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Mesolimbic Dopaminergic System Activity as a Function of Food Reward: A Microdialysis Study

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MARTEL, P. AND M. FANTINO. *Mesolimbic dopaminergic system activity as a function of food reward: A microdialysis study.* PHARMACOL BIOCHEM BEHAV **53**(1) 221-226, 1996.—The mesolimbic dopaminergic system (MDS) has been shown to be implicated in feeding behaviors. The present experiment was conducted to examine the effects of the sensory properties of food ingested on MDS activity. Microdialysis coupled to high-performance liquid chromatography with electrochemical detection was employed to measure the extracellular levels of dopamine (DA) and its main metabolites (DOPAC and HVA) in the nucleus accumbens of freely moving rats. During microdialysis sessions rats had access or not to powdered foods varying in palatability: short cakes as highly palatable (HP) food and regular chow as low palatable (LP) food. In the absence of food, there were no alterations in extracellular levels of DA, DOPAC, and HVA. During feeding, DA rose significantly with a greater rise for the HP than the LP food. Levels of DOPAC and HVA only reached significance with the HP food. The results indicate that the MDS is activated on ingestion of food, and suggest that MDS activity is related to the rewarding properties of foods.

Dopamine Nucleus sccumbens Food intake Palatability Microdialysis Food reward

AMONG the methods used to evaluate the activity of neural pathways involved in food intake (36), intracerebral microdialysis enables the study of neurotransmitters in localized brain regions in awake, freely moving animals (1,8,23,48). An increase in the extracellular level of dopamine (DA) in the nucleus accumbens, a major target of the mesolimbic dopaminergic system (15), during ingestion of food has been reported by numerous authors (19,21,34,41,53,54). This is indicative of a relationship between food intake and the activity of the mesolimbic dopaminergic system (MDS). Other studies have shown that the MDS is activated by rewarding processes (52) such as drug administration (20,37,55), self-stimulation (39), and sexual behavior (10,26). It has also been proposed that this system may be activated by food reward (20). Food reward depends in part on the hedonic component of the sensory properties of foods, i.e. their palatability (14,16). When offered a more palatable diet, most animal species eat more and may become obese (27,42,46). In most of the reported experiments on DA release associated with food intake, rats only had access to their regular food, and so the influence of food palatability was not addressed directly (20,21,29,31, 41,53). Moreover, in such experiments the rats were either 24 or 36 h food deprived (20,29,53) or were maintained at 75–80% of their basal body weight (21,31,41). As hunger makes food taste better (25), it is not clear whether the enhanced DA release in the nucleus accumbens was due to food intake per se, or to the rewarding aspect of feeding for hungry animals.

This study was designed to examine the effects of the ingestion of two foods varying in palatability on the activity of the MDS. The preference of rats for short cakes (highly palatable food) and regular chow (low palatable food) has been demonstrated in our laboratory and by other workers (4,5). MDS activity was indicated by the extracellular levels of DA and its main metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), measured by microdialysis in the nucleus accumbens.

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METHOD

Animals

The experiment was performed on nine 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 (light on at 0600 h). They had free access to regular chow (Extralabo M20 from Pietrement, France) except during the microdialysis sessions. They had access to water ad lib at all times. The experiment was conducted during the light cycle.

Feeding Conditions

The highly palatable (HP) food was short cakes (butter biscuits from Biscuits Saint-Michel-Grellier France), containing 4.1 kcal/g with 8 g/100 g proteins, 16 g/100 g lipids, and 60 g/100 g carbohydrates (33% sucrose, 67% starch). The low palatable (LP) food was regular chow (Extralabo M20), containing 2.9 kcal/g with 18 g/100 g proteins, 4 g/100 g lipids, and 60 g/100 g carbohydrates (100% starch). Both foods were powdered to obtain the same texture. Before the microdialysis sessions, the rats were habituated during 15 days to those experimental foods. Food was removed at 0800 h, and at 1300 h rats received, for 75 min, either HP food or LP food. The amount consumed during food supply (75 min) was measured.

Surgery

Under intraperitoneal pentobarbital anesthesia (60 mg/kg) each rat was stereotaxically implanted with a guide shaft aimed at the nucleus accumbens, according to the brain atlas of Paxinos and Watson (38), A: 2.2 mm anterior to bregma, L: 1.5 mm to the right of the midline, and V: 7.0 below the dura. 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 that was fixed to the cranial bones by three T-shaped stainless steel screws, according to a previously described technique (13).

Dialysis System

Probes used were CMA/10 (Canergie Medicin, Sweden) ending in a dialysis membrane (1 mm long, 0.5 mm wide) with a molecular weight cut-off of 20,000 Dalton. The relative recovery of the probes was measured regularly (9). It ranged from 7% to 10% according to the neurochemical. The microdialysis fluid, an artificial CSF consisting of 147 mM NaCl, 4.02 mM KCl, 3.42 mM $CaCl_2$, pH7, was perfused in the probe by an infusion pump (Harvard Apparatus, model 22).

Chromatographic Conditions

The HPLC system for analysis of the dialysates used a 20 μl loop to apply samples to a 125 mm $\times$ 4 mm MERCK RP-select B column (5 μm C-8 stationary phase). The mobile phase was 0.15 M anhydrous sodium dihydrogen phosphate, 1.4 mM sodium octyl sulfate, 0.8 mM EDTA, 5% methanol, at pH = 3.7. The flow rate was 1 ml/min using a Chromatofield pump (model 501). DA, DOPAC and HVA were detected with a twin cell Chromatofield detector (model ELDEC 201) at an applied potential of +0.6 V. The sensitivity was set at 0.2 nA/V for DA and 1 nA/V for DOPAC and HVA.

Experimental Procedure

After 5 days for recovery, each rat underwent three microdialysis sessions (over 3 subsequent days) that differed in their feeding conditions. Each rat thus served as its own control. At 0845 h, the probe was inserted in the previously implanted guide shaft and immediately perfused with artificial cerebrospinal fluid at a flow rate of 1.2 μl/min. Samples were collected every 25 min from 1145 to 1530 h, and immediately assayed for DA, DOPAC, and HVA by high performance liquid chromatography with electrochemical detection (HPLC-EC). During the three first samples (from 1145 am to 1300 h) and the three last samples (from 1415 to 1530 h), rats had no access to food. During food supply (from 1300 to 1415 h), rats had access to either HP food, LP food, or no food, according to a Latin-square design to balance the order of treatments.

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 cryo-microtome into 8 μm sections, which were stained with Toluidine blue. Probe placements were verified by comparing the slides to the atlas of Paxinos and Watson (38).

Statistical Analysis

Due to the large interindividual differences, the data were normalized as a percentage of the levels determined in the three dialysis samples prior to food supply. Each rat served as its own control. Results were expressed as means $\pm$ SEM. The results were subjected to one- and two-way ANOVA, followed when warranted by Newman-Keuls range test; the null hypothesis was rejected at the 0.05 level. The results of Newman-Keuls tests are shown on Figs. 2, 3, and 4. Student's t-test for paired comparison was used to compare the amounts of short cakes and regular chow ingested during the microdialysis sessions.

RESULTS

Probe Placement

Histology indicated that the dialysis probes were all located in the infero-external part of the nucleus accumbens, i.e., in the accumbens shell, as shown by a representative section in Fig. 1.

Food Intake

During the microdialysis sessions the rats ate significantly more short cakes than regular chow [3.22 $\pm$ 0.682 g vs. 1.17 $\pm$ 0.304 g; Student's t-test for paired samples (n = 9): t = 3.35, $p < 0.02$].

DA Metabolism

Basal extracellular levels (n = 9) of the measured catecholamines were 2.3 $\pm$ 0.3 pg/20 μl for DA, 823 $\pm$ 95 pg/20 μl for DOPAC and 551 $\pm$ 55 pg/20 μl for HVA.

The extracellular level of DA over time (Fig. 2) differed significantly between the three feeding conditions [two-way ANOVA: food condition effect: $F(2, 208) = 18.28$, $p < 0.0001$; time effect: $F(8, 208) = 5.25$, $p < 0.0001$; food condition $\times$ time interaction: $F(16, 208) = 2.95$, $p < 0.0003$]. Table 1 shows that in the absence of food, DA level did not change significantly over time [one-way ANOVA: $F(8, 64) = 1.26$, NS]. In contrast, DA level rose significantly as soon as the rats had access to either HP [one-way ANOVA: $F(8, 64) = 3.81$, $p < 0.001$], or LP food, [$F(8, 64) = 3.71$, $p <$

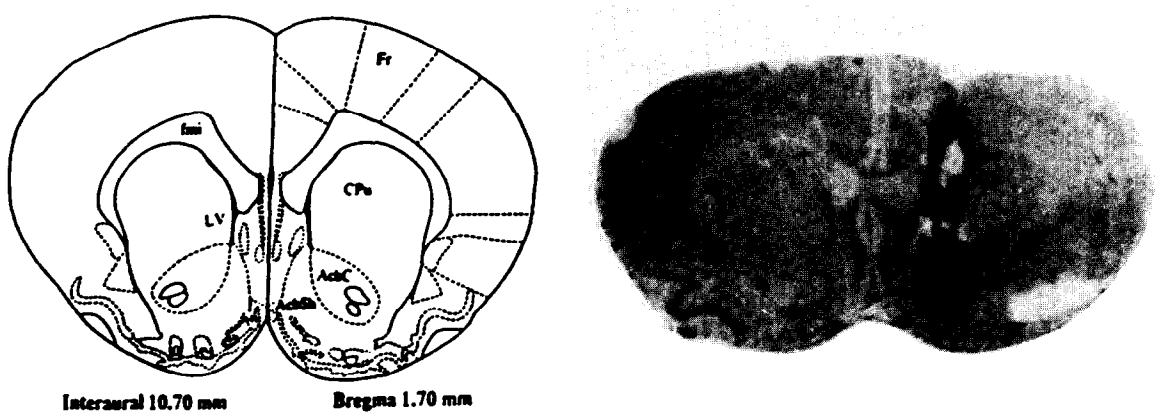


FIG. 1. Comparison of a stained brain section of one rat (left) to the corresponding slide of the Paxinos and Watson atlas (right). As a result of freezing, the left brain appears flatter than in B. The probe was well located in the nucleus accumbens shell. AcbC: nucleus accumbens, core; AcbSh: nucleus accumbens, shell; CPu: caudate putamen; fmi: forceps minor corpus callosum; Fr: frontal cortex; LV: lateral ventricle.

0.002]. Two-way ANOVA indicates that there was a significant difference over time between HP and LP sessions [food condition effect: $F(1, 136) = 7.42$, $p < 0.008$; time effect: [$F(8, 136) = 5.73$, $p < 0.0001$; food condition × time interaction: $F(8, 136) = 1.94$, NS]. The rise in DA was considerably greater with HP food, reaching 246% of the basal level (vs. 134% with LP food) during the first 25 min of food supply. With LP food, DA level peaked during the second 25 min of food supply reaching only 142% of the basal level (Table 1). At any time during access to food, one-way ANOVA showed that levels of DA differed significantly between the three feeding conditions: at 100 min $F(2, 16) = 4.15$, $p < 0.04$, at 125 min $F(2, 16) = 6.86$, $p < 0.008$ and at 150 min $F(2, 16) = 13.64$, $p < 0.0004$. However, Newman-Keuls range test indicated that this difference reached significance only during the last 25 min of food supply (α, β and θ on Fig. 2).

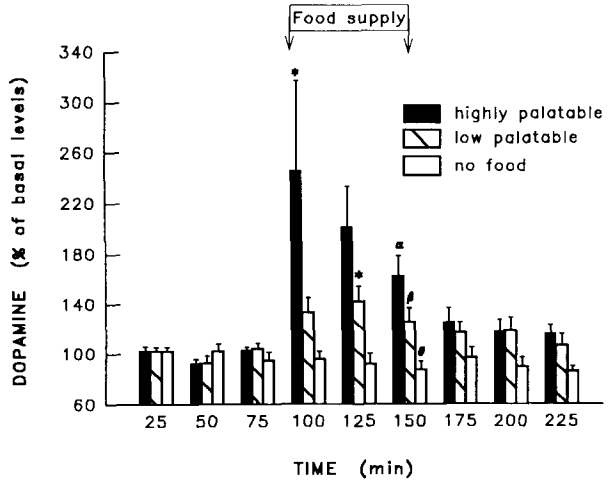


FIG. 2. Extracellular levels of DA during microdialysis sessions in the nucleus accumbens of nine rats. The results are expressed as percent of basal release (mean of samples prior to food supply ± SEM). *DA release during access to HP and LP food is significantly higher than basal levels (Newman-Keuls range test, $p < 0.05$). α, β, θ: DA release is significantly different between HP, LP, and no food sessions (Newman-Keuls 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: $F(2, 208) = 4.40$, $p < 0.02$; time effect: $F(8, 208) = 1.69$, NS; food condition × time interaction: $F(16, 208) = 1.19$, NS] and HVA [food condition effect: $F(2, 208) = 5.47$, $p < 0.005$; time effect: $F(8, 208) = 3.18$, $p < 0.003$; food condition × time interaction: $F(16, 208) = 0.76$, NS]. In the absence of food there was no significant change over time in DOPAC [one-way ANOVA: $F(8, 64) = 0.57$, NS] and HVA [$F(8, 64) = 1.04$, NS]. When the rats ate HP food, DOPAC and HVA rose significantly [respective one-way ANOVA: $F(8, 64) = 4.23$, $p < 0.0005$; $F(8, 64) = 3.77$, $p < 0.01$]. Newman-Keuls range test revealed a significant peak for DOPAC and HVA during the last 25 min of the HP meal (Figs. 3 and 4). Smaller increases in metabolites were observed when the rats had access to the LP food, only reaching significance for HVA [one-way ANOVA: $F(8, 64) = 2.27$, $p < 0.04$].

DISCUSSION

The present results are in line with previous reports showing that, during eating, extracellular levels of dopamine and its metabolites increase in the nucleus accumbens (18,19, 41,53). It has been suggested that the increase in both DA and its metabolites is a result of an increase in both firing of DA neurons ending in the accumbens and DA synthesis (2,24,54). The timing of the chemical changes (DA peaking during the first 25 min of eating, DOPAC and HVA peaking more than 50 min after the onset of the meal) has also been observed by other workers (19,20), and has been attributed to gradual increase in DA reuptake and the latency of the enzyme systems degrading DA (21,54).

In contrast, other studies observed increases in DA release in other structures but not in the nucleus accumbens during food intake (7,47). There are several possible explanations for the discrepancies between the present results and those

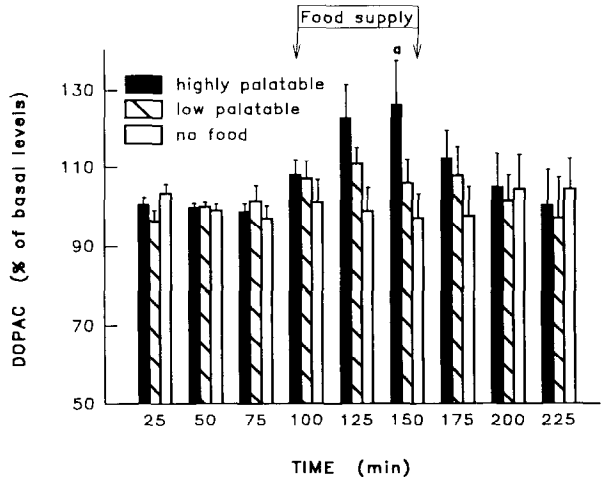
TABLE 1

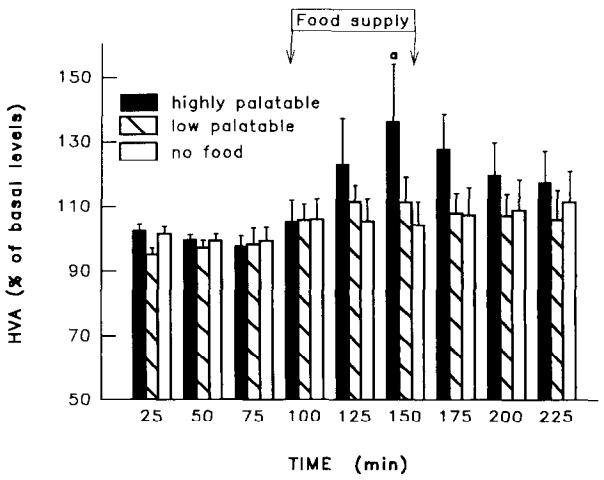
EXTRACELLULAR LEVELS OF DOPAMINE
(EXPRESSED AS PERCENT OF BASAL LEVELS ± SEM)
DURING MICRODIALYSIS SESSIONS IN THE NUCLEUS ACCUMBENS OF 9 RATS

Time (min)	High Palat. food		Low Palat. food		No food		ANOVA Food Condition
25	103 ± 2.7		102 ± 2.8		103 ± 2.9		$F(2,16) = 0.01$
	b		ac				NS
50	93 ± 3.0		93 ± 5.8		102 ± 5.7		$F(2,16) = 0.86$
	b		a				NS
75	103 ± 2.2		104 ± 4.3		95 ± 6.8		$F(2,16) = 0.94$
	b		ac				NS
100	246 ± 70.6		134 ± 11.6		96 ± 5.8		$F(2,16) = 4.15$
	a	α	bc	$\alpha\beta$		β	$p < 0.04$
125	202 ± 32.4		142 ± 11.9		92 ± 8.0		$F(2,16) = 6.86$
	ab	α	b	$\alpha\beta$		β	$p < 0.008$
150	163 ± 15.8		126 ± 11.0		88 ± 6.3		$F(2,16) = 13.64$
	ab	α	abc	β		θ	$p < 0.0004$
175	126 ± 10.7		117 ± 8.6		97 ± 7.7		$F(2,16) = 3.78$
	b	α	abc	$\alpha\beta$		β	$p < = 0.05$
200	118 ± 9.6		118 ± 10.8		90 ± 6.8		$F(2,16) = 2.62$
	b		abc				NS
225	116 ± 7.0		106 ± 9.0		86 ± 3.9		$F(2,16) = 4.89$
	b	α	ac	α		β	$p < 0.05$
ANOVA time	$F(8,64) = 3.81$ $p < 0.001$		$F(8,64) = 3.71$ $p < 0.002$		$F(8,64) = 1.26$ NS		

The food supply period (time 100, 125, 150 min) lasted 75 min with either high palatable food (short cakes), low palatable food (powdered chow), or without food. Left: one-way ANOVA according to food condition (two cells with different greek symbols are significantly different, Newman-Keuls range test $p < 0.05$). Bottom: one-way ANOVA according to time (two cells with different letters are significantly different, Newman-Keuls range test $p < 0.05$).

mentioned above. One possibility stems from the probe location within the accumbens. The accumbens is not an homogenous structure (33) and consists of two distinct territories, referred to as core and shell. The core is associated with the nigrostriatal system, while the shell is related to the mesolimbic system (11). Recent studies have provided evidence for the involvement of the shell in oral behavior (40). In our experiment, the probes were all located within the shell of the nucleus accumbens. It is perhaps worthy of note that in most of the studies that failed to find any increase in DA in the accum-





FIGS. 3-4. Extracellular levels of DOPAC (Fig. 3) and HVA (Fig. 4) during microdialysis sessions in the nucleus accumbens of nine rats. The results are expressed as percent of basal release (mean of samples prior to food supply ± SEM). (a) release is significantly higher at this time than at other times of HP session (Newman-Keuls range test, $p < 0.05$).

bens during food intake, the histological location of the probe within this structure was not indicated (7,47).

Another explanation may come from differences in feeding conditions and/or in the type of food given. Because our experiment was conducted with nonfasted rats during the light period, the physiological hyperphagia of the dark period was avoided. In the light period, differences in consumption of short cakes or regular chow will tend to depend mainly on the sensory properties of the food (35). Other studies conducted during the light period failed to find a significant increase in DA accumbens when rats ate regular chow, except when the animals were food deprived (18,20,21,31,41). The increase in DA observed in food-deprived rats could be accounted for by the larger amount of food ingested. In our study, nonfasted rats with access to powdered regular chow (LP food) only displayed a small increase in DA, and no significant increase in DA metabolites on feeding. However, DA release in the accumbens was much higher when rats ate a threefold higher amount of short cakes (HP food) than regular chow (LP food). This difference may, thus, have been due to the difference in the amount of food ingested, as well as differences in the composition and sensory properties of the food, or to the extra locomotor activity accompanying eating. Some studies have shown that motor activity increases DA metabolism in both striatum and nucleus accumbens (43). Because we have not measured motor activity, the influence of this factor on DA release was not addressed in the present experiment. It is worthy of note that we did not observe marked behavioral changes in the animals between the three feeding conditions. Furthermore, Blackburn and colleagues have not found significant differences in DA accumbens between the ingestion of a solid and a liquid diet (3), and other studies failed to find a significant increase in DA accumbens during the period of general arousal preceding food supply (41), or during locomotion (10,50). We, therefore, assumed that the alteration in extracellular levels of DA we observed reflected the effect of feeding rather than motor activity. Because the HP food has a higher energy density than the LP one (4.1 kcal/g vs. 2.9 kcal/g), postingestive effects may be involved in the DA release in the accumbens. However, sham-feeding studies have shown that the nutrient content of the diet had little influence on DA release (18,47), and indicated rather that the sensory properties of the food play an important role in the activation of the mesolimbic dopaminergic system (30,45,47). The fact that DA release during ingestion of the HP food peaked during the first 25 min of food supply is more consistent with an influence of the orosensory properties of the food than its postingestive effects (30,44). In our experiment, the enhanced DA release may have been an effect of sweetness (22,45) as short cakes are sweeter than regular chow. However, it is of interest that nonsweetened food was used in most of the studies showing an increase DA during eating (20,21,41,53). Brain dopaminergic mechanisms may be involved in sweet taste rewards, but are more probably involved in the general rewarding properties of foods.

Finally, the present results indicate that MDS activity may be involved in the rewarding aspects of feeding. For instance, it is known that DA release is potentiated by rewarding stimuli (6,51) such as drug administration (20,37,55), psychostimulant reward (12,49), sexual behavior (10,26), self-stimulation (39), as well as alimentary rewards such as periodic food presentation (31), drinking behavior in water-deprived rats (53,54), ethanol or sucrose-reinforced behaviors (22), operant schedules of reinforcement (17,32,44), and appetitively conditioned taste (30). Experiments showing an alteration in DA release in the accumbens when food palatability was modified by conditioning (28,30), point to a link between feeding reward and MDS activity. However, because food reinforcement is a function of the amount of food ingested, the enhancement of DA metabolism during ingestion of the HP food may have been due to both the sensory properties of the short cakes (i.e., palatability) and the higher amount of HP food ingested. Experiments are in progress to examine the respective roles of the sensory properties of foods and the amount ingested.

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