Original Investigation

Effects of Cigarette Smoke Exposure and Its Cessation on Body Weight, Food Intake and Circulating Leptin, and Ghrelin Levels in the Rat

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Abstract

Introduction: Smoking is associated with loss of body weight (BW) and reduced appetite, while smoking abstinence with the opposite effect. The role of peripheral signaling by appetite-controlling hormones leptin and ghrelin is not clear. In the present study, the relationship of circulating leptin and ghrelin with BW and food intake rate (FIR) changes was studied during cigarette smoke exposure (CSE) and after its cessation in the rat.

Methods: Male Wistar rats were subjected to CSE for 8 weeks by confinement to plexiglass chambers (Group S). Control animals were confined to identical chambers without smoke (Group C). During CSE and an equivalent follow-up period, BW and FIR was recorded and serum leptin and ghrelin levels were measured.

Results: A sharp decrease in BW was noted during the first 4 weeks of CSE, while FIR, after a substantial decrease noted at Week 1, returned to control levels. Thereafter, rats started to regain their BW until they reached control levels by the 1st week postCSE. BW regain was accompanied by a rebound increase of FIR, which plateaued during the first 4 weeks postCSE and then normalized. Serum leptin was decreased in Group S during both periods, normalizing at the 7th week postCSE. Ghrelin levels did not differ between groups.

Conclusions: Circulating leptin could not explain by its own BW and FIR changes during the first few weeks of CSE in rats, in contrast to the rest of the CSE period as well as after its cessation. Serum ghrelin levels did not justify BW and FIR changes.

Introduction

It is well accepted that while smoking leads to loss of appetite with subsequent weight loss (Audrian-McGovern & Benowitz, 2011; Chiolero, Faeh, Paccaud, & Cornuz, 2008; Nicklas, Tomoyasu, Muir, & Goldberg, 1999; Perkins et al., 1992), cessation of smoking without the help of nicotine substitutes usually results to the opposite effect (Moffatt & Owens, 1991; Stanford, Matter, Fell, & Papanek, 1986; Filozof, Fernandez Pinilla, & Fernandez-Cruz, 2004; Williamson et al., 1991). Although the latter side effect is considered minimal compared with the invaluable health benefits conferred by cessation of this devastating habit, it may discourage those who intend or already attempt to quit, contributing to smoking relapse (Wee et al., 2001).

Appetite-controlling hormones leptin and ghrelin play a significant role in the regulation of food intake and body weight (BW). Leptin is a protein, which is produced by adipose tissue and is secreted into the bloodstream to instruct the brain to stop food consumption and increase activity (Elmqist, Elias, & Saper, 1999; Wynne, Stanley, McGowan, & Bloom, 2005). Ghrelin, on the other hand, is an appetite-stimulating hormone, which is secreted primarily from the stomach mucosa and stimulates appetite and food intake, enhancing fat mass deposition and weight gain (Wynne et al., 2005). The role of these two hormones in the mechanism of BW and appetite changes associated with smoking and its cessation is currently under investigation (Bouros et al., 2006; Chen et al., 2005, 2006, 2008; Donahue et al., 1999; Eliasson & Smith, 1999, Fagerberg, Hultén, & Hulthe, 2003, Hodge et al., 1997; Klein, Corwin, & Ceballos, 2004; Kokkins et al., 2007; Lee et al., 2006; Nicklas et al., 1999; Oeser, Goffaux, Snead, & Carlson, 1999; Perkins & Fonte, 2002). To date, the results from clinical and animal studies are conflicting, warranting further investigation.

It is of note that studies referring to the postsmoking period face practical and ethical limitations. Since smoking is a long-term habit, these studies lack baseline measurements taken before initiation of smoking impelling investigators to employ nonsmokers volunteers that consent to smoking one or two
cigarettes (Bouros et al., 2006; Kokkinos et al., 2007). These limitations could be overcome by the use of an appropriate animal model. So far, animal studies in which nicotine was administered as a sole agent, have established that nicotine intake is associated with weight loss (Bellinger, Cepeda-Benito, & Wellman, 2003; Bishop, Parker, & Coscina, 2002; Grunberg, Bowen, & Winders, 1986). However, more than 4,000 substances, whose action has not been fully elucidated yet, have been detected in tobacco smoke. Therefore, an experimental model in which animals inhale cigarette smoke would simulate more closely the human habit. In such a model, serum levels of cotinine, the main metabolite of nicotine, should be comparable with those of active smokers and cigarette smoke abuse liability should be established.

The aim of the present study was to assess the relationship of the peripheral signaling of circulating leptin and ghrelin levels with BW and food intake rate (FIR) changes occurring during smoking and after its cessation. For this reason, a rat model of cigarette smoke exposure (CSE) was employed.

Methods

Animals

Twenty seven Wistar rats, 5 months of age, weighing 380–420 g, provided from our laboratory’s in-house breeding colony were used. They were housed in polycarbonate cages, three rats per cage, at 20–22 °C room temperature, on a 14-hr light:10-hr dark cycle (lights on from 06:00 a.m. to 20:00 p.m.) and were provided with commercial pelleted diet and tap water ad libitum.

Experimental Design

Animals were randomly assigned into three groups of nine rats each. The animals of the first group (Group S) were exposed daily for 8 weeks to interrupted sidestream cigarette smoke. Three rats at a time were confined daily in a white smoking chamber for two periods of 60 min each with a 60-min interval. The color of the chamber was that of the “nonpreferred” side as defined after a pre-exposure black versus white chamber-Conditioned Place Preference (CPP) test. Rats in the control group were confined on a daily basis for the same period in an identical chamber without exposure to smoke. The following endpoints were assessed for 16 weeks (8 week CSE period plus 8 week follow-up period): BW (weekly); FIR (weekly); cotinine serum levels (biweekly during CSE plus 2 days postCSE); leptin and ghrelin serum levels (biweekly during the CSE and the postCSE periods); CPP test (every 4 weeks during CSE). In a separate set of control experiments, nine rats were subjected for 1 week to CSE (Group S) in plexiglass chamber containing cigarette smoke, as described above and blood samples were collected at 1 hr after exposure to assess cotinine levels.

At the end of the experiments, all animals were euthanized by intracardial injection of KCl under general anesthesia. The experimental protocol was approved by the Animal Care and Ethics Committee of the local Veterinary Service since it was in compliance with Directive 86/609/EEC.

Cigarette Smoke Exposure System

The system used to expose rats to sidestream cigarette smoke consisted of a ventilator, a smoke generating chamber, and a whole body CSE chamber serially connected via silicone tubes interlined by Heimlich valves (Heimlich valve/BD, Franklin Lakes, NJ) to avoid smoke regression. The ventilator (Veterinary anesthesia ventilator/Hallowell EMC, Model 2000, Pittsfield MA) was set to provide 150 ml of air every 10 s. The smoke-generating chamber consisted of a plexiglass cylinder (8 cm radius × 27 cm height) corresponding to 5,430 cm³ total volume into which a cigarette (8 mg tar, 0.6 mg nicotine, and 9 mg carbon monoxide) at a time was kept constantly lit. Smoke was then delivered to a plexiglass white chamber (40 cm length × 20 cm width × 25 cm height) of 20,000 cm³ total volume and exhausted from a hole outlet. The level of carbon monoxide inside the CSE chamber was kept between 150 and 250 ppm by transient interruption, if needed, of the diluted sidestream smoke delivery. Carbon monoxide concentration was determined in air samples, collected from the chamber interior at 15 min intervals, using a portable carbon monoxide analyzer (piCO Smokerlyzer Breath CO monitor/Bedfont Scientific, Kent, UK). Rats were exposed to CSE between 9:00 a.m. and 12:00 p.m.

Conditioned Place Preference Test

The CPP apparatus consisted of two plexiglass chambers, a black and a white, interconnected with a door (10 cm height × 7 cm width). The dimensions of each chamber were the same with that of the CSE chamber (40 cm length × 20 cm width × 25 cm height corresponding to a volume of 20,000 cm³). Each rat was placed individually in the apparatus, at the level of the interconnecting door, and the time it chose to spend in each chamber was recorded for a period of 10 min (600 s). The chamber in which the animal spent less than 300 s was called the “nonpreferred” side.

Before commencement of the CSE period, all rats were subjected to a pre-exposure CPP test in order to determine their place preference. Thereafter, CSE (smoking group) or chamber confinement (control group) took place in identical plexiglass chambers (same color and dimensions) with that of the “nonpreferred” side. Subsequent CPP tests were considered biased and were conducted as described above. To compare the shift in place preference, the relative increase (%) of the pre-exposure time spent in the nonpreferred chamber was calculated according to the equation:

\[ \% \text{CPP shift} = \left( \frac{\text{CPP}_{\text{post}} - \text{CPP}_{\text{pre}}}{\text{CPP}_{\text{pre}}} \right) \times 100 \]

where CPP<sub>pre</sub> is CPP at a given timepoint; CPP<sub>post</sub> is pre-exposure CPP.

Calculation of Changes in BW and FIR

Body weight changes (% ΔBW), FIR per animal (FIR) and FIR changes per animal (% ΔFIR) were calculated every week according to the following equations:

\[ \% \Delta \text{BW} = \left( \frac{\text{BW}_{\text{post}} - \text{BW}_{\text{pre}}}{\text{BW}_{\text{pre}}} \right) \times 100 \]

where BW<sub>post</sub>: BW measured at a given timepoint; BW<sub>pre</sub>: initial BW

\[ \text{FIR} = \frac{\text{FW}_{\text{post}} - \text{FW}_{\text{pre}}}{n} \]

where FW<sub>post</sub>: weight of food found at a cage at a given timepoint; FW<sub>pre</sub>: standard weight of food (600 g) replaced to each cage every week; n: number of rats per cage.
Effects of cigarette smoke exposure and its cessation

% ΔFIR = \((\text{FIR}_r - \text{FIR}_i) / \text{FIR}_i\) × 100

where FIR, : FIR per animal at a given timepoint; FIR, : initial FIR per animal.

Biochemical Analysis
Blood samples were collected from the tail artery under sevoflurane anesthesia.

Collection of blood samples for cotinine measurement in Group SC was performed at 1 hr postCSE (13:00 p.m.). Collection of samples in groups S and C were performed between 08:00 a.m. and 9:00 a.m., which is approximately 20 hr after their last smoke-exposure session. Samples from groups S and C were collected in pairs of test tubes, the first assigned for ghrelin and the second for cotinine and leptin concentration determination. Immediately after collection, 1 μl of Pefabloc per 100 μl of blood was added to the aliquot assigned for ghrelin determination. Serum was separated in all samples by centrifugation at 3,000 g for 20 min. Following centrifugation, 2.5 μl of HCl 2N per 100 μl of serum were added to the ghrelin-serum aliquot. All serum samples were stored at −70°C until later analyzed. The concentrations of cotinine, leptin, and ghrelin were determined using commercially available ELISA kits (Cotinine direct ELISA/BIOQUANT, San Diego, CA; Rat leptin Assay kit/IBL, Gunma, Japan; Rat/Mouse Ghrelin (total) ELISA kit/Millipore, St. Charles, Missouri) according to the manufacturers’ instructions. The lowest detection limits were 1 ng/ml for cotinine, 10.82 pg/ml for leptin, and 0.02 ng/ml for ghrelin.

Statistical Analysis
Data were expressed as means ± SD and were subjected to repeated measures analysis of variance (repeated measures ANOVA) followed by the Student t test for comparisons between two groups or the Bonferroni test for multiple comparisons among groups. The area under the curve (AUC) was calculated using the trapezoidal rule to assess total FIR changes. A probability of less than 5% (p < .05) was considered to be statistically significant.

Results
All rats survived the 16-week experimental period.

Cotinine Levels
Serum cotinine levels at 1 hr postCSE (Group SC) ranged from 241 to 324 ng/ml (M ± SD = 285.6 ± 27.2 ng/ml). At around 20 hr postCSE, cotinine concentration was significantly increased in Group S compared with Group C at levels ≥14 ng/ml which is the cutoff value for being considered a smoker (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987). Cotinine returned to pre-exposure levels at 2 days post smoke-exposure. No changes were noted in cotinine levels in the control group (Figure 1).

CPP
According to the pre-exposure CPP test, all rats preferred the black over the white chamber (Figure 2A). During the smoke-exposure period, the time spent in the white chamber was significantly increased in both Groups S (p < .05 at Week 4; p < .001 at Week 8) and C (p < .05 at 4w; p < .05 at 8w).

Figure 1. Changes in serum cotinine concentration (means, n = 9) in rats at 20 hr post cigarette smoke exposure (Group S) or not (Group C). Error bars represent SD. Values ≤ 1 ng/ml are depicted as 1 ng/ml (minimum detection limit). S1w–S7w: smoke exposure period, PS2d: 2 days post-smoke exposure. The dotted line depicts the 14 ng/ml cutoff limit for being considered a smoker. *p < .001 versus Group C.

However, the shift in white place preference was significantly higher (p < .05) in group S compared with group C at the 8th week of exposure (Figure 2B). The white chamber remained the “non-preferred” side (<300 sec stay) throughout the study period (Figure 2A).

BW
The BW of control rats, after an initial slight decrease noted during the first 3 weeks of white chamber confinement, was incremental. The BW of rats in Group S was sharply decreased during the first 4 weeks and thereafter, although incremental, it remained significantly lower than that of control rats from the 3rd to the 8th week of CSE. BW was regained at 1 week postCSE but did not exceed that of control rats throughout the postCSE period (Figure 3A).

FIR
In the control rats, FIR remained below preconfinement values throughout the study period. In the smoke-exposed rats, after a substantial reduction in FIR (25%) at the 1st week, which was significantly lower than that of controls (12%), FIR returned to control levels. Thereafter, FIR was progressively increased, reached a plateau from the 1st to the 4th week postCSE and then returned to control levels (Figure 3B).

Although there were significant differences in BW between groups during the CSE period, these were not reflected by total FIR changes (p > .05; AUC = 48.08 ± 3.4%-w for Group S vs. 48.4 ± 3.5%-w for Group C). On the contrary, similar BWs in both groups during the postCSE period were accompanied by significantly different total FIR changes (p < .001; AUC = −13.5 ± 2.6%-w for Group S vs. −53.0 ± 3.1%-w for Group C).

Leptin Levels
The concentration of serum leptin in Group S remained significantly lower than that of control animals, ultimately normalizing at the 7th week postCSE (Figure 3C).
**Ghrelin Levels**

Serum ghrelin concentration was significantly increased in Group C from the 7th CSE week to the end of the post-CSE period, while in Group S from the 3rd to the 7th post-CSE week. However, no significant differences were noted between groups (Figure 3D).

**Discussion**

In the present experimental study, the levels of circulating leptin and ghrelin were assessed in relation to changes in BW and FIR noted during 8 weeks of CSE and an equivalent follow-up period in the rat. To our knowledge, this is the first animal study to address these issues after cessation of CSE.

In the experimental model employed, rats were exposed to daily interrupted sidestream cigarette smoke for 8 weeks. Cigarette smoke abuse liability was established before cessation of CSE by development of CPP in the smoke-exposed animals. Adequate serum cotinine levels simulated the human smoking habit, which was represented by only 2 hr of CSE each morning every day. Cotinine levels ranged around 250–300 ng/ml at 1 hr after daily CSE, which is comparable even to high values (around 300 ng/ml) reported in smokers in relevant studies (Benowitz & Henningfield, 1994). Cotinine remained above the accepted cutoff limit for being considered a smoker (≥14 ng/ml; Jarvis et al., 1987) throughout the day according to measurements in blood samples taken 20 hr post-CSE, also ensuring that daily CSE sessions started from a nonzero cotinine level.

Smokers tend to have lower BW than nonsmokers. BW is determined by the balance of caloric intake and daily energy expenditure. So far, the results from clinical and experimental studies regarding the role of caloric intake are inconsistent. Nicotine, the main addictive constituent of tobacco, has been shown to exert an anorexigenic effect (Bellinger et al., 2003; Bishop et al., 2002; Grunberg, Bowen, & Winders, 1986; Hajek, Jackson, & Belcher, 1988). Although there are studies that show a reduction in caloric intake after nicotine treatment in humans (Jessen, Buemann, Toubro, Skovgaard, & Astrup, 2005; Perkins et al., 1991) or after tobacco smoke exposure in mice (Chen et al., 2005, 2006, 2008), others have reported the opposite effect (Perkins et al., 1992). In our study, a distinct period of sharp BW decrease was noted shortly after CSE with a nadir at 4 weeks. Interestingly, FIR, after a substantial but transient decline at the 1st week of exposure, returned to control levels downgrading the role of calorie intake and suggesting an elevation in energy expenditure. There is evidence from both clinical and animal studies that smoking, via the sympathomimetic action of nicotine, increases energy expenditure (Audrian-McGovern & Benowitz, 2011; Chen et al., 2005, 2008; Hofstetter, Schutz, Jequier, & Wahren, 1986), which however is not supported by a recent clinical investigation which failed to reveal any alteration of total energy expenditure associated with smoking status (Bradley et al., 2010). Moreover, it should not be overlooked that inhalation of cigarette smoke, which is highly aversive for rats, could have acted as a stressful stimulant that contributed to the initial FIR reduction. In addition, it is well known that nicotine can have unpleasant side effects, including nausea, which has a negative impact on FIR. This effect however recedes in humans as nicotine tolerance develops (Perkins, 2002).

After the initial period of BW loss, rats started to regain their BW and gradually increase FIR while being subjected to CSE. This counterbalancing effect has been proposed to be a manifestation of the body’s adaptation after a period of negative energy balance in order to survive by increasing lipolysis of adipose tissue or reducing energy expenditure (Chen et al., 2008). Indeed, there is evidence of a rebound downregulation of energy metabolism following an initial marked elevation of energy expenditure in mice under tobacco smoke exposure (Chen et al., 2006). The development of tolerance to nicotine’s anorexigenic effect (Caggiula et al., 1991) could provide an additional plausible explanation for the restoration of feeding behavior. Moreover, the anxiolytic effect of nicotine has been shown to contribute toward this direction since nicotine treatment has been associated with restoration of food seeking behavior altered by stress factors (Cohen et al., 2009). The anxiolytic effect of cigarette smoke was manifested in our study by development of biased CPP in the smoke-exposed rats. The CPP paradigm has been primarily used to evaluate the rewarding effect of nicotine (Briemlmaier, McDonald, & Smith, 2008). Moreover, the anxiolytic effect of nicotine has also been shown by a reduction in aversion toward a previously nonpreferred environment using the CPP procedure (Torella, Badanich, Philpot, Kirstein, & Wecker 2004).

All rats used in this model had the additional stress burden of daily confinement to a normally less preferred enclosure.
color. This was reflected by a reduction in FIR in control animals when compared with preconfinement values. Progressive BW gain in the face of a fairly steady low calorie intake rate suggested a reduction in metabolic rate with age. On the other hand, BW regain in age-matched rats under CSE was accompanied by an increasing FIR, which continued up to the 4th post-CSE week. Convergent lines of evidence support the notion that the mechanism of weight gain after cessation of smoking includes increased calorie intake and decreased metabolic rate (Audrain-McGovern & Benowitz, 2011; Filozof et al., 2004; Moffatt & Owens, 1991) as well as changes in adipose tissue metabolism (Ferrara, Kumar, Nicklas, McCrone, & Goldberg, 2001). Intriguingly, after cessation of CSE the BW of rats in our study did not exceed that of control animals supporting the view that exsmokers’ weight tends to return to the levels of people who have never smoked (Williamson et al., 1991).

Leptin acts as a peripheral signaling molecule that communicates the level of adipose stores to the hypothalamus; it acts centrally to moderate metabolic activity and BW by suppressing food intake and increasing energy expenditure (Klein et al., 2004; Wynne et al., 2005). An elevation in circulating leptin levels inhibits the synthesis of hypothalamic appetite stimulating neuropeptides, such as the neuropeptide Y (NPY; Elmquist et al., 1999). Nevertheless, the role of circulating leptin signaling in smoking related-BW changes is under debate. To date, the results from clinical studies are controversial. Although, there are reports of increased (Nicklas et al., 1999) or unaltered leptin levels as a result of smoking (Donahue et al., 1999; Perkins & Fonte, 2002), epidemiological studies in different ethnic groups have shown paradoxically lower leptin levels in smokers compared with nonsmokers proposing an enhancement of leptin receptor binding or an increase in sensitivity of hypothalamic leptin receptors with subsequent modulation of leptin biosynthesis (Hodge et al., 1997; Wei, Stern, & Haffner, 1997). Moreover, there is evidence from experimental studies that cigarette smoke alters hypothalamic energy balance circuits as evidenced by a decline in NPY concentration and body fat mass in the face of unexpectedly low serum leptin levels in mice (Chen et al., 2005, 2006). In agreement with these findings, circulating leptin levels in our study were decreased in the tobacco smoke-exposed rats during the period of BW loss while FIR remained to control levels. Thereafter, the compensative increase of FIR to regain BW could be justified by the steadily low leptin profile.

Reports from clinical studies regarding the levels of serum leptin in abstinent smokers have not been consistent probably as a result of a variability in study design, population characteristics and therapeutic interventions made to aid cessation of smoking. Unchanged leptin levels have been reported in exsmokers in one study after 7 days (Oeser et al., 1999) and in another after 3 and 6 months of abstinence (Nicklas et al., 1999). The results of the latter study, however, were confounded by the use of nicotine replacement patches by 73% of the subjects enrolled in the study. On the other hand, leptin increased only in women at the 3rd week (Perkins & Fonte, 2002) or in subjects of both sexes at the 8th week post unmedicated cessation of smoking (Eliasson & Smith, 1999; Lee et al., 2006). According to the results of our study, a low leptin concentration pattern, similar to that noted during CSE, continued up to the 5th week after cessation of CSE; finally, levels of leptin normalized at the 7th week of the follow-up period. Since weight gain after smoking cessation is associated with increased body fat (Filozof et al., 2004), we can assume that circulating leptin levels reflected the result, rather than the cause, of an eventually increasing body fat mass, given that BW regain had been preceded.

Ghrelin, a potent orexigenic hormone released primarily from the stomach mucosa, stimulates food intake through the upregulation of NPY and agouti-related protein synthesis in the hypothalamus. Increased circulating ghrelin levels may be

Figure 3. Changes (mean, n = 9) in (A) body weight, (B) food intake rate, (C) serum leptin, and (D) serum ghrelin concentration in rats during and after cigarette smoke exposure (Group S) or not (Group C). BW = body weight; FIR = food intake rate *p < .05 versus Group C, **p < .01 versus Group C.
the consequence of food anticipation or may have a physiological role in initiating feeding (Wynne et al., 2005). According to our results, ghrelin levels did not differ between smoke-exposed and control rats during smoke exposure and the follow-up period despite differences in FIR between groups. These results suggest that the changes in FIR conferred by tobacco smoke-exposure were not directly associated with ghrelin signaling. Our findings confirm a previous clinical study in which no correlation between smoking status and ghrelin levels was found (Poykko et al., 2006). Furthermore, decreased ghrelin levels measured in abstinent smokers 2 months after they had quit smoking did not reflect their increased appetite suggesting a more complex regulatory mechanism of appetite control after cessation of smoking (Lee et al., 2006).

In conclusion, the findings of the present study shed some light to the relationship of peripheral metabolic signaling of circulating leptin and ghrelin with BW and FIR changes conferred by smoking and its cessation employing a rat model of CSE. Circulating leptin could not explain by its own a discrepancy between BW and FIR changes occurring during the first few weeks of CSE. Thereafter, a low leptin profile reflected the counterbalancing increase of FIR in order to regain BW during CSE as well as after its cessation. Ghrelin levels did not vary in tobacco smoke exposed versus control rats in relation to BW and FIR changes. It appears that peripheral signaling by appetite controlling hormones leptin and ghrelin could not explain by its own the underlying mechanism of weight changes related to smoking and its cessation. Additional studies are required toward the elucidation of central regulatory mechanisms of BW control, such as the expression of hypothalamic appetite controlling neuropeptides and the modulation of energy metabolism especially after the cessation of smoking. Understanding the mechanism involved in the somatic changes related to smoking and its abstinence would be invaluable for designing preventive and therapeutic strategies to deal with these effects.

Declaration of Interests

The authors declare that they have no competing interests.

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References


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