combination can account for a major portion of the standard CNV waveform. Both of these waves can be recorded individually and do not depend on paired stimuli for their appearance. The primary effects from the pairing of warning and imperative stimuli in a CNV paradigm lie, rather, in the consequent placement of these two waves in temporal juxtaposition or overlap.

Each of the two constituent waves described here can be observed separately with non-CNV procedures. By capitalizing on their distinctive topographical, temporal, and task-related features, it may be possible to design experiments that use these earmarks to make the waves individually accessible with CNV procedures as well. Certainly these individual waves, by themselves, are of interest. One wave, the negative afterwave, may provide an EEG measure of orienting or activation processes (*6, 10*). The second seems to be a movement-related potential; if so, the central determinants of motor outflow (as manifested in these potentials) may become available for scrutiny in demanding task situations, requiring movements that are made to be timed or coordinated with external events. The behaviors related to these separate waves in the CNV are, then, of considerable laboratory and clinical importance, and their assessment separately may permit the establishment of firmer relationships with psychological and motor processes than are now available.

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15. See E. Donchin and E. Heffley [in *Multidisciplinary Perspectives in Event-Related Brain Potential Research*, D. A. Otto, Ed. (Government Printing Office, Washington, D.C., 1978), pp. 555–572] for a discussion of PCA techniques. Each PCA factor represents a separate source of variance identified within the set of waveforms. All factors having an eigenvalue > 1.0 were retained and rotated using the varimax criterion, yielding 15 orthogonal factors. The readiness potential factor (factor 1) accounted for 40.6 percent of the variance, and the afterwave factor (factor 3) accounted for 9.4 percent. The factor structure was similar to that found by McCarthy and Donchin (*4*) for CNV's with a 1-second foreperiod.
16. Repeated measures analyses of variance of the separate PCA factors included as variables the CNV type (actual or synthesized), the pairing order (visual-auditory or auditory-visual), and electrode site. For the readiness potential factor, significant effects ($P < .05$) were found for the electrode site. For the negative afterwave factor, effects were found for pairing order and electrode site; the value for their interaction was .051.
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Feeding Increases Dopamine Metabolism in the Rat Brain

Abstract. *Feeding induced by food deprivation is accompanied by an increased production of the dopamine metabolite 3,4-dihydroxyphenylacetic acid in the brains of rats. This neurochemical change occurs in the nucleus accumbens, the posterior hypothalamus, and the amygdala but not in other dopaminergic nerve terminal fields such as the corpus striatum. These results indicate that the release of dopamine from particular groups of central neurons is increased during feeding and suggest that anatomically distinct subgroups of central dopaminergic neurons serve different roles in the regulation of food intake.*

Central dopaminergic neurons have been implicated in the control of food intake (*1*). Brain lesions which destroy nigrostriatal dopaminergic neurons reduce and sometimes eliminate feeding in rats (*2*). In addition, drugs such as amphetamine inhibit food intake in part by increasing the efflux of dopamine (DA) from central neurons (*3*). Although experimental alteration of central dopaminergic neurotransmission can impair feeding, such findings do not establish that these neurons normally participate in the regulation of ingestive behavior. If central dopaminergic neurons play an active role in the regulation of food intake, then changes in the functional activity of these neurons should accompany hunger, food consumption, or satiety. In order to test this hypothesis, we have monitored the neurochemical changes that normally accompany nerve impulse activity in central dopaminergic projections during food deprivation and during feeding induced by food deprivation. We now report that select populations of nonstriatal dopaminergic neurons are activated during food consumption in the rat.

Measurement of the relative rate of DA metabolism within the brain has been used to estimate the effects of drug, environmental, or behavioral influences on central dopaminergic neurotransmission (*4*). Earlier investigators who have examined DA metabolism in relation to feeding have typically focused on the hypothalamus and have reported conflicting results. Although some investigators have reported that DA metabolism within the hypothalamus is accelerated during food deprivation (*5*) or during feeding (*6*), others have failed to detect such changes (*7*). In the present studies, we have examined DA metabolism in a number of different brain regions innervated by dopaminergic projections (*8*). We have measured the accumulation of the DA metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the brain relative to the endogenous concentrations of DA as an index of the relative rate of neuro-

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nal activity in central dopaminergic projections (*9*). It has been established that changes in the DOPAC concentrations in the brain parallel changes in the rate of neuronal release and subsequent metabolism of DA (*10, 11*).

Male albino rats (Holtzman Company, Madison, Wisconsin) obtained at 90 days of age were housed individually in a room illuminated for 12 hours per day (from 0600 to 1800 hours). Rats were maintained either on continuous access to food (Purina Lab Chow pellets) or on a feeding schedule which consisted of 20 hours of food deprivation followed by 4 hours of access to food (from 1200 to 1600 hours). Rats adapted to the feeding schedule for 2 weeks were decapitated either prior to the time when food was normally presented (food-deprived rats, FD group) or after 1 hour of access to food (food-deprived rats given food, FD + F group). Rats maintained on the feeding schedule consumed approximately 16 to 20 g of food during the first hour of access compared with 30 to 36 g of food during the entire 4-hour access period. Rats maintained on continuous access to food (CA group) for 2 weeks were also decapitated in parallel with these groups. Brains were dissected as described elsewhere (*12*), and the amounts of DOPAC and DA in brain regions were determined by radioenzymatic assay (*13*).

We first estimated the rates of DA metabolism within brain regions of FD rats, FD + F rats (given 1 hour of access to food), and CA rats (Table 1). Food deprivation alone did not alter the content of DOPAC or DA in the brain regions of any of these groups. However, access to food after food deprivation significantly increased the accumulation of DOPAC in the nucleus accumbens by 61 percent, in the hypothalamus by 19 percent, and in the amygdala by 131 percent above the concentrations present in tissues from CA rats. In contrast, no feeding-induced changes in DOPAC accumulation occurred in other dopaminergic terminal fields including the caudate putamen, the olfactory tubercle, the frontal cortex, or the septum. Subsequent studies revealed that feeding-induced increases in hypothalamic DA metabolism were restricted to the posterior half of the hypothalamus, no changes being detected within the anterior hypothalamus (*14*).

The changes in brain DOPAC concentrations seen in rats engaged in feeding do not appear to be due to alterations in the rate of DOPAC transport from brain or to changes in alternative metabolism pathways for DOPAC. Groups of FD rats and FD + F rats (given 1 hour of access to food) were given pargyline hydrochloride (50 mg/kg, intraperitoneally), a drug that inhibits the conversion of DA to DOPAC. Six rats from each group were killed at 1, 15, or 30 minutes after pargyline administration, and the DOPAC concentrations were determined in the nucleus accumbens, posterior hypothalamus, amygdala, and caudate putamen. The slopes of the linear curves which described the decline of DOPAC from each brain region with time were found not to differ in the FD and FD + F groups (*15*). These results support the notion that the feeding-induced increases in DOPAC accumulation that we observed are due to an increase in DOPAC production subsequent to an increased rate of DA release from central neurons (*16*). In addition, the unchanged rate of elimination of DOPAC from the caudate putamen of rats engaged in feeding suggests that our failure to detect changes in DOPAC accumulation in this tissue was not due to a feeding-induced increase in the rate of DOPAC elimination.

Although we cannot identify the stimulus responsible for the feeding-induced increases in brain DA metabolism, we have found that the increased production of DOPAC in the amygdala, but not in the nucleus accumbens or posterior hypothalamus, may be due to postingestional factors. The FD + F rats given 1 hour of access to a liquid food solution comprised of powdered Purina Lab Chow and 0.9 percent saline (4:1, by weight) showed greater concentrations of DOPAC within the nucleus accumbens, posterior hypothalamus, and amygdala than were seen in FD rats (Table 2). Rats tube-fed with a similar amount of food (20 g) and those tube-fed with 20 g of saline showed increased concentrations of DOPAC in the amygdala, comparable to the increase seen in the FD + F rats. In contrast, neither the tube-feeding of food nor the tube-feeding of saline altered the metabolism of DA in the nucleus accumbens or posterior hypothalamus. These results suggest that the nutrient content of the diet is not responsible for the feeding-induced changes in brain DA metabolism. Furthermore, other postingestional effects of food do not appear to mediate the feeding-induced increase in DA metabolism within the nucleus accumbens or the posterior hypothalamus. Although the

Table 1. Dopamine (DA) metabolism (means ± the standard error of the mean) within brain regions during food deprivation and access to food after deprivation. Groups of eight rats each were maintained on continuous access to food (CA) or on a feeding schedule of 4 hours per day. Food-deprived rats (FD) were killed prior to the time food was normally presented; food-deprived rats given food (FD + F) were killed 1 hour after access to food. Rats given access to food consumed a mean (± standard error of the mean) of 18.7 ± 0.7 g of food pellets.

Group	DOPAC (ng per mg of protein)	DA (ng per mg of protein)	DOPAC/DA ($\times 10^2$)
		Caudate putamen	
CA	10.62 ± 0.74	105.9 ± 4.3	10.03 ± 0.47
FD	10.27 ± 0.78	102.8 ± 5.8	9.98 ± 0.55
FD + F	10.03 ± 0.79	103.8 ± 4.5	9.81 ± 0.86
		Nucleus accumbens	
CA	9.95 ± 0.86	100.4 ± 4.4	10.31 ± 0.51
FD	11.18 ± 0.72	94.6 ± 4.8	11.84 ± 0.63
FD + F	16.01 ± 1.38*	103.5 ± 6.8	15.81 ± 1.31*
		Olfactory tubercle	
CA	13.22 ± 0.85	60.9 ± 5.2	22.07 ± 1.71
FD	14.21 ± 0.91	66.2 ± 4.2	21.61 ± 1.56
FD + F	14.11 ± 1.09	68.1 ± 2.0	20.41 ± 1.51
		Septum	
CA	1.40 ± 0.15	11.5 ± 1.3	12.24 ± 1.01
FD	1.45 ± 0.19	11.8 ± 1.1	12.45 ± 1.21
FD + F	1.41 ± 0.21	11.4 ± 1.5	12.49 ± 0.73
		Frontal cortex	
CA	0.08 ± 0.01	0.42 ± 0.02	19.79 ± 2.42
FD	0.07 ± 0.01	0.38 ± 0.03	19.07 ± 2.65
FD + F	0.08 ± 0.01	0.46 ± 0.03	18.44 ± 1.74
		Amygdala	
CA	0.16 ± 0.02	1.14 ± 0.07	14.08 ± 1.12
FD	0.19 ± 0.02	1.28 ± 0.13	15.14 ± 0.69
FD + F	0.37 ± 0.04*	1.34 ± 0.04	30.20 ± 2.80*
		Hypothalamus	
CA	0.51 ± 0.01	2.33 ± 0.18	21.89 ± 1.51
FD	0.46 ± 0.04	2.02 ± 0.09	22.77 ± 1.80
FD + F	0.61 ± 0.05*	2.20 ± 0.12	27.73 ± 1.95*

*Differs significantly from CA and FD groups; $P < .05$ (two-tailed t-test).

Table 2. Dopamine (DA) metabolism (mean ± the standard error of the mean) in brain regions of rats after access to food or tube-feeding. Groups of six rats each were maintained on a feeding schedule of 4 hours per day. Food-deprived rats (FD) were killed prior to access to food. Food-deprived rats given food (FD + F) were killed 1 hour after access to a liquid food suspension. These rats consumed a mean (± standard error of the mean) of 20.3 ± 2.6 g of the suspension. Rats tube-fed food (TFF) were killed 1 hour after intragastric intubation of 20 g of the food suspension. Rats fed saline (TFS) were killed 1 hour after intragastric intubation of 20 g of 0.9 percent saline.

Group	DOPAC (ng per mg of protein)	DA (ng per mg of protein)	DOPAC/DA ($\times 10^2$)
	Nucleus accumbens		
FD	11.65 ± 0.94	86.51 ± 5.32	13.97 ± 1.27
FD + F	22.59 ± 3.60*	84.32 ± 3.58	27.13 ± 4.57*
TFF	12.88 ± 1.12	88.06 ± 4.51	15.33 ± 1.78
TFS	12.38 ± 1.57	82.03 ± 3.12	15.03 ± 1.74
	Amygdala		
FD	0.14 ± 0.02	1.04 ± 0.09	14.46 ± 1.58
FD + F	0.26 ± 0.04*	1.19 ± 0.04	21.85 ± 1.62*
TFF	0.25 ± 0.02*	1.18 ± 0.05	21.19 ± 1.89*
TFS	0.23 ± 0.03*	0.96 ± 0.05	23.96 ± 1.99*
	Posterior hypothalamus		
FD	0.32 ± 0.03	1.57 ± 0.17	22.95 ± 2.15
FD + F	0.43 ± 0.02*	1.41 ± 0.16	32.29 ± 2.88*
TFF	0.39 ± 0.04	1.77 ± 0.16	22.20 ± 2.09
TFS	0.32 ± 0.04	1.32 ± 0.22	24.77 ± 2.85

*Differs significantly from the FD group; $P < .05$ (two-tailed t-test).

gastric distension which accompanies food consumption as well as tube-feeding of food or saline may account for the metabolic changes seen in the amygdala, we cannot exclude the possibility that separate mechanisms underlie the effects of voluntary food intake and intragastric intubation on DA metabolism within the amygdala.

These results suggest that feeding after food deprivation is accompanied by an increased rate of DA metabolism in specific dopaminergic nerve terminal fields including the nucleus accumbens, the posterior hypothalamus, and the amygdala. The restriction of the feeding-induced increases in hypothalamic DA metabolism to the posterior hypothalamus suggests activation of tuberinfundibular dopaminergic neurons of the arcuate nucleus rather than the incertohypothalamic neurons which terminate in the anterior hypothalamus (*8*). The increase in DA metabolism within the nucleus accumbens and the absence of such an increase in the caudate putamen suggest that mesocortical but not nigrostriatal neurons are activated during feeding. The absence of metabolic changes in other terminal fields of the mesocortical dopaminergic system, such as the frontal cortex, septum, and olfactory tubercle, suggests that functionally distinct subgroups of mesocortical neurons may be activated during feeding.

Our findings are in agreement with earlier observations that feeding produces increased metabolism of DA within the hypothalamus (*6*) or the whole brain (*17*) and, as such, support suggestions that brain dopaminergic neurons are active in the control of normal feeding. Earlier investigators have emphasized the importance of intact nigrostriatal dopaminergic neurons for the expression of normal feeding (*2*) or have proposed that anorectic drugs may act by increasing the release of DA from central neurons (*3*). In contrast, our findings suggest that dopaminergic neurons which project to the nucleus accumbens or the posterior hypothalamus may, through increased release of DA, facilitate feeding under physiological conditions.

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