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Effects of nicotine on body weight and food consumption in rats

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Abstract. Recent human and animal studies have found that cigarette smoking or nicotine administration is accompanied by decreased consumption of sweet-tasting, high caloric foods. Cessation of smoking or nicotine is accompanied by increased consumption of these foods. Changes in consumption of these specific foods may partially account for the inverse relationship between smoking or nicotine and body weight. The present research was designed to determine whether consumption of nonsweet food is affected by nicotine and whether continuous access to only nonsweet foods attenuates the body weight changes associated with nicotine administration and cessation of nicotine administration. Alzet miniosmotic pumps were implanted SC to administer saline or three different concentrations of nicotine to male Sprague-Dawley albino rats for 2–3 weeks. Two studies on a total of 80 rats found an inverse dose-response relationship between nicotine administration and body weight without changes in bland food or water consumption. After cessation of nicotine administration, there were no differences in food consumption or body weight changes between groups. The effects of nicotine on body weight, both during and after drug administration, were attenuated in comparison to the results of studies that provided sweet-tasting foods.

Key words: Nicotine – Body weight – Food consumption – Water consumption

It is well established that cigarette smokers weigh less than comparably aged nonsmokers, and that smokers who quit smoking gain weight (Grunberg 1982; Wack and Rodin 1982). Although this relationship between cigarette smoking and body weight is clear, the reasons for it are not. Some writers believe that smokers eat less food than do nonsmokers and exsmokers (e.g., Birch 1975), others argue that smoking increases the metabolic rate and thereby alters body weight (e.g., Comroe 1960), and still others report that exsmokers consume increased amounts of sweet-tasting, high caloric foods (e.g., Myrsten et al. 1977). However, few empirical studies have carefully examined these hypotheses and even fewer studies have pitted one explanation against another.

A recent series of human and animal studies examined the two behavioral explanations – changes in general food consumption and changes in consumption of specific foods. In the context of a taste-judgment study, cigarette smokers who were allowed to smoke ate significantly less sweet-tasting foods but similar amounts of bland and salty foods as did nonsmokers and smokers who were not allowed to smoke. An accompanying rat study found an inverse dose-response relationship between nicotine administration and body weight. Similar to the results of the human study, rats receiving nicotine consumed significantly less sweet-tasting foods but identical amounts of laboratory chow as control animals receiving saline. After cessation of nicotine administration, the body weights of animals that had received nicotine increased at a substantially greater rate compared to controls. In addition, animals in nicotine "withdrawal" increased their consumption of sweet foods significantly compared to controls. There were no diffferences between groups in consumption of bland laboratory chow. The changes in consumption of sweet foods throughout this experiment accounted for significant changes in caloric intake that contributed to the changes in body weight (Grunberg 1982). These findings are corroborated by epidemiologic data indicating a significant negative correlation between cigarette and sugar consumption in the United States between 1964 and 1977 (Grunberg and Morse, in press). Taken together, these studies strongly suggest that changes in body weight with cigarette smoking and abstinence from smoking may be explained by changes in specific food consumption. General food consumption does not seem to be affected by cigarette smoking or nicotine administration.

These studies suggest that if exsmokers are not allowed access to sweet-tasting foods, they will not increase their food consumption and therefore will not gain much weight. We write "much weight" instead of "any more weight than controls" because we have not examined the effects of nicotine administration or cessation of nicotine administration on energy utilization. Therefore, even if restriction to nonsweet foods results in no changes in caloric intake between experimental and control groups, changes in caloric utilization could occur and could thereby result in changes in body weight. Unfortunately, the animal study cited above does not definitely rule out an effect of nicotine on general food consumption because bland food was never presented alone. Glucose solutions and bland food were both continuously available to animals. It remains possible that consumption of nonsweet foods might be affected by nicotine administration if these were the only available foods. Similarly, the human laboratory study and human epidemiological study show that specific food consumption is affected by cigarette smoking, but they do not rule out the possibility that restriction to nonsweet foods might show

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changes in consumption of these foods in the absence of sweet foods.

The present research was designed to determine whether consumption of nonsweet food is affected by nicotine when no other foods are available, and whether continuous access to only nonsweet foods attenuates the body weight changes associated with nicotine administration and cessation of nicotine administration. Based on previous work, we expected no effects of nicotine administration or cessation on food consumption and an attenuation of nicotine-related body weight changes.

Study 1

Materials and methods

Subjects. Subjects were 32 male Sprague-Dawley albino rats obtained from Charles River, Inc. (Wilburn, MA, USA). The subjects were approximately 6 months old and weighed about 400 g at the beginning of the study. Animals were individually housed in standard polypropylene shoebox cages ($35.6 \times 15.2 \times 20.3$ cm) fitted with metal grill lids and elevated metal floors above absorbent wood Pine-Dri shavings. All cages were placed on a four-shelved double-sided rack in a room with overhead fluorescent lighting. The room was kept at approximately 22° C and 50% relative humidity with a 12-h light-dark cycle. Rat chow (Charles River RMH 3200 meal) and tap water were continuously available. The food was provided in stainless steel cups (6.4 or 8.9 cm in diameter) fitted with lids that had a hole in the middle. Water was provided in plastic bottles fitted with stainless-steel drinking tubes in rubber stoppers. Water bottles lay on the wire lids of the cages with spouts protruding into the cages. Cages were changed twice a week and food cups were washed once a week.

Drug administration. Alzet miniosmotic pumps (Model 1702) were implanted SC to deliver nicotine or saline at a constant rate of 0.5 µl/h for 12 ±1 days (Theeuwes and Yum 1977). Physiological saline was used to make the nicotine solutions (made from nicotine dihydrochloride, J. T. Baker Chemical Co., Phillipsburg, NJ, USA) and was the control solution. Drug dosages were based on previous research (Grunberg 1982; Schechter and Cook 1976; Becker and King 1966). Miniosmotic pumps were used because animals may receive drug each day without the trauma of daily injections, and because the slow infusion rate establishes and maintains fairly constant concentrations of drug for many days (in contrast to bolus injections of toxic drug, which result in tremendous differences in drug concentrations between injections). In addition, this paradigm for administering nicotine has produced animal results comparable to studies of human smokers (cf. Grunberg 1980, 1982).

Procedure. After an initial gentling period, daily measurements were made of body weight, food consumption, and water consumption using a Sartorius 1264 MP electronic scale with model 7042 programmer. To ensure accurate body weight measurements, the mean of ten weighings taken once a second over a 10-s period was recorded. Food cups and water bottles were weighed once upon removal from each cage and once after they were refilled as necessary before returning them to the cages. This procedure lasted 2 weeks ("before drug" administration period).

Next, animals were anesthetized with methoxyfluorane and Alzet miniosmotic pumps were implanted SC in each rat between the head and back. Eight rats each received saline (control group), 4 mg, 8 mg, or 12 mg nicotine (computed as base) per kilogram body weight per day. Body weight, food consumption, and water consumption were measured and recorded daily. Experimenters who made the daily measurements were blind to the experimental conditions. This phase of the study lasted roughly 2 weeks ("during drug" administration period).

At the end of the drug administration period, half of the animals from each group were killed for use in other investigations separate from the present research. Daily measurements of body weight, food consumption, and water consumption were made for the remaining animals for 2 weeks after cessation of nicotine administration.

Results

The miniosmotic pumps require a number of days to establish constant drug concentrations, and the models used may be empty after 12 days. This information is based on specifications and technical reports provided by Alza Corporation, the manufacturer of the mini-osmotic pumps. Therefore, the data gathered on the days immediately after surgery were not used in the analyses. Based on the specifications provided by the manufacturer, the "during drug" period (for the purpose of data analysis) included all data for the 6 days during which the pumps definitely were delivering constant levels of drug. The "before drug" period included all data for the 6 days preceding surgery. The "after drug" period included all data for the first 6 days after the pumps definitely were empty. Six-day periods were chosen to ensure that the values being compared were stable. Using these 6-day values, difference scores were computed for each animal for the changes in body weight, food consumption, and water consumption 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 between groups. Significance levels were determined using two-tailed values. In addition to these analyses of 6-day periods, the data were summarized and analyzed as single days from each period, 3-day means from each period, and 9-, 6-, and 9-day means before, during, and after drug administration, respectively. These other analyses were performed because they had also been included in Grunberg (1980, 1982) who developed the methodological paradigm used in these studies. Because all analyses revealed the same results, only the 6-day means are presented.

Body weight. Figure 1 presents the mean body weight for each experimental group before, during, and after drug administration. The body weights of the four groups of animals did not differ during the predrug period. During the drug administration period there was an inverse dose-response relationship betweeen the concentration of nicotine administered and body weight. Comparing the changes in body weight from before-drug to during-drug administration, the saline group gained significantly more weight than did all three nicotine groups (interaction $t = 5.58$, 4.87, 2.46 for 12 mg, 8 mg, 4 mg; $df = 14$; $P < 0.001$, 0.001, 0.05, respectively). In addition, the 4-mg group gained significantly more weight compared to the 8-mg and 12-mg groups (interaction $t = 2.81$, 3.96; $df = 14$, $P < 0.05$, 0.01, respectively). The 8-mg group gained somewhat more weight than the 12-mg group (interaction $t = 1.96$, $df = 14$,

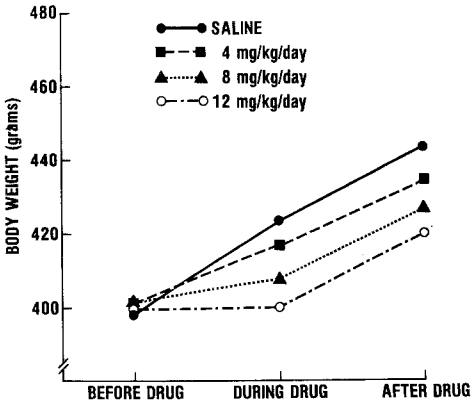

Fig. 1. Body weights averaged over 6-day periods before, during, and after drug administration (Study I)

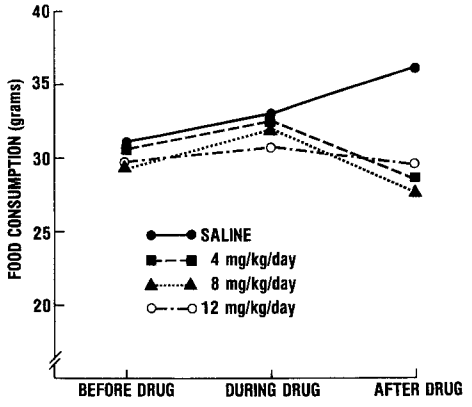

Fig. 2. Average consumption of laboratory chow during 6-day periods before, during, and after drug administration (Study I)

$P < 0.10$). Although the body weights of all groups were virtually identical before drug administration, the high nicotine group weighed significantly less than the control group during drug administration ($t = 2.38$, $df = 14$, $P < 0.05$).

In contrast, all groups showed similar increases in body weight from during to after drug administration. That is, the parallel lines for all the groups indicate that the rate of growth after cessation of nicotine was virtually identical to the rate of growth of the control group that had received saline (all *P*s N.S. comparing each nicotine group to control and comparing nicotine groups to each other).

Food consumption. Figure 2 presents the mean food consumption for each experimental group before, during, and after drug administration. There were no differences between groups during any phase of the experiment (all *P*s N.S.). Further, there were no differences between groups in the changes in amount of chow eaten from before to during drug administration or from during to after drug administration (all *P*s N.S.). Although food consumption after cessation of drug administration may appear different between the saline and nicotine groups, the ranges of individual values overlap completely. In addition, the higher mean value for the saline and nicotine groups, the ranges of individual animal.

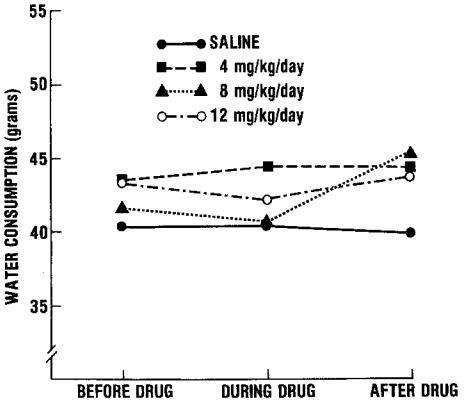

Fig. 3. Average water consumption during 6-day periods before, during, and after drug administration (Study I)

Water consumption. Figure 3 presents the mean water consumption for each experimental group for each phase of the study. As with food consumption, there were no differences between groups during any phase of the study and no differences in change scores in the amount of water consumed from one phase of the study to another (all *P*s N.S.).

Discussion

It is clear from this study that nicotine administration decreases normal gains in body weight. These changes in body weight cannot be explained by changes in general food consumption because there were no changes in consumption of bland laboratory chow or water. In addition, cessation of nicotine administration had no effect on body weight different from the normal body weight growth of animals that had received saline. After drug administration, rats that had received nicotine gained weight at the same rate as control animals.

These findings add two new pieces of information to previous research on the nicotine/body weight relationship. Specifically, the effects of nicotine administration on body weight (i.e., the *decrease* in body weight gains) in the present study were less than the effects in the earlier rat study, which allowed animals access to sweet-tasting high caloric glucose solutions (Grunberg 1982). That is to say, dose for dose the inverse relationship between nicotine and body weight was more striking in the previous study in which rats had access to glucose solutions. In addition, in that previous research on the nicotine/body weight relationship between nicotine administration and consumption of glucose solutions, which caused an inverse relationship between nicotine administration and caloric intake.

The second new piece of information from the present study is the finding that weight gains after drug administration for the nicotine and saline groups are similar when only bland laboratory chow is available. In contrast, when glucose solutions are provided, animals in "withdrawal" from nicotine eat significantly more glucose solutions than controls, consume significantly more calories than controls, and gain weight at a substantially faster rate than controls (Grunberg 1980, 1982).

Before generalizing from these data, we felt that a replication of these findings was important. Study II used a larger

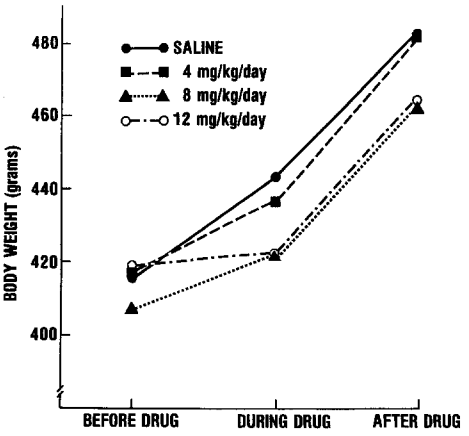

Fig. 4. Body weights averaged over 6-day periods before, during, and after drug administration (Study II)

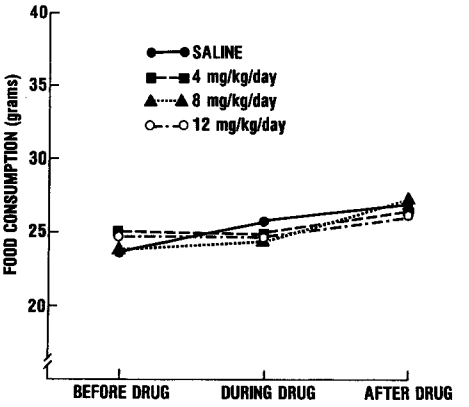

Fig. 5. Average consumption of laboratory chow during 6-day periods before, during, and after drug administration (Study II)

subject population and modified the duration of drug administration to make sure that the results were not confined to specific nicotine administration or withdrawal intervals.

Study II

Materials and methods

Subjects. The subjects were 48 male Sprague-Dawley albino rats. All other subject information is identical to Study I.

Drug administration. Alzet miniosmotic pumps (Model 2002) were used in this study. These pumps release their contents at a rate of roughly 0.5 µl/h for 19 ± 2 days. All other drug administration information is identical to Study I.

Procedure. The procedure was similar to Study I except that Model 2002 pumps delivered their contents for 1 week longer than the 1702 pumps used in Study I.

Results and discussion

As in Study I, for purposes of data analysis the "before drug" period included the 6 days preceding implantation of miniosmotic pumps. The "during drug" period included data from the 6 days during which the pumps were definitely delivering constant levels of drug that were comparable to the "during drug" period of Study I. The "after drug" period included all data for the first 6 days after the pumps definitely were empty. Because the pumps used in this study lasted 1 week longer than the pumps used in Study I, the "after drug" period is different from Study I; that is, the "after drug" period of Study II began roughly 3 weeks after implantation of pumps (compared to 2 weeks after implantation of pumps in Study I). Data are presented in this form to be directly comparable to Study I. Besides the additional analyses described in the Results section for Study I, data from the "extra" week of Study II also were examined. All analyses revealed the same results. Therefore, only the 6-day means are presented.

Body weight. Figure 4 presents the mean body weight for each experimental group before, during, and after drug administration. The body weights of the four groups of animals did not differ during the predrug period. During the drug-administration period there was an inverse dose-response relationship between the concentration of nicotine administered and body weight. Comparing the changes in body weight from before drug to during drug administration, the saline group gained significantly more weight than did the 12-mg and 8-mg nicotine groups (interaction $t = 7.31, 2.47$; $df = 22$; $P < 0.001, 0.05$, respectively) and slightly more weight than did the 4-mg nicotine group (interaction $t = 1.25$, $df = 22$, N.S.). In addition, the 4-mg group gained significantly more weight compared to the 12-mg group (interaction $t = 2.91$, $df = 22$, $P < 0.01$). The 4-mg group gained more weight than did the 8-mg group (interaction $t = 1.95$, $df = 22$, $P < 0.10$) and the 8-mg group gained more weight than did the 12-mg group (interaction $t = 1.95$, $df = 22$, $P < 0.10$).

In contrast, all groups showed similar increases in body weight from during to after drug administration (all *P*s N.S.). As in Study I, the rate of growth after cessation of nicotine was virtually identical to the rate of growth after cessation of saline (all *P*s N.S.).

Food consumption. Figure 5 presents the mean food consumption for each experimental group before, during, and after drug administration. As in Study I, there were no differences between groups during any phase of the experiment (all *P*s N.S.). Also, there were no differences between groups in the changes in amount of chow eaten from before to during drug administration or from during to after drug administration (all *P*s N.S.).

Water consumption. Figure 6 presents the mean water consumption for each experimental group for each phase of the study. Comparing the groups, mean consumption of water was within 8 g (equivalent to 8 ml) throughout the study. The saline group drank significantly less water than did the 12-mg group before drug administration ($t = 2.94$, $df = 21$, $P < 0.01$), but no other comparisons of water consumption were significantly different before, during, or after drug administration. A comparison of changes in water consumption from before to during drug administration revealed only one significant difference: the saline group increased water consumption from the before to during

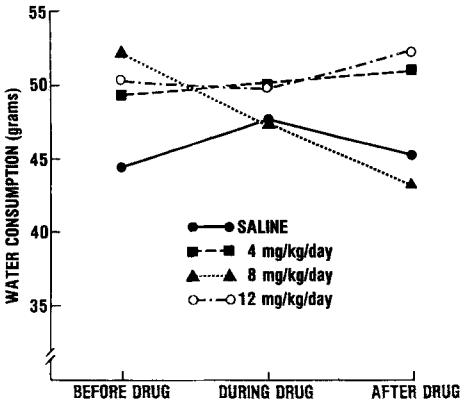

Fig. 6. Average water consumption during 6-day periods before, during, and after drug administration (Study II)

drug periods significantly more than did the 8-mg group ($t = 3.11$, $df = 21$, $P < 0.01$). No other comparisons approached significance.

The results of this study replicate those of Study 1. Nicotine administration decreases normal gains in body weight. These effects on body weight occur without changes in consumption of bland food or water. When only bland food and water are available, postnicotine body weight changes are identical to normal weight gains of animals never exposed to nicotine. This study administered nicotine for a longer period of time than in Study I, yet the results were virtually identical. The one difference from the body weight, food consumption, and water consumption results of Study I was in the water-consumption data. This difference could not account for the effects of nicotine on body weight because only the middle nicotine group (8 mg/kg per day) changed water consumption compared to the control group; the low and high nicotine groups did not differ from controls on this variable.

General discussion

The present research was designed to answer specific questions about the effects of nicotine administration and cessation of nicotine administration on body weight and food consumption. As hypothesized, nicotine had no effect on consumption of bland food even when this was the only food available. This finding is consistent with previous reports that nicotine alters consumption of specific foods but not of all foods (Grunberg 1982; Grunberg and Morse, in press). Studies that have concluded that nicotine or tobacco use affects general appetite have examined food consumption by animals for a short period of time immediately after an injection of nicotine – a toxic chemical (e.g., Münster and Bättig 1975); have relied on food consumption self-reports of humans (e.g., Gaudet and Hugli 1969; Lincoln 1969) or have failed to examine whether specific foods account for any changes in food consumption by humans (e.g., Pangborn and Trabue 1973). A more recent rat study, which concluded that nicotine affects food consumption (McNair and Bryson 1983), gave three bolus injections of nicotine each day, did not include important control groups (i.e., animals receiving only saline throughout the study), and reported significant effects for less than half of the groups in the study. The present findings corroborate the conclusion that nicotine does not affect general food consumption and are consistent with the argument that changes in body weight with cigarette smoking and cessation of smoking result partially from changes in consumption of specific foods and not from changes in general appetite or food consumption.

Also, as expected, the body-weight changes that accompany nicotine administration and cessation of nicotine administration were attenuated when only bland food was available (compared to the weight changes when bland food plus glucose solutions were available in Grunberg 1982). This attenuation was particularly pronounced after cessation of nicotine. In fact, the rate of growth of all nicotine groups was identical to the rate of growth of the control animals. This finding complements the results reported by Grunberg (1982, 1980) in which the rate of growth after cessation of nicotine was greater than controls in a dose-response fashion when glucose solutions also were available. The decreases in body weight growth during nicotine administration were somewhat less in the present studies than in Grunberg (1982) when glucose solutions also were available. Because the dosages of nicotine used in Grunberg (1980, 1982) (2.5, 5.0, 10.0 mg/kg per day) were somewhat different from the dosages used in the present studies, no statistical values from the previous work are reported here for direct comparison. Instead, qualitative statements of the relative differences are made based on comparisons of all analyses of the data sets. Detailed statistical information of the earlier results are reported in Grunberg (1980, 1982).

This new observation, that weight gains after cessation of nicotine administration are identical to weight gains of control animals when only bland food is available, has practical implications. Possibly cigarette smokers can quit smoking and avoid weight gains by restricting the types of foods that they eat and not worry about how much they eat; the animals had continuous access to the laboratory chow and did not show unusual weight gains. Future studies should continue to investigate what foods or nutrients can be made available to exsmokers (or ex-nicotine-administered animals) continuously and not result in unusual weight gains. In addition, investigations of why consumption of only specific foods change with nicotine administration/cigarette smoking and cessation of nicotine/smoking should be conducted.

Another finding that appeared in Studies I and II was that nicotine administration can affect body weight without changing caloric intake. In both studies there was a dose-effect relationship between nicotine administration and body weight without changes in food consumption. Earlier studies using different techniques for nicotine administration also have reported this finding (e.g., Evans et al. 1967; Passey et al. 1961; Passey et al. 1959; Schechter and Cook 1976). Therefore, changes in energy intake *alone* cannot account for the decreases in body weight that accompany nicotine administration. Future studies should carefully examine factors that influence energy expenditure, including changes in physical activity and metabolism.

In summary, the results of both Studies I and II are clear: nicotine administration decreases gains in body weight, nicotine administration does *not* affect consumption of bland food, and cessation of nicotine results in gains in body weight similar to controls when only bland food is available. These findings may help to explain the changes in body weight that accompany tobacco use and abstinence

from habitual tobacco use. Further, these findings have implications for how to control the marked gains in body weight that plague many exsmokers.

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