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Food-Related Stimuli Increase the Ratio of 3,4-Dihydroxyphenylacetic Acid to Dopamine in the Hypothalamus

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SIMANSKY, K. J., K. A. BOURBONAIS AND G. P. SMITH. *Food-related stimuli increase the ratio of 3,4-dihydroxyphenylacetic acid to dopamine in the hypothalamus.* PHARMACOL BIOCHEM BEHAV. **23**(2) 253–258, 1985.—Rats were restricted for three weeks to a schedule of 4-hr daily access to food. The regional concentrations of dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC) in the forebrain were then determined after the rats: (1) were food-deprived overnight; (2) ate for the first hour of the scheduled feeding period; or (3) remained in their cages without receiving food but while other rats fed. A group of controls had food available continuously. The DOPAC/DA ratio, a metabolic index of DA activity, increased in the hypothalamus of rats that fed and in the rats exposed to food-related stimuli without eating. This ratio did not change in the striatum, olfactory tubercle, amygdala-pyriform lobe or nucleus accumbens. Furthermore, this index did not differ from controls in any region of the forebrain in deprived rats that were not exposed to stimuli signalling the availability of food. Together, these data suggest that environmental stimuli associated with feeding after deprivation, and not the act of feeding, increased dopaminergic activity in the hypothalamus.

Dopamine Feeding Food-related stimuli DOPAC Stimulus control of DA
Schedule-induced feeding DOPAC/DA ratio Hypothalamic DA DA turnover

DURING the past fifteen years, numerous studies established that pharmacological or surgical manipulations which decreased the activity of dopaminergic mechanisms in the brain impaired appetitive and consummatory responding for food by rats [6, 10, 16, 21, 29, 31, 32, 39, 40]. These observations led to proposals that dopaminergic neurons mediated the activation, expression or reinforcement of feeding and other motivated behaviors [18, 23, 30, 37]. It was arguable, however, whether the behavioral effects due to perturbing dopaminergic function adequately reflected neurochemical processes that normally controlled feeding.

A complementary tactic involved determining the neurochemical changes associated with eating in neurally intact, undrugged animals. Using this approach, Heffner *et al.* [8] obtained evidence that feeding elicited by food deprivation stimulated dopaminergic neurons in regions of the forebrain. These investigators employed the ratio of the concentration of 3,4-dihydroxyphenylacetic acid (DOPAC), an acidic metabolite of dopamine (DA), to the concentration of DA as a metabolic index of DA turnover [14,16]. They detected increases in the DOPAC/DA ratio in the hypothalamus, nucleus accumbens and amygdala after rats fed for one hour following twenty hours of food deprivation. Feeding appeared to alter the activity of only some components of the dopaminergic systems in the forebrain because no changes occurred in the striatum, frontal cortex, septum or olfactory tubercle. Furthermore, the apparent increases in the regional turnover of DA were not due solely to food deprivation because the ratios were identical in controls fed ad lib and in deprived rats that were sacrificed without having access to food.

These findings agreed with previous studies in which feeding elicited by deprivation elevated the level of DOPAC in whole rat brain [5] and increased the efflux of labeled DA from the hypothalamus [15]. The results appeared to conflict with the failure to obtain increases in DA efflux during feeding in another study [33]. In this latter experiment, however, rats were fed after a single overnight period of food deprivation. By contrast, in each of the studies in which DA efflux or turnover increased [5, 8, 15], the rats were first adapted to a regimen of limited daily access to food.

Although these data suggest that scheduled feeding can stimulate dopaminergic mechanisms, the precise stimuli eliciting this neural activity remain unclear. For example, it was recently reported that the rate at which DOPAC accumulated in the hypothalamus was uncorrelated with either the duration of access to food or the amount of food eaten [9]. These investigators concluded that dopaminergic activity in the hypothalamus mediated some aspect of ingestive behavior without directly reflecting the states of hunger or

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TABLE 1

EFFECTS OF FEEDING REGIMENS ON INGESTIVE BEHAVIOR AND BODY WEIGHT

Feeding Regimens and Experimental Groups	Food and Water Intakes (ml)			Body Weight (g)	
	4-hr Milk Diet	4-hr Water	20-hr Water	Final	Change
Continuous Access to Food					
CAF	1.8 ± 0.4*	0.2 ± 0.2*	6.7 ± 3.2	429 ± 17*	59 ± 8*
Restricted Access to Food	24.8 ± 1.0	4.0 ± 0.5	5.9 ± 1.0	350 ± 6	−2 ± 2
FD	23.4 ± 1.9	4.1 ± 0.8	7.0 ± 2.2	347 ± 12	−2 ± 4
FD + F	25.2 ± 1.8	4.0 ± 0.9	5.2 ± 1.7	346 ± 7	0 ± 2
FD + S^D	25.8 ± 1.5	3.8 ± 0.7	5.5 ± 1.1	356 ± 14	−4 ± 4

Values are means ± standard errors for rats that had a milk-based liquid diet available either continuously (CAF, N=6) or for only 4 hr daily (Restricted Access, N=24). The data for the restricted access group are also subdivided according to the experimental treatments of the same rats on the day they were sacrificed for neurochemical assay (N=8 per treatment). Four-hour milk and water intakes were determined for all rats from 1100–1500 3 weeks after initiating the feeding schedules. Twenty-hour water intakes were measured during the ensuing period from 1500–1100 when rats with limited access to food were deprived of milk. Final body weights were obtained immediately before the rats were sacrificed. Body weights of rats in the CAF and FD + F groups were corrected for the food and water they ingested from 1100–1200 before being killed: FD + F rats ate more (22.2 ± 1.6 ml) than CAF rats (1.7 ± 1.4 ml; $t(12)=9.24$, $p<0.001$) but their water intakes (1.5 ± 0.6 and 0.2 ± 0.2 ml, respectively) were not different ($p>0.10$). The change in weight refers to the difference between the initial and final body weights for each rat.

*Differs from mean of the combined data of the 24 rats that had restricted access to food ($p<0.001$; Student's t-test, two-tailed) and from each of the means of the individual groups that were maintained with restricted access to food ($p<0.001$; Least Significant Difference Test, two-tailed).

satiety. One possible hypothesis is that these neurons are conditioned or sensitized during adaptation to the feeding schedule. Increases in the turnover of DA have been correlated with other conditioning processes [11, 22, 27]. If the changes in dopaminergic activity are associated with the control of discriminative stimuli (S^D) for feeding, and not the specific act of ingestion, then increases in the regional DOPAC/DA ratio should occur in rats that are exposed to food-related stimuli but not allowed to eat. In the present study, we report that the metabolism of DA within hypothalamic neurons appears to be entrained by scheduled feeding.

METHOD

Animals and Feeding Regimens

Thirty male albino rats (Hormone Assay Co., Chicago, IL) weighing 292–434 g were housed individually in suspended wire mesh cages in a colony in which the temperature was regulated at 22±1°C and fluorescent lighting was on from 0730–1930. The rats were maintained on tap water and a liquid diet consisting of one can (300 ml) Magnolia Brand sweetened condensed milk, 300 ml water, 0.5 ml formaldehyde solution (37% w/v) and 1.0 ml Poly-Vi-Sol Multiple Vitamins with Iron (a gift of Mead-Johnson, Evansville, IN). Fresh milk diet and tap water were provided on the front of the cage at 1100 each day in inverted 100-ml graduated glass cylinders fitted with a rubber stopper and stainless steel spout (Wahman Manufacturing Co., Timonium, MD). During the first week in the colony, all rats had free access to food and water. After this interval, 24 of the rats were restricted to a single 4-hr feeding period from 1100–1500 daily although water was available at all times; the remaining 6 rats continued to have unlimited access to both food and water. The initial body weights of the rats permitted to eat for only 4 hr each day (352±6 g, mean±S.E.) did not differ from those of the rats allowed continuous access to food (370±12 g).

Experimental Treatments

The two groups of rats were maintained on their respective feeding regimens for three weeks after which we determined the regional concentrations of DA and DOPAC in the forebrain. Rats given continuous access to food (CAF group) were sacrificed for biochemical assay 1 hr after fresh milk diet was provided. The rats that had food for 4 hr daily were assigned randomly to be sacrificed under one of the following conditions: (1) just before fresh milk was placed on the cage at the end of the 20-hr period of food deprivation (FD group); (2) 1 hr after fresh milk was provided (FD + F group); or (3) 1 hr after milk was presented to the CAF and FD + F groups (FD + S^D group). Rats in the FD + S^D group, therefore, did not have access to milk diet but were exposed to complex discriminative stimuli associated with the presentation of food or with feeding.

Food and water intakes were recorded for the first four and last two days of the three week interval before the biochemical assays; body weights were determined at the beginning of the experiment and immediately before each rat was sacrificed. The data revealed that the rats adapted quickly to the schedule with limited access to food: 3 days after initiating this regimen the 24 rats consumed 26.3±0.8 ml of milk during the 4-hr feeding period whereas 18 days later they consumed 24.8±1.0 ml. These food intakes greatly exceeded the amount of milk ingested during the same time of the day by the rats given continuous access to food (Table 1) but were 60% less than the total daily food intake of the CAF group (43.0±2.5 ml). The data in Table 1 demonstrated that the rats maintained with limited access to food also differed from those in the CAF group with respect

to a number of other measures of ingestive behavior and body weight. Nonetheless, for purposes of this study, it was far more important that there were no differences in these measures among the three treatment groups that were deprived of food for 20 hr each day.

Neurochemical Determinations

The concentrations of DA and DOPAC in the hypothalamus, striata, amygdala-pyriform lobes, olfactory tubercles and nuclei accumbens were determined using an aluminum oxide adsorption procedure for extracting catechols [1] followed by high performance liquid chromatography (HPLC) coupled with electrochemical detection [19]. For these assays, the rats were decapitated with a guillotine and the brains dissected on a cold plate over dry ice immediately after being removed from the calvarium. The olfactory tubercles were pinched off the base of the brain with fine microdissection forceps. The amygdala-pyriform lobes were then removed bilaterally by a transverse cut with a spatula blade along the rhinal sulcus, a coronal cut at the level where the lateral olfactory tract leaves the surface of the cortex, and a longitudinal cut along the lateral edge of the optic tract thereby separating the pyriform lobe from the diencephalon; the pyriform lobe was then peeled caudally away from the rest of the brain.

A section containing the two accumbens nuclei was dissected from the basal forebrain with the aid of a 2-mm long knife constructed by bending the beveled end of a 26-ga syringe needle at a right angle to the shaft. This section included tissue posterior to the appearance of the forceps minor and the genu of the corpus callosum (level A 10050 in [13]), rostral to the anterior commissure at level A 7890, ventral to the inferior aspect of the lateral ventricles and between two sagittal planes lying 0.5 and 2.0 mm lateral to the midline in each hemisphere. Striata were dissected bilaterally on the basis of their distinctive appearance [7].

After discarding the optic nerves and any remaining meninges, the boundaries of a block of hypothalamic tissue were delineated by cutting along the descending columns of the stria medullaris anteriorly, along the caudal edge of the mammillary bodies posteriorly, and along the medial edge of the optic tracts laterally. The hypothalamic section was removed after making a horizontal cut at the level of the descending columns of the fornix on the anterior surface of the block of tissue.

The fresh weights of the tissue sections were: 24±1 mg, for the olfactory tubercles; 158±3 mg, for the amygdala-pyriform lobes; 40±2 mg, for the region containing the accumbens nuclei; 104±4 mg for the combined striata; and 55±1 mg, for the hypothalamus. The mean weights of the regions did not differ among the four experimental groups (all p values >0.10 by Analysis of Variance).

After weighing, the tissue samples were homogenized in 10 volumes of solvent consisting of equal parts of 0.1 M perchloric acid and 1 M Tris (hydroxymethyl)-aminomethane (Tris, Sigma 7-9), pH 8.6, containing 1 mg/ml dithiothreitol as an antioxidant. Dihydroxybenzylamine hydrochloride (DHBA) in 0.05 M perchloric acid (1 ng salt/μl acid) was added to the homogenate as an internal standard in a ratio of 1:10 (v/v). The homogenate was centrifuged at 23,000×g at 4°C in a Sorvall RC-5 centrifuge equipped with an SM-24 head, after which a 500 μl aliquot of supernatant was transferred to a 1.5 ml conical Eppendorf microcentrifuge tube containing 30 mg washed alumina. The samples were then vortexed briefly, shaken for 5 min, and centrifuged at 4°C in an IEC Clini-Cool Centrifuge at 1125×g. The supernatant was then discarded, the alumina washed twice with 400 μl distilled-deionized water, and the DA, DOPAC and DHBA were eluted with 150 μl of 0.1 M phosphoric acid. The eluate was then vortexed, shaken for 5 min, and centrifuged at 4°C for 10 min at 1125×g; 100 μl of the eluate was frozen in WISP vials (Waters Associates; Milford, MA) fitted with limited volume inserts and stored at −40°C until injected into the chromatograph (within 72 hr).

The DA, DOPAC and DHBA contents of the eluate fractions were determined by isocratic HPLC at ambient temperature (22°C) with a Hewlett-Packard Model 1081A Liquid Chromatograph using a Whatman octadecylsilane reverse-phase precolumn, a 30-cm Bondapak C-18 reverse phase column, and a 0.1 M dibasic phosphate buffer mobile phase (pH 5.0) containing 1 mM EDTA and 0.25 mM heptanesulfonic acid as an ion pairing agent to optimize resolution of the catechol species. Thirty to 50 μl of the eluate was injected by a Waters WISP automatic sample injector onto the chromatograph, with the column pressure adjusted to approximately 1500 psi in order to maintain a flow rate of 1.2 ml/min. Electrochemical detection was by a TL-5 glassy carbon electrode (Bioanalytical Systems; West Lafayette, IN) and a Metrohm VA-Detector E-611 (Brinkmann; Westbury, NY) with the detector potential set at +0.70 V vs. a Ag/AgCl reference electrode. The detector sensitivity was 30 nA/V with the signal recorded by a Houston Omniscribe strip-chart recorder.

The DA, DOPAC and DHBA were identified by comparing the retention times of their peaks to those of authentic catechols injected directly into the chromatographic system. The retention times were: 15.8 min (DA); 7.2 min (DOPAC); and 9.6 min (DHBA). Standard curves were constructed by chromatographing a series of internal standards consisting of the fixed amount of DHBA and four concentrations of DA and DOPAC added to the homogenizing solvent. The concentrations of DA and DOPAC were calculated from the ratio of their peak heights to that of the DHBA in each sample using the slope and intercept of the standard curve. This procedure corrected implicitly for variations in recovery among the samples. Concentrations of DA and DOPAC were expressed as nmol catechol per g fresh tissue. The ratio of the concentration of DOPAC to that of DA in each region of the forebrain was determined from the data for the individual rats.

Statistical Analyses

The data were subjected to analysis of variance for comparing the means of the individual groups that were maintained on a restricted feeding regimen with the mean of the rats allowed continuous access to food. Post hoc comparisons were made by two-tailed t-tests (Least Significant Difference Test [12]). Orthogonal tests of the differences between the mean of the CAF group and that of the entire group of rats that were restricted to 4-hr of food daily were made by two-tailed Student's t-tests. The level of significance for each analysis was set at $p<0.05$.

RESULTS

The DOPAC/DA ratio increased in the hypothalamus of rats that were allowed to eat for 1 hr after food deprivation (FD + F group) and in the rats that were only exposed to stimuli associated with feeding (FD + S^D) when

compared to the value for animals having food available continuously (CAF group) (Table 2). By contrast, this ratio was unchanged in the hypothalamus of food-deprived rats that were killed before food was brought into the animal colony (FD). Thus, the DOPAC/DA ratios were also larger in the hypothalami of rats in the FD + F and FD + S^D groups—by 51% ($p<0.05$) and 86% ($p<0.01$), respectively—than in the FD group. A similar pattern of results was obtained in the amygdala-pyriform lobe. Nonetheless, these differences were not statistically significant, $F(3,26)=1.33$, $p>0.10$, nor did the DOPAC/DA ratio change systematically in any other regions of the forebrain (all p values for analyses of variance exceeded 0.10). The elevated DOPAC/DA ratios in the hypothalami of rats in the FD + F and FD + S^D groups resulted from apparent increases in the concentration of DOPAC and decreases in DA content in this region. However, only the values for hypothalamic DA in these two groups differed significantly from that of the CAF group.

TABLE 2

EFFECTS OF FEEDING AND STIMULI ASSOCIATED WITH FEEDING ON THE CONCENTRATIONS OF DOPAC AND DA AND THEIR RATIO IN REGIONS OF THE FOREBRAIN

Group	Concentration (nmol/g Tissue) DOPAC	DA	DOPAC/DA (× 100)
	Hypothalamus		
CAF	1.13 ± 0.12	5.29 ± 1.04	23.5 ± 2.3
FD	1.01 ± 0.06	4.51 ± 0.26	23.0 ± 1.0
FD + F	1.31 ± 0.12	3.79 ± 0.20*	35.1 ± 2.7*
FD + S	1.31 ± 0.12	3.20 ± 0.26†	42.8 ± 5.2†
	Amygdala-Pyriform Lobe		
CAF	1.19 ± 0.12	4.90 ± 0.46	25.8 ± 2.1
FD	1.07 ± 0.06	4.58 ± 0.52	26.7 ± 4.2
FD + F	1.43 ± 0.12	4.44 ± 0.26	31.9 ± 1.4
FD + S	1.25 ± 0.06	4.25 ± 0.39	32.2 ± 3.7
	Striatum		
CAF	7.14 ± 0.72	75.0 ± 9.0	10.0 ± 1.3
FD	7.68 ± 0.61	75.8 ± 4.8	10.3 ± 0.9
FD + F	8.57 ± 0.82	75.4 ± 4.5	11.6 ± 1.4
FD + S	7.32 ± 0.76	75.0 ± 5.0	9.8 ± 1.0
	Olfactory Tubercle		
CAF	7.38 ± 0.24	69.2 ± 7.3	11.2 ± 1.3
FD	8.33 ± 0.60	58.6 ± 3.4	14.5 ± 1.1
FD + F	7.80 ± 0.36	68.0 ± 6.8	12.0 ± 0.8
FD + S	8.33 ± 0.60	64.8 ± 5.0	13.1 ± 0.7
	Nucleus Accumbens		
CAF	7.92 ± 1.13	57.1 ± 6.2	14.2 ± 1.4
FD	9.40 ± 2.20	43.7 ± 5.9	20.1 ± 2.5
FD + F	8.75 ± 0.71	54.5 ± 5.3	16.5 ± 1.7
FD + S	8.57 ± 0.60	51.0 ± 6.3	17.1 ± 1.7

All values are means ± standard errors for 6–8 rats in the experimental groups described in the legend to Table 1. The DOPAC/DA ratios were derived from the data for the individual rats in each group.

*Differs significantly from the means of the CAF and FD groups: *$p<0.05$; †$p<0.01$; Least Significant Difference Test, two-tailed.

DISCUSSION

The results of this investigation confirmed the previous report [8] that scheduled feeding after food deprivation was accompanied by an increase in the DOPAC/DA ratio in the hypothalamus. The data extended that finding by demonstrating that the DOPAC/DA ratio also increased in the hypothalamus of rats that were not provided with food but were exposed to extrinsic stimuli associated with feeding. This ratio did not change in the brains of a third group of rats that were killed in the absence of stimuli related to feeding. The three groups were adapted equally to the regimen of limited access to food before the experiment was conducted. In addition, these groups did not differ with respect to their initial or final body weights, the amount of milk diet they ingested during the four-hour feeding period, the volume of water they drank, or in their relative distribution of drinking during the periods of feeding and food deprivation. Thus, the neurochemical differences among these groups were clearly not due simply to food deprivation or to the nutritional status of the animals. Accordingly, the data established that neither access to food nor the act of feeding were necessary to increase the DOPAC/DA ratio in the hypothalamus of rats that were entrained to a feeding schedule. Instead, the present study suggested that the experimental setting for feeding was sufficient for altering this index of dopaminergic activity.

The effect of stimuli that set the occasion for feeding on dopaminergic neurons in the hypothalamus was anatomically specific because no similar changes were detected in the other areas measured. The failure to obtain increased DOPAC/DA ratios in the amygdala-pyriform lobe and nucleus accumbens conflicted with the results reported previously by Heffner *et al.* [8]. In that investigation, rats were fed dry food pellets after deprivation whereas a liquid milk diet was used in the present experiment. Thus, the disparity between their neurochemical findings and ours may have resulted from differences in the palatability, nutritional composition or physical properties of the foods employed. Perhaps a more likely explanation was that the data reflected the dissimilar methods used for dissecting the regions of the forebrain in the two studies. For example, we did measure equivalent nonsignificant increases in the DOPAC/DA ratio in the pyriform lobes of the two groups of rats that were sacrificed one hour after the beginning of the feeding period. Thus, it was possible that DA turnover increased in a discrete portion of the amygdala. Similarly, it was conceivable that the size of our tissue section that included the nucleus accumbens diluted local neurochemical effects within that region.

The DOPAC/DA ratios increased in the hypothalami of the two groups of rats exposed to food-related stimuli because of significant reductions in the concentration of DA and a trend for opposite effects on the content of DOPAC. The identical pattern of changes in DA and this acidic metabolite has been reported in the frontal cortices of rats exposed to electric foot shock [14]. Those investigators concluded from the resulting increase in the DOPAC/DA ratio that shock activated the dopaminergic neurons innervating the mesocortex. By analogy, the current data suggest that presenting stimuli which reliably predicted access to food activated dopaminergic neurons in the hypothalamus.

Theoretically, though, the DOPAC/DA ratio serves most appropriately as an index of the functional activity of dopaminergic neurons under steady state conditions [2]. Furthermore, the relationship between the accumulation of DOPAC and the turnover of DA has been established most firmly in the nigrostriatal and mesolimbic systems in the rat [26,36]. Since the increases in the DOPAC/DA ratio in the current study occurred in the hypothalamus and in the absence of a steady state, the inference that this neurochemical change reflected an enhancement of dopaminergic activity is offered with caution. Even with this proviso, however, the present results are consistent with the hypothesis that the metabolism or rate of turnover of DA in the hypothalamus is subject to control by discriminative stimuli for feeding.

A considerable amount of support exists for the proposal that environmental stimuli influence the dynamics of central monoaminergic systems [28]. For example, in one particularly relevant experiment, discriminative stimuli for food elicited bursting activity in some dopaminergic cells in the mesencephalic tegmentum and medial substantia nigra [17]. Furthermore, the notion that the activity of hypothalamic neurons can be brought under stimulus control using a paradigm employing food as a reward is not new [20]. To our knowledge, however, the present study is the first to suggest that dopaminergic neurons in the hypothalamus may mediate the effects of external stimuli on physiological or behavioral responses involved in feeding (e.g., [25, 35, 38]). Such a mechanism could provide a neurochemical substrate for cognitive, or nonhomeostatic, factors in initiating meals [3, 24, 34]. These speculations require further study in which well-defined stimuli and controls for nonassociative conditioning factors are included.

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