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Meal patterns and body weight after nicotine in male rats as a function of chow or high-fat diet

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Abstract

Studies of the effects of nicotine (NIC) on meal patterns in rats often employ chow pellet diets that contain little fat, whereas humans using NIC commonly consume diets relatively rich in fat. The aim of the present study was therefore to compare the impact of NIC administration and NIC cessation on meal pattern in adult male rats offered a standard powdered chow (CHOW: 10.9% fat by calories) diet or a palatable high-fat (HIFAT: 58.3% fat by calories) diet. Computerized meal pattern analyses were conducted for male rats treated for 14 days with injections of either saline or 1.4 mg/kg/day of NIC (as the free base given in 5 equal amounts) during the dark phase and continued for 10 days after NIC cessation. The suppression of daily caloric intake by NIC was larger in HIFAT-NIC rats than in CHOW-NIC rats ($p < .01$), such that NIC induced a greater suppression of body weight in HIFAT-NIC rats, relative to CHOW-NIC rats ($p < 0.02$). NIC administration reduced MS in both CHOW and HIFAT rats. CHOW fed rats showed a gradual increase in meal number in response to NIC, whereas HIFAT fed rats showed a significant initial suppression of meal number, which returned to control levels by day 4 of the 14 day NIC treatment period. In addition, NIC increased water intake more in HIFAT fed rats than in CHOW rats. Cessation of NIC resulted in transient increases in daily caloric intake in CHOW and in HIFAT rats. The present study demonstrates that NIC actions on food intake suppression, meal patterns, and weight reduction differ depending on whether the rats are fed low- or high-fat diets.

Keywords: Meal size; Meal number; Hypophagia; Smoking; Body weight; Water intake; High-fat diet

1. Introduction

Nicotine (NIC) exerts important inhibitory actions on eating and body weight in humans and animals (Benowitz and Hatsukami, 1998; Blaha et al., 1998; Grunberg et al., 1986, 1987; Levin et al., 1987; Nicklas et al., 1999; Perkins et al., 1987; Pomerleau and Kurth, 1996). The central mechanisms by which NIC reduces eating are still under active study (Bellinger et al., 2003b; Frankish et al., 1995; Guan et al., 2004; Jo et al., 2002; Kane et al., 2000, 2001; Li et al., 2000a,b; Miyata et al., 1999; Yang et al., 1999). Of particular interest is the determination of NIC action in rat models that simulate the use of NIC by smokers. In a recent study of meal patterns during and after NIC administration in the dark phase, Bellinger et al. (2003a) reported that meal size was initially suppressed by 1.4 mg/kg/day NIC (dose calculated as the free base), but that meal number increased after 9 days of NIC treatment so as to normalize total daily caloric intake.

Animal studies of NIC action on feeding and body weight typically maintain control and NIC rats on a form of chow pellet diet (i.e. Bellinger et al., 2003a,b; Bellinger et al., 2005; Blaha et al., 1998; Miyata et al., 1999; Miyata and Meguid, 2000). Chow pellets commonly contain relatively low amounts (~4% by weight) of dietary fat. By way of contrast, humans consume diets that are rich in calories derived from fat sources. In a recent metanalysis comparing dietary patterns in smokers, relative to non-smokers, Dallongeville et al. (1998) noted that smokers consume more calories from fat and alcohol sources than do non-smokers, with only small differences in relative consumption of carbohydrates. An important concern is whether the fat content of the maintenance diet would result

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in variation of meal pattern effects noted during NIC administration and after cessation of NIC.

The intent of the present study was therefore to contrast the impact of 1.4 mg/kg/day NIC on meal patterns in adult male rats maintained on a ground chow diet similar in composition to that used in earlier NIC ingestive behavior studies (Bellinger et al., 2003a,b; Grunberg et al., 1986; Yang et al., 1999; Zarrindast and Oveisi, 1997) or a palatable diet containing 58.3% fat (by calories: Corbit and Stellar, 1964; Wellman et al., 1982). Meal pattern analyses were conducted using BioDAQ feeding cages (Farley et al., 2003) that were adapted for maintaining rats on a powdered chow (CHOW) diet or a high-fat (HIFAT) diet (details presented in Wellman et al., 2004).

2. Methods

2.1. Animals

The procedures of the animal studies were approved by the Texas A&M University Laboratory Animal Care Committee. Adult male Sprague–Dawley rats (Harlan, Houston, TX) weighing 250–321 g at the start of the experiment were housed individually in hanging wire rodent cages. Each cage was modified to allow for the continuous monitoring of food intake (see apparatus description below). The colony room was maintained at 23.0+1 °C under a 12 h/12 h illumination schedule (lights off at 1200 h). Dim illumination was provided within the colony room (during dark phase injection procedures) by a red light bulb (15 W) mounted above the rodent rack.

2.2. Drugs

The NIC solution was prepared by dissolving 0.8 mg NIC hydrogen tartrate (Sigma Chemical Company, St. Louis, MO), calculated as the salt, into 1 ml of 0.9% SAL vehicle. The pH of the NIC solution was adjusted to 7.0 using sodium hydroxide.

2.3. Diets

Two maintenance diets that varied in fat content were used in the present study. The low-fat diet consisted of a finely ground rodent chow (Teklad 8604W: http://www.teklad.com/rodent/standard/8604.htm). The high-fat diet consisted of two parts by weight of ground chow and one part melted vegetable shortening (Hill Country Farms, San Antonio, TX) and was prepared fresh every third day. The high-fat diet was thoroughly mixed while hot, allowed to cool and then remixed and stored at room temperature. The nutritional content of the chow diet (by weight) was 4.5% fat and 24.8% protein; with a calculated gross energy content of 3.3 Kcal/g. In contrast, the high-fat diet contained about 35.9% fat (by weight) and 16.3% protein and its calculated energy content was 5.28 Kcal/g. These diets vary considerably along the physical dimensions of greasiness, texture, ease of consumption, fat content, and energy content as well as along perceptual dimensions related to palatability and taste (Corbit and Stellar, 1964; Wellman et al., 1982).

2.4. BioDAQ system

Our laboratory has modified the BioDAQ system to use a commercially available aluminum food cup (Lab Products, 50 mm high × 70 mm wide) with a stainless steel cover (see Fig. 1; details are available in Wellman et al., 2004). Each of the 12 automated feeding units was interfaced to a serial bus

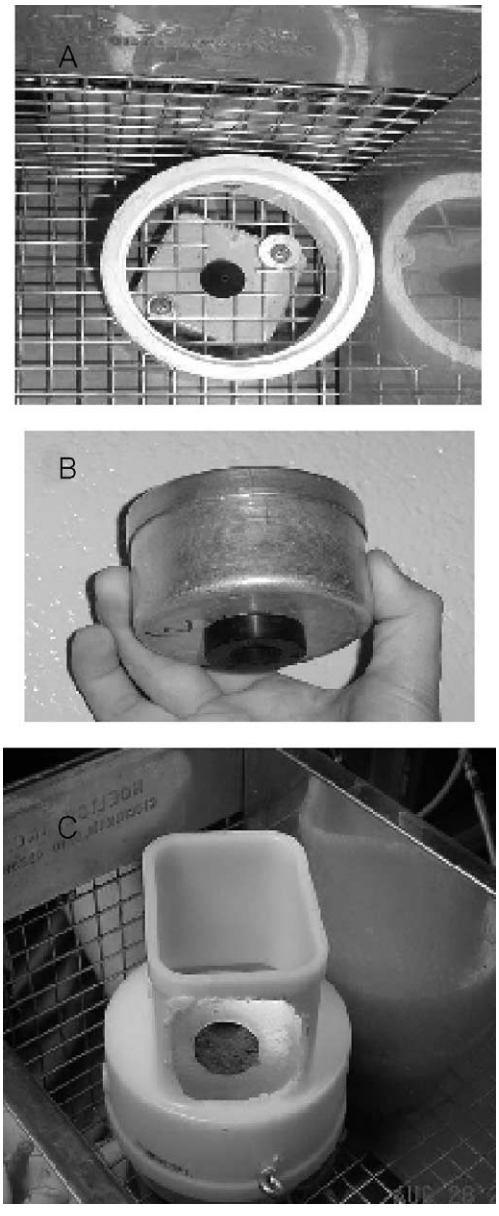

Fig. 1. A–C: (A) View of a rodent cage from the top. A strain gauge is affixed to the cage floor using two bolts and washers. The retaining ring is affixed to the cage wall and to the cage front using stainless steel bolts, washers, and nuts. The black circle in the center of the retaining ring is a conical mount positioned within the strain gauge. (B) Ventral view of an aluminum food cup to which a solid mounting disk has been fixed to the cup using self-tapping bolts. The food cup is weighted using a series of stainless steel washers (~125 g) placed inside the cup. (C) A view of the cage from the top rear, illustrating the placement of the adaptor on the retaining ring, and the placement of the food cup within the ring.

controller, which in turn reported data to a microcomputer. A proprietary software program (Research Diets, Inc.; New Brunswick, NJ) was used to analyze the meal pattern data. In this system, a meal was initiated upon movement of the food hopper. A meal was deemed to have terminated when there were no additional movements of the food hopper for 240 s (Castonguay et al., 1986). The minimum meal amount was set at 0.05 g. Meal number, average meal size (g), and total food intake (g) data were reported over the 12 h dark period and an 11 h light period (with the system down for 1 h for maintenance at the end of the light period).

2.5. Procedure

The rats were maintained in a colony room for 7 days prior to the start of behavioral testing, so as to acclimate them to colony maintenance procedures, including daily weighing and handling. The rats were randomly assigned to either a CHOW group ($n=15$) or a HIFAT group ($n=12$) and were adapted to the respective diet for 3 days (in the home-cage). The rats were then transferred to one of the BioDAQ feeding cages and offered 23 h per day access to a metal food cup filled either with the CHOW diet or the HIFAT diet for the remainder of the experiment.

On days 5–7 of the baseline period, the rats were adapted to the injection protocol, which consisted of daily dark-phase injections (IP) of 0.9% saline (SAL, 1 ml/kg) administered at 1200, 1400, 1600, 1800, and 2000 h. On days 1–14 of the drug treatment period, rats within the CHOW group and the HIFAT group were randomly assigned to receive five daily injections of either SAL (forming groups CHOW-SAL or HIFAT-SAL) or 1.4 mg/kg/day NIC, free base (forming groups CHOW-NIC or HIFAT-NIC). The dose for each rat was based on the highest body weight for that rat during the injection period, using the procedures of Bellinger et al. (2003a). Our choice of a 1.40 mg/kg NIC dose was based on a number of considerations. One factor is that 70–75% of NIC given by the i.p. route used in the present study would be removed by the liver during a single pass (Svensson, 1987) and thus would not reach the brain. Humans smoking one to three packs of cigarettes per day take a total daily dose of approximately 0.3–0.5 mg/kg/day of NIC through their lungs Benowitz and Jacob, 1984; Perez-Stable et al., 1998). Therefore the effective NIC dose used in the present study that would reach the rat brain would be about ~0.42 mg/kg/day and is in the range of that used spontaneously by human smokers. To ensure that changes in feeding and drinking were not due to termination of daily injections (as opposed to cessation of NIC treatments), all rats received SAL injections during the 10 day recovery period. Because only 12 feeding modules were available in this laboratory, rats from each diet-drug group were run in squads until the proper group sizes were reached.

At 1100 h of each test day, the software system was terminated and data stored for subsequent analysis. The final volume of each drinking tube was recorded to the nearest ml. Each rat was weighed to the nearest gram and transferred to a separate clean holding cage with access to water, but not food. Each food cup was weighed to the nearest 0.1 g and then refilled, reweighed, and returned to the test cage. Food spillage was collected on paper placed beneath each cage and recorded to the nearest 0.1 g (water intakes were not corrected for spillage, but the pads below the cages were dry). Additionally, the daily procedure involved system maintenance including calibration of each strain gauge and verification that movement of the food cup did not alter the baseline weight reported for the system for that cup (i.e. a "zero meal" check). At the start of the dark cycle (1200 h), each rat received its first appropriate injection and was returned to the feeding cage, and its feeding was monitored until the next morning at 1100 h.

2.6. Data analyses

The overall design of the experiment included between-group factors of maintenance diet (CHOW vs. HIFAT) and NIC dose (0 (SAL) vs. 1.4 mg/kg/day) and a within-group factor of day (NIC treatment days 1–14; recovery from NIC treatment days 1–10). Separate three-way analyses of variance were computed using SPSS (Version 11.5, SPSS, St. Louis, MO) comparing differences among the groups for the dependent variables of body weight, water intake, food intake, and meal parameters. Additional contrasts between group means were made using the Bonferroni procedure. Difference probabilities <0.05 were deemed to be statistically significant. Preliminary analyses indicated that there were no significant differences among the SAL and NIC groups in any meal parameter during the 2 days prior to the start of the drug treatment period.

3. Results

3.1. Food intake and meal patterns

The BioDAQ system measure of total food intake was validated by an actual weighing of the food cup at the start and end of the 23 h testing period. In most cases, the discrepancy between the two methods of measure resulted from spillage from the food cup (meal parameters were not corrected for food spillage: Farley et al., 2003). The average (±S.E.M.) spillage from the CHOW and HIFAT groups over a 23-h period was 0.6 (±0.2) and 0.4 (±0.05) g, respectively. These spillage values are about 2 kcal/day for the CHOW and the HIFAT groups and represent about one-third of the average meal size per day (in kcal). It should be noted that the amount of chow diet spillage is greater than that obtained (<0.12 g) using a pellet-based eatomer (Bellinger et al., 2003a,b; Guan et al., 2004). The food intakes were recorded to the nearest 0.1 g daily and were converted into caloric intakes for subsequent data analyses.

As expected, HIFAT-SAL rats consumed significantly more calories during the 14 day treatment period ($F(1,12)=16.95$, $p<0.001$), than did CHOW-SAL rats (see Fig. 2A). The ANOVA of the daily caloric intakes revealed a significant effect of NIC treatment ($F(1,23)=27.60$, $p<0.001$) and a significant interaction between diet and NIC treatment ($F(1,23)=7.21$, $p<0.02$). The impact of NIC on total daily caloric intake was evident on day 1 of treatment and was

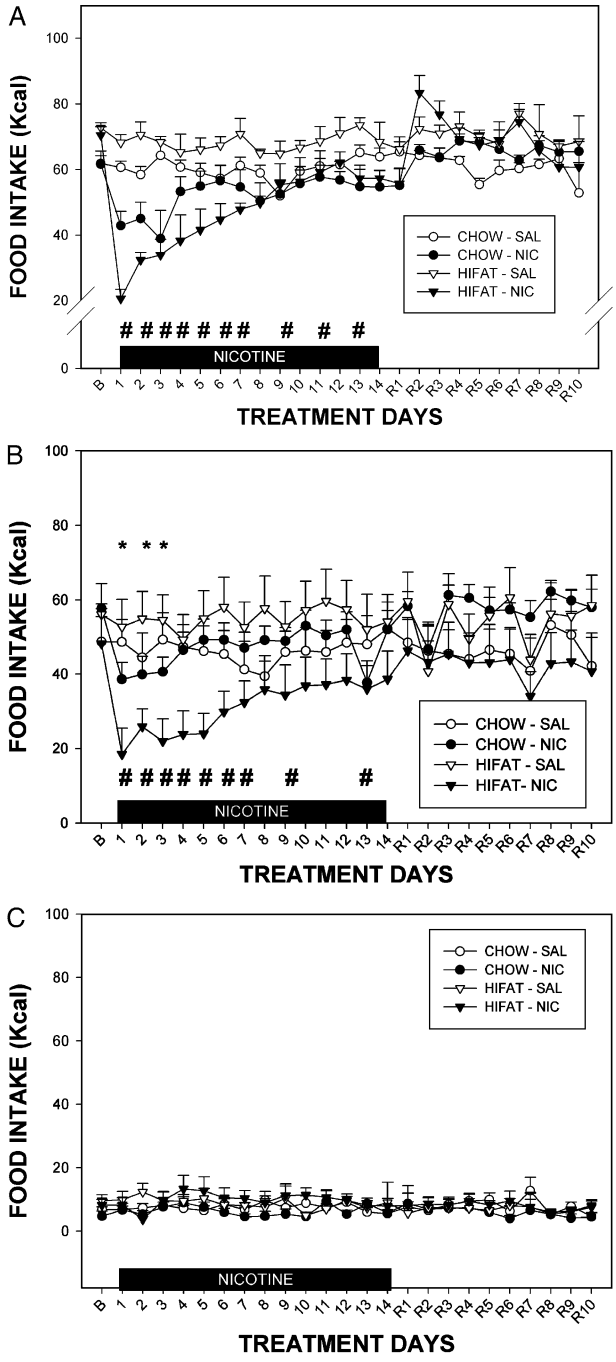

Fig. 2. Mean group caloric intake in kcals (KCALS) in male rats treated for 14 days with either 0.9% saline (SAL) or 1.4 mg/kg free base nicotine (NIC) maintained on either a chow (CHOW) or high-fat diet (HIFAT). During the 10 days after cessation of NIC, all rats were injected daily with SAL. The vertical line above or below each symbol represents the SEM. An * denotes a significant ($p<0.05$) difference between CHOW-NIC and CHOW-SAL groups, whereas a # represents a significant ($p<0.05$) difference between HIFAT-NIC and HIFAT-SAL groups. Panel A: Total daily caloric intake; Panel B: Dark phase caloric intake; Panel C: Light phase caloric intake. Treatment days: B=Baseline day; 1–14=drug treatment days; R1–R10=Recovery days.

significantly greater for rats maintained on the HIFAT diet than CHOW-fed rats ($t(11)=2.51$, $p<0.03$). Interestingly, the capacity of NIC to suppress eating waned over the 14 day treatment period more rapidly for rats fed the CHOW diet than for rats fed the HIFAT diet. The difference between NIC and SAL groups was significant for the first 3 days of the 14 day period for the CHOW groups, but was significant for the first 7 days of the 14 day period for the HIFAT groups (Fig. 2A).

A similar pattern of greater NIC-induced hypophagia for rats fed a HIFAT diet as compared to rats fed a CHOW diet was evident in the dark-phase caloric intakes (Fig. 2B), whereas there were no obvious differences among the groups in caloric intake during the light phase (Fig. 2C). As expected, the rats consumed a large portion of their daily food intakes during the dark phase, and this was so for both the CHOW rats as well as for the HIFAT rats (Fig. 2B).

Although discontinuation of NIC on day 14 resulted in increased caloric intakes in both CHOW-NIC and HIFAT-NIC groups, these changes were not significantly different for each NIC group relative their control group ($p>0.05$).

3.2. Meal size

As expected, NIC produced an immediate suppression of dark phase meal size (Fig. 3B), but did not significantly affect light phase meal size (Fig. 3C). The ANOVA of the dark-phase meal size data indicated a significant effect of diet ($F(1,23)=6.70$, $p<0.02$) and of NIC treatment ($F(1,23)=12.70$, $p<0.002$), but no interaction among these factors ($p=0.91$). Dark phase meal size was higher in rats fed the HIFAT diet than rats fed the CHOW diet, regardless of NIC treatment. Contrasts indicated significant inhibition of dark phase meal size on 5 of 14 days for the HIFAT group and for 7 of 14 days for the CHOW group. A similar pattern of results were noted for the 23 h meal size data with significant effects of diet ($F(1,23)=9.20$, $p<0.01$) and of NIC ($F(1,23)=4.80$, $p<0.04$), but no interaction between these factors ($p=0.77$). For these contrasts, only day 1 of NIC treatment was significant for the CHOW group (Fig. 3A). ANOVA indicated no significant effect of NIC treatment on light phase meal size (Fig. 3C) ($p=0.72$), nor was there an interaction between the factors of diet and NIC treatment ($p=0.63$). Following cessation of NIC, there were no significant differences in meal size during the dark phase as a function of prior NIC treatment ($p=0.9$) or of diet ($p=0.20$), nor was there an interaction among these factors ($p=0.468$). The 23 h meal size of the NIC-HIFAT group increased significantly on the first day after termination of NIC (Fig. 3A), but not thereafter.

3.3. Meal number

Dark-phase meal number (Fig. 4B) and 23 h meal number (Fig. 4A) slightly decreased from baseline in the CHOW-SAL group, but increased in the CHOW-NIC group across days 1–14. The ANOVA of the dark phase meal number data revealed a significant interaction between the factors of diet and NIC administration ($F(1,23)=4.62$, $p<0.03$). Contrasts of dark phase meal number indicated significantly higher meal number values for the CHOW-NIC group relative to the CHOW-SAL group on days 8, 12, and 13. After NIC termination, meal number values converged such that there were no differences between CHOW groups. In stark contrast, NIC administration

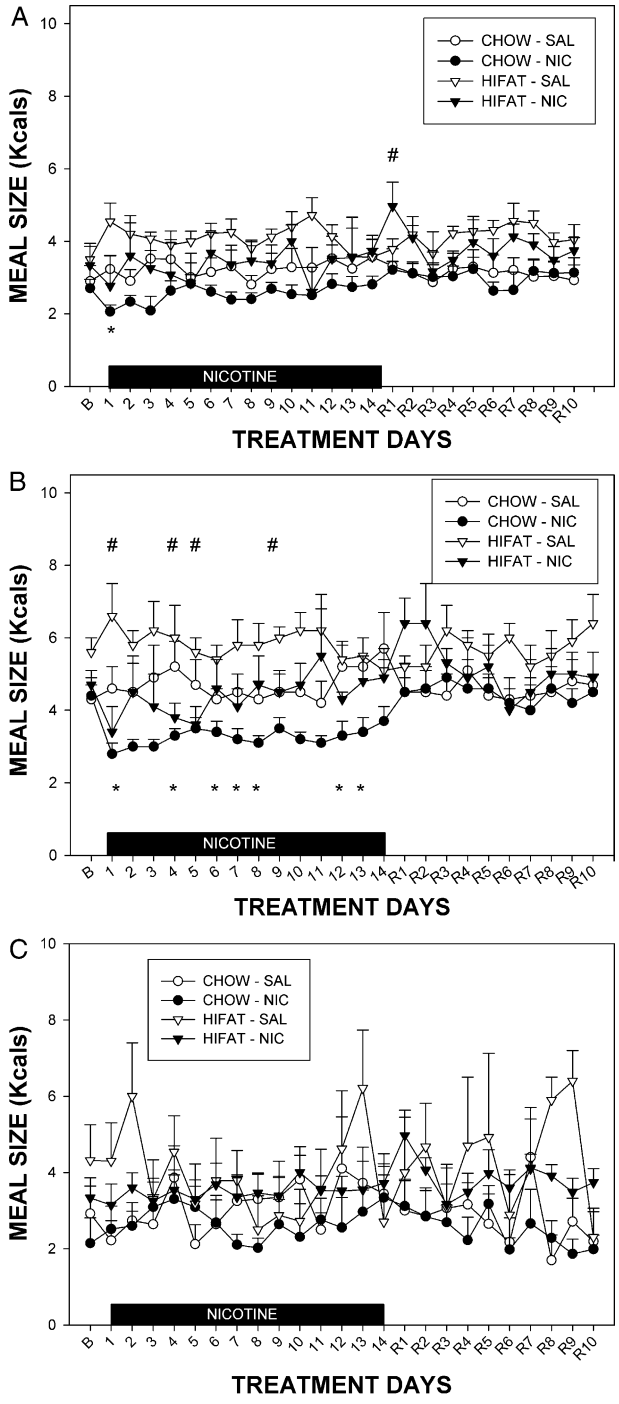

Fig. 3. Mean group meal size in male rats treated for 14 days with either SAL or NIC maintained on either a CHOW or HIFAT. During the 10 days after cessation of NIC, all rats were injected daily with SAL. Panel A: Total daily caloric intake; Panel B: Dark phase caloric intake; Panel C: Light phase caloric intake. Means±S.E.M., see Fig. 2 for abbreviations and explanations.

initially suppressed 23 h and dark phase meal number in rats fed the HIFAT diet and this effect waned across the treatment period. Dark-phase and 23-h meal number was significantly suppressed on days 1 and 2 in the HIFAT-NIC group relative to the HIFAT-SAL group, but not thereafter.

During the 10 day recovery period, regardless of measurement period, there were no overall differences in meal number as a function of diet, NIC administration, nor was there a significant interaction between diet and NIC administration.

3.4. Body weight

As expected (Fig. 5), rats in the CHOW-SAL group gained weight at a significantly slower rate than did rats in HIFAT-

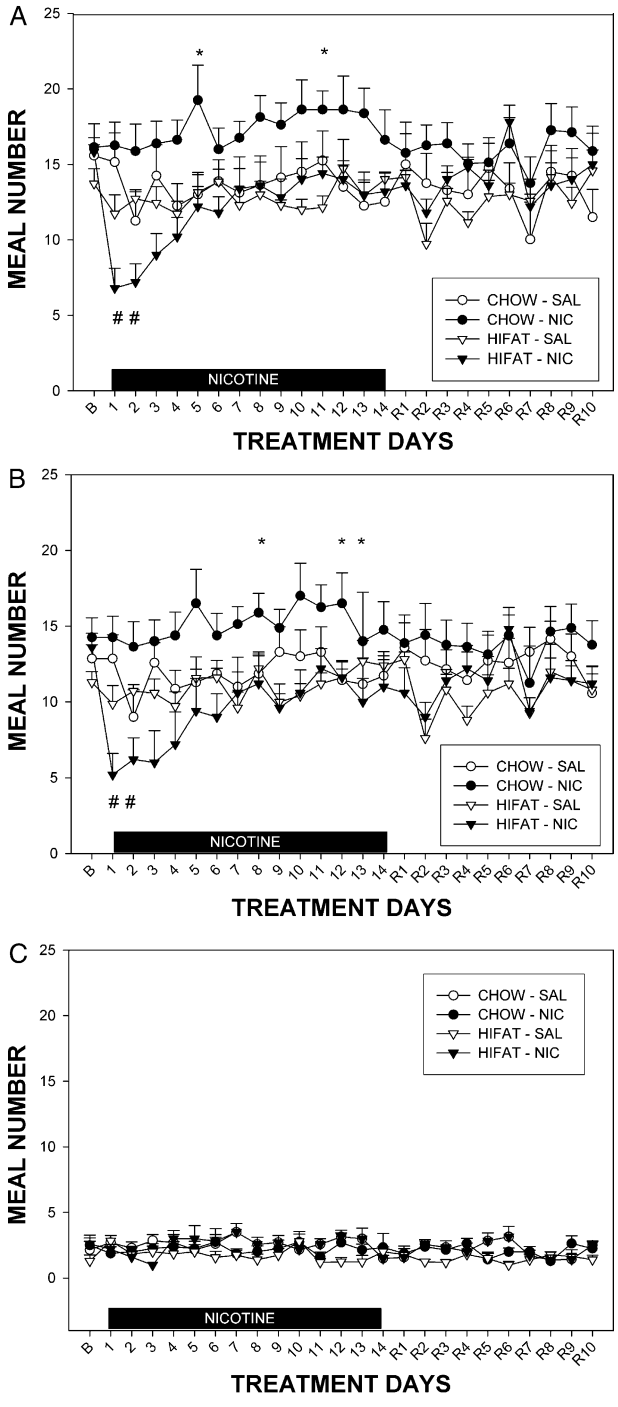

Fig. 4. Mean group meal number in male rats treated for 14 days with either SAL or NIC maintained on either a CHOW or HIFAT. During the 10 days after cessation of NIC, all rats were injected daily with SAL. Panel A: Total daily caloric intake; Panel B: Dark phase caloric intake; Panel C: Light phase caloric intake. Means±S.E.M., see Fig. 2 for abbreviations and explanations.

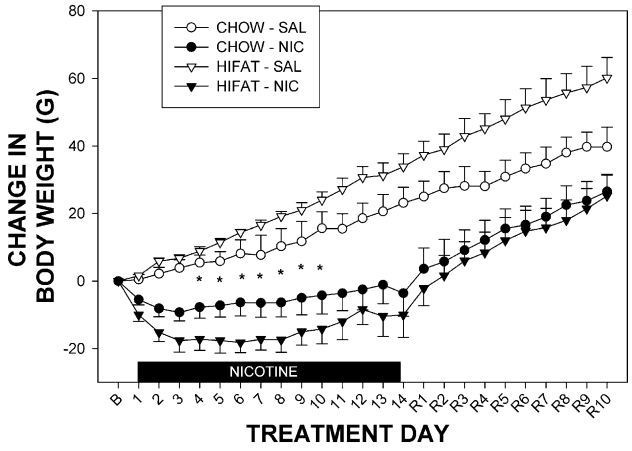

Fig. 5. Mean group changes in body weight (g) in male rats treated for 14 days with either SAL or NIC maintained on either CHOW or HIFAT. During the 10 days after NIC, all rats were injected daily with SAL. Means ± S.E.M., see Fig. 2 for abbreviations and explanations.

SAL group ($F(13,156)=2.02$, $p<0.03$). The ANOVA of body weight change during the 14 day drug treatment period revealed a significant effect of NIC administration ($F(1,23)=46.00$, $p<0.001$), but not of diet. The capacity of NIC to reduce body weight was greater in the HIFAT group than the CHOW group, as evident in a significant interaction between the factors of diet and NIC administration ($F(1,23)=5.10$, $p<0.02$). Termination of NIC administration resulted in weight gain in the CHOW-NIC and HIFAT-NIC groups, but by the end of the 10 day recovery period, the body weights of these groups remained below the levels of their respective SAL control groups.

3.5. Water intakes

As expected, rats in the CHOW-SAL group consumed more water than did rats in the HIFAT-SAL group across the treatment and recovery phases (Fig. 6). Administration of NIC increased water intake, particularly in the HIFAT-NIC group, relative to the HIFAT-SAL group ($F(1,23)=17.90$, $p<0.001$). After termination of NIC water intake was affected by diet ($p<0.00001$), but not by prior exposure to NIC. There was no a significant interaction between the factors of diet and NIC administration during the recovery period.

4. Discussion

In the present study, administration of NIC during the dark phase, at a free base dose of 1.4 mg/kg/day, produced a significant suppression of food intake, and of body weight in adult male rats fed CHOW or HIFAT diets, but these effects were significantly larger in rats fed the HIFAT diet. In spite of the greater palatability and caloric density of the high-fat diet, NIC produced a larger suppression of daily caloric intake relative to the changes noted in rats fed the chow diet. The hypophagic effect of NIC in CHOW-fed and in HIFAT-fed rats waned across days with repeated NIC administration. As in our earlier study (Bellinger et al., 2003a), NIC immediately suppressed meal size in CHOW-fed rats; whereas meal number was not initially altered in CHOW-fed rats, but increased above baseline with repeated NIC administration. This increment of meal number in CHOW-NIC rats tended to return caloric intake back to baseline levels, in spite of continued dark phase administration of NIC. Cessation of NIC resulted in a transient but nonsignificant increase in daily caloric intake in CHOW-fed and HIFAT-fed rats (Fig. 2A), and a transient but significant increase in meal size for rats fed the HIFAT diet (Fig. 3A). These results generally parallel the transient changes in chow diet intake for male rats after termination of NIC in our earlier study (Bellinger et al., 2003a).

Importantly, the present study addressed the concern that diets used in earlier studies of NIC effects on caloric intake and meal patterns are not representative of diets ingested by human smokers (cf. Dallongeville et al., 1998). The tendency of rats to prefer the high-fat diet resulted in greater daily caloric intakes and a greater rate of weight gain in the HIFAT-SAL group relative to the CHOW-SAL group. These differences in caloric intake and body weight gain stand in stark contrast to the significantly larger suppressions of daily caloric intake and reduced weight gain noted in the HIFAT-NIC group relative to that of the CHOW-NIC group. These results suggest that the hypophagic and weight-reducing properties of NIC are augmented when rats are fed a HIFAT diet as opposed to a CHOW diet. Such a result is somewhat surprising given that many of the features of the high-fat diet (i.e. greater palatability, easier to consume) would be predicted to attenuate the hypophagic action of NIC.

The ground-chow diet and the high-fat diet chosen for this study are clearly different along a number of dimensions including texture, greasiness, palatability, taste, dryness, caloric density and relative proportions of carbohyrate/protein/fat (Blundell and Lawton, 1995; Corbit and Stellar, 1964; Wellman et al., 1982). The differential effect of NIC on caloric intake and body weight cannot be attributed to some non-specific change in overall ingestive behavior, inasmuch as NIC induced significantly greater daily water intakes, but reduced

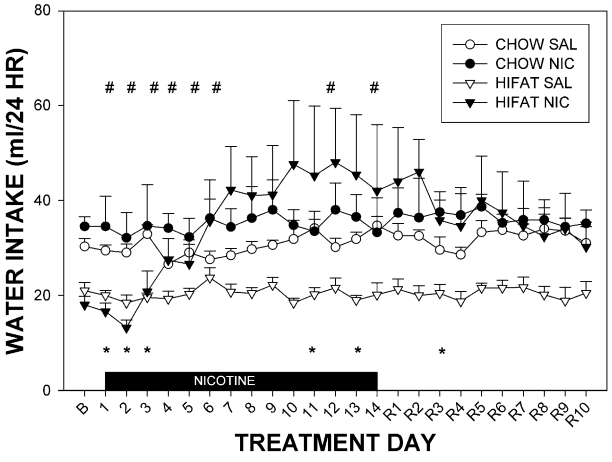

Fig. 6. Mean 23 h water intake values (mls) in male rats treated for 14 days with either SAL or NIC maintained on either CHOW or HIFAT. During the 10 days after cessation of NIC, all rats were injected daily with SAL. Means ± S.E.M., see Fig. 2 for abbreviations and explanations.

food intake in HIFAT rats relative to CHOW rats. It is also unclear as to whether the differences in the present study reflect a general action of HIFAT maintenance on drug-induced hypophagia. The present results for NIC are similar to studies summarized by Blundell and Lawton (1995) in which the serotonergic agent dexfenfluramine produced stronger suppressions of food intake and weight gain in rats fed a high-fat diet (50–60% as fat) relative to a low-fat (4–5%) diet. Yet, other studies have noted either no change in hypophagia after systemic amphetamine in rats fed a HIFAT diet (Wellman et al., 1982) or have noted a diminished hypophagic response in HIFAT rats receiving acute ICV administration of drugs that activate MC3/MC4 receptors in brain (Clegg et al., 2003). As noted earlier, these diets vary in multiple dimensions in addition to fat content (Corbit and Stellar, 1964) thereby precluding specification of the factors that resulted in the present interaction between diet type and NIC-induced hypophagia and weight gain.

In the present study NIC suppressed meal size in the HIFAT-NIC group and in the CHOW-NIC group. The effect of NIC on meal number, however, depended on which diet the rats were offered. Meal number was significantly elevated in the CHOW-NIC group relative to the CHOW-SAL group, but suppressed by NIC in rats offered a HIFAT diet. This latter finding is novel in that other studies using pelleted chow diets in sound attenuated feeding modules (Bellinger et al., 2003a,b) showed that NIC initially suppressed meal size and food intake, but did not immediately alter meal number. Only later did meal number increase over baseline, in a compensatory manner, to normalize the chow intake of these male rats (Bellinger et al., 2003a,b). In the present study, NIC administration suppressed meal size in both the CHOW and HIFAT fed groups. The joint impact of NIC on reducing meal size and meal number of the HIFAT fed group greatly attenuated their body weight. The 23 h food intake of the HIFAT-NIC group only recovered when meal number returned to normal. In summary, giving NIC in the same dose and manner to rats fed chow vs. a high-fat diet results in differences in meal patterns and body change. The present study and earlier findings (Bellinger et al., 2003a,b) show chow fed rats receiving NIC initially show a prolonged suppression of meal size that does not recover during NIC treatment. These rats then show a compensatory increase in meal number such that around day 9 food intake has normalized, but meal patterns are aberrent. Around day 9, the body weight of these rats begins to parallel the controls, while remaining significantly below that of saline controls. The HIFAT-NIC rats of the present study show a somewhat different pattern. Their meal size is also reduced, but not as long as found in chow fed rats receiving NIC. In contrast to the elevation of meal number in NIC treated chow fed rats the meal number of HIFAT-NIC is reduced and daily caloric intake only recovers to normal when both meal size and meal number return to baseline. Because both meal size and meal number are attenuated in HIFAT-NIC rats, body weight is impacted more in these rats than in CHOW fed rats.

It should be noted that body weight levels in the NIC treatment groups remained below those of SAL treated rats at the end of the 14 day drug treatment period, even as the caloric intakes of these groups were similar. This observation suggests a metabolic basis for the continued impact of NIC on body weight (Lupien et al., 1988; Perkins, 1992). One might speculate that chronic exposure to NIC eventually results in a set of physiological adaptations that allow an organism to weigh less in spite of consuming amounts of fat and energy that produce weight gain in non-NIC treated organisms (Dallongeville et al., 1998).

In the present study, NIC was administered during the dark phase, but not during the light phase. There was no evidence of compensation during the light phase for caloric intake (Fig. 2C), meal size (Fig. 3C), or meal number (Fig. 4C) when NIC was not administered. These findings support our earlier study in which our dark-phase model of administration did not result in light-phase compensation in caloric intake or meal patterns (Bellinger et al., 2003a).

The brain mechanisms by which NIC inhibit eating are mostly unknown, although there is evidence linking NIC hypophagia to activation of brainstem nicotinic receptors (Guan et al., 2004). A number of recent studies indicate that mice and rats that shifted to various high-fat diets exhibit changes in circulating hormone levels (Leibowitz et al., 2004) as well as changes in neuronal activity in brain (Chang et al., 2004; Heshka et al., 2001; Wang et al., 1999), which could alter the propensity of NIC to impact ingestive behavior, metabolism, and ultimately body weight. The present study suggests important interactions between dietary fat and NIC actions on eating and body weight, although the pathways through which these effects occur are as yet unknown.

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