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Influence of the Amount of Food Ingested on Mesolimbic Dopaminergic System Activity: A Microdialysis Study

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MARTEL, P. AND M. FANTINO. *Influence of the amount of food ingested on mesolimbic dopaminergic system activity: A microdialysis study.* PHARMACOL BIOCHEM BEHAV **55**(2) 297–302, 1996.—The mesolimbic dopaminergic system (MDS) has been shown to be activated by ingestive behaviors, and it has been suggested that this activation may be related to the rewarding properties of foods. Because rats eat more when given a more palatable diet, this study was undertaken to determine the relationship between the amount of food ingested and DA release in the nucleus accumbens of freely moving rats. The extracellular levels of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were measured by high-performance liquid chromatography with electrochemical detection on microdialysis samples from the nucleus accumbens. Each rat underwent three microdialysis sessions that differed in feeding conditions: on the first day they had access to a highly palatable diet (short cakes) ad lib; on the second day they were given half the amount consumed on the previous day of the same food; and on the third day they were deprived of food. In the absence of food, there were no significant alterations in extracellular levels of DA, DOPAC, and HVA. During feeding, levels of DA and its two metabolites rose. DA release in the nucleus accumbens was related to the amount of food ingested. As the amount ingested is a component of the reinforcement associated with food intake, this result is consistent with a direct relationship between MDS activity and food reward.

Dopamine Nucleus accumbens Food intake Palatability Quantity Microdialysis Food reward

THERE is considerable evidence for an association between feeding behaviors and the release of dopamine (DA) in the nucleus accumbens (11,12,22,28,32,34). In a previous study we examined the effect of ingestion of two foods differing in palatability on this neurochemical response (21). We have found that DA release in the nucleus accumbens was significantly higher in rats with access to a highly palatable (HP) diet than to regular chow, and we suggested that activity of the mesolimbic dopaminergic system (MDS) was related to the rewarding properties of foods. However, because our rats ate more HP food than chow (21), this raised the question of the respective roles of the sensory properties of food and the amount ingested in the activation of the MDS. The role of the quantity ingested has been addressed indirectly in the reports mentioned above: in most of the experiments the rats were either 24 or 36 h food deprived (12,34) or were maintained at 75–80% of their basal body weight (22,28) and, consequently, ate large amounts of food (28). Furthermore, the hungrier the animals on access to food, the greater the activity of the MDS (32). It has also been reported that high periodic food presentation (during which rats ate 2 g of regular chow) induced higher DA release in the nucleus accumbens than low periodic food presentation when the rats ate a quarter as much (22). The DA release reported in those studies may, thus, have been a response to food intake per se or to the larger amount of food ingested. It has also been reported that microinjection of DA into the nucleus accumbens stimulates food intake and lever press for food in a dose-dependent manner (5,24), which is consistent with a relationship between the amount of food ingested and MDS activity.

The present study was designed to examine the effects of the ingestion of different quantities of the same highly palat-

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able food on the activity of the MDS. Extracellular levels of DA and its main metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were measured in the nucleus accumbens, a major target of the MDS, by in vivo microdialysis in freely moving rats.

METHOD

Animals and Feeding Conditions

The experiment was carried out on five male Sprague–Dawley rats (from Iffa-Credo, l'Arbresle, France) weighing 270 to 310 g. The animals were individually housed under a 12 L:12 D cycle (lights on at 0600 h). The experiment was conducted during the light cycle. The rats had free access to regular chow (Extralabo M20 from Pietrement, France) except during the microdialysis sessions performed on rats that were food deprivred from 0800 to 1300 h. During the feeding period of microdialysis sessions they received powdered short cakes (butter biscuits containing 4.1 kcal/g with 8 g/100 g proteins, 16 g/100 g lipids, and 60 g/100 g carbohydrates), which we have previously shown to be highly palatable to rats (4). For 15 days before the microdialysis sessions, the animals were habituated to this highly palatable (HP) food, receiving it ad lib from 1300 to 1325 h each day. They had access to water ad lib at all times.

Surgery

Under intraperitoneal pentobarbital anesthesia (60 mg/kg) the rats were stereotaxically implanted with a guide shaft aimed at the nucleus accumbens, using the skull surface coordinates: A, 2.2 mm anterior to bregma; L, 1.5 mm to the right of the midline; and V, 7.0 below the skull surface. The microdialysis probe to be inserted later extended 1 mm beyond the guide shaft. The guide shaft was embedded in a pad of synthetic resin fixed to the cranial bones by three T-shaped stainless steel screws.

Dialysis System

The tips of the CMA/10 probes (Canergie Medicin, Sweden) were capped with a dialysis membrane (1 mm long, 0.5 mm wide), with a molecular weight cutoff of 20,000 Dalton. The relative recovery of the probes was measured regularly, and was found to range from 7 to 10% according to the neurochemical. The microdialysis fluid was an artificial CSF consisting of 147 mM NaCl, 4.02 mM KCl, 3.42 mM $CaCl_2$, pH7.35.

Chromatographic Conditions

The high-performance liquid chromatography (HPLC) system for analysis of the dialysates used a 20 μl loop to apply samples to a 125 × 4 mm MERCK RP-select B column (5 μm C-8 stationary phase). The mobile phase was 75 mM anhydrous sodium dihydrogen phosphate, 1.2 mM sodium octyl sulfate, 20 μM EDTA, 8% methanol, at pH = 3.3. The flow rate was 1 ml/min using a ESA pump (model 508, Eurosep Instrument). Products were detected using a Coulochem electrochemical detector 5200A′ (Eurosep Instrument) with the working electrode (model 5014, Eurosep Instrument) set at −0.2 V. DA, DOPAC, and HVA were detected at an applied sensitivity of 1, 500, and 10 nA/V, respectively.

Experimental Procedure

After 5 days recovery, each rat underwent three microdialysis sessions (over three subsequent days) differing in feeding conditions. Each rat, thus, served as its own control. At 0800 h, regular chow was removed, and the probe was inserted in the previously implanted guide shaft and immediately perfused with the artificial CSF by an infusion pump (Harvard Apparatus, model 22) at a flow rate of 1.2 μl/min. Samples were collected every 25 min from 1020 to 1440 h, and immediately assayed for DA, DOPAC, and HVA by HPLC coupled to electrochemical detection. During the four first samples (from 1020 to 1300 h) and the three last samples (from 1325 to 1440 h), rats had no access to food. During food supply (from 1300 to 1325 h), rats had access: a) either to the HP food ad lib (HP ad lib session); b) or they received the same diet but half the amount it had ingested during the HP ad lib session (limited HP); c) or they remained food deprived (deprived session). Because the order of repeated measurements in a previous study with similar experimental procedure did not induce any significant change in DA release in the nucleus accumbens (21), all the rats in the present experiment underwent the same experimental design, for instance., HP ad lib on the first day, limited HP on the second day, and no food on the third one.

Histology

At the end of the experiment, the rats were sacrificed, their brains were quickly removed, and stored at −20°C. The brain was then sliced with a cryomicrotome into 8 μm sections, which were stained with toluidine blue for localization of the probe placements.

Statistical Analysis

Due to the large interindividual differences, the data were normalized as a percentage of the levels determined in the four dialysis samples collected prior to food supply. Each rat served as its own control. The results were subjected to one- and two-way ANOVA for repeated measurements, followed, when warranted, by Newman–Keul's range test; the null hypothesis was rejected at the 0.05 level.

RESULTS

Probe Placement

Histology indicated that the dialysis probes were all located in the inferointernal part of the nucleus accumbens, for instance, in the accumbens shell (23). The location of the probe routes and tips are presented in Fig. 1.

Food Intake

During the ad lib microdialysis sessions the rats ate 2.1 ± 0.6 g. During the limited food sessions, due to spillage (which was carefully measured), rats ate less than the 1 g of HP food given and only consumed 0.6 ± 0.1 g.

DA Metabolism

The extracellular level of DA (Fig. 2) differed significantly over time and between the three feeding conditions [two-way ANOVA: food condition effect: $F(2, 64) = 29.38$, $p < 0.001$; time effect: $F(7, 64) = 4.41$, $p < 0.001$; food condition × time interaction: $F(14, 64) = 7.95$, $p < 0.001$]. In the absence of food, DA levels progressively decreased over time [one-way ANOVA: $F(7, 28) = 2.48$, $p < 0.05$], although the Newman–Keul's range test did not identify any significant difference between the dialysis samples (Table 1). In contrast, DA levels

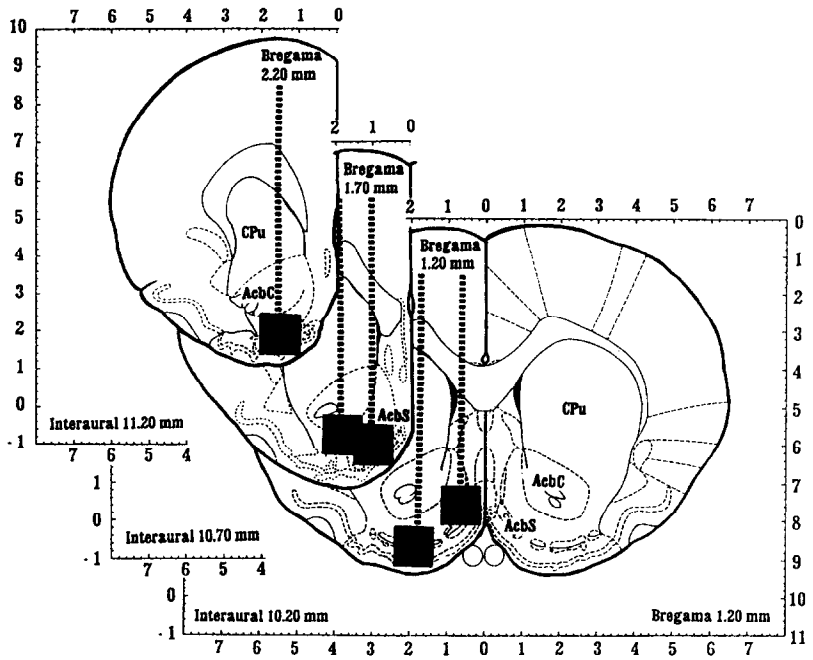


FIG. 1. Coronal sections of the rat brain (drawn from the Paxinos and Watson atlas, Academic Press, 1986) showing the location of the microdialysis probe in the five animals (AcbC: accumbens nucleus, core; AcbS: accumbens nucleus, shell; CPu: caudate putamen).

rose significantly over time, as soon as the rats had access to either ad lib HP [one-way ANOVA: $F(7, 28) = 9.24$, $p < 0.001$] or to limited HP [one-way ANOVA: $F(7, 28) = 2.50$, $p < 0.05$]. Newman–Keul's range test indicated that DA reached a significant higher level than baseline during the first 25 min following food supply only with ad lib HP (Fig. 2). One-way ANOVA (Table 1) showed that DA levels differed significantly between the three feeding conditions as well as during food supply [100–125 min: $F(2, 8) = 4.94$, $p < 0.05$] than during the two following 25 min time intervals [125–150 min: $F(2, 8) = 24.48$, $p < 0.001$; 150–175 min: $F(2, 8) = 6.33$, $p < 0.05$]. The greatest difference occured during the first 25 min following food supply (125–150 min) when DA reached 183% of its basal level for ad lib HP, 127% for limited HP, and 91% in the no food condition (Fig. 2).

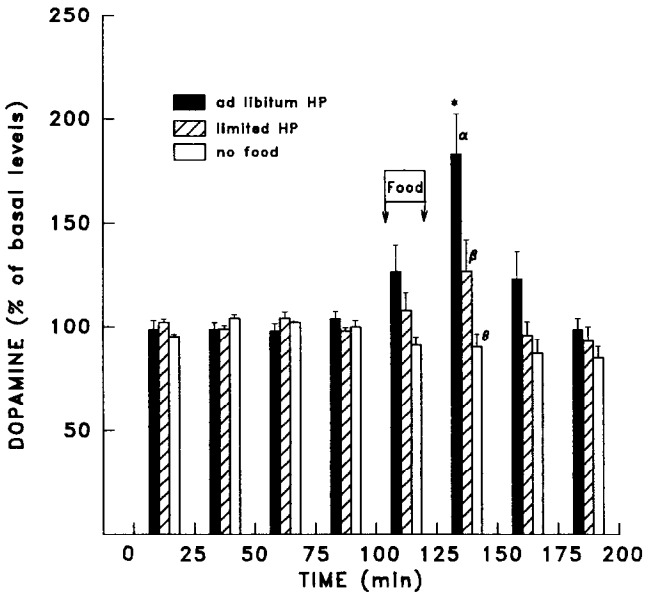


FIG. 2. Extracellular levels of DA during microdialysis sessions in the nucleus accumbens of five rats. The results are expressed as percent of basal release (mean of samples prior to food supply ± SEM). *DA release during access to ad lib HP is significantly higher than basal levels (Newman–Keul's range test $p < 0.05$). α, β, θ; DA release is significantly different between ad lib HP, limited HP, and no food sessions (Newman–Keul's range test $p < 0.05$).

The change in extracellular levels of DOPAC (Fig. 3) and HVA (Fig. 4) resembled that of DA. Two-way ANOVA indicated significant differences between the three feeding conditions for DOPAC [food condition effect: $F(2, 64) = 18.47$, $p < 0.001$; time effect: $F(7, 64) = 3.16$, $p < 0.02$; food condition × time interaction: $F(14, 64) = 3.40$, $p < 0.001$] and HVA [food condition effect: $F(2, 64) = 22.74$, $p < 0.001$; time effect: $F(7, 64) = 4.49$, $p < 0.002$; food condition × time interaction: $F(14, 64) = 4.63$, $p < 0.001$]. In the absence of food there was no significant change over time in DOPAC and HVA (Figs. 3 and 4). DOPAC and HVA rose progessively on feeding, but the increase only reached significance with ad lib HP [one-way ANOVA for DOPAC: $F(7, 28) = 11.42$, $p < 0.001$; for HVA: $F(7, 28) = 11.93$, $p < 0.001$]. One-way ANOVA indicated that DOPAC and HVA levels with ad lib HP differed significantly from the other two feeding conditions during the two 25 min intervals following food supply [at 125–150 min: $F(2, 8) = 7.98$, $p < 0.05$ for DOPAC; $F(2, 8) = 20.69$, $p < 0.001$ for HVA; at 150–175 min respective one-way ANOVA: $F(2, 8) = 9.70$, $p < 0.01$; $F(2, 8) = 8.58$, $p < 0.05$].

DISCUSSION

The present results are in line with previous reports showing that extracellular levels of dopamine (DA) and its metabo-

TABLE 1

EXTRACELLULAR LEVELS OF DOPAMINE DURING MICRODIALYSIS SESSIONS IN THE NUCLEUS ACCUMBENS OF 5 RATS

Time (min)	Ad Libitum HP Food	Limited HP Food	No Food	ANOVA Food Condition
0–25	99 ± 4.1	102 ± 1.8	95 ± 1.3	$F(2, 8) = 1.37$
	a	a	a	NS
25–50	99 ± 3.2	99 ± 1.6	104 ± 1.9	$F(2, 8) = 1.04$
	a	a	a	NS
50–75	98 ± 3.6	104 ± 3.3	102 ± 0.7	$F(2, 8) = 0.81$
	a	a	a	NS
75–100	104 ± 3.4	98 ± 1.8	100 ± 3.2	$F(2, 8) = 1.23$
	a	a	a	NS
100–125	127 ± 12.6	108 ± 8.4	91 ± 4.1	$F(2, 8) = 4.94$
	a α	a αβ	a β	$p < 0.05$
125–150	183 ± 19.6	127 ± 15.3	90 ± 6.5	$F(2, 8) = 24.48$
	b α	a β	a θ	$p < 0.0005$
150–175	123 ± 13.7	96 ± 6.5	87 ± 6.9	$F(2, 8) = 6.33$
	a α	a β	a β	$p < = 0.05$
175–200	99 ± 5.2	93 ± 7.1	85 ± 5.6	$F(2, 8) = 1.66$
	a	a	a	NS
ANOVA time	$F(7, 28) = 9.24$ $p < 0.001$	$F(7, 28) = 2.50$ $p < 0.05$	$F(7, 28) = 2.48$ $p < 0.05$	

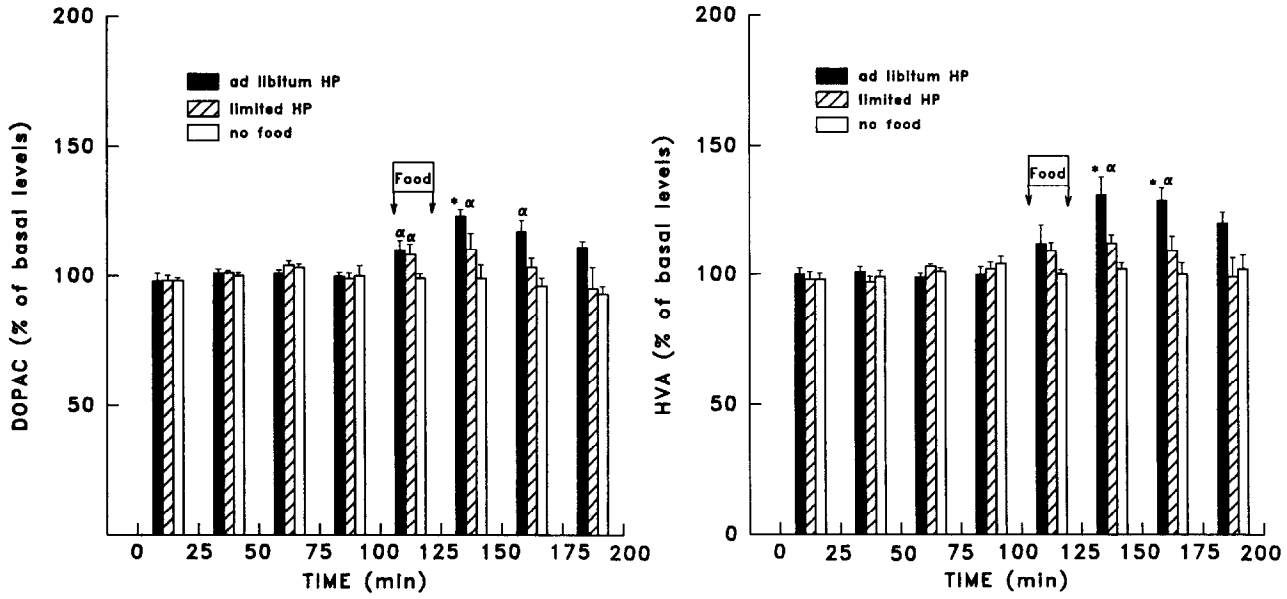
Values are expressed as percent of basal levels ± SEM. The food supply period (stippled cells) lasted 25 min with either high palatable food ad lib or same food in limited quantity, or without food. Left: one-way ANOVA with respect to food condition (two cells with different Greek symbols are significantly different, Newman–Keul's range test, $p < 0.05$). Bottom: one-way ANOVA with respect to time (two cells with different letters are significantly different, Newman–Keul's range test, $p < 0.05$).

lites increase in the nucleus accumbens during feeding (11,28,32,34). In addition, they are the first to demonstrate the influence of the amount of food ingested on the activity of the mesolimbic dopaminergic system (MDS). Indeed, when the rats ate ad lib HP food, DA significantly increased, reaching 183% of basal level 25 min after access to food, whereas it only reached 127% when the rats ate half the amount of the same food. Although this level did not differ significantly from basal level, it was significantly higher than DA level in no food condition (Table 1). These results indicate that DA release is a direct function of the amount of food ingested. This is in accordance with the more indirect evidences mentioned in the introduction (12,22,28,32,34), and raises the question of the mechanism of action. At least three possibilities may be considered: locomotor activity accompanying food intake, postingestive effects of food, and food reward.

Several authors have described an association between locomotor activity and the meso-accumbens DA pathway (9,16), although other workers failed to detect any significant increase in DA in the nucleus accumbens during locomotion (7,17,33). In addition, the shell accumbens, where our probes were located, has been shown to be involved in oral behaviors such as chewing, grooming (27) or feeding (21), whereas the core is associated with the nigrosriatal system and motor activity (8). Furthermore, other authors failed to observe any significant DA release in the nucleus accumbens during the period of general arousal preceding food ingestion (25,28). We, therefore, assumed along with Zhang (35) that the alteration in extracellular levels of DA we observed was a reflection of the effect of feeding rather than motor activity per se. Although the size of the dialysis membrane was small (1 × 0.5 mm), we cannot definitively exclude the possibility that measurement of DA levels were not strictly restricted to the shell accumbens.

Because the rats absorbed about four times more calories during the ad lib HP food sessions than in the limited HP sessions (8.5 vs. 2.5 kcal), postingestive effects may be involved in the MDS activation. So, the occurence of the DA peak during the first 25 min after feeding suggests that it may be more related to satiety mechanisms than to sensory properties of the food (32). However, it is worthy to note that, although unsignificantly, DA level began to increase during food supply reaching 127% of basal level, and that in a previous study with similar experimental procedure (21) DA level peaked during food supply. In addition, there are arguments, provided by sham-feeding studies, which indicate that the nutrient content of the diet has little influence on DA release (29,30), and finally, conditioned taste preference experiments have shown that postingestive effects are not directly involved in this neurochemical response (20). All these observations are in favor of a role of the sensory properties of the food in DA release in the nucleus accumbens (20,29,30) and are consistent with the hypothesis that the amount ingested may act via the reward it induces. Because the reinforcement is a direct function of the appetitive stimulus (15), the amount of food ingested may be assumed to be a component of the reward associated with ingestive behaviors.

There is evidence for a specific link between reward and MDS activity. Accumbens DA release has been shown to be potentiated by many non alimentary rewarding stimuli such as psychostimulant drug administration (10,12,17,26), sexual behavior (7,18), electrical stimulation of the lateral hypothalamus (11), and ethanol administration (6,13). When rats are



FIGS. 3 and 4. Extracellular levels of DOPAC (Fig. 3) and HVA (Fig. 4) during microdialysis sessions in the nucleus accumbens of five rats. The results are expressed as percent of basal release (mean of samples prior to food supply ± SEM). *DOPAC and HVA releases are significantly higher at this time than at other times of ad lib HP session (Newman–Keul's range test $p < 0.05$). α DOPAC and HVA releases are significantly different between ad lib HP, limited HP, and no food sessions (Newman–Keul's range test $p < 0.05$).

administered compounds that facilitate DA neurotransmission, they increase responding for conditioned reward (2,5,31), whereas they show an impairment of such responses when administered compounds that block DA neurotransmission (1). The relationship between MDS activity and reward, especially food reward, is also supported by the observation that DA receptor antagonists, such as pimozide or raclopride, reduce ingestion of palatable foods (13,14), and that DA release in the nucleus accumbens is altered when food palatability is modified by conditioning (19,20). The role of the amount of food ingested as a component of food reward in MDS activity is consistent with the notion that when an organism comes into contact with a relevant appetitive stimulus (e.g., food), further contact with that stimulus (e.g., consummatory response of eating, i.e., quantity ingested) will enhance the reward activation (3). We, therefore, suggest that an augmentation in reinforcement by whatever mechanism will give rise to an increase in DA release in the nucleus accumbens.

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