Pharmacology Biochemistry & Behavior, Vol. 25, pp. 1131–1136, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

Nicotine's Effects on Female Rats' Body Weight: Caloric Intake and Physical Activity

DEBORAH J. BOWEN,[1] SHARON E. EURY AND NEIL E. GRUNBERG

Department of Medical Psychology, Uniformed Services University of the Health Sciences

Received 3 June 1986

BOWEN, D. J., S. E. EURY AND N. E. GRUNBERG. *Nicotine's effects on female rats' body weight: Caloric intake and physical activity*. PHARMACOL BIOCHEM BEHAV **25**(6) 1131–1136, 1986.—Caloric intake and physical activity contribute to the inverse relationship between nicotine and body weight in male rats. In contrast, the relative contribution of these behavioral variables to the nicotine/body weight relationship in female rats has not been investigated. Recent research indicates that males and females respond differently to nicotine. The present study was designed to determine the role of physical activity and food consumption in body weight changes associated with nicotine administration in female rats. Nicotine or saline was administered chronically to 24 female rats for 19 days. Body weight, food consumption, water consumption, and physical activity were measured before, during, and after nicotine administration. Body weight and food consumption decreased during and increased after nicotine administration. However, there were no changes in physical activity that could account for these changes in body weight. These results corroborate the report that males and females respond differently to nicotine.

Nicotine Body weight Food consumption Water consumption Physical activity Females

CALORIC intake and physical activity contribute to the inverse relationship between nicotine and body weight in male rats [2–4]. Chronic nicotine administration significantly decreases consumption of sweet-tasting and high carbohydrate foods; slightly increases physical activity; but does not alter consumption of bland, low carbohydrate foods. After cessation of nicotine, male rats significantly increase consumption of sweet-tasting and high carbohydrate foods; significantly decrease physical activity; but do not alter bland food consumption [4–6]. However, females may be differentially affected by nicotine. A recent study indicates that, for female rats, there is an inverse relationship between nicotine and body weight and between nicotine and bland food consumption [7]. Because of the marked difference in the effects of nicotine on bland food consumption in males and females, it is unknown, without empirical evidence, what the effects of nicotine would be in females on other variables (e.g., physical activity) that contribute to the nicotine/body weight relationship. Also, without empirical evaluation it is impossible to know the relative contributions of caloric intake and physical activity to the inverse relationship between nicotine and body weight in female rats.

The present study was designed to examine the effects of nicotine on body weight, food consumption, water consumption, and physical activity of female rats. Nicotine was administered subcutaneously for 19 days via osmotic minipumps. This technique was chosen because it provides results consistent with the effects of cigarette smoking on body weight and eating behavior [2,8]. Physical activity was examined for 24-hour periods to allow conclusions regarding the contributions of changes in physical activity to nicotine's effects on body weight. This paradigm has been successfully used to examine the contributions of physical activity to nicotine's effects on body weight of male rats [4]. In contrast, previous studies of nicotine's effects on physical activity [1, 10, 13, 15, 16] could not speak to the body weight issue convincingly because these earlier studies: did not measure body weight; used bolus injections of nicotine for less than a week; measured physical activity for less than 45 minutes a day; and did not measure physical activity after cessation of nicotine.

METHOD

Subjects and Housing

The subjects were 24 virgin female Sprague-Dawley rats purchased from Hilltop Laboratory Animals (Scotdale, PA). Animals weighed roughly 200 g at the start of the study. Animals were individually housed in polypropylene shoebox cages (35.6×15.2×20.3 cm) fitted with metal grill lids and elevated metal floors above absorbant wood Pine-Dri shav-

[1]Requests for reprints should be addressed to Dr. Deborah J. Bowen at her present address: Department of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104.

ings. Cages were kept on a four-shelved metal rack in a 6×3 m room with overhead fluorescent illumination. The room was maintained on a 12-hour light/dark cycle (lights on at 0900 hours and off at 2100 hours) at approximately 22 degrees C and 50% relative humidity. Animals were provided with continuous access to tap water and to ground chow (Charles River RMH 3200) in stainless steel cups with fitted lids. When animals were in the activity monitor cages (see the Activity Monitoring section), tap water and pellet chow (Charles River RMH 3500) were continuously available.

Drug Administration

Immediately preceding surgery animals were anesthetized by inhalation of methoxyflurane (Metofane). Alzet miniosmotic pumps (Model 2002, Alza Corporation, Alza, CA) were implanted subcutaneously between the shoulders to deliver nicotine or saline at a constant rate of 0.5 μl/hr for 20±2 days [17]. This infusion technique provides constant, chronic levels of nicotine without the trauma of several daily injections. Physiological saline was used to make the nicotine solutions (made from nicotine dihydrochloride) and was the control solution. Equal numbers of animals received saline, 4, 8, or 12 mg nicotine/kg/day (values computed as nicotine base). These dosages were used to be comparable to previous research on nicotine and physical activity in male rats [4] and to be comparable to studies of the effects of nicotine on body weight and eating behavior [2, 5, 6].

Activity Monitoring

Physical activity was monitored for nine 24-hour periods (beginning at 1015 hours) evenly spaced before, during, and after nicotine administration. The monitoring period included days 1, 7, and 13 before drug; days 3, 9, and 15 during drug administration; and days 2, 8, and 14 after cessation of nicotine. These days were the same for all subjects. Digiscan Optical Digital Sensor Activity Monitors equipped with Datalogger 8000 data collection devices (Omnitech Electronics Inc., Columbus, OH) were used to measure activity. These monitors consist of a metal frame containing an 8×8 grid of infrared light beams projected 2.5 cm above the cage bottom to measure horizontal activity. A second set of beams projected infrared light across the cage 15 cm above the floor to measure vertical activity. Whenever one of these beams was crossed, the Datalogger incremented one unit for the appropriate activity type. At the end of each monitoring period, a printout of data in counts per hour was removed from the Datalogger and the counters were reset for the next day's collection. While activity was being monitored, animals were housed in 40.6 cm square Plexiglas cages with Plexiglas tops set inside the activity monitors.

Procedure

After animals were gentled for a week, they were assigned in equal numbers to each experimental group (0, 4, 8, and 12 mg nicotine/kg body weight/day) such that the body weights of each group were similar. Body weight was measured daily using Sartorius electronic balances (Model 1264-MPBCD) programmed to provide the mean of 10 separate weighings. Food and water consumption were measured on weekdays by weighing food cups and water bottles upon removal from each cage and again after cups and bottles were refilled. Vaginal smears were taken daily by the lavage method and were read immediately for cell types under a light microscope to determine stage of estrus cycle [9]. Physical activity was measured for 24-hour periods in four activity monitors placed on tables in the room in which the rats were housed. (Rats were habituated to these chambers before beginning the study.) Three days of physical activity data were collected for each animal during each of the three phases of the experiment: before, during, and after drug administration. These nine days were evenly spaced within each phase. On any given day, one animal from each of the four experimental groups was simultaneously in one of the four activity monitors. The activity monitors were cleaned and prepared with fresh food, water, and bedding every day after animals were returned to their home cages. After 19 days of pre-drug measurements, miniosmotic pumps were implanted to infuse nicotine or saline. All measurements continued during the 19 day drug administration period. Minipumps were subsequently removed and measurements continued for the after drug period.

RESULTS

Data Analyses

The results of this study for body weight, food and water consumption were analyzed in two ways. The first type of analysis used body weight and consumption data from nine days comparable to the days that physical activity was monitored. This analysis allowed for comparison of the relative contributions of physical activity and eating behavior to nicotine's effects on body weight. The second type of analysis used values from six days before, six days during, and six days after nicotine administration. This analysis was performed to allow direct comparison with previous studies of the effects of nicotine on body weight and eating behavior [2, 5–7]. In all types of analyses, difference scores were computed for each animal for the changes in body weight, food consumption, water consumption, and physical activity from the "before drug" to "during drug" periods and from the "during drug" to "after drug" periods. Grouped t-tests were performed on these difference scores. Significance levels were determined using two-tailed values.

Body Weight

Activity days. Figure 1a presents body weight data for each experimental group before, during, and after nicotine administration. Before drug administration, body weights for all drug groups were similar. During nicotine administration there was an inverse dose-response relationship between dosage of nicotine and body weight. Comparing the changes in body weight from before drug to during drug administration, the saline group gained more weight than did the nicotine groups [interaction $t(10)=4.56, 2.11, 0.89$ for 12 mg, 8 mg, and 4 mg, respectively; $p<0.001, 0.10$, ns]. In addition, the 4 mg and 8 mg groups gained significantly more weight than did the 12 mg group [interaction $t(10)=4.86, 2.28$, respectively; $p<0.001, 0.05$]. Comparing the changes in body weight from during to after drug administration, the 4 mg and 12 mg groups gained more weight than did the saline group, but these differences were not significant.

Six-day means. Figure 1b presents body weight six-day means. Similar to the activity days analyses, the body weights for all groups did not differ before drug administration and there was an inverse dose-response relationship dur-

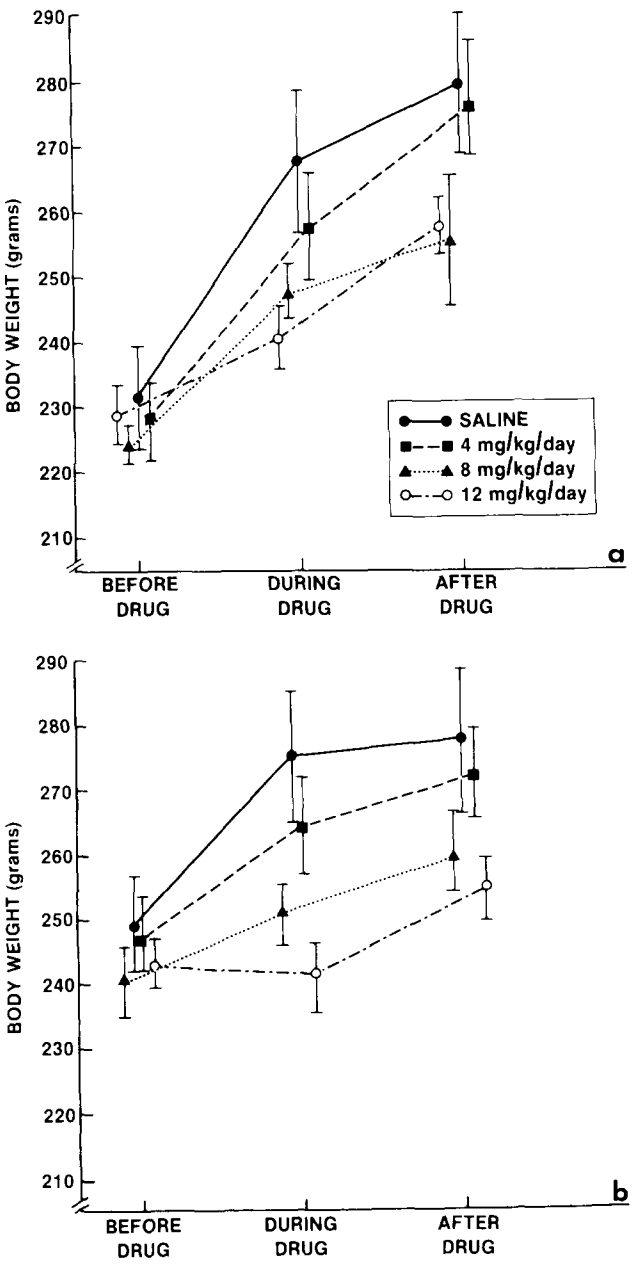

FIG. 1. (a) Body weight averaged across physical activity days before, during, and after drug administration. (b) Body weight averaged over 6-day periods before, during, and after drug administration.

ing drug administration. Comparing the changes in body weight from before drug to during drug administration, the saline group gained more weight than did the nicotine groups [interaction $t(10)=7.53$, 3.33, 2.08 for 12 mg, 8 mg, and 4 mg, respectively; $p<0.001$, 0.01, 0.10]. After cessation of nicotine, the 12 mg group gained significantly more weight than did controls [interaction $t(10)=5.63$, $p<0.001$]. The 8 mg group also gained somewhat more weight than did controls [interaction $t(10)=1.87$, $p<0.10$].

Food Consumption

Activity days. Figure 2a presents food consumption data for each experimental group before, during, and after nicotine administration. Before drug administration, food consumption by all groups was similar. During nicotine administration, there was an inverse dose-response relationship between dosages of nicotine and food consumption. Comparing the changes in food consumption from before drug to during drug administration, all nicotine groups decreased significantly compared to saline [interaction $t(10)=3.97$, 3.99, and 3.10, for 12 mg, 8 mg, and 4 mg, respectively; $p<0.01$, 0.01, 0.05]. Comparing the changes in food consumption from during to after nicotine administration, all nicotine groups increased significantly compared to saline [interaction $t(10)=5.32$, 9.34, 2.58, for 12 mg, 8 mg, and 4 mg, respectively; $p<0.001$, 0.001, 0.05].

Six-day means. Figure 2b presents food consumption six-day means. The 12 mg and 8 mg nicotine groups decreased food consumption during drug administration compared to controls. However, these changes were not significantly different from controls. Comparing the changes in food consumption from during to after drug administration, all nicotine groups increased compared to controls [interaction $t(9,10,10)=2.70$, 1.96, 1.02, for 12 mg, 8 mg, 4 mg, respectively; $p<0.05$, 0.10, ns].

Water Consumption

Activity days. Figure 3a presents water consumption data for each experimental group before, during, and after nicotine administration. The 8 mg group decreased water consumption during nicotine administration, while other groups showed no change. Comparing the changes in water consumption from before to during nicotine administration, the difference between the 8 mg and saline groups approached significance [interaction $t(10)=2.09$, $p<0.10$] but no other comparisons approached significance. Comparing the changes from during to after drug administration, the 8 mg and 12 mg groups increased water consumption compared to controls [interaction $t(10)=2.71$, 1.56, $p<0.05$, ns, respectively].

Six-day means. Figure 3b presents water consumption six-day means. Comparing the changes from before to during drug administration, the 12 mg and 8 mg groups decreased compared to saline but these differences were not significant. In contrast, comparing these changes from during to after drug administration, the 12 mg nicotine group increased compared to all other groups [interaction $t(10)=4.53$, 4.22, 2.19; for saline, 4 mg, 8 mg, respectively; $p<0.01$, 0.01, 0.10]. In addition, the 8 mg group increased compared to saline [interaction $t(10)=1.85$, $p<0.10$].

Physical Activity

Figure 4 presents the horizontal physical activity data before, during, and after drug administration. There were no differences between the nicotine and saline groups in the changes in physical activity from before to during drug or from during to after drug administration. The only significant differences between groups were decreases in physical activity from before to during drug administration for the 12 mg group compared to the 8 mg and 4 mg groups [interaction $t(10)=2.28$, 2.41, respectively; $p<0.05$]. Similar to the horizontal physical activity analyses, there were no significant differences between the nicotine and saline groups from before to during drug or from during to after drug administration for vertical physical activity. The only significant differ-

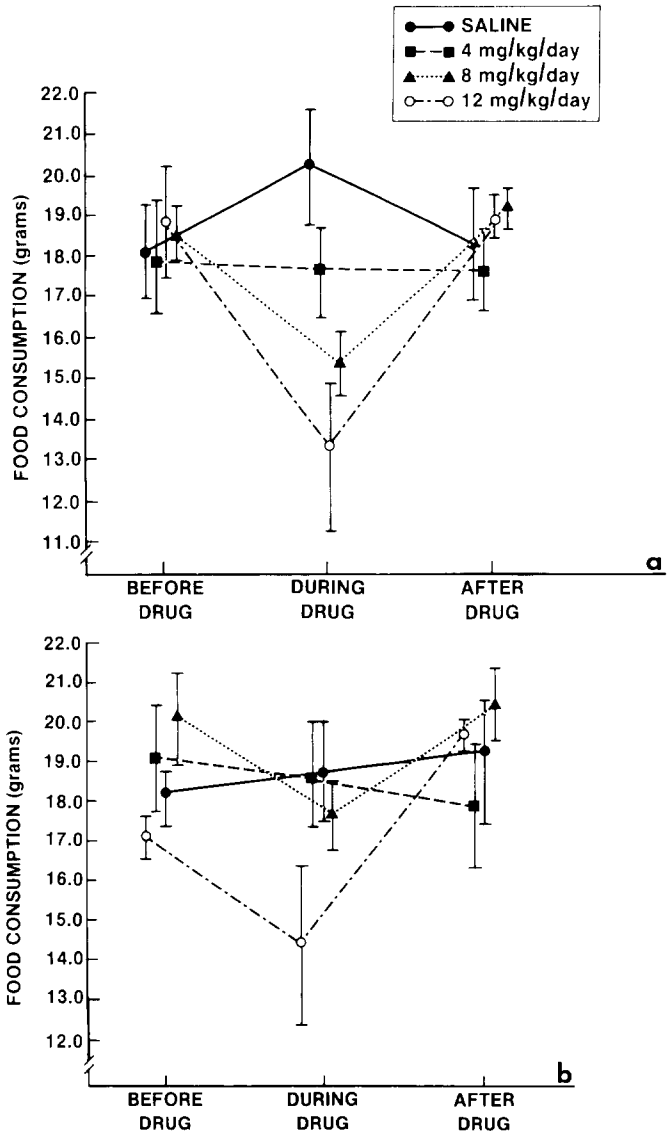

FIG. 2. (a) Food consumption averaged across days comparable to physical activity monitoring before, during, and after drug administration. (b) Food consumption averaged over 6-day periods before, during, and after drug administration.

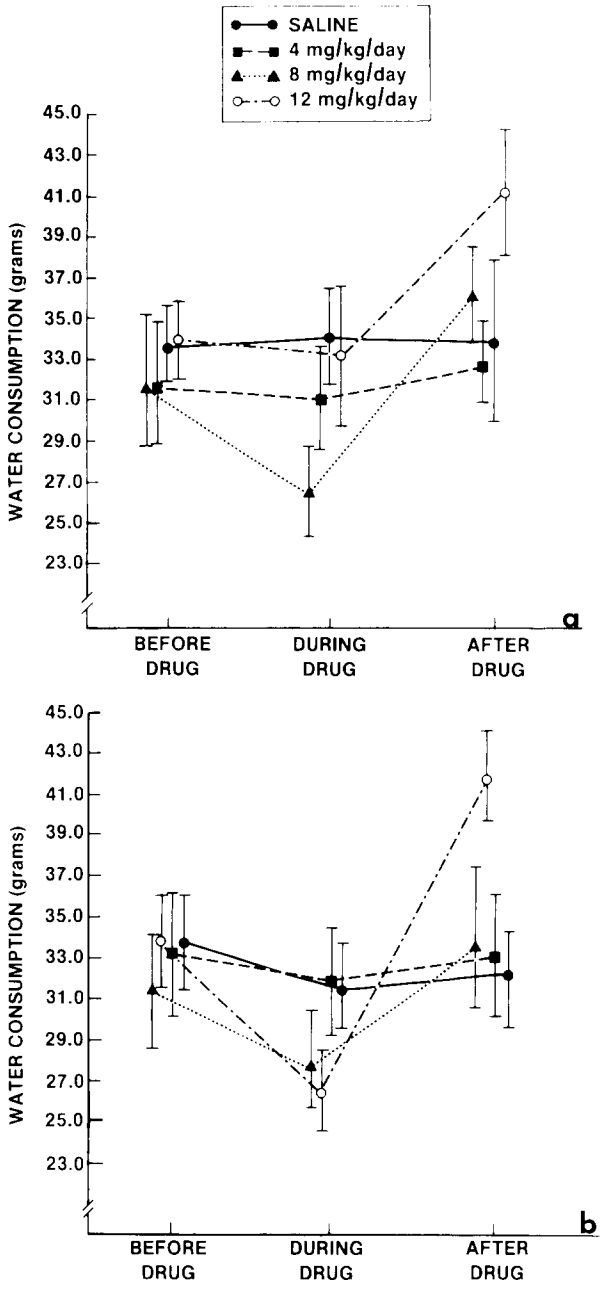

FIG. 3. (a) Water consumption averaged across days comparable to physical activity monitoring before, during, and after drug administration. (b) Water consumption averaged over 6-day periods before, during, and after food consumption.

ences in vertical physical activity were between the 12 mg and 4 mg groups. From before to during nicotine administration, the 12 mg group decreased while the 4 mg group increased [interaction $t(10)=3.24$, $p<0.01$]. From during to after nicotine administration, the 12 mg group increased in comparison to the decrease in physical activity by the 4 mg group [interaction $t(10)=2.60$, $p<0.05$]. Physical activity data (horizontal and vertical) also were analyzed by 12 hour light and dark periods. These analyses yielded similar results to those presented by 24-hour periods.

Cycle Phase Analyses

All variables were analyzed by estrous cycle phase. The results reported for nicotine's effects on body weight, food consumption, and water consumption were indistinguishable

throughout the estrous cycle. Nicotine administration slightly increased activity during estrus and slightly decreased activity during diestrus. However, these trends were not significant.

DISCUSSION

In the present study, there was an inverse dose-response relationship between nicotine and body weight. After cessation of nicotine, animals generally gained more weight than did controls. These changes in body weight were partially a result of changes in caloric intake; compared to controls, food consumption decreased during nicotine administration and increased after cessation of nicotine. In contrast, the changes in body weight did not result from changes in physical activity. In fact, physical activity actually decreased during administration of 12 mg of nicotine at the same time that body weight decreased.

The body weight and caloric intake data replicate a previous study of nicotine's effects in female rats [7]. These findings are markedly different from a study of the effects of nicotine on male rats [6]. One key to the sex difference in the effects of nicotine appears to be the taste of the food available. When the food was bland, females decreased caloric intake and body weight during nicotine administration and increased caloric intake and body weight after cessation of nicotine. Males showed no changes in consumption of bland food during or after nicotine administration and there were no post-nicotine excessive body weight gains. In addition, the present study reveals that there also are sex differences in nicotine's effects on physical activity. For males, physical activity increased during nicotine administration and decreased after cessation of nicotine. For females, there were no changes in physical activity that could account for the decreases in body weight during nicotine or the increases in body weight after cessation of nicotine. These sex differences in the effects of nicotine may reflect differences in sensitivity to nicotine, sex differences in pharmacokinetics and pharmacodynamics of nicotine, or a variety of, as yet, unexplored possibilities. (See [7] for a fuller discussion of this point.)

Considering these studies together, it appears that the effects of nicotine on body weight in male and female rats result from different behavioral variables. If these data are relevant to human smokers (a possibility that we entertain in light of previous corroboration of this animal model with human studies [2, 8, 11, 12]), then women who quit smoking should be particularly careful not to increase caloric intake while males who quit smoking should be sure to maintain or to increase physical activity. Perhaps, these practices (as well as the avoidance of sweet-tasting, high caloric foods [2,5]) will help avoid excessive weight gain after cessation of smoking.

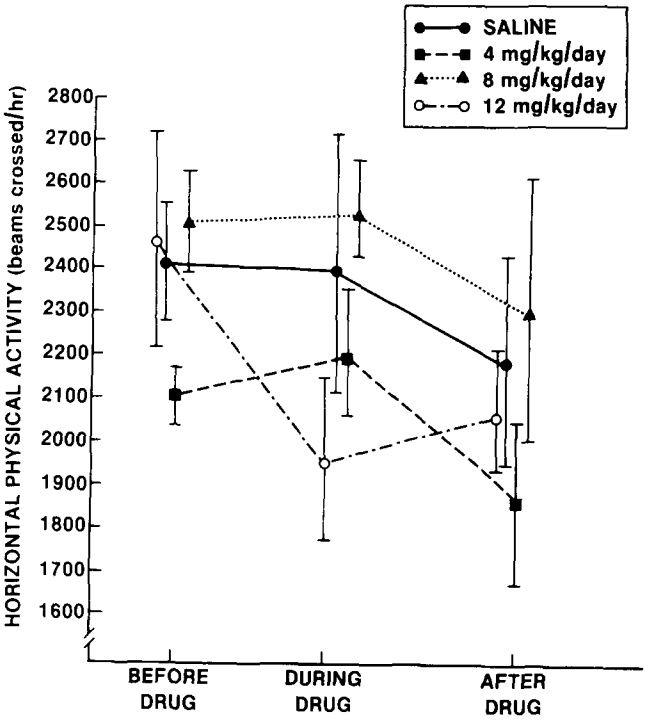

FIG. 4. Horizontal physical activity averaged across all monitoring days before, during, and after drug administration.

ACKNOWLEDGEMENTS

This work was supported by the USUHS Protocol CO7223. The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the DoD, the USUHS, or Fred Hutchinson Cancer Research Center. We are especially grateful to Alicia Harschfield and Diana Platt for their invaluable assistance conducting this experiment.

REFERENCES

1. Bryson, R., D. M. Biner, E. McNair, M. Bergondy and O. R. Abrams. Effects of nicotine on two types of motor activity in rats. *Psychopharmacology (Berlin)* **73**: 168–170, 1981.
2. Grunberg, N. E. The effects of nicotine and cigarette smoking on food consumption and taste preferences. *Addict Behav* **7**: 317–331, 1982.
3. Grunberg, N. E. Nicotine, cigarette smoking and body weight. *Br J Addict* **80**: 369–377, 1985.
4. Grunberg, N. E. and D. J. Bowen. The role of physical activity in nicotine's effects on body weight. *Pharmacol Biochem Behav* **23**: 851–854, 1985.
5. Grunberg, N. E., D. J. Bowen, V. A. Maycock and S. M. Nespor. The importance of sweet taste and caloric content in the effects of nicotine on specific food consumption. *Psychopharmacology (Berlin)* **87**: 198–203, 1985.
6. Grunberg, N. E., D. J. Bowen and D. E. Morse. Effects of nicotine on body weight and food consumption in rats. *Psychopharmacology (Berlin)* **83**: 93–98, 1984.
7. Grunberg, N. E., D. J. Bowen and S. E. Winders. The effects of nicotine on body weight and food consumption in female rats. *Psychopharmacology (Berlin)* **90**: 101–105, 1986.
8. Grunberg, N. E. and D. E. Morse. Cigarette smoking and food consumption in the United States. *J Appl Soc Psychol* **14**: 310–317, 1984.
9. Handelmann, G., R. Ravizza and W. J. Ray. Social dominance determines estrous entrainment among female hamsters. *Horm Behav* **14**: 107–115, 1980.
10. Hatchell, P. C. and A. C. Collins. The influence of genotype and sex on behavioral sensitivity to nicotine in mice. *Psychopharmacology (Berlin)* **71**: 45–49, 1980.

11. Klesges, R. Personal communication, 1985.
12. Rodin, J. Weight change following smoking cessation: The role of food intake and exercise. *Addict Behav*, in press.
13. Rodgers, R. J. Effects of nicotine, mecamylamine and hexamethonium on shock-induced fighting, pain reactivity, and locomotor behavior in rats. *Psychopharmacology (Berlin)* **66:** 93–98, 1979.
14. Schechter, M. P. and P. G. Cooke. Nicotine-induced weight loss in rats without an effect on appetite. *Eur J Pharmacol* **38:** 63–69, 1976.
15. Schlatter, J. and K. Bättig. Differential effects of nicotine and amphetamine on locomotor activity and maze exploration in two rat lines. *Psychopharmacology (Berlin)* **64:** 155–161, 1979.
16. Schlatter, J. and K. Bättig. The adrenergic role in the manifestation of nicotine effects on maze ambulation in Roman High- and Roman Low-avoidance rats. *Br J Addict* **76:** 199–209, 1981.
17. Theeuwes, F. and S. I. Yum. Principles of the design and operation of generic osmotic pumps for the delivery of semisolid or liquid drug formulations. *Ann Biomed Eng* **4:** 343–353, 1977.