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Increased Dopamine Metabolism in the Nucleus Accumbens and Striatum Following Consumption of a Nutritive Meal but not a Palatable Non-Nutritive Saccharin Solution

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BLACKBURN, J. R., A. G. PHILLIPS, A. JAKUBOVIC AND H. C. FIBIGER. *Increased dopamine metabolism in the nucleus accumbens and striatum following consumption of a nutritive meal but not a palatable non-nutritive saccharin solution.* PHARMACOL BIOCHEM BEHAV **25**(5) 1095–1100, 1986.—This study examined the concentrations of dopamine (DA) and its metabolites homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) in the striatum and nucleus accumbens of rats that were either 20 hr food deprived or had been given 1 hr of access to food pellets, a liquid diet, or a palatable 0.4% saccharin solution. Significant increases were observed in the HVA/DA ratio in both structures following ingestion of either liquid diet or food pellets. Increases in the DOPAC/DA ratio were observed only after the ingestion of liquid diet. Ingestion of saccharin solution had no effect on any index of DA activity. These results indicate that the type of food ingested can influence dopaminergic responses to feeding, and argue against an exclusive role for motor or reward processes in determining DA activity.

Dopamine DOPAC/DA ratio Nucleus accumbens DOPAC HVA Striatum Saccharin HVA/DA ratio Feeding behaviour

FOOD intake is a complex process controlled by both internal and external stimuli [31,33]. Numerous studies employing either pharmacological or surgical disruption of dopaminergic neurotransmission suggest a role for dopamine (DA) in the neural regulation of feeding behaviour [6, 11, 15, 16, 20, 22, 29, 30, 32, 38]. At present, there is uncertainty as to the relationship between dopaminergic activity and the various components of feeding behaviour including the production of motor behaviours required for feeding, the perception of the reward value of food [36,37], or the stimulus control of feeding [4,33].

Recent attempts to clarify the role of DA in feeding behaviour have utilized biochemical analyses of dopaminergic activity in localized regions of the brain. For example, Heffner *et al.* [13] have observed increases in DA metabolism in various brain regions following consumption of a meal. DA turnover was estimated by the ratio of the concentration of the DA metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) to the concentration of DA. The DOPAC/DA ratio was increased significantly in the hypothalamus, nucleus accumbens, and amygdala 1 hr after the onset of a daily meal of food pellets in rats maintained on a 20 hr food deprivation schedule. No effects were attributed to food deprivation itself, as similar levels of DA utilization were observed in groups of rats either maintained on a food deprivation schedule and sacrificed prior to the daily feeding session or maintained on ad lib access to food. The nutrient content of the food and postingestional events were also discounted as relevant factors. In contrast to increases observed following oral consumption of a liquid suspension of powdered Purina lab chow, gastric intubation of this diet was not accompanied by an increase in DA utilization in either the nucleus accumbens or posterior hypothalamus. The restricted pattern of feeding-related increases in DA utilization

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in selected brain regions suggested that only a subset of central dopaminergic neurons were activated by some aspect of feeding behaviour, specifically those in the mesotelencephalic pathway and hypothalamus.

Subsequent attempts to define the precise relationship between feeding and DA activity have examined changes in DA utilization under different feeding conditions. Although the accumulation of DOPAC was shown to be increased in the second to fourth hr of access to food pellets, these changes were not correlated with the duration of access to food, the amount of food consumed, latency to onset of feeding or the termination of the meal. Therefore these data were incompatible with a role for DA in either hunger or satiety [14]. A recent effort to resolve this conundrum compared changes in DA metabolism in groups adapted to a daily feeding regimen and sacrificed either prior to presentation of a milk diet, 1 hr after food was provided, or following exposure to a set of discriminative stimuli associated with the presentation of a meal, but with no opportunity to feed [28]. Comparable increases in DA metabolism were observed in both groups exposed to feeding-related discriminative stimuli, regardless of whether or not feeding occurred. This pattern of results was interpreted as evidence that increases in DA activity are entrained to environmental stimuli associated with scheduled feeding behaviour. These increases in DA activity were observed in the hypothalamus, but not in the nucleus accumbens, striatum or amygdala-pyriform lobe.

Collectively these studies raise a number of issues worthy of further investigation. The first concerns the relationship between the presentation of feeding-related stimuli, consumption of a meal, and increased metabolism of DA. The stimulus control of feeding should have a maximum effect immediately prior to and at the onset of the meal, yet DA activity has been observed to increase in the period between 1 and 2 hr after food was provided. It might be argued that the first hour of food presentation serves as a cue for the availability of food for another 3 hr period. Alternatively, the changes in DA activity which accompany the presentation of feeding-related stimuli may be distinct from those associated with the oral ingestion of a meal. Second, it has not yet been determined whether similar increases in DA metabolism would be observed following ingestion of comparable quantities of a non-nutritive substance. Third, can the consumption of a meal trigger increases in DA activity associated with the rewarding properties of the food [36,37]? A final issue concerns the ambiguity surrounding the anatomical locus of feeding-related increases in DA metabolism. Specifically, do such increases occur only in the hypothalamus [28], or can they also be observed reliably in the nucleus accumbens [7,13] and the striatum? [7].

The present experiment was designed to address some of these issues by measuring changes in DA metabolism in tissue samples from the nucleus accumbens and striatum 1 hr after consumption of food pellets, liquid diet, or palatable (0.4%) saccharin solution. Ingestion of the saccharin solution should be rewarding, and requires the same motor responses as ingestion of liquid diet, but has no post-ingestive nutritive effects. Liquid diet and food pellets are both nutritive, but require notably different motor responses for their consumption.

METHOD

Subjects

Male hooded rats obtained from Charles River Laboratories of Canada were used. All rats were experimentally naive, weighed 350–450 g at the start of the experiment and were housed individually in wire stainless steel cages.

Apparatus

Feeding materials consisted of standard Purina lab chow pellets, Sustacal (Mead Johnson) liquid diet and 0.4% sodium saccharin (Fisher) solution. Fluids were presented to the rats in 50 ml Nalgene tubes fitted with stainless steel drinking spouts that were attached to the front of the cages. Food pellets were delivered into food hoppers mounted on the outside of the cage.

Procedure

The feeding regimen was modified from that described by Heffner *et al.* [13]. Water was freely available to all rats at all times. Rats were randomly assigned to four groups (n=6 for each group), and were then adapted for two weeks to a feeding schedule in which they received food for only 4 hr/day in their home cages. The feeding period occurred near the middle of the 12 hr lights-on period in the colony. As it has previously been demonstrated that DA utilization is increased by cues previously paired with feeding [5,28], feeding times were varied by up to 2 hr on successive days to minimize the association between temporal cues and feeding.

Rats in the food deprived (FD) and pellet (Pel) groups received food pellets in each daily 4 hr feeding period. The rats in one group (LD) received liquid diet during the 4 hr feeding period on the fourth day. They also received the liquid diet in the first hr of this period on the 8th and 12th days, followed by 3 hr access to pellets. Rats in the final group (Sac) were treated in exactly the same manner as those in group LD except that 0.4% saccharin solution was substituted for liquid diet. This procedure ensured that rats in the four restricted feeding groups were maintained at equivalent levels of deprivation, while allowing the rats in groups Sac and LD to become familiar with the solutions they were to consume on the test day.

On the test day, the 15th day of restricted food intake, all the rats were sacrificed by cervical fracture. Rats in group FD were sacrificed when they had been deprived of food for about 20 hr, before food was delivered on the test day. Care was taken to avoid exposing these control rats to odours or sounds signaling food delivery, as such cues have been shown to increase DA utilization [5,28]. Rats in groups Pel, LD and Sac were sacrificed 1 hr after they had been given pellets, liquid diet or a saccharin solution, respectively. During the hour in which food was available the LD rats consumed 24.2±0.7 ml of the liquid diet, while the Sac rats consumed 27.6±1.9 ml of the saccharin solution.

Tissue Extraction

Following sacrifice the brains were rapidly removed and frozen with CO_2 on a microtome. Two consecutive 1-mm coronal slices were taken and placed in ice so that the rostral surface was face up. By the atlas of König and Klippel [17], the rostral extent of the anterior slice was approximately at the level of A9820 μ and the rostral limit of the second slice was approximately at A8620 μ. The nucleus accumbens was dissected from the rostral slice. The structure was defined as being ventral to the genu of the corpus callosum and dorsal to the olfactory tubercle (demarcated by small fiber bundles forming the olfactory radiations). The anterior commisure

was included in the sample. The mean weight of the nucleus accumbens samples was 7.8 mg. The striatum was dissected from the caudal slice and was defined dorsally and laterally by the corpus callosum. The medial border was formed by the lateral ventricles. The ventral limit was imposed by making a horizontal cut at the level of the anterior commisure. The mean weight of the striatal samples was 12.3 mg. Following weighing, the tissues were sonicated for 30 sec in 0.2 M $HClO_4$ with 0.15% $Na_2S_2O_5$ and 0.5% Na_2-EDTA. Following centrifugation at 30,000 g for 15 min (+4°C), the supernatant was removed and stored at −80°C. Assay of the precipitate [19] indicated that the mean protein content of the nucleus accumbens samples was 10.7% by weight, while that of the striatal samples was 11.2%.

Neurochemical Analysis

Regional brain analysis of DOPAC, HVA and DA was performed by reverse phase high pressure liquid chromatography with electrochemical detection (HPLC-EC). The HPLC-EC system consisted of a Beckman model 100A pump, LC-4B amperometic controller with a glassy carbon electrode (BAS), a 3390A recorder integrator (Hewlett-Packard) and a μBondapak C18 column (10 μm, 150×3.9 mm; Waters). The detector potential was set at +0.75 V versus a Ag/AgCl reference electrode and the sensitivity was set at 10–20 nA/V full scale. The mobile phase consisted of 0.1 M KH_2PO_4 buffer solution (pH 3.6) containing 0.2 mM sodium octanesulfonic acid, 0.15 mM Na_2-EDTA and 9.5% methanol.

The concentrations of DA, DOPAC and HVA were determined by comparing the peak area of the sample with that of a known standard. The detection limit of the system was approximately 0.5 pmol/20 μl of tissue sample.

Data Analysis

One-way ANOVAs were conducted for the concentrations of DA and its metabolites, DOPAC and HVA, and also for the ratio of each metabolite to the parent molecule in both of the brain regions. Each measure was taken as the average of the two hemispheres. When the ANOVA indicated a significant effect, Dunnett's test [12] was used to compare each of the feeding groups to the FD animals.

RESULTS

The concentrations of DA and its metabolites, DOPAC and HVA, are shown in Table 1 for both of the brain regions. The analysis of variance indicated that the concentration of DA, in either the accumbens or the striatum, was not significantly affected by the different feeding conditions (Fs<1). There was a significant difference between DOPAC concentrations in the nucleus accumbens, $F(3,20)=6.44$, $p<0.005$, these being higher in the LD group, relative to the FD rats ($p<0.01$). A significant difference between the groups was also observed for DOPAC in the striatum, $F(3,20)=4.14$, $p<0.05$, however Dunnett's test did not indicate that the levels for any group differed significantly from those of the LD controls. HVA differed significantly between groups in both the nucleus accumbens, $F(3,20)=10.71$, $p<0.001$, and the striatum, $F(3,20)=7.70$, $p<0.005$. In the case of the nucleus accumbens, HVA was significantly elevated for both the Pel ($p<0.05$) and LD ($p<0.01$) groups, relative to the FD controls. In the striatum only the Pel group had significantly elevated HVA ($p<0.01$).

TABLE 1

EFFECTS OF INGESTING FOOD PELLETS, LIQUID DIET OR SACCHARIN SOLUTION ON LEVELS OF DA, HVA AND DOPAC IN THE NUCLEUS ACCUMBENS AND STRIATUM

	Concentration (nmol/g tissue)		
Group	DA	HVA	DOPAC
	Nucleus Accumbens		
FD	57.77 ± 1.94	5.32 ± 0.26	14.91 ± 0.63
Pel	58.65 ± 2.06	6.55 ± 0.39*	15.79 ± 0.65
LD	58.55 ± 0.96	6.94 ± 0.26†	17.80 ± 0.55†
Sac	54.92 ± 1.22	4.77 ± 0.74	14.68 ± 0.32
	Striatum		
FD	77.26 ± 3.89	6.27 ± 0.32	13.74 ± 0.64
Pel	76.31 ± 2.21	7.77 ± 0.37†	13.49 ± 0.27
LD	73.78 ± 1.98	7.15 ± 0.69	15.16 ± 0.46
Sac	70.62 ± 2.07	5.85 ± 0.23	12.89 ± 0.41

All values expressed as mean ± standard error (n=6). FD: Food deprived for 20 hr prior to sacrifice. Pel: Consumed food pellets in the hour prior to sacrifice. LD: Consumed liquid diet in the hour prior to sacrifice. Sac: Consumed 0.4% saccharin solution in the hour prior to sacrifice.

*Different from FD: $p<0.05$. (Dunnett's test).

†Different from FD, $p<0.01$. (Dunnett's test).

DOPAC/DA ratios are shown in Fig. 1. There were significant differences between groups in both the nucleus accumbens, $F(3,20)=3.60$, $p<0.05$, and the striatum, $F(3,20)=3.95$, $p<0.05$. In each case the ratio was increased significantly only for the LD group (ps<0.05).

The HVA/DA ratios are shown in Fig. 2. The ANOVA indicated significant group differences in both the nucleus accumbens, $F(3,20)=8.79$, $p<0.001$, and the striatum, $F(3,20)=5.38$, $p<0.001$. Compared to the FD controls, ratios were significantly elevated for the Pel groups in both brain regions ($p<0.05$ in each case). Consumption of the LD was also associated with increased HVA/DA ratios in both the nucleus accumbens and the striatum (ps<0.05).

DISCUSSION

The present data confirm that increases in DA activity are associated with the consumption of food. It should be noted, however, that changes in the two indices of DA activity employed in the present study varied as a function of the type of food ingested. For example, ingestion of food pellets was associated with increases in the HVA/DA ratio in both the nucleus accumbens and the striatum, whereas no increases were observed in the DOPAC/DA ratios. The latter result is consistent with a recent report of a failure to find significant increases in this index of DA activity in the hypothalamus 1 hr after the start of a meal of food pellets although significant changes were observed after 2 hr [14]. Consumption of liquid diet, on the other hand, was associated with a significant increase in both the HVA/DA and DOPAC/DA ratios in both brain regions sampled, 1 hr after the start of a meal. In the present experiment, these differences may be attributable to different influences of the types of food ingested on DA release and metabolism. Alternatively, as movement through

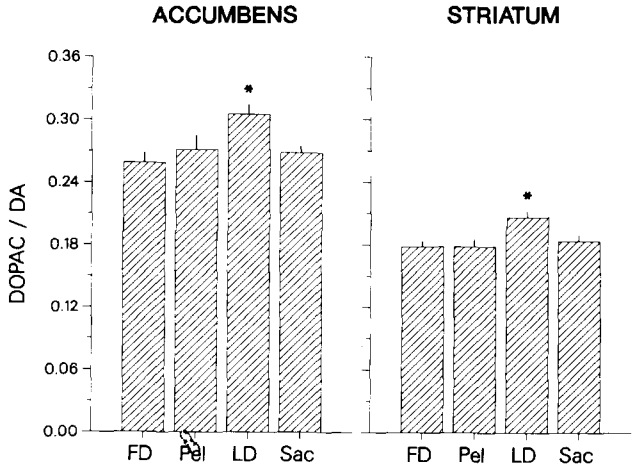

FIG. 1. Ratio of DOPAC to DA (both calculated as nmol/g tissue) in the nucleus accumbens and striatum following ingestion of food pellets, liquid diet or saccharin solution. Bars represent mean for six rats. Vertical lines represent standard error of the mean. FD: Food deprived for 20 hr prior to sacrifice. Pel: Consumed food pellets in the hour prior to sacrifice. LD: Consumed liquid diet in the hour prior to sacrifice. Sac: Consumed 0.4% saccharin solution in the hour prior to sacrifice. *Different from FD, $p<0.05$ (Dunnett's test).

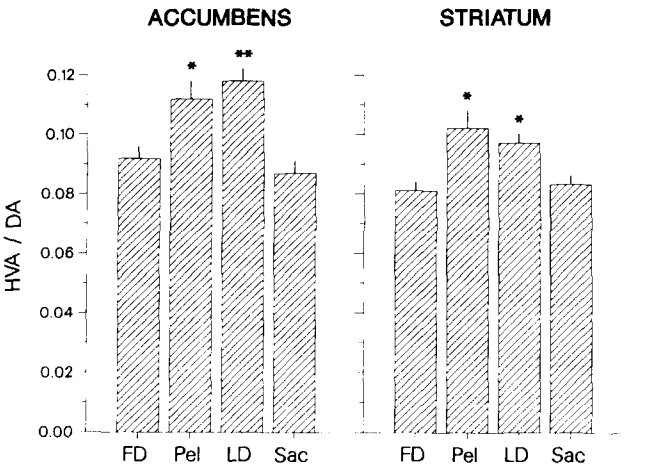

FIG. 2. Ratio of HVA to DA in the nucleus accumbens and striatum following ingestion of food pellets, liquid diet or saccharin solution. Abbreviations as in Fig. 1. *Different from FD, $p<0.05$ (Dunnett's test). **Different from FD, $p<0.01$ (Dunnett's test).

the DA metabolite pools is dynamic, differences in the rates at which the foods are digested and metabolized could affect the time course of their impact on dopaminergic systems.

The present results do not indicate any selectivity in alterations of DA activity between the mesolimbic and nigrostriatal DA systems as similar elevations were observed in both brain regions. This finding is consistent with one previous report [7], but differs from other studies that have reported increases only in the nucleus accumbens [13] or no change in either structure [28]. Further experiments will be necessary to reveal if analytic procedures, types of food, or other factors such as time of sampling are critical parameters for determining which brain region will show signs of increased DA activity.

The present results bear on the analysis of which components of feeding behaviour are related to these changes in brain chemistry. Previous research has indicated that a single day of food deprivation does not result in an increase in DA utilization [3, 13, 14, 28]. Nor can increases be attributed to a particular pattern of motor activity. In the present experiment biting and chewing of solid food was associated with comparable increases in HVA/DA ratios to those produced by lapping a liquid diet from a spout. On the other hand, when motor responses identical to those involved in the ingestion of liquid diet were executed during the consumption of saccharin solution, no such increases were observed. This finding rules out the possibility that the motor sequences involved in consuming a liquid diet were associated with the changes in DA metabolism.

The observed increases in DA activity may be related to post-ingestive events. This hypothesis would be compatible with the recent observation that DOPAC/DA ratios rose markedly during the second hour of a feeding session, despite the fact that only a small amount of food was consumed during this period [14]. Post-ingestive effects could either be related to the increased availability of specific nutrients or to increased energy stores. It seems improbable that increased energy availability could be directly responsible for the observed increases in DA activity as several studies have reported decreased dopaminergic activity following infusions of glucose [10, 25, 34], whereas severe glucoprivation produces increases in DA utilization [1, 2, 8, 9, 24, 26].

Reward is an additional factor that has been proposed as a candidate for producing changes in DA activity [36]. This hypothesis is challenged by the failure to find an increase in DA utilization associated with saccharin intake. Saccharin solution is avidly consumed by rats, and is an adequate reward to maintain high rates of operant behaviour [27]. Clearly, engaging in activities associated with hedonically positive states is not sufficient to increase DA utilization as estimated by the present methods.

The present data are also relevant to a previously proposed role for DA in the production of responses to appetitive stimuli [4]. Other studies have indicated that DA utilization is increased when rats are exposed to stimuli that reliably predict the availability of food [5,28]. Precautions were taken in the present experiment to ensure that the food-deprived control subjects were not exposed to such feeding-related stimuli, whereas the delivery of the food pellets, liquid diet and saccharin solution was accompanied by the familiar sounds and odours of the feeding sessions. The increases observed in DA utilization in the brains of rats that had consumed pellets or liquid diet may thus be interpreted in terms of appetitive, incentive-based responses. In this case, the absence of any increase following saccharin ingestion would have to be attributed to an inability on its part to be associated with appetitive behaviour. In fact, saccharin solutions are unusual in that, unlike other rewards such as sucrose solutions, they are incapable of producing conditioned place preferences [35]. Different effects of saccharin and sucrose solutions in conditioned reinforcement, even when they are equated for preference [21,35], may be related to saccharin's inability to increase DA utilization.

Although different events may lead to increases in DA activity observed prior to a feeding session, as opposed to after a meal, these factors could be related. One possibility is that the release of DA in the wake of a meal occurs as an

unconditioned response to some biochemical stimulus. In an adult animal, stimuli predicting the delivery of food could act as conditional stimuli to which the release of DA would be a conditioned response. This pre-feeding release may be related to the animals' preparation for feeding. Powley [23] has proposed a similar mechanism to account for pre-feeding increases in insulin release.

In conclusion, the present data indicate that changes in DA activity associated with feeding differ with the substance ingested and with the index of DA activity employed. Although it was not varied in this study, the precise time at which biochemical activity is sampled in relation to initiation of feeding behaviour [3,14] appears to be an important factor in determining which DA metabolite will provide the most sensitive index of DA activity. Ideally, sequential biochemical measurements should be taken from several brain regions during the preparatory, consummatory and post-ingestive phases of feeding behaviour, involving the consumption of different types of food. These and other important issues may be best addressed through the use of *in vivo* techniques, including chronoamperometric detection, in conjunction with chronically implanted catecholamine selective electrodes [18].

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