SYSTEMIC NICOTINE ADMINISTRATION SUPPRESSES FOOD INTAKE VIA REDUCED MEAL SIZES IN BOTH MALE AND FEMALE RATS

Vladimír Bláha, Zhongjin Yang, Michael Mecpal, Jaroslav Chalí and Zdeněk Zadák

Department of Metabolic Care and Gerontology, Charles University, Faculty of Medicine and Teaching Hospital, Hradec Králové, Czech Republic; (Head: prof. MUDr. Z. Zadák, CSc.) Neuroscience Program, Surgical Metabolism and Nutrition Laboratory, Department of Surgery, University Hospital, SUNY Health Science Center, Syracuse, NY 13210, USA; (Head: prof. J. Parker, MD, PhD)

Summary: The appetite suppressing effect of tobacco products, via the main pharmacological agent nicotine, is a major reason for its usage both by woman and man. Food intake (FI) could be changed by altering either meal size (MZ) or meal number (MN), which are regulated dependently in a reciprocal manner. The present study investigated the effect of systemic nicotine administration on the rat feeding pattern. Because of gender differences in the effects of nicotine, both male and female rats were studied. Alzet miniosmotic pumps (Model 20101) and the automated rat eatometer were used to evaluate the feeding pattern of male and female Fischer 344 rats during seven days of systemic nicotine infusion (6mg/kg b.w. s.c.). The main findings are: 1) systemic nicotine infusion decreased food intake in both sexes; 2) the decreased food intake was due to significantly reduced meal sizes while meal numbers were not altered significantly in either male or females. 3) the cyclical pattern of vaginal smears, food intake, meal number and meal size of female rats was not affected by nicotine administration. We conclude that the feeding suppressive effect of nicotine, which is due to reduced meal sizes and thus satiation, is not sex-hormones related.

Key words: Nicotine; rats, Male and female; feeding pattern; Meal size, Meal number, Food intake; Miniosmotic pump

Introduction

The appetite suppressing effect of smoking, via its main pharmacological agent nicotine, is a major reason for its usage both by woman and man. Food intake (FI) could be changed by altering either meal size (MZ) or meal number (MN), which are regulated dependently in a reciprocal manner. The present study investigated the effect of systemic nicotine administration on the rat feeding pattern. Because of gender differences in the effects of nicotine, both male and female rats were studied. Alzet miniosmotic pumps (Model 20101) and the automated rat eatometer were used to evaluate the feeding pattern of male and female Fischer 344 rats during seven days of systemic nicotine infusion (6mg/kg b.w. s.c.). The main findings are: 1) systemic nicotine infusion decreased food intake in both sexes; 2) the decreased food intake was due to significantly reduced meal sizes while meal numbers were not altered significantly in either male or females. 3) the cyclical pattern of vaginal smears, food intake, meal number and meal size of female rats was not affected by nicotine administration. We conclude that the feeding suppressive effect of nicotine, which is due to reduced meal sizes and thus satiation, is not sex-hormones related.

Additionally, some sex differences in the effects of nicotine per se were reported in human studies of smoking behavior (13) and of sex-dependent metabolism and excretion of nicotine (2,3,28). Animal studies of food consumption during nicotine administration showed contrasting results, depending not only on the experimental conditions, dose of nicotine, age, but also on the sex (8,9,16,17,23,37). As has been recently reported, the female estrous cycle significantly affects meal number and meal size in a reciprocal fashion (14,32). The food intake and feeding pattern in the female rat is related to the fluctuations in the circulatory system (3). The appetite suppressing effect of nicotine in the female rat is related to the fluctuations in the circulatory system (3). The appetite suppressing effect of smoking, via its main pharmacological agent nicotine, is a major reason for its usage both by woman and man. Food intake (FI) could be changed by altering either meal size (MZ) or meal number (MN), which are regulated dependently in a reciprocal manner. The present study investigated the effect of systemic nicotine administration on the rat feeding pattern. Because of gender differences in the effects of nicotine, both male and female rats were studied. Alzet miniosmotic pumps (Model 20101) and the automated rat eatometer were used to evaluate the feeding pattern of male and female Fischer 344 rats during seven days of systemic nicotine infusion (6mg/kg b.w. s.c.). The main findings are: 1) systemic nicotine infusion decreased food intake in both sexes; 2) the decreased food intake was due to significantly reduced meal sizes while meal numbers were not altered significantly in either male or females. 3) the cyclical pattern of vaginal smears, food intake, meal number and meal size of female rats was not affected by nicotine administration. We conclude that the feeding suppressive effect of nicotine, which is due to reduced meal sizes and thus satiation, is not sex-hormones related.
nicotine acts on the rat feeding pattern to suppress appeti-
tive; (ii) to study gender differences, if any, whereby nicoti-
ne influences the feeding pattern in male and female rats; (iii) to see whether nicotine decreases FI by affecting post-
prandial satiety and hunger via decreasing MN, or by in-
roducing premature satiation thereby decreasing ME, or both.

Material and methods

Subjects
Adult male and female Fischer-344 rats (Taconic Farm Co., Germantown, NY; male weighing 250-270g; female
weighing 140-160g; 10 wks old) were housed in holding
cages for 1 wk after purchase to acclimatize them to the
constant study environmental conditions: 12 h light-dark
cycle (lights on at 0600), 26 ± 1°C room temperature, and
45% humidity. Tap water and standard rat chow (diet
5008, Ralston Purina, St. Louis, MO) were available ad li-
bitem.

After initial acclimation, rats were placed in individual
cages equipped with an automated computerized rat eater
cage (ACREM), previously described in detail (19).

Measurement of feeding pattern

Food intake and feeding-related indexes were measured
daily and expressed as grams per 24 h study period. The fol-
lowing indexes were measured: food intake (FI; g) =
amount of food consumed per study period; meal number
= total number of meals in each study period (MN); and
meal size (g/meal) = total amount of food consumed
per total meal number in each study period. Food intake
corresponded a series of bites. A bite was defined as an access
to the food dish that resulted in food consumption of 60 mg.
Consequently, a meal was defined as a bite or a series of bi-
tes preceded and followed by at least 5 min of feeding inac-
tivity (19,20).

Vaginal smears
Female rats, showing regular 5 days cycling, were used in
the study. Female estrous cycles were monitored by dia-
l vaginal smears, done between 0800 and 1000 AM. After
being stained, smears were observed under light microsco-
y and the phase of the estrous cycle was determined. Briefly,
estrous phase was identified by the presence of the presence of polymorphonuclear leukocytes, nuclea-
ted cells and a few cornified epithelial cells present together
with stringy mucus, and on late proestrus only with nucle-
ated cells present; and estrous phase was identified when
cornified epithelial cells were only present, except in the
very early stages when a few irregularly shaped nucleated
cells may also be seen (35).

Nicotine administration

Alzet mini-osmotic pumps (Model 2001) were implant-
ted subcutaneously to deliver nicotine solutions or saline
at a constant rate of 1 µl/h for 7 days. Physiological saline
was used to prepare the nicotine solutions and was the
control solution. Animals received 6 mg of nicotine [(+]-
Nicotine Hydrogen Tartrate Salt, Sigma, St. Louis, MO) per
kg body weight per day (nicotine group) or saline (con-
trol group).

Experimental Design

After an initial acclimatization period, daily measure-
ments of food intake and feeding patterns were done using
the ACREM (19). Body weights were recorded daily.

The rats were randomly assigned to the four experi-
mental groups: controls infused with saline (male control,
n=4; female control, n=8) or nicotine infused rats (male ni-
cotine, n=5; female nicotine, n=8). Because of cycling in fe-
male, control data were collected from Day -6 to Day -1.

On Day 0, the rats had Alzet mini-osmotic pumps im-
planted under Fentanyl inhalation anesthesia. Each of
the female rat was operated upon at the day of metestrous,
to synchronize its estrus-cycle dependent food intake,
meal number and meal size. The skin in the operation area
was shaved and prepared with Povidone-Iodine 10% (Betadine®). Mini-osmotic pumps were placed subcutane-
ously in the nape of the neck by making a small incision
(roughly 1 cm), placing the pump, and closing the incisi-
on with 9 mm wound clips. Food intake, feeding patterns
and body weights were recorded for the following seven
days from mini-osmotic pumps insertion (Day 1 to Day 7).

On Day 8, the minipumps were removed under light
anesthesia (similar procedure to pump implantation) and
the data were collected for another period after cessation
of nicotine or saline administration (Day 9 to Day 14).

Experimental protocol has been approved by local
Ethical Committee.

Statistical Analysis

Because infusions in females were all started on a parti-
cular day of their 5-days estrous cycle (metestrous - see abo-
ve), the data are expressed as related to cycle-synchronized
data. To describe the data from the period of nicotine infusi-
on (Day 1 to Day 7), means ± SE were calculated for body
weight, food intake, meal number and meal size. Furth-
more, the means were expressed as the percentage of
control data (Table 1).

The data in female rats are presented per complete four
estrus cycles (Day 6 to Day 14), to demonstrate their par-
ticular cyclical feeding pattern, while the data in naturally
non-cycling males are shown from Day 1 to Day 11.

All data are expressed as mean ± SE. The twotailed
Student’s t test was used to compare control vs. nicotine
rats.

Table 1: Body weight, food intake, meal number and meal size during nicotine administration. Data are presented as
average ± SE for the total of 7 day period of nicotine infusion
(Day 1 to Day 7). The percentage change in nicotine trea-
ted animals, assuming the values in control rats being 100%.

|          | Male            | Female          |
|----------|-----------------|-----------------|
|          | Body weight     | Body weight     |
|          | (g)             | (g)             |
| Male     |                |                |
| Control  | 105 ± 2         | 170 ± 3         |
| Nicotine | 96 ± 4          | 192 ± 3         |
| Nicotine as a percentage of Control | 93% | 113% |
| Male     |                |                |
| Control  | 100 ± 4         | 170 ± 2         |
| Nicotine | 95 ± 4          | 188 ± 5         |
| Nicotine as a percentage of Control | 96% | 111% |

Results

Body weight

The body weights in male (284 ± 3 g in control vs. 283
± 3 g in nicotine group) and female (177 ± 2 g in control vs.
178 ± 2 g in nicotine group) did not differ significantly
before nicotine administration on Day 0. During the period
of nicotine administration there was an inverse relation-
ship between nicotine administration and body weight.

Both sexes gained significantly less body weight compared
to the controls. The daily average weight gain was 97 % of
control values in female and 96 % in male nicotine treated
rats (Table 1). After cessation of nicotine administration,
all rats increased the body weight gain. In spite of this, the
body weight in nicotine-administered vs. control rats was
still significantly lower on Day 11 (male rats: 297 ± 4 g in
control vs. 279 ± 7 g in nicotine group, p<0.05; female rats:
183 ± 2 g in control vs. 177 ± 2 g in nicotine group, p<0.05).

Food Intake

The average daily food intake during nicotine administ-
ration was 88 % of the control values in male and 87 % in fe-
male rats (Table 1). As shown in Figure 1, daily food intake
in the female rats fluctuated. Before nicotine administrati-
on, peak food intake was reached during the metestrous
and diestrous phases, while a nadir occurred during late pro-
estrous and estrous phases. Anesthesia and surgery on Day
0 decreased the food intake in both sexes. The female rats
did not lose their cyclical pattern during the period of ni-
cotine infusion from Day 1 to Day 8. The food-depressing ef-
flect of nicotine was significant on Days 1, 2, 3, 4, 6 and 8
in females and/or by Days 1 and 4 in males vs. controls.

The food intake in the male and female rats returned to nor-
mal by Day 9.

Fig. 1: Daily means ± SE of food intake in male (top) and female (bottom) rats before (Day -6 to Day -1), during (Day
1 to Day 7) and after cessation of nicotine administration (Day 9 to Day 14). The mini-osmotic pumps for nicotine de-
livery were surgically inserted on Day 0 and removed on Day 8. Statistical significance of the difference at p<0.05 ni-
cotine vs. control is indicated by asterisks above relevant
data points. The period of nicotine administration is indi-
cated by shadow bars. The numbers on X axis indicate the
days from mini-osmotic pumps insertion, and are used both
for male and female. The letters on X axis indicate the pha-
ses of the female estrus cycle: M, metestrous; D, diestrous;
P early or late proestrous; E, estrous.

Effect of Systemic Nicotine Infusion on Food Intake

Meal Number

In spite of the decreased food intake during nicotine ad-
ministration, the meal number did not change significantly
in either male and female rats, as compared vs. controls
(Figure 2). The average meal number during nicotine ad-
ministration was 104 % of the control values in male and
110 % in female rats (Table 1). In females, daily meal num-
ber fluctuated. Before nicotine administration, peak meal
number was reached during the late proestrus phase, and
this cyclical pattern was not changed during nicotine admi-

nicotine acts on the rat feeding pattern to suppress appeti-
tive; (ii) to study gender differences, if any, whereby nicoti-
ne influences the feeding pattern in male and female rats; (iii) to see whether nicotine decreases FI by affecting post-
prandial satiety and hunger via decreasing MN, or by in-
roducing premature satiation thereby decreasing MZ, or both.

Material and methods

Subjects

Adult male and female Fischer-344 rats (Taconic Farm Co., Germantown, NY; male weighing 250-270g; female weighing 140-160 g; 10 wks old) were housed in holding cages for 1 wk after purchase to acclimatize them to the constant study environmental conditions: 12 h light-dark cycle (lights on at 0600), 26 ± 1°C room temperature, and 45% humidity. Tap water and standard rat chow (diet 5008, Ralston Purina, St. Louis, MO) were available ad li-
bitum.

After initial acclimation, rats were placed in individual cages equipped with an automated computerized rat eater meter (ACREM), previously described in detail (19).

Measurement of feeding pattern

Food intake and feeding-related indexes were measured continuously and expressed per 24 h study period. The fol-
lowing indexes were measured: food intake (FI; g) = amount of food consumed per study period; meal number = total number of meals in each study period (MN); and meal size (MS; g/meal) = total amount of food consumed per total meal number in each study period. Food intake comprised a series of bites. A bite was defined as an access to the food dish that resulted in food consumption. Body weight gain. In spite of this, the food intake in the male and female rats returned to nor-
mal by Day 9.

Vaginal smears

Female rats, showing regular 5 days cycling, were used in the study. Female estrous cycles were monitored by dai-
ly vaginal smears, done between 0800 and 1000 AM. After being stained, smears were observed under light microsco-
py, and the phase of the estrous cycle was determined. Briefly, metestrous phase was identified by the presence of pavement cells only; diestrous phase was identified by the presence of mostly polymorphonuclear leukocytes present with little or no mucus; proestrous phase was identified by the presence of polymorphonuclear leukocytes, nulea-
ted cells and a few cornified epithelial cells present together with stringy mucus, and on late proestrus only with nucle-
ated cells present; and estrous phase was identified when cornified epithelial cells were only present, except in the very early stages when a few irregularly shaped nucleated cells may also be seen (35).

Nicotine administration

Azjet mini-osmotic pumps (Model 2001) were implant-
ted subcutaneously to deliver nicotine solutions or saline at a constant rate of 1 µl/h for 7 days. Physiological saline was used to prepare the nicotine solutions and was the control solution. Animals received 6mg of nicotine (-)-
Nicotine Hydrogen Tartrate Salt (Sigma, St. Louis, MO) per kg body weight per day (nicotine group) or saline (con-
trol group).

Experimental Design

After an initial acclimatization period, daily measurements of food intake and feeding patterns were done using the ACREM (19). Body weights were recorded daily.

The rats were randomly assigned to the four experi-
mental groups: controls infused with saline (male control, n=5; female control, n=5) or nicotine infused rats (male ni-
cotine, n=5; female nicotine, n=8). Because of cycling in fe-
males, control data were collected from Day -6 to Day -1.

On Day 0, the rats had Azjet mini-osmotic pumps im-
planted under Fentanyl inhalation anesthesia. Each of the female rat was operated upon at the day of metestrous,

Results

Table 1: Body weight, food intake, meal number and meal size during nicotine administration. Data are presented as average ± SE for the total of 7-day period of nicotine infusion (Day 1 to Day 7). The percentage change in nicotine trea-
ted animals, assuming the values in control rats being 100%, is also indicated.

|          | Body weight at start (g) | Food intake (g) | Meal number | Meal size (g) |
|----------|--------------------------|-----------------|-------------|--------------|
| Male     |                          |                 |             |              |
| Control  | 274.4±8.4                | 14.01±1.4       | 18.9±1.8    | 1.49±0.1     |
| Control  | 286.4±8.3                | 15.91±1.5       | 15.5±1.7    | 1.58±0.1     |
| Nicotine | 60.9±1.6                 | 0.16±0.0        | 0.16±0.0    | 0.06±0.0     |
| Nicotine | 74.6±2.1                 | 0.81±0.4        | 1.9±0.2     | 0.81±0.0     |
| Female   |                          |                 |             |              |
| Control  | 174.2±2.1                | 9.2±0.5         | 19.1±2.1    | 0.52±0.0     |
| Control  | 176.2±2.3                | 17.4±0.8        | 17.4±0.8    | 0.65±0.0     |
| Nicotine | 79.0±2.9                 | 0.16±0.0        | 0.16±0.0    | 0.06±0.0     |
| Nicotine | 79.0±2.9                 | 0.16±0.0        | 0.16±0.0    | 0.06±0.0     |

Table 1: Body weight, food intake, meal number and meal size during nicotine administration. Data are presented as average ± SE for the total of 7 period of nicotine infusion (Day 1 to Day 7). The percentage change in nicotine trea-
ted animals, assuming the values in control rats being 100%, is also indicated.

Daily meal (± SE) of body weight, food intake, meal number and meal size during nicotine or saline infusion (Day 1 - Day 7).

Food intake (g/day)

Because infusions in females were all started on aparti-
tion (Day 1 to Day 7). The percentage change in nicotine trea-
ted animals, assuming the values in control rats being 100%, is also indicated.

Daily meal (± SE) of body weight, food intake, meal number and meal size during nicotine or saline infusion (Day 1 - Day 7).

Food intake (g/day)

Because infusions in females were all started on aparti-
tion (Day 1 to Day 7). The percentage change in nicotine trea-
ted animals, assuming the values in control rats being 100%, is also indicated.

Daily meal (± SE) of body weight, food intake, meal number and meal size during nicotine or saline infusion (Day 1 - Day 7).

Food intake (g/day)

Because infusions in females were all started on aparti-
tion (Day 1 to Day 7). The percentage change in nicotine trea-
ted animals, assuming the values in control rats being 100%, is also indicated.

Daily meal (± SE) of body weight, food intake, meal number and meal size during nicotine or saline infusion (Day 1 - Day 7).

Food intake (g/day)

Because infusions in females were all started on aparti-
tion (Day 1 to Day 7). The percentage change in nicotine trea-
ted animals, assuming the values in control rats being 100%, is also indicated.

Daily meal (± SE) of body weight, food intake, meal number and meal size during nicotine or saline infusion (Day 1 - Day 7).

Food intake (g/day)

Because infusions in females were all started on aparti-
tion (Day 1 to Day 7). The percentage change in nicotine trea-
ted animals, assuming the values in control rats being 100%, is also indicated.

Daily meal (± SE) of body weight, food intake, meal number and meal size during nicotine or saline infusion (Day 1 - Day 7).

Food intake (g/day)

Because infusions in females were all started on aparti-
tion (Day 1 to Day 7). The percentage change in nicotine trea-
ted animals, assuming the values in control rats being 100%, is also indicated.

Daily meal (± SE) of body weight, food intake, meal number and meal size during nicotine or saline infusion (Day 1 - Day 7).

Food intake (g/day)

Because infusions in females were all started on aparti-
tion (Day 1 to Day 7). The percentage change in nicotine trea-
ted animals, assuming the values in control rats being 100%, is also indicated.
Fig. 2: Daily means ± SE of meal number in male (top) and female (bottom) rats before (Day -6 to Day -1), during (Day 1 to Day 7) and after cessation of nicotine administration (Day 9 to Day 14). The mini-osmotic pumps for nicotine delivery were surgically inserted on Day 0 and removed on Day 8. There was no statistical significance of the differences between means. The period of nicotine administration is indicated by shadow bars. The numbers on X axis indicate the days from mini-osmotic pumps insertion and are used both for male and female. The letters on X axis indicate the phase of the female estrous cycle: M, metestrous; D, diestrous; P, early or late proestrous; E, estrous.

Fig. 3: Daily means ± SE of meal size in male (top) and female (bottom) rats before (Day -6 to Day -1), during (Day 1 to Day 7) and after cessation of nicotine administration (Day 9 to Day 14). The mini-osmotic pumps for nicotine delivery were surgically inserted on Day 0 and removed on Day 8. Statistical significance of the difference at p<0.05 nicotine vs. control is indicated by asterisks above relevant data points. The period of nicotine administration is indicated by shadow bars. The numbers on X axis indicate the days from mini-osmotic pumps insertion, and are used both for male and female. The letters on X axis indicate the phase of the female estrous cycle: M, metestrous; D, diestrous; P, early or late proestrous; E, estrous.

Effect of Systemic Nicotine Infusion on Meal Number

Effect of Systemic Nicotine Infusion on Meal Size

The findings of this study indicate that nicotine administration decreases food intake via a selective suppression of meal size, and thus satiation. It has been suggested that satiation of feeding is the principal mechanism of food regulation and is primarily responsible for the adjustment of food intake to the extent of a nutritional deficit (6). However, our results did not address the mechanisms that may underlie the influence of nicotine on meal size. We propose both a peripheral and a central interaction: The first possibility is that nicotine affects the brain areas regulating food intake by a systemic nicotine and its agonists, through an interaction at nicotine receptors in brain, facilitate the release of many neurotransmitters, including acetylcholine, noradrenaline, dopamine and serotonin (27,29,36,42). Among the neurotransmitters, dopamine release in lateral hypothalamic area (LHA) was significantly increased by eating (40), and the degree of increase correlated with meal size (22). LHA-dopamine is a potent eating-inhibitory neurotransmitter (15), and consistent evidence indicates that LHA-dopamine controls meal size via the modulation of gut motility (26).

The second possibility is that systemic nicotine increases the brain serotonin release (27,36). Serotonin is a well-established eating-inhibitory neurotransmitter in medial hypotalamus (15). In vivo microdialysis studies report that setting up satiation during the meal is mediated by sharp secretion of serotonin in this hypothalamic area (24), thus probably regulating meal size.

The third aspect of the central interaction of systemic nicotine and meal size regulation comprises the influence of nicotine upon the lomotor activities connected with feeding. High doses of nicotine reduce spontaneous locomotor activity (11), and decrease food intake, the time spent in the feeding area, the time eating and grooming, but increase the time spent resting (16). Moreover, systemic nicotine influences other centrally regulated mechanisms, which might decrease food intake via reduced meal size, by decreasing the water ingestion (16,34), by acting as a substitute for oral behaviors (12), by altering taste perception (6) or by increasing the metabolic rate (33). In the periphery, the delayed gastrointestinal transit time or the hormonal changes of decreased feeding may account for the reduced meal size in our study. Therefore, we hypothesize that the central feeding suppressing effect of nicotine might be mediated via 1) increased hypothalamic dopaminergic and/or serotoninergic activity, 2) decrease in locomotor activity, 3) by acting as a substitute for oral behaviors or by altering taste perception, or 4) by increasing the metabolic rate (33).

Finally, nicotine influences peripheral bioavailability of nutrients. Such interaction could decrease meal size by promoting early satiation. Thus gastrointestinal secretion and motility has been reported to be delayed in individuals who smoke (30). Since the gastric emptying rate, as reflected by the number of pellets expelled per time, was reduced in rats given nicotine (23), this might affect nutrient absorption and thus feeding due to the reduced meal size. How nicotine enhances satiation via a suppression of meal size may include its effect on fat stores (37), or by a significant decrease in circulating insulin levels and increase in catecholamines and glucose (10). The resulting hyperglycemia and/or higher rate of fat catabolism could be associated with early satiation, and thereby with decrease of individual meal size.

Feeding in female rats is primarily influenced by sex-linked hormones (32), reflecting their cyclical pattern (5,14,38). Nicotine induced changes in feeding were suggested to be gender-related (8,9), and interaction of nicotine with sex steroids was proposed (18). Evidence from the present study does not support the hypothesis that the feeding suppressive effect of nicotine in the rat is mediated via female sex-linked hormones. The average decrease in daily food intake was similar in both sexes, as shown in Figures 1 and 3 and Table 1. The feeding suppressive effect of nicotine was due to the reduced meal size both in male and female rats. The daily vaginal smears in the females showed regular 5 day cycles, as did the cyclical feeding pattern. Thus, nicotine administration did not alter the female estrous cycle, which is regulated via female sex hormones.

The effect of nicotine on regulation of feeding behavior is a complex process that includes both central and peripheral mechanisms, although our study was not designed to elucidate the particular mechanisms. A selective effect of nicotine on satiation via decrease in meal size accounted for the depressed food intake in our study. Therefore, we hypothesize that the central feeding suppressive effect of nicotine might be mediated via 1) increased hypothalamic dopaminergic and/or serotoninergic activity, 2) decrease in locomotor activity, 3) by acting as a substitute for oral behaviors or by altering taste perception, or 4) by increasing the metabolic rate (33). In the periphery, the delayed gastrointestinal transit time or the hormonal changes of decreased feeding may account for the reduced meal size during nicotine administration. The particular role of hypothalamic feeding-related centers and their neurotransmitters in mediating the central feeding suppressive effect of nicotine is currently under investigation. Recognition of this suggests the possibility of applying appropriate control of drugs. Instead of searching for compounds that inhibit food intake, an alternative strategy would be to consider compounds that intensify the satiating power of food. In other words, drugs would not work to directly block intake but would work synergistically or additively with food itself to create an enhanced satiating efficacy.

Acknowledgment

We thank Darlene Thompson and William G. Hammond for their editorial assistance.

This work was supported in part by grant IGA MH CR 4548-3.

References

1. Audrain JE, Kleges RC, Kleges LM. Relationship between obesity and the metabolic effects of smoking in women. Health Psychol 1993;14:116-23.
2. Beckert AH, Gorrod JW, Jenner P. The effect of smoking on nicotine metabolism in vivo in man. J Pharm Pharmacol 1971;23:626-678.
The food-depressing effect of nicotine in both sexes was due to the significantly decreased meal size (Figure 3) on Days 1, 3, 4, 5 and 7 in females vs. controls and/or on Days 1 and 4 in males vs. controls. After cessation of nicotine administration, the meal size became normal. The average meal size during nicotine administration was 85% of the control values in male and 80% in female rats (Table 1). In females, daily meal size fluctuated. Before nicotine administration, a nadir was reached during the late proestrus phase, and this cyclical pattern was not changed during nicotine administration.

**Meal Size**

The findings of this study indicate that nicotine administration decreases food intake via a selective suppression of meal size, and thus satiation. It has been suggested that satiation of feeding is the principal mechanism of food regulation and is primarily responsible for the adjustment of food intake to the extent of a nutritional deficit (6). However, our results did not address the mechanisms that may underlie the influence of nicotine on meal size. We propose both a peripheral and a central interaction: The first possibility is that nicotine and its agonists, through an interaction at nicotine receptors in brain, facilitate the release of many neurotransmitters, including acetylcholine, norepinephrine, dopamine and serotonin (27,29,36,42). Among the neurotransmitters, dopamine release in lateral hypothalamic area (LHA) was significantly increased by eating (40) and the degree of increase correlated with meal size (22); LHA-dopamine is a potent eating-inhibitory neurotransmitter (15), and consistent evidence indicates that LHA-dopamine controls meal size via the modulation of gastric motility (26).

The second possibility is that systemic nicotine increases the brain serotonin release (27,36). Serotonin is an established eating-inhibitory neurotransmitter in medial hypothalamus (15). In vivo microdialysis studies report that setting up satiation during the meal is mediated by sharp serotonin release in this hypothalamic area (24), thus probably regulating meal size.

The third aspect of the central interaction of systemic nicotine and meal size regulation comprises the influence of nicotine upon spontaneous locomotor activities connected with feeding. High doses of nicotine reduce spontaneous locomotor activity (11), and decrease food intake, the time spent in eating the food, the food intake, and time rearing and grooming, but increase the time spent resting (16). Moreover, systemic nicotine influences other centrally regulated mechanisms, which might decrease food intake via reduced meal size, by decreasing the water ingestion (16,34), by acting as a substitute for oral behaviors (12), by altering taste perception (6) or by increasing the metabolic rate (33). In the periphery, the delayed gastrointestinal transit time or the hormonal changes of decreased growth hormone and resulting hyperglycemia or increased fat catabolism, might account for the reduced meal size during nicotine administration. The particular role of hypothalamic feeding-related centers and their neurotransmitters in mediating the central feeding suppressive effect of nicotine is currently under investigation. Recognition of this suggests the promise of approaching appetite control by drugs. Instead of searching for compounds that inhibit food intake, an alternative strategy would be to consider compounds that intensify the satiating power of food. In other words, drugs would not work to directly block intake but would work synergistically or additively with food itself to create an enhanced satiating efficiency.

**Discussion**

The effect of nicotine on regulation of feeding behavior is a complex process that includes both central and peripheral mechanisms, although our study was not designed to elucidate the particular mechanisms. A selective effect of nicotine on satiation via decrease in meal size accounted for the depressed food intake in our study. Therefore, we hypothesize that the central feeding suppressive effect of nicotine might be mediated via 1) increased hypothalamic dopaminergic and/or serotonergic activity, 2) decrease in motor activity, 3) by acting as a substitute for oral behaviors or by altering taste perception, or 4) by increasing the metabolic rate (33). In the periphery, the delayed gastrointestinal transit time or the hormonal changes of decreased growth hormone and resulting hyperglycemia or increased fat catabolism, might account for the reduced meal size during nicotine administration. The particular role of hypothalamic feeding-related centers and their neurotransmitters in mediating the central feeding suppressive effect of nicotine is currently under investigation. Recognition of this suggests the promise of approaching appetite control by drugs. Instead of searching for compounds that inhibit food intake, an alternative strategy would be to consider compounds that intensify the satiating power of food. In other words, drugs would not work to directly block intake but would work synergistically or additively with food itself to create an enhanced satiating efficiency.

**Acknowledgment**

We thank Darlene Thompson and William G. Hammond for their editorial assistance.

This work was supported in part by grant IGA MH CR 4548-E-3.

**References**

1. Auvrard JE, Klesges RC, Klesges LM. Relationship between obesity and the metabolic effects of smoking in women. Health Psychol 1995;14:116-23.
2. Beckett AH, Gorrod JW, Jenner P. The effect of smoking on nicotine metabolism in vivo in man. J Pharm Pharmacol 1971;23:626-675.
6. Collier G. The economics of hunger, thirst, satiety, and regulation. Ann N Y Acad Sci 1989;575:136-54.
7. Grunberg N. The effects of nicotine and cigarette smoking on food consumption and taste preferences. Addict Behav 1992;7:317-31.
8. Grunberg NE, Bowen DJ, Morse DE. Effects of nicotine on body weight and food consumption in rats. Psychopharmacology 1984;83:93-8.
9. Grunberg NE, Bowen DJ, Windsers SE. Effects of nicot ine on body weight and food consumption in female rats. Psychopharmacology 1986;90:101-5.
10. Grunberg NE, Poop KA, Bowen DJ, Nespor SM, Windsers SE, Eury SE. Effects of chronic nicotine administra tion on insulin, glucose, epinephrine, and norepinephrine. Life Sci 1988;42:161-70.
11. Grunwald F., Schrock H., Theilen H. Biber A., Kuschnisky W. Local cerebral glucose utilization of the awake rat during chronic administration of nicotine. Brain Res 1988;456:350-6.
12. Jacobs MA., Knapp PIH., Anderson LS., Karsin N., Meissner R., Richman SJ. Relationship of oral frustration factors with heavy cigarette smoking in male college students. J Nerv Ment Dis 1965;141:161-71.
13. Kozlowski LT, Director J, Harford MA. Tobacco dependence; restraint and time to the first cigarette of the day. Addict Behav 1981;6:307-12.
14. Laviano A, Meguid MM, Gleason JR, Yang ZJ. Reinype T. Comparison of longterm feeding pattern between male and female Fischer 344 rats: influence of estrus cycle. Am J Physiol 1991;260:R413-R419.
15. Leibowitz SF. Brain monoamines and peptides: role in the control of eating behavior. Feder Proc 1986;45:1396-1403.
16. Levin ED, Ellison GD, Salem C, Jarvik M, Gritz E. Behavioral effects of acute hexamethonium in rats chronically intoxicated with nicotine. Physiol Behav 1988;44:355-9.
17. Levin ED, Briggs SJ, Christopher NC, Rose JE. Sertraline attenuates hyperphagia in rats following nicotine withdrawal. Pharmacol Biochem Behav 1993;44:31-6.
18. McNair E, Brysson R. Effects of nicotine on weight change and food consumption in rats. Pharmacol Biochem Behav 1983;18:341-4.
19. Meguid MM, Kawashima Y, Campos ACL et al. Automated computerized rat eater meter: description and application. Physiol Behav 1990;48:759-63.
20. Meguid MM, Chen TV, Yang ZJ, Campos ACL, Hitch DC, Gleason JR. Effects of continuous graded total paren- teral nutrition on feeding indexes and metabolic concomit ants in rats. Am J Physiol 1991;260:E126-E140.
21. Meguid MM, Gleason JR, Yang ZJ. Orbitofrontal bulbecto my in rats modulates feeding pattern but not total food intake. Physiol Behav 1993;54:471-9.
22. Meguid MM, wed ZJ, Kokosi M. Eating induced rise in LHA dopamine correlates with meal size in normal and bulbectomized rats. Brain Res Bull 1995;36:487-90.
23. Minnis LCH, Ferrer JT, Wanyun Z, Haley NJ. Nicotine administration to rats: methodological considerations. Life Sci 1987;17:1699-1708.
24. Orosco M, Niculides S. Spontaneous feeding-related monoamine changes in the rostromedial hypothalamus revealed by microdialysis. Pharmacol Behav 1992;52:1015-9.
25. Qiu BS, Cho CH, Ogil CW. The influence of chronic nic otine on stress-induced gastric ulceration and emptying rate in rats. Expereientia 1992;48:389-91.
26. Ralph TL, Sawchenko PE. Differential effects of lateral and ventromedial hypothalamic lesions on gastrointestinal transit in the rat. Pharmacol Behav 1978;3:11-4.
27. Ribetino EB, Bittker RL, Bogdanov M, Wurtman RJ. Effect of systemic nicotine on serotonin release in rat brain. Brain Res 1993;621:311-8.
28. Rosecrans J. A. Brain area nicotine levels in male and female rats with different levels of spontaneous activity. Neuropharmacology 1972;11:863-70.
29. Rowell PP, Winkler DL. Nicotinic stimulation of [1H]acetylcholine release from mouse cerebral cortical synap tosomes. J Neurochem 1984;43:159-8.
30. Scott AM, Franq JEC, Franq GME, Nolan JM, Jones MP. Cigarette smoking and nicotine delay postprandial mouth-cecum transit time. Digest Dis Sci 1992;37:1544-7.
31. Stolerman IP, Mirza NR, Shoaib M. Nicotine psychopharmacology: addiction, cognition and neuroadaptation. Med Res Rev 1995;1:47-72.
32. Wace GN, Schneider JI. Metabolic fuels and reproduction in female mammals. Neurosci Biobehav Rev 1992;16:233-72.
33. Wack JT, Rodin JR. Smoking and its effects on body weight and the systems of caloric regulation. Am J Clin Nutr 1982;35:366-80.
34. Wager-Stirling SA, Levine AS, Morley JE, Hoidal JR, Niewoehner DE. Effects of cigarette smoke and nicotine on feeding and energy. Physiol Behav 1984;32:389-95.
35. Waynforth HG, Flecknall PA. Reproducitive parameters. In: Harcourt, Brace: Jovanovich, eds. Experimental and Surgical Technique in the Rat. New York: Academic Press; 1992.
36. Westfall PJ, Grant H, Perry H. Release of dopamine and 5-hydroxytryptamine from rat striatal slices following activation of nicotinic cholinergic receptors. Gen Pharmacol 1983;14:321-5.
37. Windsers SE, Grunberg NE. Effects of nicotine on body weight, food consumption and body composition in male rats. Life Sci 1990;40:1523-30.
rats. Life Sci 1990;46:1523-30.
20.Meguid MM, Chen T-Y, Yang Z-J, Campos ACL, Hitch DC, Gleason JR. Effects of continuous graded total paren-teral nutrition on feeding indexes and metabolic concomi-
tants in rats. Am J Physiol 1991;260:E126-E140.
21.Meguid MM, Gleason JR, Yang Z-J. Olfactory bulbecto-
my in rats modulates feeding pattern but not total food int-
ake. Physiol Behav 1993;54:471-9.
22.Meguid MM, Yang Z-J, Koseki M. Eating induced rise in LHA dopamine correlates with meal size in normal and
bullectomized rats. Brain Res Bull 1995;36:487-90.
23.Murin LCH, Ferrer JT, Wanyun Z, Halye NJ. Nicotine administration to rats: methodological considerations. Life-
scie 1987;17:1699-1708.
24.Orosco M, Nicolaidas S. Spontaneous feeding-related monoaminoergic changes in the rostromedial hypothalamus
revealed by microdialysis. Physiol Behav 1992;52:1015-9.
25.Qiu BS, Choh CH, Ogle CW. The influence of chronic ni-
cotine on stress-induced gastric ulceration and emptying
rate in rats. Experiemta 1992;48:389-91.
26.Ralph TL, Sawchenko PE. Differential effects of lateral
and ventromedial hypothalamic lesions on gastrointestinal
transit in the rat. Physiol Behav 1978;3:11-4.
27.Ribeiro EB, Bettker RL, Bobdanov M, Wurtman RJ. Ef-
fect of systemic nicotine on serotonin release in rat brain.
Brain Res 1993;621:311-8.
28.Rosecrans J. A. Brain area nicotine levels in male and fe-
male rats with different levels of spontaneous activity.
Neuropsychopharmacology 1972:11:86-7.
29.Rowell PP, Winkler DL. Nicotinic stimulation of
rate in rats. Experientia 1992;48:389-91.
30.Scott AM, Fracp JEK, Fracp GME, Nolan JM, Jones
MP. Cigarette smoking and nicotine delay postprandial
mouth-cecum transit time. Digest Dis Sci 1992;37:1544-7.
31.Stolerman IP, Misra NR, Shoaib M. Nicotine psychop-
harmacology: addiction, cognition and neuroadap-
tion. Med Res Rev 1995;1:47-72.
32.Wade GN, Schneider J. Metabolic fuels and reproduc-
tion in female mammals. Neurosci Biobehav Rev 1992;16:235-72.
33.Wack JF, Rodin JR. Smoking and its effects on body
weight and the systems of caloric regulation. Am J Clin Nutr
1982;35:366-80.
34.Wagner-Strat SA, Levine AS, Morley JE, Hoidal JR, Niewoehner DE. Effects of cigarette smoke and nicotine on
feeding and energy. Physiol Behav 1984;32:389-95.
35.Waynforth HG, Flecknell PA. Reproducive parameters.
In: Harcout; Brace; Jovanovich, eds. Experimental and
Surgical Technique in the Rat. New York: Academic Press;
1992.
36.Westfall PJ, Grant H, Perry H. Release of dopamine and
5-hydroxytryptamine from rat striatal slices following acti-
vation of nicotinic cholinergic receptors. Gen Pharmacol
1983:14:321-5.
37.Winders SE, Grunberg NE. Effects of nicotine on body
weight, food consumption and body composition in male
rats. Life Sci 1990;46:1523-30.
38.Wingkar KC. Alterations in feeding and sexual behavior
during reproductive cycle in female rats. Indian J Physiol
Pharmacol 1992;36:178-6.
39.Yang ZJ, Meguid MM. LHA dopaminergic activity in
obese and lean Zucker rats. Neuropeor 1993:8:1191-4.
40.Yang Z.J, Meguid MM. Nicotine-induced release of
noradrenaline from hypothalamic synaptosomes. Brain
Res 1980;182:361-8.

Submitted July 1998.
Accepted October 1998.

MUDr. Vladimir Bláha, CSc.,
Dept. of Metabolic Care and Gerontology,
Charles University, Faculty of Medicine
and Teaching Hospital,
500 05 Hradec Králové,
Czech Republic.