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# Infusion of Nicotine Into the LHA Enhances Dopamine And 5-HT Release and Suppresses Food Intake

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YANG, Z.-J., V. BLAHA, M. M. MEGUID, A. OLER AND G. MIYATA. *Infusion of nicotine into the LHA enhances dopamine and 5-HT release and suppresses food intake.* PHARMACOL BIOCHEM BEHAV **64**(1) 155–159, 1999.— Nicotine administration induces hypophagia. Because of the involvement of hypothalamic neurotransmitters in food intake control, we hypothesized that increased activity of the lateral hypothalamic dopamine (LHA-DA) and/or serotonin (LHA-5-HT) may be responsible for nicotine-induced hypophagia. Either 4 mM nicotine or vehicle was administered via reverse microdialysis technique into the LHA of overnight food-deprived rats for 60 min; then food was provided for 40 min. The LHA-DA, 5-HT and their intermediate metabolites, DOPAC and 5-HIAA, were continuously measured during 20-min intervals before, during, and after nicotine administration. Continuous nicotine administration for 60 min increased LHA-DA and DOPAC concentrations during the first 40 min, and induced a long-lasting increase in LHA-5-HT release, until 120 min after the start nicotine administration, even when nicotine administration was stopped. The food intake during the 40-min refeeding period was significantly lower when rats received nicotine. Eating induced a significant and short-lasting increase in the LHA-DA and a long-lasting increase in the LHA-5-HT. These findings indicate that nicotine enhances dopaminergic and serotonergic activity in the LHA, and that the enhanced LHA-5-HT activity may contribute to nicotine-induced hypophagia. © 1999 Elsevier Science Inc.

Microdialysis Lateral hypothalamic area Nicotine Dopamine Serotonin Hypophagia Food intake

DESPITE the fact that most people are aware of the health risks associated with using tobacco products, approximately one-fourth of adults use tobacco products (2). Obviously, there must be some compelling reasons for people to use tobacco products. One frequently cited reason is the belief that the tobacco products can suppress appetite and control body weight gain. Epidemiological studies have suggested that smokers weigh consistently less than persons who have never smoked. There are also studies documenting weigh gain after the cessation of smoking (28). Nicotine is the most pharmacologically active component of tobacco products and is believed to be responsible for the tobacco using-induced inhibitory effect on feeding in addition to the psychostimulant properties of nicotine. Grunbert et al. (3), Levin et al. (9) and also Morgan et al. (16) demonstrated that chronic nicotine infusion or injection decreased body weight due to decrease of food intake in female Sprague–Dawley rats and cessation of nicotine infusion increased food consumption and normalized body weight.

Evidence indicates that nicotine has significant effects on brain neurotransmitter release via either systemic or central administration (1,6,9,15,20,21,27), and hypothalamic neurotransmitters, among them dopamine (DA) and serotonin (5-HT), are involved in food intake control (4,8,11,31). We previously hypothesized that the LHA-DA may play a dual role in food intake control to enhance or inhibit ongoing feeding, depending on the DA levels (35). The present study was designed to examine our hypothesis that nicotine may be modulating the LHA dopaminergic and/or serotonergic activities to affect food intake and body weight gain. In vivo microdialysis was

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used to measure DA, 5-HT, and their intermediate metabolites levels in the LHA before, during, and after administration of nicotine via reverse microdialysis concomitantly with food intake.

## METHOD

### *Subjects*

Adult male Fischer-344 rats weighing 285–305 g (Taconic Quality Laboratory Animals and Services for Research, Germantown, NY) were housed in holding wire cages for 10 days to acclimate them to the study surroundings. The environmental conditions were kept constant (12L:12D cycle; room temperature of 26 ± 1°C; 45% humidity). Rats were allowed free access to standard rat chow (Diet # 5008; Ralston Purina, St. Louis, MO) and water.

### *Lateral Hypothalamic Area (LHA) Cannulation*

After acclimatization, rats were anesthetized with a mixture Ketamine, Xylazine, and Acepromazine (150:30:5 mg/ml at 0.7 ml/kg body weight intramuscularly), and were placed in a stereotaxic device. A guide cannula was implanted unilaterally into the left LHA. The stereotaxic coordinates of the LHA: 0.2 mm anterior to the bregma; mediolateral, 2.0 mm from the midline; and dorsal–ventral, 8.9 mm ventral from the surface of the dura (19). The guide cannula was fixed to the skull with acrylic dental cement. After operation, each rat was kept individually in a plastic metabolic cage (Nalgene Company, Rochester, NY); 10 days were allowed for recovery, following which the rats were randomized into the study group ($n = 7$) and the control group ($n = 6$).

### *Microdialysis Procedure*

The CMA/10 microdialysis probe was used (BAS, West Lafayette, IN). The microdialysis membrane was 1 mm long, 400 μm i.d., 520 μm o.d., and 20,000 Dalton molecular weight cutoff. According to our in vitro calibration test, a relative recovery rates for DA and 5-HT was about 10–12% and 5–8% at a flow rate of 1 μl/min, respectively. A Ringer-type solution containing 147.0 mM $Na^+$, 2.4 mM $Ca^{2+}$, 4.0 mM $K^+$, and 155.8 mM $Cl^-$ was used for perfusing by a CMA/100 microinjection pump (BAS, West Lafayette, IN). The flow rate of 1 μl/min allowed the collection of one 20-μl sample every 20 min.

### *Experimental Procedure*

The schedule of the microdialysis is shown in Fig. 1. All rats were food deprived overnight. At 0700 h, the rat was placed into a bowl-like cage (CMA/120 Awake Animal System, BAS, West Lafayette, IN). A microdialysis probe was inserted into the guide cannula at 0800 h, extending 1 mm beyond the cannula into the LHA. After a 120-min stabilization period, three 20-min baseline dialysates were collected and measured to make sure that the baseline DA and 5-HT levels were constant. Then, for study group rats, 4 mM (−)-Nicotine di-(+)-tartrate salt (Sigma) dissolved in perfusion solution was perfused into the LHA via the microdialysis probe for 60 min. The control rats were perfused with Ringer solution. Thereafter, food pellets were provided and the activity of the rat was monitored by the investigator. The food intake during the 40-min refeeding period was measured. For 20 min the LHA dialysates were continuously collected and measured; all samples were analyzed immediately after collection. DA, 5-HT, and their intermediate metabolites, DOPAC and 5-HIAA, were detected using reverse-phase liquid chromatography with an ESA Model 5014 high-sensitivity analytical cell and ESA Hypersil ODS column (15 cm × 4.6 mm i.d.). The mobile phase consisted of 75mM $NaH_2PO_4H_2O$, 1.4 μM OSA, 10 μM EDTA, and 10% acetonitrile. Buffer pH was adjusted to 3.1 with $H_3PO_4$.

### *Histology*

At the end of the experiment, the rats were anesthetized and perfused with normal saline followed with 10% formalin. The brain was removed and fixed, and serial coronal sections were cut, mounted, and stained. Locations of dialysis probes in LHA were confirmed using Pellergrino's rat brain atlas (19).

### *Data Analysis*

The levels of DA, DOPAC, 5-HT, and 5-HIAA were expressed in pg per 10 μl dialysate. Data were also calculated as percent change from dialysate baseline levels; 100% was defined as the mean value of three consecutive samples prior to nicotine perfusion. All data are expressed as MEAN±SE. Data were analyzed by one- and two-way analysis of variance (AVOVA) with repeated measures, followed by the Newman–Keuls test for multiple comparisons. Data were also analyzed by Student *t*-test for comparison between study and control rats.

## RESULTS

### *Food Intake*

Food intake before food deprivation was similar in both group rats (control: 16.1 ± 0.7 g/day vs. nicotine: 15.0 ± 0.6 g/day, respectively; $p > 0.2$). When food was provided during the microdialysis, the rats started eating immediately. During the 40-min refeeding period, cumulative food intake was significantly higher in control rats than in nicotine infused rats, being 4.1 ± 0.4 g and 2.8 ± 0.3 g, respectively ($p < 0.02$).

### *Dopamine and DOPAC Release*

As shown in Figure 2 during the baseline period, LHA-DA and DOPAC concentration were similar in both groups in 10 μl of analyzed dialysates (DA: 8.4 ± 0.8 pg vs. 8.3 ± 0.8 pg; DOPAC: 16.0 ± 2.2 pg vs. 17.5 ± 2.7 pg, respectively). During nicotine perfusion period, LHA-DA increased to 249 ±

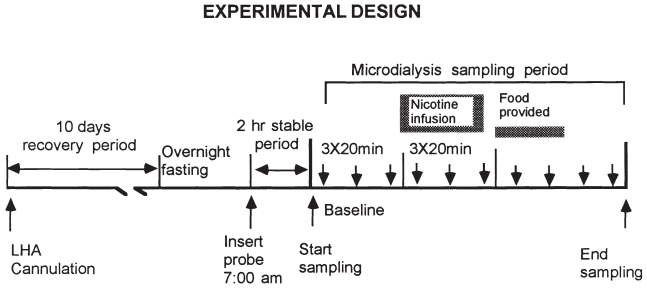


FIG. 1. After recovery from operation and overnight food deprivation, the rat was placed in a bowl-like cage at 0700 h, and a microdialysis probe was inserted into the LHA. After a 2-h stabilization period, three 20-min basal dialysates were collected and measured. Then 4 mM nicotine was administered via the microdialysis probe at 1 μl/min for 60 min. Food pallets then were provided for 40 min. Twenty-minute dialysates were continuously collected and analyzed.

42% ($p < 0.01$) and 178 ± 35% ($p < 0.05$) of baseline, respectively. DOPAC also increased to 207 ± 64% ($p = 0.1$) and 164 ± 58% of baseline level, respectively, although these differences did not reach significance. Eating significantly increased LHA-DA in both the nicotine infused rats and the control rats, being 150 ± 19% ($p < 0.05$) and 152 ± 10% ($p < 0.01$) of baseline, respectively. DOPAC also significantly increased to 180 ± 21% ($p <$) and 144 ± 15% ($p < 0.05$) of baseline in the control rats, and also slightly increased in the nicotine-treated rats, being 127 ± 22% and 157 ± 30% of baseline, respectively. In both groups, the LHA-DA and DOPAC level returned to baseline when eating stopped.

### *5-HT and 5-HIAA Release*

5-HT and 5-HIAA levels before, during, and after nicotine infusion and eating in both groups of rats are shown in Fig. 3. Mean baseline LHA-5-HT and 5-HIAA concentrations were similar in both groups in 10 μl of analyzed dialysates (5-HT: 0.55 ± 0.09 pg vs. 0.83 ± 0.15 pg; 5-HIAA: 74.2.0 ± 13.4 pg vs. 91.1 ± 22 pg, respectively). The LHA-5-HT levels increased to 1,128 ± 437% ($p < 0.05$), 548 ± 171% ($p < 0.05$), and 793 ± 364% ($p < 0.06$) of baseline during the entire nicotine administration period. The LHA-5-HT levels were still higher during the refeeding period until 40 min after eating. In control rats, eating gradually increased the LHA-5-HT level, reached significance 20 min after refeeding (144.7 ± 10.8%, $p < 0.05$), and then returned to baseline level.

In both the nicotine-infused rats and the control rats, no significant changes in LHA-5-HIAA levels were observed during nicotine administration and eating.

## DISCUSSION

Animal studies have revealed that the central administration of nicotine via the microdialysis probe enhanced DA release in many brain regions including the nucleus accumbens and the ventral tegmental area (15,17) and 5-HT release in the cingulate and frontal cortex (27). The same techniques were used in the present study to examine possible linkages among nicotine, the LHA neurotransmitters, and food intake. The main findings were: (a) continuous nicotine administration for 60 min increased LHA-DA and DOPAC release during the first 40 min; (b) nicotine administration induced a long-lasting increase in LHA-5-HT release; (c) LHA nicotine administration significantly decreased food intake; (d) eating

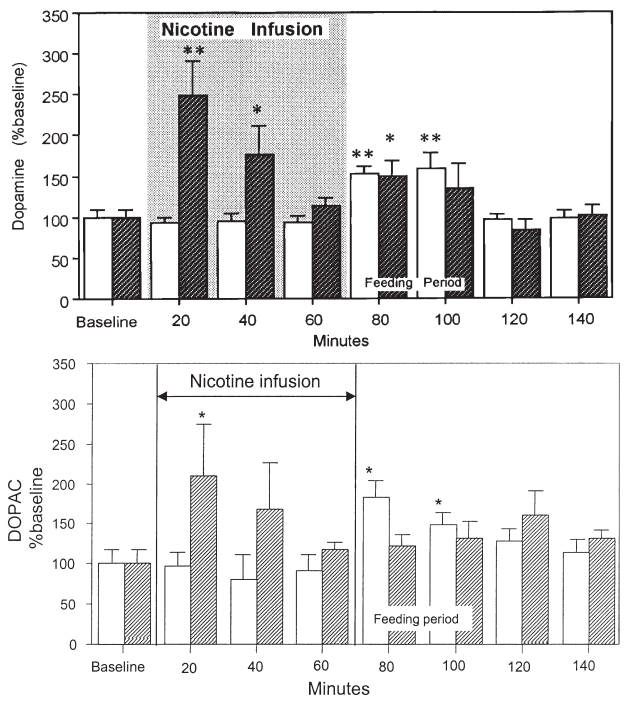


FIG. 2. Dopamine and DOPAC levels in the LHA before, during, and after the nicotine administration and eating. The basal DA and DOPAC levels are means of three consecutive samples before nicotine administration. Data are presented as percent of baseline and expressed as mean ± SE. The 60 min of nicotine administration significantly increased LHA-DA levels for 40 min, which then returned to baseline level, although nicotine was continuously administered. The LHA-DOPAC levels also correspondingly increased, although without reaching significance because of wide variations. Eating induced an immediate increase in LHA-DA, and the magnitude of the increase corresponded to the amount of food consumed. Shaded bar: nicotine-treated rats; open bar: control rats. *$p < 0.05$ and **$p < 0.01$ vs. the baseline level.

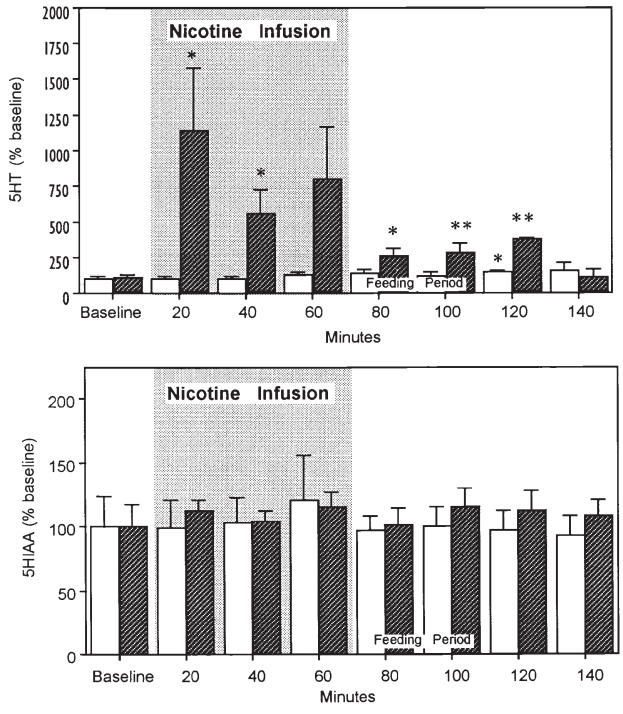


FIG. 3. Serotonin and 5-HIAA levels in the LHA before, during, and after nicotine administration and eating. The basal 5-HT and 5-HIAA levels are means of three consecutive samples before nicotine administration. Data are presented as percent of baseline and expressed as mean ± SE. The 60-min nicotine administration induced a long-lasting increase in LHA-5-HT levels even after nicotine administration stopped. There was no significant change in LHA-5-HIAA levels during the entire experiment. Eating induced an immediate and long-lasting increase in the LHA-5-HT level of nicotine-treated rats. The increase in LHA-5-HT of control rats was gradual, and reached significance 20 min after eating stopped. Shaded bar: nicotine-treated rats; open bar: control rats. *$p < 0.05$ and **$p < 0.01$ vs. the baseline level.

increased LHA-DA and DOPAC release during the eating period; (e) eating produced a long-lasting increase in LHA-5-HT release; and (f) there were no changes in LHA-5-HIAA release during nicotine administration and eating.

The magnitudes of the LHA-DA and 5-HT increases during the nicotine administration were different, for example, the increase of LHA-5-HT was greater than LHA-DA increase. This was probably due to the relatively larger 5-HT content in the LHA. It has also been observed that the duration of increased DA release in response to continuous nicotine administration differs among the different regions in the brain. Nisell et al. reported that nicotine infusion in the ventral tegmental area for 80 min produced a long-lasting increase in accumbal DA, whereas a similar nicotine infusion in the nucleus accumbens increased DA levels only within the first 20 min of administration (17). The present study showed that continuous nicotine administration for 60 min increased DA release in the LHA only during the first 40 min of administration. Although the reason for differences in duration of DA responses to nicotine administration are unknown, the number of DA neurons in the vicinity of the probe (29) and the rapid decrease in sensitivity of the nicotine receptors located on DA terminals (17) have been postulated to be responsible for the transient increase in DA release during continuous nicotine administration. That the LHA-DOPAC release also increased during nicotine administration and that the duration of the increase was similar to DA suggests increased dopaminergic activity.

Schwartz et al. reported that eating increased extracellular 5-HT in the lateral hypothalamus (23). We also reported previously that eating increased LHA-DA. The increase correlated to the size of a meal (12–14,24,32–34,35). The pattern of eating-induced LHA-DA and 5-HT changes in our present study is in agreement with these previous reports. In present study, the increased level of 5-HT was gradual, and reached to the peak value after eating had stopped. The reasons for the difference are probably: (a) the dialyzed region was more medial in their study (1.4 mm lateral to the midsagittal sinus) than ours (2.0 mm from the midline); (b) the rats in their study were trained to eat a palatable mash of sweetened condensed milk and chow for 2 h before the experiment, whereas no such pretraining or preconditioning occurred in our study.

Evidence has implicated dopaminergic mechanisms in the effects of nicotine at the neurochemical and behavioral level (5,18). The central DA, particularly in the hypothalamus, has been well documented to participate in regulating food intake (4). The function of the LHA-DA in food intake control remains undefined, whereas some have reported that LHA-DA inhibits food intake, others report a stimulation of food intake (7,22,26). We previously proposed that the LHA dopaminergic neurons might play a dual role in feeding control, especially regarding meal size. Phenylpropanolamine, an adrenergic agonist, which is believed to act in part via hypothalamic DA (22), has also been used to treat postnicotine cessation weight gain with some success (30), suggesting that the impact of nicotine on food intake and body weight may be in part via modulating hypothalamic dopaminergic activities. However, in the present study, eating induced a similar increase of LHA-DA release in both the nicotine-treated and control rats, and the LHA-DA level increased only during eating (in agreement with our previous reports), and suggests that: (a) the LHA-DA might not directly be involved in the nicotine-induced hypophagia; and (b) the transient-enhanced LHA-DA activity may initiate a cascade reaction to activate other feeding-related neuromodulators, consequently induce hypophagia.

A great amount of pharmacological, biochemical, and behavioral evidence over the last 2 decades has demonstrated that increased 5-HT activity in the brain has an inhibitory influence on eating behavior both in animals and in humans. Extensive mapping and lesion studies indicate that 5-HT acts within the hypothalamus to inhibit eating, and is believed to act on satiation, suppressing food intake by decreasing meal size and duration (25). The fact that 5-HT reuptake inhibitors, such as fluoxetine and setraline, have been found to reduce nicotine withdrawal-induce hyperphagia and weight gain (10,20) suggests the involvement of hypothalamic 5-HT in nicotine-induce hypophagia. The function of the LHA-5-HT in food intake is still unclear. The gradual increase of 5-HT in the LHA reached a much higher level after eating, which may reflect that satiation was gradually during eating and postprandial satiety was maintained. The finding in this present study suggests that the significantly higher LHA-5-HT after cessation of nicotine administration may be responsible for nicotine-induced hypophagia. The long-lasting enhanced LHA-5-HT activity induced by nicotine may also explain the chronic effect of tobacco product use on appetite because of ready access of nicotine to the brain.

In summary, the present findings demonstrated that nicotine directly administered into the LHA induces a long-lasting increase in 5-HT levels and a relatively short period of increase in DA levels. We hypothesize that these nicotine-induced long-lasting neurotransmitter changes may contribute to nicotine-induced hypophagia.

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