays of below 8%. Saliva samples were also collected at the beginning of each session using Salivette® tubes (Sarstedt, Rommelsdorf Germany) and were assayed for cotinine. Cotinine was assayed using EIA (DRG Diagnostics, Marburg, Germany) which produced CV values less than 12%. Expired CO was collected at both time points using a MicroCO™ monitors (Micro Direct, Inc., Auburn, Maine).

Procedures

All participants attended two laboratory sessions scheduled between noon and 2:00 pm to control for diurnal phase. The smokers were asked to smoke their preferred brand prior to reporting to the laboratory on the first session (ad libitum session). All participants were

instructed to eat a small meal 2 hours prior to coming to the lab. They were also instructed to refrain from exercise and alcohol consumption for 24 hours and to avoid caffeine for 4 hours prior to each lab. During each lab session they provided blood and saliva samples for later analysis and then completed a standardized stress manipulation reported on elsewhere (al'Absi et al. 1997; al'Absi et al., 2013). The second session, which was scheduled approximately two weeks later, was identical to the first with the exception that it took place during the initial phase of smoking cessation. Participants were required to be abstinent from smoking for at least 48 hours prior to the second lab session. Absence from smoking was verified biochemically with cotinine and exhaled CO. Subjects were also interviewed approximately 28 days post-quit to assess relapse and to collect cotinine and CO for confirmation of smoking status. Relapse was defined as smoking 7 consecutive days. A comparison group of nonsmoking individuals were also asked to complete the two laboratory and follow-up sessions in the same sequence except for smoking-related events, in parallel with the examination of smokers. All participants were paid for their participation in compliance with the guidelines of Human Subjects Review Board at the University of Minnesota.

Data analysis

The data was restricted to smokers with confirmed carbon monoxide (CO) levels less than 8 ppm at the time of 48 hour abstinence session (7 cases eliminated). The mean CO level for these 7 cases was 13.43 ppm (SE = 1.46) with a range of 9 to 20 ppm. Examination of box plots and Kolmogorov-Smirnov tests of normality revealed that the leptin values at both laboratory sessions were skewed and contained a few extreme values. The data was square root transformed and 2 extreme values removed (raw leptin > 30 ng/ml). Relapse was defined as having smoked for 7 days consecutively at any time point in the first 28 days following quitting, which was confirmed at the post-quit laboratory visit conducted approximately 28 days after smoking cessation. Classification of abstainer required that there was no period of 7 consecutive days of smoking during the 28 day period and the lab CO levels were less than 8 ppm. The final sample consisted of 102 subjects with 34 non-smokers (15 female), 28 abstainers (15 females), and 40 relapsers (17 females). Baseline demographics, depression, anxiety and pre-quit descriptive smoking variables were analyzed as simple one way analysis of variance (ANOVA) with smoking status at 28 days as the independent variable. Bivariate correlations and partial correlations controlling for BMI were also used to examine the relationship between baseline leptin, leptin change across the two time points (post quit minus baseline), age, and the symptom reports (MNWS, craving, QSUB) using the overall group and separately within relapse subgroups (relapsing and abstaining smokers).

The primary analysis of interest was an assessment of leptin in response to 48 hours of smoking cessation in the prediction of relapse. This was conducted using a mixed ANCOVA with repeated measures. Lab sessions (ad libitum smoking, 48-hour abstinence) were the within subjects variable (repeated factor) and smoking status at 28 days (non-smokers, relapsers and abstainers) and gender (women, men) were the between subject variables. The dependent variable consisted of the square root transformed leptin. To further clarify the effects of relapse status and confirm that any significant group by time or gender

interactions were not unduly influenced by the nonsmokers, an additional model with just the smokers split by relapse status (relapser vs. abstainer) were also conducted using the same mixed ANCOVA model. Significant interactions from the restricted model (smokers only) were followed up using mixed ANOVA split by lab session and by gender. Lab site (Duluth and Minneapolis) was used as a covariate. Given that leptin is typically correlated with age and BMI, a secondary analysis was conducted to assess the impact of these variables on the results. Cox regression was also used to further explore the leptin association with relapse. Data from the smokers only was used to predict days to relapse at 28 days and gender, leptin change (48-hour minus ad libitum) and a leptin change by gender interaction term as predictors. We report the regression coefficient representing the relative effect of gender and leptin change (ad libitum to abstinence) on the survival function (time to event, here defined as relapse). Site was again entered as a covariate. Eta squared will be presented as estimates of effect size ($p\eta^2 > .059$ are medium, $p\eta^2 > .138$ are large). All significance levels were set to 5% with the exception of the final 4 follow-up paired t-Tests which were Bonferroni corrected to $p < .0125$. SPSS v21 was used in this analysis. Occasional missing data affected sample sizes and subsequent degrees of freedom.

Results

Group differences on descriptive variables

The smoking status groups were equivalent on basic demographics such age, BMI, years of education and average hours of sleep over the two laboratory sessions. The smokers who maintained abstinence through 28 days reported at screening that they consumed more coffee ($F(2, 95) = 4.18, p < .05$) and other caffeine beverages ($F(2, 95) = 6.21, p < .01$) than the non-smokers (see Table 1). Coffee and other caffeinate beverage consumption of the relapsers was not significantly different from either the non-smokers or abstainers. Within the smoking groups (relapsers, abstainers), there were no baseline differences in nicotine dependence, cotinine, years at the current rate of smoking, average number of cigarettes smoked, hours since the last cigarette, desire to quit on a 7 point scale, or age at the first cigarette. Sleep prior to each lab session did not differ between the relapse groups, nor was there a correlation with leptin at either session (all $ps > .10$). Transformed leptin values at session 1 positively correlated with both age ($r(106) = .23, p < .05$) and BMI ($r(103) = .46, p < .001$). At the second session only BMI correlated with leptin ($r(103) = .43, p < .001$). Equal numbers of male and female smokers maintained their abstinence (18 female, 19 male abstainers; 26 female, 28 male relapsers; $\chi^2 < 1.0, p > .10$).

Leptin and withdrawal

The mixed ANCOVA restricted to just the two relapse groups (relapsers vs. abstainers) indicated a significant relapse status by gender by session interaction ($F(1,67) = 3.99, p < .05; p\eta^2 = .06$). As shown in figure 1, further analysis of the interaction per group revealed a significant interaction between session and gender for the abstainers only ($F(1, 25) 4.89, p < .05; p\eta^2 = .16$). Only the female abstainers showed a significant change in leptin across sessions ($t(14) = 4.02, p < .001$), but neither the male abstainers ($t(12) = 2.283, p > .0125$) nor the relapsers were significant (both $t < 1.0, p > .10$). At the abstinent lab sessions there were no gender or relapse status differences. The relapsers failed to show a significant effect

of session or session by gender interaction ($F_s < 1.0$). There was also a significant effect of gender whereby females produce more leptin than males ($F(1, 67) = 24.298, p < .001; \eta^2 = .27$). Within nonsmokers the gender effect was also apparent ($F(1, 31) = 42.034, p < .001; \eta^2 = .58$), but there was no effect of session nor session by gender interaction ($F_s < 1.5, p_s > .10$). There was also no change in leptin across the sessions for nonsmokers ($F < 1.0, p > .10$).

The Cox regression analysis indicated a significant overall model ($\chi^2(3, N = 71) = 13.84, p < .01$). The leptin change from ad libitum to abstinence, but not gender nor gender by leptin change interaction, was a significant predictor of relapse ($B = -.86, HR = 0.48, p < .05$). These results indicate that as leptin increased by one point over the two sessions, the risk of relapse decreased by 48% (see Figure 2).

Given the differences between the groups on BMI and age, an analysis was conducted to rule out the possibility that either of these could have accounted for the leptin effect demonstrated above. Using these factors in the same ANOVA model as continuous covariates did not change the overall finding. In some cases, the effect sizes increased. For example, in the uncorrected model the effect size for the time by group interaction was 11% ($\eta^2 = .11$). With BMI and age added to the model, the time by group interaction remained significant and effect size slightly increased to 13% ($F(2, 92) = 6.70, p < .01; \eta^2 = .13$).

Leptin and subjective experience correlations

Correlational analysis shows that the change in leptin was negatively correlated with the change in withdrawal symptoms for the abstainers ($r(26) = -.49, p < .01$). As leptin increased, withdrawal symptoms decreased over time for the abstainers. There was no relationship between leptin and withdrawal change for relapsers ($r(38) = .11, p > .10$). The change in leptin did not correlate with changes in craving or smoking urges ($F1$ or $F2$) either as a smoking group overall or separately within the relapsers and abstainers. Leptin change did not correlate with any of these variables (withdrawal, craving, $F1$ or $F2$) when split by gender.

Discussion

We demonstrate here that leptin is increased following 48-hours of smoking withdrawal, but only for female smokers who are able to successfully abstain from smoking during the study period. This finding is independent of group differences in BMI and age. Furthermore, the leptin response to abstinence from smoking was specific to withdrawal symptoms, at least for the abstainers. It is not clear why the relapse group had no association between leptin and withdrawal, particularly given the prior work showing the relapsed smokers had higher withdrawal symptoms and more distress. Urges or cravings were not related to leptin change over time, either as a total group or within the relapsers and abstainers. These findings add to the growing literature on appetite regulators and smoking cessation. In an earlier publication with a different cohort of smokers, we showed that circulating leptin obtained only after quitting did not predict relapse but craving scores at 24 hours post cessation were positively associated with leptin from that time period (al' Absi et al. 2011) and following an acute stress challenge (Potretzke et al. 2014). Furthermore, in a separate cohort leptin was

responsive to an acute stress challenge and it correlated negatively with cortisol (Potretzke et al. 2014). The current study adds further clarity to this literature by demonstrating that prospective tracking revealed that the acute change in response to abstinence, but not the actual circulating level, predicts later relapse independent of changes in craving or smoking urges.

The current study demonstrates that the previously shown positive correlations between leptin, craving and smoking urges after 24-abstinence (al'Absi et al. 2011) are not present across the two sessions for either relapsers or abstainers. The leptin increase in female abstainers shown here contradicts an earlier indication that leptin is not related to smoking abstinence (Stadler et al. 2014). It is important to note, however, that the current study examined leptin changes during the initial quit attempt relative to pre-quit levels across both controls and smokers while other studies used a single group to assess both leptin and withdrawal severity. Also, the larger sample size in the current study (here 28 abstainers) and the shorter follow-up period might account for this discrepancy. It is reasonable to propose that leptin levels may change early in abstinence but normalize by the one to three month follow up used by others (Stadler et al. 2014; Won et al. 2014).

In this study we demonstrate that, regardless of smoking, women produce more leptin than men regardless of smoking status. We also demonstrate that women who abstain show an increase in leptin from the ad libitum to 48-hour abstinent period but men did not regardless of relapse status. The higher leptin in women regardless of smoking status has been demonstrated by others as well (Klein et al. 2004). This gender by relapse effect is unique and does not appear to be the result of gender-based differences in relapse, which has been found elsewhere (Ward et al. 1997) but not in this study. While leptin changes with menstruation have been documented (Ajala et al. 2013; Asimakopoulos et al. 2009), an equal number of women were in the luteal phase versus the follicular phase during testing and there was no association between menstrual phase and relapse status (al'Absi et al. 2015). Other studies of addiction have shown that leptin increases with abstinence from alcohol abuse equally across both genders, though correlations with craving in females but not males has been found in some (Kraus et al. 2004) but not all studies (Hillemecher et al. 2007). In this study we do not find correlations for craving either in the whole sample (smokers and nonsmokers) or within just the smokers. This lack of correlation is not consistent with other studies of leptin during ad libitum smoking and nicotine craving (von der Goltz et al. 2010). These discrepancies between our results and other reports may be due to differences in the addictive substance studied (e.g. alcohol), sample size issues, or the nature of the psychological test instruments used to assess craving. We also do not replicate the correlations between craving and leptin in previous studies of ad libitum smoking (al'Absi et al. 2011), but it is important to point out that in this study our analysis utilized a dynamic assessment of change from baseline scores. We do, however, show that for abstainers only the increases in leptin were related to decreases in withdrawal symptoms over time.

Given the low probability of success for smokers attempting to quit, it is difficult to obtain large numbers of abstinent smokers across a period of one month. The current study was larger than other preliminary studies in this field, but further enhancement of sample sizes

could be quite important, especially in examining the interaction between gender and relapse groups. This is particularly important given the evidence that gender has been shown to be critical in predicting relapse and assessing the relationship between stress (biological and psychological) and relapse (al'Absi et al. 2015, al'Absi 2006; Allen et al. 2009; Cepeda-Benito et al. 2004). Our choice to assess participants in the early afternoon, a time when leptin is at its lowest, was made given the interest in the HPA axis as reported in the primary study (al'Absi et al. 2014b). It is not known how this affected the leptin results reported here, but cortisol testing in the afternoon can be preferable (Kudielka et al. 2004). In addition, the current study controlled for diurnal rhythm and pre-session food consumption, but there was no direct assessment of diet or eating patterns across the quit attempt nor was there an assessment of insulin sensitivity. The addition of prospective analysis of changes in insulin sensitivity, feeding patterns and macronutrient selection has been informative in other studies (Stadler et al. 2014; Won et al., 2014) and it would enhance our current understanding of leptin and smoking cessation in future studies. Clarifying the role of abnormal eating behaviors in response to nicotine cessation might further elucidate important relationships between leptin and post cessation negative affect as has been demonstrated by others (Koopmann et al. 2011).

We demonstrate here that leptin is responsive to the early phase of smoking abstinence and this response seems to be specific to those who were successful in abstinence from smoking at 28 days. Self-reported symptom experience was not related to leptin levels, though the expected differences in distress were found within the relapse group. This highlights the value of concurrent measurement of both psychobiological and subjective experience. We have also shown in previous publications that elevated ghrelin during the early abstinence period, but not PYY, predicted an increased risk of relapse (al'Absi et al. 2014a). As with leptin in the current study, men produce lower ghrelin than women (al'Absi et al. 2014a) but gender was not a significant predictor of time to relapse in either study. Thus, there is consistent evidence that gender differences, though significant in cross-sectional analysis, for both leptin and ghrelin are not important in the prediction of relapse risk. As this knowledge base on the role of each of these and other appetite regulators expands and becomes clearer, it will be important in future studies to test how these appetite regulators and other factors, such as insulin sensitivity, gender, craving and negative affect, work independently and in concert to predict relapse.

In conclusion, leptin increased during the first 48 hours of abstinence but only for female smokers who ultimately will be able to abstain from smoking. Increased leptin change over this 48-hour period was also predictive of lower risk to relapse. Leptin correlated negatively with symptoms of withdrawal, which may indicate a protective effect of this rise in leptin. Leptin was not, however, correlated with cravings when assessed as a change from pre-quit levels. We also demonstrate that leptin differs both as a function of gender and as a function of abstinence for women, but not men. Given the negative relationship between leptin and the HPA axis (Roubos et al. 2012), future studies are needed to examine whether this relationship explains the relapse and leptin effects demonstrated here. Targeting leptin production, particularly in women, will be an important avenue for further smoking cessation research.

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Fig. 1.

The results indicate a significant relapse group by gender by time interaction for transformed leptin levels across ad libitum smoking and 48-hour abstinence ($p < .05$; $\eta^2 = .06$). Follow up analysis revealed that the female abstainers were the only group to show significant differences across time, here characterized as an increase in leptin during the 48-hr abstinence that was not evident in either the males relapsers. Females also produce more leptin than males ($p < .001$).

Fig. 2.

The change in leptin from ad libitum smoking to 48-hour abstinence predicted relapse ($B = -.86$, $HR = 0.48$, $p < .05$) but neither gender nor the gender by leptin change interaction did ($ps > .10$).

Table 1

Group differences on basic demographics and smoking variables expressed as means (standard error).

	Smoking Status Groups		
	Non-smokers (n = 34)	Abstainers (n = 28)	Relapsers (n = 40)
Age	30.15 (1.97)	36.86 (2.32)	34.83 (1.76)
BMI	24.32 (0.53)	25.77 (0.85)	25.67 (0.68)
Education	15.82 (0.61)	14.09 (0.50)	14.77 (0.43)
Average sleep	7.34 (0.11)	7.08 (0.14)	7.08 (0.15)
Caffeine (cups) ^a	.70 (0.17)	2.11 (0.36)**	1.50 (0.27)
Cups of coffee/day ^a	1.10 (0.26)	3.04 (0.83)*	2.52 (0.30)
Depressive affect	.53 (0.42)	1.29 (0.47)	1.75 (0.49)
Anxiety	33.64 (1.53)	36.26 (2.01)	37.90 (1.41)
Nicotine Dependence		5.70 (0.38)	5.08 (0.31)
Years smoked at this rate		10.25 (1.56)	12.38 (1.63)
Average cigarettes per day		18.87 (1.40)	16.99 (0.73)
Hours since last cigarette		.76 (0.22)	1.43 (0.47)
Age at first cigarette		16.64 (0.62)	16.33 (0.52)

^a Significant smoking status effect