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An Appetitively Conditioned Taste Elicits a Preferential Increase in Mesolimbic Dopamine Release

GREGORY P. MARK, SABRINA E. SMITH, PEDRO V. RADA AND BARTLEY G. HOEBEL[1]

Department of Psychology, Princeton University, Princeton, NJ 08544-1010

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MARK, G. P., S. E. SMITH, P. V. RADA AND B. G. HOEBEL. *An appetitively conditioned taste elicits a preferential increase in mesolimbic dopamine release.* PHARMACOL BIOCHEM BEHAV **48**(3) 651-660, 1994.—Rats were prepared with intragastric (IG) cannulae for infusing a nutrient into the stomach and microdialysis guide shafts in the nucleus accumbens (NAC) and striatum (STR) for measuring changes in extracellular dopamine. Prior to dialysis, subjects were trained to prefer the mildly bitter taste of sucrose octaacetate (SOA; CS+) by pairing voluntary intake with automatic IG infusions of nutritive polycose. The mildly sour taste of citric acid (CS−) was paired with IG water infusions as a control. Unconditioned animals received four exposures to SOA and citric acid on counterbalanced, alternating days. After training, dialysis samples were collected every 30 min before, during, and after intake of the CS+ or CS− in response to 14 h water deprivation on counterbalanced, consecutive days. Voluntary intake of the CS+ for 30 min significantly increased extracellular DA in the NAC but not in the STR of conditioned subjects. Intake of the CS− did not alter DA efflux at either site. Unconditioned, control rats also showed no DA response to either taste. These results show selective activation of the mesolimbic dopaminergic projection system as a consequence of a conditioned taste stimulus paired with a nutritive gastric load. This suggests that conditioned DA release may play a role in learned ingestive behavior based on the postingestive effects of food.

Microdialysis Nucleus accumbens Striatum Intragastric Rat Conditioned taste preference Dopamine

THE ability of animals to associate taste cues with gastrointestinal consequences is well documented. In the familiar conditioned taste aversion paradigm, animals readily learn to avoid a novel taste after a single pairing with an aversive consequence (21) [for review see (22)]. This capacity is not limited to associations between tastes and illness. Animals demonstrate preferences for flavors that are associated with nutritional benefit. In some of the first conditioned taste preference (CTP) experiments animals learned to prefer tastes that were paired with substances that compensated for physiological deficits (20,48,63). The effects of pharmacological agents such as morphine and ethanol were also demonstrated to be effective unconditioned stimuli (USs) for inducing taste preferences (35,42). Rats also prefer a taste previously paired with a calorie-rich meal as the US (5,6,9,27,41,53), and the strength of this preference can be directly proportional to the caloric density of the US (6).

Olfactory and taste cues associated with the US are not necessary to the development of the preference, since animals can be trained to inject a liquid diet directly into the stomach via a nasoesophageal tube (11,28). Moreover, Puerto et al. (45) have shown that rats develop a preference for a taste that is paired with the intragastric (IG) infusion of a nutritive mixture. Taste preferences have also been demonstrated for solutions paired with IG infusions of a pure starch, such as polycose (10,52). Taken together, these results demonstrate that a calorie-rich US can be sufficient to induce a CTP, but the ability of such a stimulus to modify neurotransmitter release has not been examined.

The role of central dopamine (DA) systems in modulating behavior has been the subject of intense investigation for many years. Several current theories of mesolimbic/mesostriatal DA function have been derived from behavioral data following DA depletion (e.g., by administration of the catecholaminergic toxin 6-OH-DA) or pharmacological blockade of DA receptors (primarily with neuroleptics). Historically, theories based on this experimental strategy have tended to fall into one of two categories, one emphasizing a sensorimotor

[1] Requests for reprints should be addressed to Bartley G. Hoebel, Department of Psychology, Green Hall, Princeton University, Princeton, NJ 08544-1010.

integration or arousal function of DA (55,56,59) and the other proposing that DA is responsible for mediating various aspects of positive and negative reinforcement (12,60). Several investigators have also suggested that DA, particularly in the nucleus accumbens (NAc), may be more prominently involved in signaling the salience of secondary or conditioned cues associated with ingestion rather than unconditioned stimuli (3, 44,49,50,51).

In the present study we have combined the CTP paradigm with in vivo microdialysis to determine whether DA efflux in the NAc and dorsolateral striatum (STR) could be correlated with the presentation of an appetitively conditioned taste stimulus (CS+) that had previously been paired with IG infusions of a calorie-rich, maltooligosaccharide solution (Polycose). DA released as a function of CS+ intake was compared to that induced by the taste of a CS− which had previously been paired with IG infusions of water. As a further control, DA was measured following each taste stimulus in unconditioned animals.

MATERIALS AND METHODS

Subjects

Twenty-nine male Sprague–Dawley rats (375–425 g) were housed individually on a 12-h reversed day–night schedule (lights off 0800–2000). Animals had ad lib access to food and water during recovery from surgery. They were deprived of water but not food from 0900 to 1300 daily during training and testing. During each dialysis session, animals were deprived of food and water, with the exception of the 30 min during which the cue solution was presented.

Surgery

Subjects were pretreated with atropine (0.5 mg/kg), anesthetized with sodium pentobarbital (20 mg/kg, IP) supplemented by ketamine HCl (40 mg/kg, IP), and fitted with a gastric cannula using a procedure modeled after Kraly et al. (34) and Elizade and Sclafani (10). The cannula consisted of a stainless steel cylinder (o.d., 8 mm; length, 14 mm) threaded on the inside to accept a stainless steel screw. One end of the cylinder was flanged (o.d., 16 mm) and a slot (1 × 2 mm) was placed in the rim of the flange to facilitate entry of the cannula into the stomach. A steel washer and springclip, placed against the skin, held the cannula in position. All stainless steel parts were sterilized before surgery.

A guide shaft (10 mm, 21-gauge stainless steel) was stereotaxically aimed at either the left or right NAc (anterior [A]: 10.2 mm, lateral [L]: 1.2 mm, ventral [V]: 4.0 mm) (43) with reference to the interaural line (A), midsagittal sinus (L), and level skull surface (V), and a contralateral guide shaft was aimed at the dorsolateral striatum (A: 8.7 mm, L: 3.0 mm, V: 2.5 mm) in each subject. Microdialysis probes which were inserted later extended an additional 5 mm to reach the target sites. Cannulae were attached to the skull with dental cement anchored by stainless steel screws. A metal shield to protect dialysis probes was placed anterior to the cannulas and attached to the assembly with dental cement. A stylet constructed of plugged stainless steel tubing (20.5 mm, 26 gauge within 10 mm, 21 gauge) was placed in each cannula. Animals were given an injection (0.1 ml) of penicillin (300,000 units penicillin G benzathine/ml) at the conclusion of surgery and allowed to recover for at least seven days before training began.

Training

Prior to training, the stainless steel screw in the cannula was replaced with a stainless steel connector and flexible coiled spring (0.145 in. o.d.) which housed a 50 cm length of PE-20 tubing. The tubing extended through a slot in the cage floor to a fluid swivel attached to a 20-cc syringe placed in a syringe pump below the floor of the animal's cage. The length of the protective spring and tubing was sufficient to allow the animal complete freedom of movement within the cage.

On days 1 and 2 animals were familiarized with the apparatus. A graduated cylinder of water with a sipper tube was placed in the cage, and each lick detected by a drinkometer triggered a 2-s nonoverlapping IG infusion of deionized water (20 μl/s). On days 3 and 5, 0.03% sucrose octaacetate (SOA; Sigma Chemical Co., St. Louis) solution in a graduated cylinder with a sipper tube was presented as the CS+. Intake of this flavor was accompanied by IG infusions of 32% Polycose (Ross Laboratories, Columbus, OH) solution. On days 4 and 6 the CS− was presented in an identical sipper tube that contained 0.05% citric acid (Fisher Scientific, Fair Lawn, NJ). The CS− flavor was paired with IG administration of deionized water. The presentation of one of two liquids (CS+ or CS−) was paired with IG infusions for 20 h per day in counterbalanced order. Animals had access to water during all test phases except during the remaining 4 h each day (0900 to 1300). Food pellets were available ad lib during training. Both oral and IG fluid intake were measured daily.

An unconditioned control group (n = 10), without IG cannulae, was treated identically to the conditioned groups with daily exposures to SOA and citric acid on days 2 and 4 and 3 and 5, respectively, but without IG infusions.

Microdialysis

Microdialysis probes were constructed of silica glass tubing (37 μm i.d.; Polymicro Tech Inc.) inside a 26-gauge stainless steel tube with a microdialysis tip of cellulose tubing (0.2 mm o.d. by 3 mm long for NAc, 4 mm for STR) sealed at the end with epoxy cement. The microdialysis fiber had a 6000 MW cutoff (Spectrum Med. Inc., Los Angeles, CA). Detailed descriptions of this probe design are published elsewhere (26,40).

At least 16 h prior to each experiment, microdialysis probes were inserted in the NAc and contralateral STR. Probes were perfused with a Ringer solution (145 mM NaCl, 4.0 mM KCl, 1.2 mM $CaCl_2$, degassed pH 5.6) at a flow rate of 1.0 μl/min. The outlet branch of the probes led to 400-μl vials clipped to a flexible coiled spring 25 cm above the head of the rat. Samples were collected every 30 min for analysis. On the evening preceeding each dialysis session, animals were deprived of water at 2300, and food was removed when the session began. Each animal participated in two dialysis sessions on consecutive days beginning at 1100 daily during the dark cycle. After a stable baseline was measured for DA (three consecutive 30-min samples within ±10%), subjects were allowed access to either the CS+ or CS− solution for 30 min. IG water infusions were paired with both solutions during dialysis. The order of the presentation of the CS+ and CS− solutions was counterbalanced. Animals were not included in the study unless they consumed a minimum of 5 ml of at least one of the solutions. Dialysis samples were collected for 2 h after the solution was removed.

At the conclusion of dialysis sessions, 13 rats were given two-bottle preference tests on each of two days to evaluate the strength of the taste preference. On one day the animals were exposed to the CS+ and water; on the other day they were

exposed to the CS− and water. The order of presentation and the side of the cage on which each solution was presented were counterbalanced. The intake of each test solution in a 24-h period was calculated as a percentage of total fluid consumption.

Dopamine Assay

DA and metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were analyzed by reverse-phase, high-performance liquid chromatography with electrochemical detection (HPLC-EC). Samples were injected directly into an HPLC system which used a 50-μl sample loop leading to a 10-cm column with 3.2-mm bore and 3-μm, C-18 packing (Brownlee Co., Model 6213). The mobile phase contained 60 mM sodium phosphate, 100 μM ethylenediaminetetraacetic acid (EDTA), 1.24 mM heptanesulfonic acid, and 5–6% v/v methanol. Once separated, compounds were measured with an ESA Co. model 5100A coulometric detector (conditioning cell, Model 5021: +500 mV; E_1: +100 mV; E_2: −400 mV).

Statistical Analyses and Histology

This experiment measured the animals' preference for the CS+ versus CS− and extracellular DA following CS+ versus CS− intake. The taste preference was evaluated using Student's t test. Absolute, basal recovery of DA varied considerably between subjects. For this reason, peak heights were converted to a percent of the mean of three baseline samples. Data were then analyzed by two-way analysis of variance (Condition × Time) followed by post hoc t tests when justified. Histology was performed to verify probe placement in the NAc and STR. Subjects received an overdose of sodium pentobarbital and were perfused with 0.9% saline followed by formalin. Brains were removed and frozen, and sections 40 microns thick were taken from the anterior lobe caudally until probe tracks were identified.

RESULTS

Animals consumed comparable amounts of the CS+ and CS− solutions during dialysis sessions, but the CS+ that had been associated with IG calories released more DA in the NAc than the CS− that had been associated with water. Mean intakes of each taste solution during dialysis test sessions for conditioned subjects were SOA (CS+) 12.7 ± 1.0 ml (mean ± SEM) and citric acid (CS−) 11.6 ± 1.0 ml. For unconditioned subjects intakes were SOA 11.6 ± 0.9 ml and citric acid 12.1 ± 1.9 ml.

For the nucleus accumbens, ingestion of the CS+ by conditioned animals was associated with a statistically reliable 28% increase in DA efflux compared to unconditioned subjects, $F(1, 27) = 4.47$, $p < 0.05$. Post hoc analysis revealed that this significant increase occurred in the time period during which the CS+ was consumed, $F(1,7) = 8.89$, $p < 0.01$ (see Fig. 1, top). No change in extracellular DA was apparent during ingestion of the CS− (Fig. 2). Extracellular levels of DA metabolites DOPAC and HVA showed smaller, nonsignificant increases in the samples following CS+ ingestion: DOPAC, $F(1, 27) = 1.46$, NS; HVA, $F(1, 27) = 1.69$, NS (Fig. 1, middle and bottom).

In the striatum neither DA, $F(1, 27) = 0.95$, NS (Fig. 3, top), nor its metabolites—DOPAC, $F(1, 27) = 0.97$, NS; HVA, $F(1, 27) = 0.68$, NS (Fig. 3, middle and bottom)—exhibited any significant interaction between condition and time for either the CS+ or CS− (Fig. 4).

Absolute, mean basal levels of DA, DOPAC, and HVA were calculated for the first day of measurement in each site. These figures are shown in Table 1.

Preference tests were conducted on days following dialysis sessions. Animals were given access to two drinking tubes with SOA (CS+) and water on one day, and citric acid (CS−) and water on a counterbalanced, second day. When conditioned animals were given the CS+ and water for 24 h, average intake of the CS+ was 73% of total fluid intake. In comparison, animals exposed to the CS− and water showed a mean CS− intake that was 45% of total fluid consumption. While the preference for SOA compared to water was not statistically significant, $t(7) = 0.52$, NS, the mean percentage intake of SOA was greater than either citric acid or water. Elizade and Sclafani (10) reported a comparable percentage intake of SOA after four days of training in a similar paradigm. By necessity, each subject in the present experiment was exposed to one extinction trial during dialysis, which may have contributed to the lack of significance in post hoc, preference testing.

DISCUSSION

The studies presented here demonstrate that DA efflux is preferentially increased in the NAc by presentation of a taste (CS+) which was previously paired with IG infusions of nutritive Polycose. This increase was not apparent following presentation of a taste (CS−) previously paired with IG water infusions or in unconditioned subjects who were previously exposed to the CS+ without IG Polycose infusions.

DA release in the dorsolateral striatum was affected by neither of the tastes, suggesting that the nigrostriatal DA system is not as involved as the mesolimbic system in the establishment or maintenance of conditioned taste preferences. However, the nigrostriatal DA system is sensitive to some factors affecting ingestive behavior. For example, Church et al. (7) found that interval feeding elevated DA in the STR of food-deprived animals, and Bakshi and Kelley (1) reported that haloperidol microinjected into the ventrolateral but not the dorsolateral striatum could block food intake. On the other hand, Hernandez and Hoebel (24) reported that extracellular DA in STR did not increase detectably during a bar-press feeding task when an increase was evident in the NAc. Differences in paradigms and probe locations within the STR may account for these differences. The present results showed no change in striatal DA in the area sampled when a stimulus was presented that predicted nutritive postingestive effects.

The results of several studies have suggested that DA activity in the ventrolateral striatum (8,30,32) and NAc (31,33) is involved in oro-motor functions. However, DA released into the caudal-medial portion of the NAc examined in the present study did not increase nonspecifically in response to oral behavior because consumption of the CS− in conditioned animals and the CS− and CS+ in unconditioned animals failed to alter DA efflux. The specificity of the DA response to presentation of the CS+ in conditioned animals could not be attributed to the volume of solutions consumed because intake of the CS+, while slightly higher in conditioned subjects, was comparable to that of the CS− in both conditioned and unconditioned groups. This suggests that DA was released preferentially in the NAc by the taste of a stimulus reminiscent of positive postingestional aftereffects.

Determining the function of mesolimbic DA in controlling motivated behavior has been the subject of a considerable research effort. One persuasive hypothesis in this field suggests that DA is responsible (or necessary) for mediating the

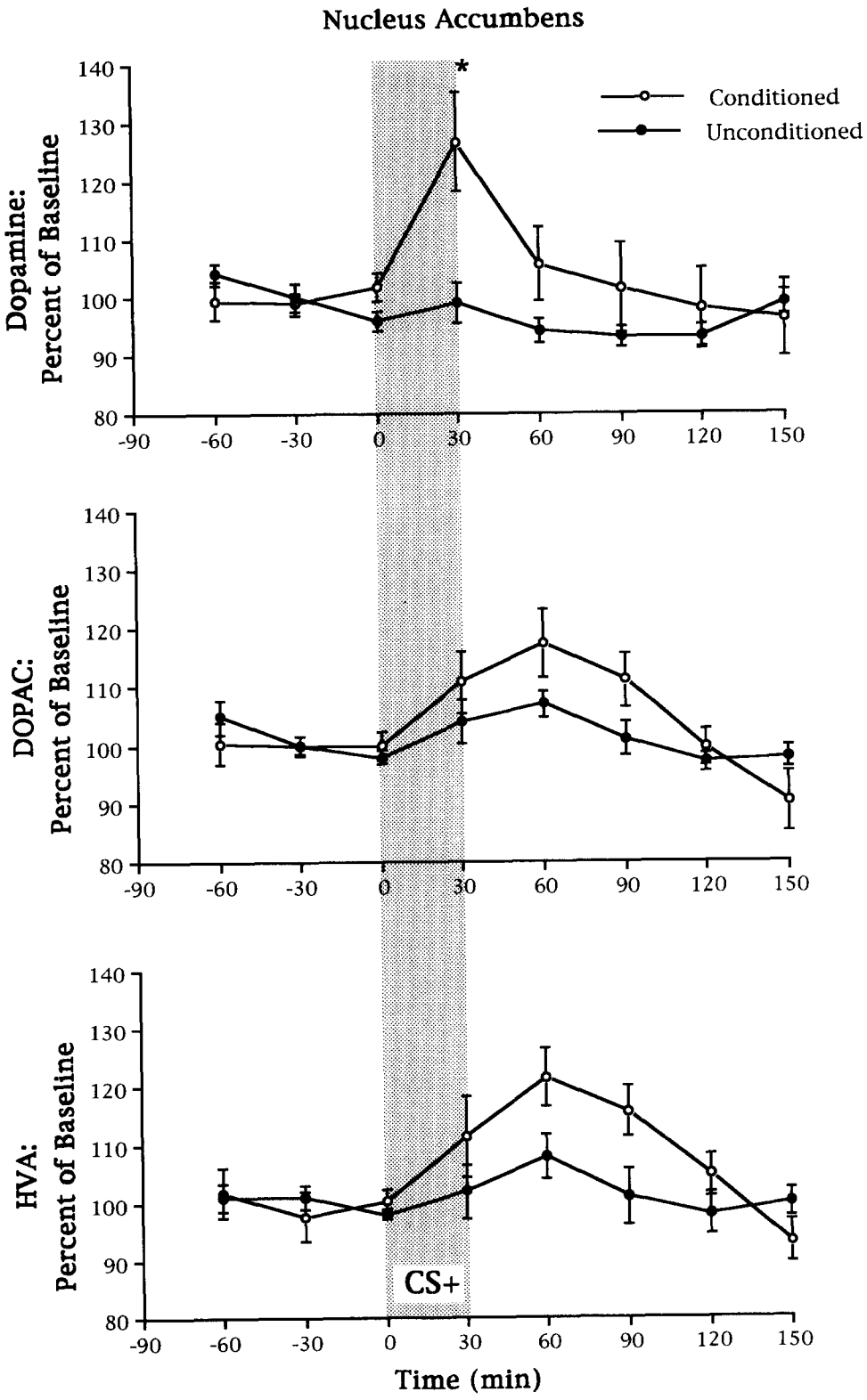

FIG. 1. (Top) Nucleus accumbens extracellular levels of dopamine expressed as percentage of mean baseline before, during, and after presentation of the CS+ in conditioned (n = 10) and unconditioned (n = 6) rats. Dopamine increased significantly in conditioned subjects during CS+ intake (*$p < 0.01$). (Middle and bottom) Extracellular levels of DA metabolites (DOPAC) and homovanillic acid (HVA) in the nucleus accumbens before, during, and after presentation of the CS+ in conditioned and unconditioned subjects. While DOPAC and HVA increased following CS+ presentation, this increase was not statistically significant.

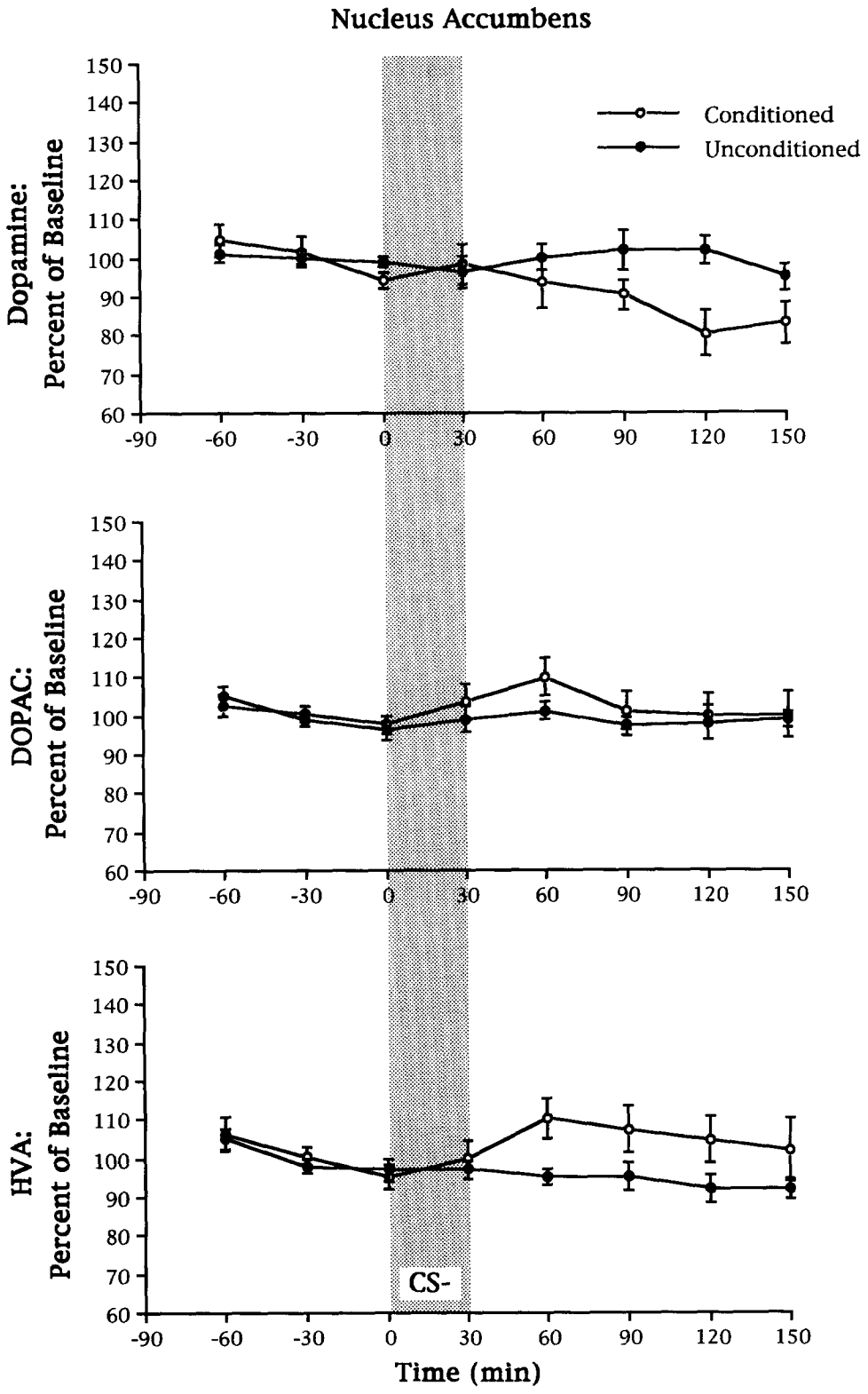

FIG. 2. Nucleus accumbens extracellular levels of dopamine (top) and metabolites (middle and bottom), expressed as percentage of mean baseline, before, during, and after presentation of the CS− in conditioned (n = 12) and unconditioned (n = 5) rats. There were no statistical differences associated with presentation of this stimulus.

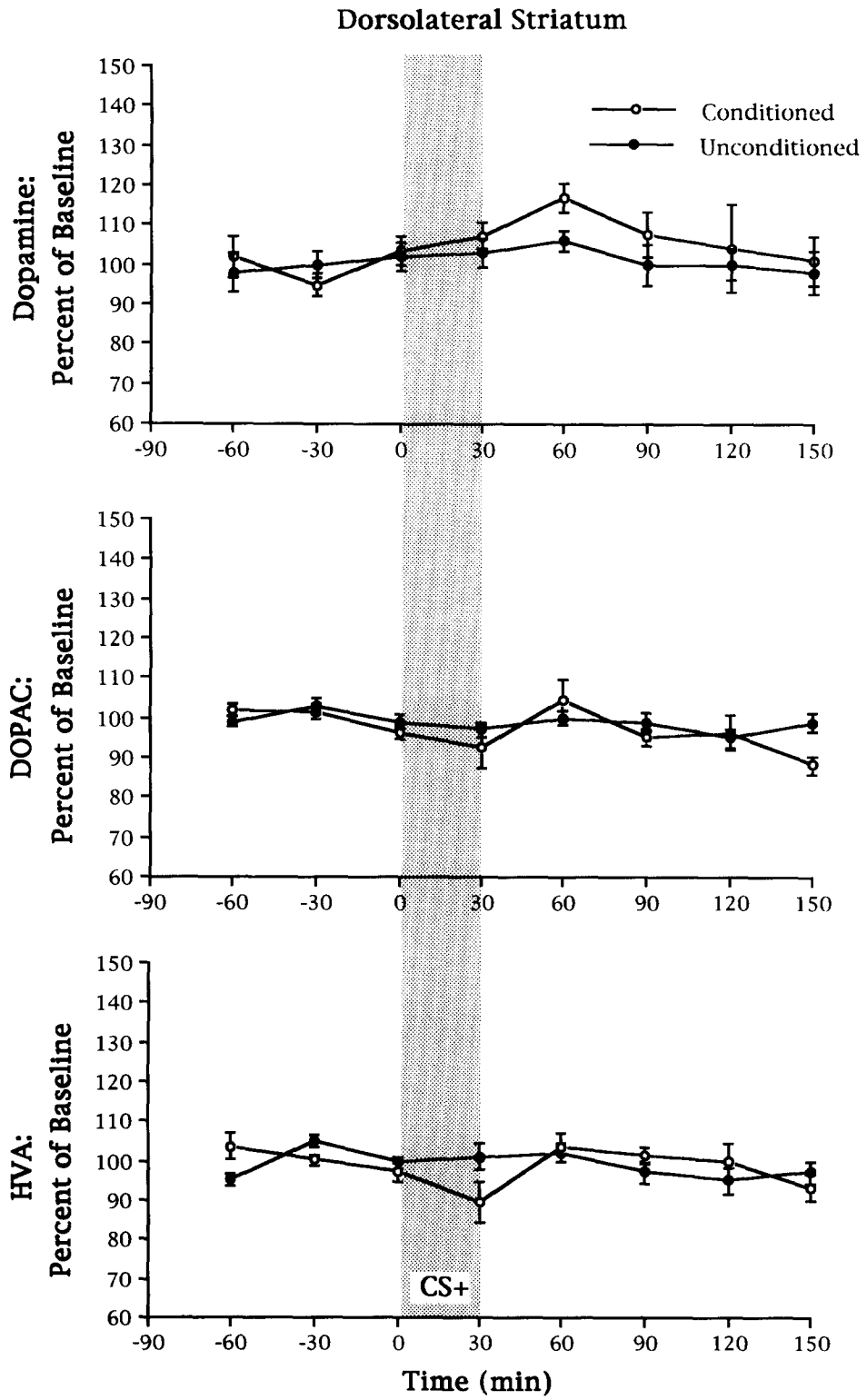

FIG. 3. (Top) Striatal extracellular levels of dopamine, expressed as percentage of mean baseline, before, during, and after presentation of the CS+ in conditioned (n = 5) and unconditioned (n = 6) rats. Dopamine increased slightly after administration of the CS+ in conditioned rats, but this change was not statistically significant. Extracellular levels of DA metabolites dihydroxyphenylacetic acid (DOPAC, middle) and homovanillic acid (HVA, bottom) in the striatum before, during, and after presentation of the CS+. Neither metabolite was significantly affected by fluid intake.

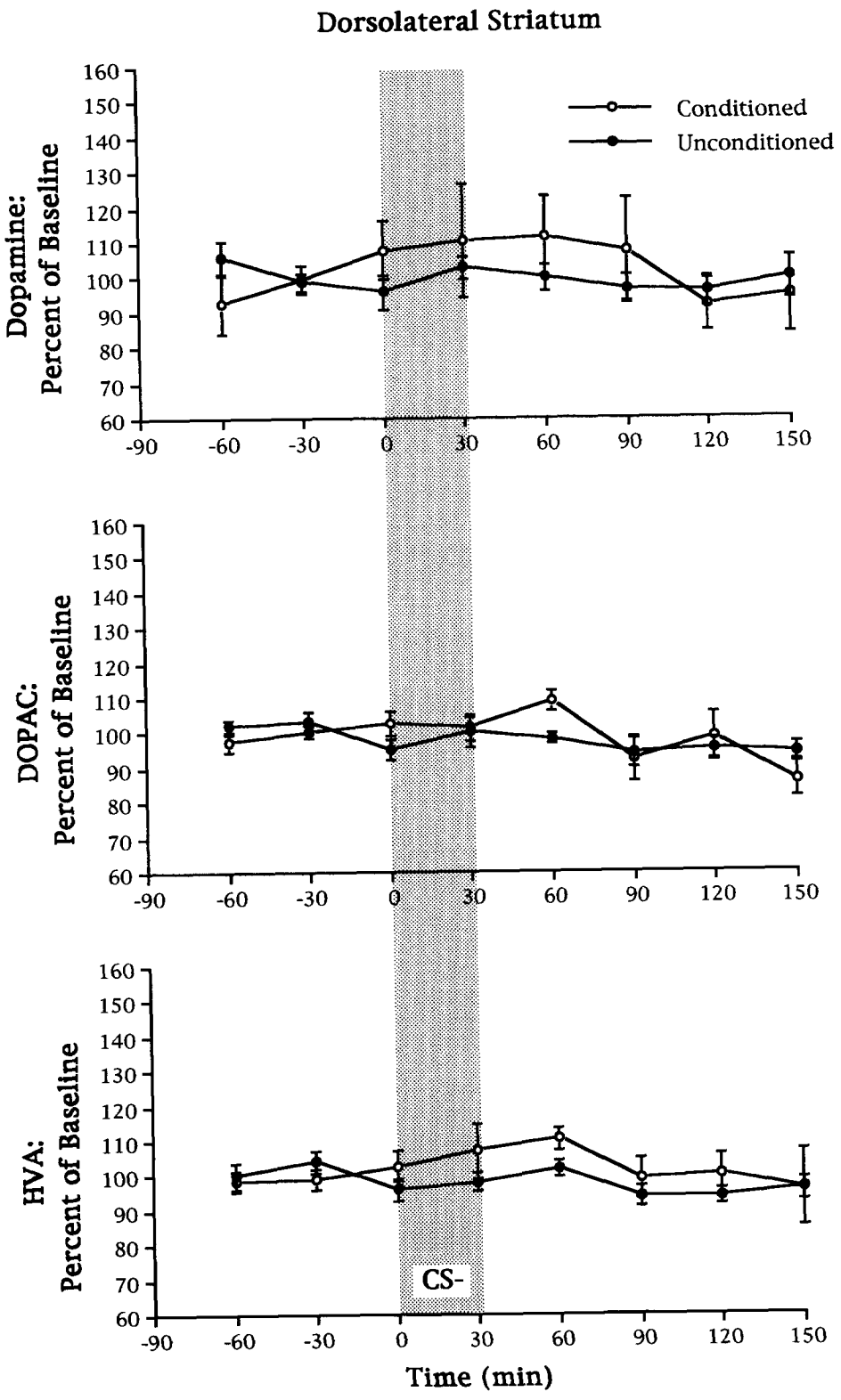

FIG. 4. Striatal extracellular levels of dopamine (top) and metabolites (middle and bottom), expressed as percentage of mean baseline, before, during, and after presentation of the CS− in conditioned (n = 5) and unconditioned (n = 5) rats. There were no statistical differences associated with presentation of this stimulus.

"hedonic" quality of reinforcers (13,54,60–62). This theory has received support from observations that the pattern of behavioral disruption following neuroleptic treatment is similar to that caused by reward attenuation (e.g., during extinction (12,15,17–19,23). This theory was originally offered as an alternative to suggestions that behavioral deficits resulting from DA receptor blockade or DA lesions were a function of motor impairments (14,16,46,47,57). More recently, several researchers have stressed the distinction between unconditioned consummatory actions from more complex, learned instrumental behaviors supported by conditioned or incentive stimuli (2,3,50,51,58). According to these theories, DA functioning is required for mediating the response-eliciting properties of conditioned stimuli, whereas primary, unconditioned consummatory behaviors are less dependent on mesolimbic DA transmission. Several studies have demonstrated that instrumental responding for food or water is disrupted by neuroleptics at doses below those necessary to impair food or water consumption (16,36,37,47). Blackburn et al. (4) have shown that pimozide disrupts entry into a food niche in response to a cue light without affecting food consumption once inside the niche. Moreover, Berridge et al. (3) have suggested that DA may be necessary for the attribution of salience to previously neutral stimuli which acquire new significance as a consequence of experience. In this view, the subsequent ability of these reprogrammed "incentive" stimuli to evoke ingestive behavior may depend more heavily on DA transmission than primary, consummatory stimuli. The results of the present study lend support to this theory and corroborate the interpretation of the pharmacological experiments mentioned above in that the simple consumption of fluid was not a distinguishing factor in eliciting DA efflux, but rather the CS+ developed the ability to enhance extracellular DA as a consequence of its previous association with IG calories.

The data presented here are also consistent with the suggestion of Whishaw and Kornelsen (58) that the NAc participates in behavior directed toward secondary, incentive cues associated with food. They observed that NAc-lesioned rats will carry food to eat immediately but will not transport food to a refuge to eat later as normal rats do. This finding led Whishaw and Kornelsen to suggest an "incentive motivation" theory of NAc function in which the integrity of the accumbens is required for mediating the secondary, perhaps conditioned, stimuli associated with food and is less involved in the primary reinforcement features. Our microdialysis results suggest that DA may be a mediating transmitter in this regard.

While the precise meaning of the change in transmitter release described here is not known, it is possible that information about the positive nature of a CS is expressed through enhanced extracellular DA in the accumbens, whereas a decrease in DA release signals a negative event. We have reported that exposure to an aversively conditioned taste is associated with a *decrease* in DA efflux in the NAc (39). This finding was confirmed by Louilot et al. (38), who also demonstrated a decrease in extracellular levels of DA in the accumbens in response to an aversively conditioned olfactory stimulus. Taken together, these results and the data presented here not only demonstrate the sensitivity of the mesolimbic DA system to conditioned stimuli associated with ingestion, but also suggest that its activity is modifiable in a manner consistent with the "affective valence" of a conditioned stimulus.

TABLE 1

AVERAGE, ABSOLUTE LEVELS (NOT CORRECTED FOR PROBE RECOVERY) OF DA (in pg/30μl) AND METABOLITES (in ng/30 μl) FROM THE NUCLEUS ACCUMBENS AND STRIATUM

Neurochemical	Site	Amount/30 μl	SEM	Range
DA	NAc	2.61	0.42	0.4 - 4.6
	STR	3.65	0.22	3.0 - 4.1
DOPAC	NAc	2.28	0.37	0.59- 4.44
	STR	4.41	1.01	1.12- 6.23
HVA	NAc	2.75	0.43	0.71- 5.73
	STR	8.04	2.21	2.83–15.6

The increase in accumbens DA reported here is only one component of a complicated system that develops and drives learned, ingestive behaviors. For example, the involvement of the mesocortical DA system in ingestive behaviors has been demonstrated electrophysiologically in primates trained to press a bar to receive food. Prefrontal cortical cells that were sensitive to local application of DA became active during the bar-press task (29). This suggests that cortical DA plays a role in food-seeking behavior. Furthermore, DA turnover has been shown to increase in the rat prefrontal cortex during and after feeding (25). Both of these findings implicate cortical DA in the acquisition or ingestion of food; therefore, exposure to a stimulus associated with a caloric substance might also increase DA in the prefrontal cortex as shown here for the NAc.

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