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Bilateral Hypothalamic Dopamine Infusion in Male Zucker Rat Suppresses Feeding Due to Reduced Meal Size

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YANG, Z.-J., M. M. MEGUID, J.-K. CHAI, C. CHEN AND A. OLER. *Bilateral hypothalamic dopamine infusion in male Zucker rat suppresses feeding due to reduced meal size.* PHARMACOL BIOCHEM BEHAV **58**(3) 631–635, 1997.—Lateral hypothalamic area dopamine activity (LHA-DA) appears to play a contributory role in regulating food intake, in particular, meal size. In this study we examined our hypothesis that bilateral LHA-DA injection induced depression of food intake via reduced meal size. Dopamine (11 mg/ml) or vehicle was infused into bilateral LHA at 0.5 μl/h via two osmotic minipumps in six study or six control obese male Zucker rats for 13 days, respectively. Meal size, meal number, as well as food intake were continuously measured before, during, and after dopamine infusion. Intra-LHA-DA infusion significantly depressed food intake. The decreased food intake was solely caused by a significant and profound reduction in meal size. There was a modest compensatory rise in meal number that gradually increased food intake so that it reached control level on 10th dopamine infusion day. However, feeding pattern did not normalize until dopamine infusion ceased. The findings support our hypothesis that LHA-DA may participate in regulating meal size. Data also demonstrate that meal size and meal number are regulated in a reciprocal and independent manner to compensate for each other. © 1997 Elsevier Science Inc.

Dopamine Lateral hypothalamic area Male Zucker rats Feeding pattern Meal size Meal number Food intake Minipump

THE genetically obese Zucker rats are characterized by a number of behavioral, endocrinological, and metabolic abnormalities, including disturbed dopamine (DA) function in the hypothalamus (23,24). This is in keeping with evidence showing that in the normal state hypothalamic dopamine is involved in food intake control in general, but more specifically in the inhibition of food intake control in the lateral hypothalamic area (LHA) (11,13).

In previous work, using in vivo microdialysis in Fischer-344 rats (21), we showed the correlation between physiological endogenous LHA-DA levels and meal size. LHA-DA levels rise rapidly and are maintained at higher levels during eating, returning to baseline when eating stops. The magnitude of this rise is proportionate to the size of the meal. This correlation also existed in genetically obese Zucker rats whose food intake is significantly higher than their lean litter mate. In these obese Zucker rats, endogenous LHA-DA levels were significantly higher with a larger meal size (32). In contrast, a single injection of a pharmacological dose of dopamine into the LHA of normal rats suppresses food intake (13).

Food intake (FI) is the product of meal size (MZ) and meal number (MN) [FI = MZ × MN]. Under physiological conditions in both male and female rats, meal size and number appear to be regulated in a reciprocal manner, so that

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food intake is modulated by altering meal size or meal number or both (12,17,34). In general, a decrease of one is compensated for by an increase in the other. Some examples of the different types of relationship between meal size and meal number observed in our past studies are as follows: a) following olfactory bulbectomy, anosmatic male rats maintain their daily food intake by an altered feeding pattern. Meal size is approximately 50% less in bulbectomized rats than in control rats, but by increasing meal number almost twofold, a normal food intake is maintained (17). b) Similar events occur following hepatic vagotomy in normal male rats. Relative to controls, vagotomized rats do not change their daily food intake, although meal size decreases and meal number increases (34). If the perturbation is beyond the compensatory ability, then food intake changes. c) In a methylcholanthrene (MCA)-induced sarcoma male rat model, during tumor growth meal number is first to decrease. By a compensatory increase in meal size, daily food intake is maintained for a while. Thereafter, when the meal size can no longer compensate and start to decrease, daily food intake decreases and the anorexia of cancer occurs (19). In these anorectic tumor male rats, temporarily blocking LHA function or VMN function restores food intake via an increase in meal size and meal number, respectively (preliminary data). d) In the normal female Fischer rat, there is a reciprocal trade off between meal size and number during each estrous cycle (12). e) Furthermore, in normal male rats, temporarily blocking VMN function increased meal number and food intake (preliminary data). f) Finally, another example of the meal size/meal number relationship is found in the genetically obese Zucker rats. Obese Zucker rats vs. their lean controls consume the same meal number per day, but have a very large meal size, resulting in very high food intake. Based on the sum of these data, we hypothesize that meal size and meal number appear to be regulated in a reciprocal manner and that the LHA-DA is involved in regulating meal size. Consequently, suppressed food intake induced by LHA-DA injection should be due to a reduced meal size. We used the obese Zucker rat as a model in this study because of its property of eating large meal sizes, which would allow perturbations in this feeding index to be readily observed.

The availability of osmotic mini-pump implant technique permits the testing of this hypothesis by continuously infusing a pharmacological dose of dopamine into the LHA of obese Zucker rats for a prolonged period, while measuring meal size, meal number, while determining the interaction of these two products on food intake. Because it was recently suggested that the development of obesity in obese Zucker rats may be associated with OB (leptin) receptor gene defect (6), data from our present study may help us understand the role of dopamine in food intake control.

METHODS

Animals

The experiment was approved by the SUNY Health Science Center, Syracuse Committee for the Humane use of Animals, and was in accordance with the guideline established by National Institutes of Health.

All rats used in this study were 9-week-old males. They were housed in holding wire cages following purchase (Harlan Sprague–Dawley, Inc., Indianapolis, IN) for 10 days to acclimatize them to the study surroundings. Environmental conditions were kept constant (12-h light/dark cycle; room temperature of 26 ± 1°C; 45% humidity). Rats were allowed free access to standard coarsely ground rat chow (Diet#5008; Ralston Purina, St. Louis, MO) and water.

Experimental design

Experiment #1: dopamine infusion study. Two minipumps were implanted, as described below, in 12 male obese Zucker rats. Either dopamine (n = 6) or vehicle (n = 6) was infused into bilateral LHA. Rats were individually placed into cages equipped with the automated computerized rat eater meter (ACREM) as previously described in detail (18,20). These continuously measured the feeding indexes of meal size, meal number, as well as food intake, for 17 days. Body weight of the rats was measured every 4 days.

Experiment #2: measuring concentration of dopamine in the LHA. To confirm that the delivery of doapmine and the increased concentrations of dopamine measured in the LHA were associated with changes in food intake, six male Fischer-344 rats each with a minipump containing dopamine were studied. Another six rats were used as normal control.

Rats were killed on the 10th dopamine delivery day after implanting minipump. The brain was rapidly removed and whole hypothalamus was harvested and immediately frozen in liquid nitrogen.

Experiment #3: comparative feeding patterns in obese Zucker rats. For comparative purposes, eight obese (fa/fa) and eight lean (Fa/−) acclimated male Zucker rats were individually placed into ACREM cages and food intake and feeding indexes continuously measured for 7 days.

Measuring food intake, meal size, and meal number. The ACREM used in each experiment is based on commercially available metabolic cage (Lab Products, Inc., Maywood, NJ; model #LC-176) in which the supplied feeding cup has been replaced by an electronic scale balance and two photocells. The cells are centered just above the food dish to detect accesses. A remote computerized data collection system records the information on feeding related parameters as detected from the photoelectric cells and the scale with the real time. The equipment and its function has been previously described in detail (18,20).

A meal is defined as a bite or a series of bites preceded and followed by at least 5 min of feeding inactivity. If a bite or series of bites is not followed by 5 min feeding inactivity, then it is considered part of the preceded meal. Using this definition, the following feeding indexes were measured: food intake = amount of food (g) consumed during 24 h; meal number = total number of meals during 24-h period; meal size = amount of food consumed per meal (g/meal) during 24-h period.

Measuring dopamine concentrate in LHA. Each hypothalamic sample of rats in Experiment 2 was weighed and put into 2 ml of 0.05 M perchloric acid to homogenize and centrifuged at 14,000 rpm for 45 min at 0°C. The supernatant was collected and stored at −70°C until analysis. The stored supernatant was thawed and deproteinated with 50% sulfosalicylic acid and centrifuged for 20 min at 5,000 rpm at 0°C. The supernatant was then filtered through a 0.2 mm Gelman syringe filter. Dopamine was analyzed using a reverse-phase liquid chromatography with electrochemical detection and a BAS Phase II ODS 10 cm column. The mobile phase contained 100 mM monochloroacetic acid, 0.5 mM EDTA, 0.15 mM octyl sodium sulfate, 2.5% v/v acetonitrile at pH 3.0.

LHA cannula and minipump implantation. In Experiments #1 and #2, the rats were anesthetized with a rodent anesthesia mixture (Ketamine HCl, 100 mg/ml; Xylazine HCl, 30 mg/ml; Acepromazine 10 mg/ml; 1 ml/kg, intramuscularly). Four

stainless screws were anchored into the skull, and two stainless steel cannula (0.64 mm in outer diameter) were implanted into the bilateral LHAs using the following stereotaxic coordinates: 0 mm anterior to the bregma; media–lateral, +2.0 mm from the middle line; and dorsal–ventral, 9.0 mm ventral from the surface of the dura (26).

Two osmotic minipumps (Model 2002, Alza Corp., Palo Alto, CA) were placed subcutaneously in the nape of neck and attached to the cannula with medical-grade vinyl tubing (size V/3; Biolab Inc., Lake Havasu City, AZ). In the study rats, the pump, and tubing were filled with dopamine HCL (11 mg/ml) dissolved in sodium metabisulfite (1 mg/ml) solution (7) and were primed at room temperature overnight in normal saline solution. The stability of dopamine in sodium metabisulfite solution was verified using HPLC (ESA) after 13 days at 37°C. In control rats, the delivery system was filled with the sodium metabisulfite vehicle only. Then the cannula and connected tubing were fixed to the skull with acrylic dental cement. Each pump delivers 0.5 μl/h for 13 days into the rat, according to the manufacturers quality control (QC) specifications, and then ceased to function.

After the implant operation, all rats were replaced into their metabolic cages and feeding indexes were continuously measured for 17 days.

Histology. After conclusion of Experiment #1, rats were anesthetized and perfused with normal saline and 10% formalin. The brain was removed and further fixed in 10% formalin and then serial coronal sections were cut, mounted, and stained. Locations of cannula in both LHAs were verified using the Rat Brain Atlas (26).

Data analysis. The daily feeding indexes of food intake, meal size, and meal number were analyzed by performing repeated measures one-way analysis of variance for each group. Contrast *t*-tests were used to compare the mean at each of days 1–17 (test and posttest periods) with the mean of day −2 to 1 (pretest or baseline period). Data represent each feeding index and its mean ± standard error on each experimental day.

RESULTS

Experiment #1

Body weight. Table 1 shows the changes in body weight during the study. Body weight gain was lower ($p < 0.055$) in dopamine infused obese Zucker rats than in vehicle infused rats during the infusion period. Had body weight been measured daily, significant differences might have been detected sooner. Three days after the dopamine infusions ceased, there was no difference in body weight between the two groups.

TABLE 1

EFFECT OF LHA-DA INFUSION ON BODY WEIGHT GAIN (MEAN ± SE)

	Day	Body Weight (g)		Between Two Groups
		Dopamine	Vehicle	
Preinfusion	−2	320.8 ± 5.2	322.0 ± 5.1	NS
During infusion	2	314.2 ± 10.8	325.1 ± 3.9	NS
	6	335.0 ± 7.9	352.8 ± 4.7‡	$p = 0.055$
	10	363.3 ± 14.2*	374.0 ± 6.1‡	NS
Postinfusion	14	381.7 ± 15.7†	381.8 ± 7.1‡	NS
	17	393.3 ± 14.6‡	404.6 ± 7.1‡	NS

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ vs. preinfusion body weight.

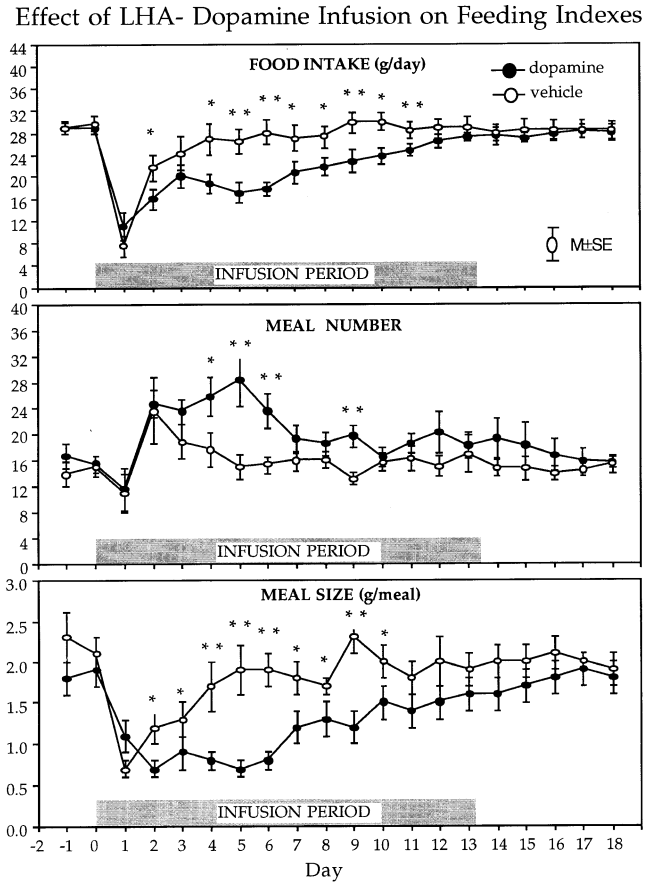

FIG. 1. Comparison of meal daily feeding index pre-, during, and postdopamine or vehicle infusion. Food intake, meal number, and meal size significantly decreased in both groups immediately after surgery for pump placement. One day thereafter, while meal size was still low, meal number sharply increased, resulting in a modest increase in food intake in both groups. Thereafter, in the control group, meal size quickly increased while meal number gradually decreased and returned to preoperative level on the third infusion day. In dopamine infused rats, meal size continued to decrease and remained at this level until the seventh infusion day when it gradually increased and reached that of control rats on the 13th infusion day. Meal number remained continuously at a higher level for the first 6 days of dopamine infusion, then declined to the level of controls. The gradual increase of food intake in the dopamine rats after surgery for pump placement was initially due to increased meal number during the first 6 days, and thereafter it was due to a gradual increase in meal size. *$p < 0.05$ and **$p < 0.01$ between dopamine infused and vehicle infused rats.

Feeding indexes. The changes which occurred in the feeding indexes in response to the LHA infusion are shown in Fig. 1. Following anesthesia and operation, meal size, meal number, and food intake significantly decreased in both groups, by similar proportions. But, 1 day after surgery, while meal size was still low, meal number sharply increased resulting a modest increase in food intake in both groups. Thereafter, in the control group, meal size quickly increased and was accompanied by a gradual decrease in meal number. Both indexes returned to preoperative level and normalized food intake by third vehicle infusion day.

In the LHA-DA–infused rats, meal size continued to further decrease to about 35% of preinfusion level and remained at this level until 7th postinfusion day then gradually increased and reached the control rats level on 13th postinfusion day. Meal number was continuously at a higher level until the sixth dopamine infusion days. Thereafter, it declined to the control level. The gradual increase of food intake was due to increased meal number during first 6 days, and thereafter was due to gradually increased meal size.

Histology. Microscopic studies of the needle tracts show bilateral tracts through the lateral hypothalamic areas. The tracts are broadest at the base. They are 0.1 mm in width superiorly and 0.25 mm at the base inferiorly. Superiorly the tracts appear empty and collapsed; an effect seen secondary to histological fixation of the tissues. Inferiorly the tracts contain RBCs and WBCs. Also present are macrophages. At the edge of the tract there is an incomplete one cell layer of myofibroblasts, and also a one to two cell layer of microglial cells. These were most prominent inferiorly.

Experiment #2

Following 10-day minipump infusion, dopamine concentration was significantly higher in dopamine-infused rats than in control rats, being 853 ± 145 pg/10 μl vs. 41 ± 6.8 pg/10 μl, respectively ($p < 0.001$).

Experiment #3

The mean of 7-day feeding indexes, when comparing obese vs. lean Zucker rats, are summarized in Table 2. The higher food intake in obese Zucker rats is solely due to a considerably enlarged meal size.

DISCUSSION

A similar profile of monoaminergic changes in the hypothalamus following feeding among obese Zucker rats and nonobese Wistar (25,32) and Fischer (21) rats has been observed, although the kinetics and magnitudes of the changes were different. Based on the data in this study of the role of LHA-dopamine in food intake control obtained from obese Zucker rats, we arrive at the same conclusion.

The characteristic feeding pattern of genetically obese Zucker rats, as previously documented by others and by this laboratory, include enlarged meal size and the disappearance of predominantly nocturnal feeding (3,5,9,16,18). The 24-h feeding pattern of genetically obese Zucker rats, as observed in our study, was similar to that documented by others. However, slight differences exist in reported feeding patterns of obese Zucker rats among different laboratories. For instance, in Alingh-Prins' study, meal size of obese Zucker rats was larger and meal number were fewer when compared to our findings (1). This is probably due to the different experimental environment and different definition of a meal. Thus, in Alingh-Prins' study, the room temperature for rats was 21°C, and 15 min of no feeding activity was considered the definition of a separate meal; in our experiments, they were 26°C and 5 min, respectively, emphasizing the need for caution when comparing feeding pattern data among laboratories.

TABLE 2

COMPARISON OF MEAN 7-DAY FEEDING INDEXES BETWEEN OBESE AND LEAN ZUCKER RATS (MEAN ± SE)

Feeding Index	Obese	Lean	
Food intake (g/day)	27.4 ± 1.0	19.4 ± 1.2	$p < 0.05$
Meal number	16.3 ± 1.4	16.1 ± 1.9	NS
Meal size (g/meal)	1.7 ± 0.2	1.2 ± 0.2	$p < 0.01$

Food intake is the product of meal size and meal number. Hence, changes of either meal size or meal number or both would affect food intake. And, the importance of studying meal patterns instead of merely measuring daily food intake to elucidate the neural controls of ingestive behavior has been emphasized (4). Mapping studies have demonstrated that central injections of a pharmacologic dose of dopamine suppresses feeding, the suppressive effect being a site-specific phenomenon. The area of greatest sensitivity was found to be the perifornical region of the LHA (13). Our findings support these studies by further showing the inhibitory effect of dopamine in the LHA in reducing food intake is solely via reducing meal size.

Because rats regulate long-term food intake carefully and because rats consume food in a series of discrete meals, such regulation must ultimately be affected through variation in size of the meal, the interval between meals, or both. As pointed out by Becker and Kissileff (4), there are counterbalancing controls for each feeding index such that under normal metabolic circumstances, a change in one, a change in the other, is likely to occur to preserve the consistency in daily food intake, i.e., meal size and meal number are regulated in an independent and reciprocal manner. Several reports have shown that energy regulation is achieved primarily by changing meal size and not meal number so that meal size is postulated to be involved in the adjustment of energy homeostasis (8,15,30,31). Meal pattern studies in rats have demonstrated that the injection of the hypothalamic paraventricular nucleus with norepinephrine or neuropeptide Y potentiates feeding primarily through an increase in meal size and meal duration, rather than meal number, while the latency of feeding onset is unaltered (14,27,29). Serotonin suppresses feeding primarily through a decrease in meal size and duration (28). Evidence that neuropeptide Y and dopamine interact antagonistically in the perifornical hypothalamus in food intake control in rats (10) suggests that these factors may influence meal size via modulating dopamine activity or interact with dopamine system.

Our study in obese male Zucker rats also shows that the LHA-DA infusion-induced hypophagia is due to reduced meal size, which is determined by the factors modulating the cessation of a meal. In a pilot study, a similar observation was made in nonobese Fischer and Sprague–Dawley rats. LHA-DA may play a dual role in food intake control as we previously speculated (32). When eating is initiated, the release of the LHA-DA increases; when eating continues, dopamine release continues to increase to enhance the eating process, until it appears to reach a "threshold" level, at which time it acts as a terminating signal, which together with other signals, end the meal (22). A slight increase in the LHA-DA level would enhance the eating activity, therefore increasing food intake. This is supported by our recent data in which rats implanted with LHA-DA rich fetal cells consumed more food and gain more body weight (33) vs. controls. In contrast, the infusion of dopamine induced higher dopamine levels in the LHA as shown in this study, and may thus act as a premature terminating signal to end a meal; resulting in a very smaller meal size.

In the present study, while meal size is reduced during the LHA-DA infusion, meal number significantly increased, once more suggesting that a compensatory reciprocally functioning mechanism exists in energy homeostasis, so that both meal

size and meal number may be able to accommodate each other to regulate food intake. To function as a compensatory mechanism it is likely that meal size and meal number are independently regulated in different anatomic sites of the brain in a way analogous to the reciprocal innervation controlling spinal reflexes. The dual center theory, often dismissed as outmoded, states that feeding activity is influenced by a LHA feeding center and a ventromedial hypothalamic nucleus (VMN) satiety center (2). More recent studies demonstrate that eating induces reciprocal changes in dopamine level in the LHA and VMN (22). In the LHA, eating induces a temporary endogenous and physiological increase in dopamine level; in the VMN, it induces a prolonged decrease in dopamine level. Because the LHA-DA level increases only during eating, it therefore closely relates to meal size (21). On the other hand, if VMN-DA level is maintained at a depressed level for a prolonged period after eating has ceased, it appears to therefore be closely associated to meal number (22).

In summary, the inhibitory effect of dopamine infusion in a pharmacological dose into the LHA on food intake is solely due to a reduced meal size, supporting our hypothesis that the LHA-DA may be involved in regulating meal size.

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