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Acquisition of Conditioned Reward Blocked by Intra-Accumbens Infusion of PD-140548, a CCK_A Receptor Antagonist

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JOSSELYN, S. A. AND F. J. VACCARINO. *Acquisition of conditioned reward blocked by intra-accumbens infusion of PD-140548, a CCK_A receptor antagonist.* PHARMACOL BIOCHEM BEHAV **55**(2) 439–444, 1996.—Cholecystokinin (CCK) is an endogenous peptide that is colocalized with dopamine (DA) in some mesolimbic neurons projecting to the nucleus accumbens (NAC). DA has been implicated in the acquisition of conditioned rewarding properties by neutral stimuli [conditioned stimuli (CS)] associated with a primary reward (such as food). A variety of experimental evidence suggests that exogenously applied CCK, acting at the CCK_A receptor, potentiates the function of DA in the NAC. Thus, the present experiment examined the role of endogenous CCK_A mechanisms in the NAC in the development of conditioned reward. The CCK_A receptor-selective antagonist PD-140548 was microinjected into the NAC during the CS–food pairing phase of a conditioned reward experiment. In the test session, animals that previously received vehicle microinjections into the NAC or PD-140548 microinjections into areas surrounding the NAC pressed a lever that produced the CS more often than did a control lever. The CS had gained conditioned rewarding properties. However, animals that received PD-140548 microinjections into the NAC did not exhibit a preference for the CR lever. Results suggest that blockade of CCK_A receptors in the NAC impairs the development of conditioned reward. These findings support a role for endogenous CCK_A mechanisms in the NAC in the acquisition of stimulus–reward associations. **Copyright © 1996 Elsevier Science Inc.**

Conditioned reward CCK_A receptors PD-140548 Nucleus accumbens Reward-related learning

FOOD or water, as well as other primary rewarding stimuli, can exert powerful control over behavior. Motivationally neutral stimuli paired with primary rewards may acquire rewarding properties such that these stimuli elicit approach and other responses through an incentive learning process (2,5). Thus, in the conditioned reward paradigm, a previously neutral stimulus [conditioned stimulus (CS)] comes to exert a rewarding effect on behavior by virtue of an association with a primary reward. During a test phase, following CS–food pairings, two novel levers are introduced and rats may press one lever [the conditioned reward (CR) lever] to present the reward-associated stimulus alone or another lever (the non-CR or NCR lever), depression of which produces no programmed consequence. Demonstration of the acquisition of this type of reward-related learning is offered on a drug-free test day if the animal presses the CR lever more often than the NCR lever.

Converging evidence suggests a role for dopamine (DA) in the acquisition of reward-related learning in general, and conditioned reward, specifically (2,3). Systemic administration of the DA antagonist pimozide before CS–food pairings prevents the acquisition of conditioned reward (14). Cholecystokinin (CCK) is extensively colocalized with DA in a large subpopulation of mesencephalic neurons arising from the ventral tegmental area (VTA) (A10 cell group) and the substantia nigra (SN) (A9 cell group) and terminating in limited forebrain areas including the nucleus accumbens (NAC) [e.g., (15,16)]. Two CCK receptors have been identified, cloned, and classified into CCK_A and CCK_B subtypes (10,17,22,32). Microiontophoretic application of CCK onto the cell bodies of mesolimbic DA neurons increases the firing rat (26). In the NAC, exogenous application of CCK-8S increased firing rate of neurons, especially in the medial posterior NAC, an effect that is inhibited by DA application (31,33). However, CCK-8S, but not CCK8-US or CCK-4, increases K^+-evoked DA release in posterior NAC slices, an

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effect that is blocked by low doses of a CCK_A-selective but not CCK_B receptor–selective antagonist (21). CCK-8S potentiates DA-induced activation of adenylate cyclase in the posterior NAC (27). Furthermore, exogenous application of CCK_A receptor–selective peptide fragments into the medial posterior region of the NAC potentiates DA or agonist-induced hyperlocomotion (7–9,30). Together these results suggest that endogenous CCK acting at CCK_A receptors in the NAC may potentiate the function of DA [see (29) for review].

As intact mesolimbic DA functioning has been implicated in the acquisition of reward-related learning [see (1,18)] and NAC CCK_A receptor–mediated events seem to potentiate the function of DA within the NAC, the possibility that endogenous CCK_A mechanisms in the NAC might play a role in the acquisition of conditioned reward is raised. We recently reported that systemic injections of the CCK_A receptor–selective antagonist devazepide, but not the CCK_B receptor–selective antagonist L-365,260, blocked the acquisition of conditioned reward (19). Although these results suggest that endogenous CCK acting at the CCK_A receptor is critically involved in the acquisition of conditioned reward, the neuroanatomic substrate mediating this effect remains to be determined.

The present experiments sought to extend the previous findings by examining the effects of microinjecting a CCK_A receptor antagonist directly into the NAC on the acquisition of conditioned reward. As devazepide has poor water solubility, this compound has limited use in microinjection studies. Thus, the dipeptoid PD-140548 that readily dissolves in water was used. PD-140548 is a potent and selective CCK_A receptor antagonist [IC_{50} for CCK_A receptors = 2.82 nM, IC_{50} for CCK_B receptors = 259 nM (25)]. Immediately before four conditioning sessions, PD-140548 was microinjected into the NAC. On a subsequent test day, the acquisition of conditioned reward was assessed.

METHODS

This research has been carried out with due regard for the Animals for Research Act, the Guidelines of the Canadian Council on Animal Care, and relevant University policy.

Animals

Male albino Wistar rats (n = 51, obtained from Charles River, Montreal, Canada) were singly housed and maintained in a controlled environment on a 12 L:12 D cycle (lights on at 0600 h) at a temperature of 21°C. Animals were slowly reduced to 85% of their free-feed weight by a limited-access feeding schedule. Water was available in the home cage throughout the experiment.

Surgery

Animals were bilaterally implanted with stainless-steel guide cannulae (23 ga) aimed at the posterior region of the NAC [coordinates 0.7 mm anterior to bregma, 1.0 mm lateral to the midline, and 6.5 mm ventral to the surface of the skull, with the incisor bar set at 3.2 mm below the horizontal plane passing though the interaural line (23)]. Rats were anaesthetized with sodium pentobarbital (65 mg/ml; 1 ml/kg body wt., IP). Cannulae were anchored to the skull with stainless-steel screws and dental cement. When not in use, the guide cannulae were occluded with wire pins.

Central Injections

Hamilton microsyringes (5.0 μl), mounted in an infusion pump, were used to infuse the drugs at a constant rate of 0.25 μl/min. The volume of all injections including vehicle was 0.5 μl. Injection cannulae (30 ga) were constructed of stainless-steel tubing and cut to extend 1.0 mm beyond the tips of the guide cannulae. Polyethylene tubing attached the microsyringe to the injection cannulae. Following the injection, cannulae were maintained in position for an additional minute to ensure diffusion of the drug.

Drugs

PD-140548 [CAM 1481-5-013; AdOC–(Ia/Me)Ltrp–(D-3-Bzl)b Ala.D-MeGluc] was provided by the Neuroscience Research Center at Parke-Davis (Cambridge, UK). The compound was dissolved in saline. Four doses of PD-140548 were used [vehicle (n = 9); PD-140548 (1.0 μg in 0.5 μl, n = 3); PD-140548 (10.0 μg in 0.5 μl, n = 26); and PD-140548 (20.0 μg in 0.5 μl, n = 13)].

Apparatus

Eight standard operant chambers (Med Associates, Inc., Georgia, VT) measuring 26.5 × 22 × 20 cm were used. Each operant chamber was constructed of two Plexiglas and two aluminum sides with a wire rod floor. A pellet dispenser was attached to each operant chamber and delivered food pellets (45-mg sucrose pellets; BioServ, Frenchtown, NJ) into a food cup. A ventilating fan was contained on one wall and the entire chamber was housed in a sound-attenuating outer compartment to minimize external noise. Two retractable levers on either side of the food cup were located beneath two red stimulus lights. A houselight was located near the center of the opposite wall. The operant chambers were attached to a personal computer that was responsible for controlling the activities of the operant chambers as well as data collection.

Experimental Procedure

Behavioral evaluation was carried out in three distinct phases, taking place over 7 consecutive days.

Habituation Phase. In the two 15-min preliminary sessions with the operant levers in the retracted position, animals habituated to the operant chambers with several of the novel food pellets available in the food cups.

Conditioning Phase. During four daily conditioning sessions, rats were trained to associate food presentation [the reward or unconditioned stimulus (UCS)] with a neutral CS. A reinforcement schedule (random time 30-s schedule of presentation) was used in which there were 30 presentations of the CS (houselight off, red stimulus lights on for 3 s followed by a 0.1-s tone) immediately followed by delivery of a food pellet. During this phase the levers were in the retracted position. Five minutes before conditioning sessions, rats were administered the appropriate drug injection.

FIG. 1. Coronal sections showing the injector tips for all rats. "Hits" (those tips located in the NAC) = ●; "misses" (those tips located outside the NAC) = ○. (A) Vehicle group (hits = 7, misses = 2). (B) PD-140548 1.0-μg group (hits = 3). (C) PD-140548 10.0-μg group (hits = 21, misses = 5). (D) PD-140548 20.0-μg group (hits = 8, misses = 5). Drawings are adapted from Paxinos and Watson (29); numbers beside each section indicate the distance (mm) anterior to bregma.

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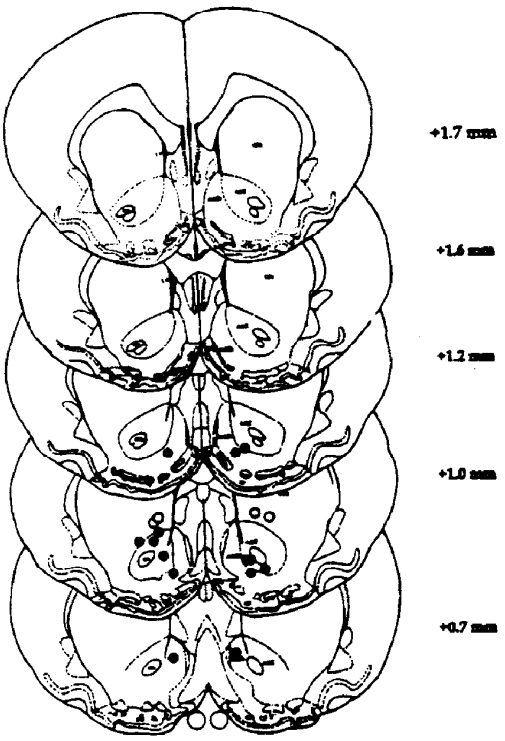
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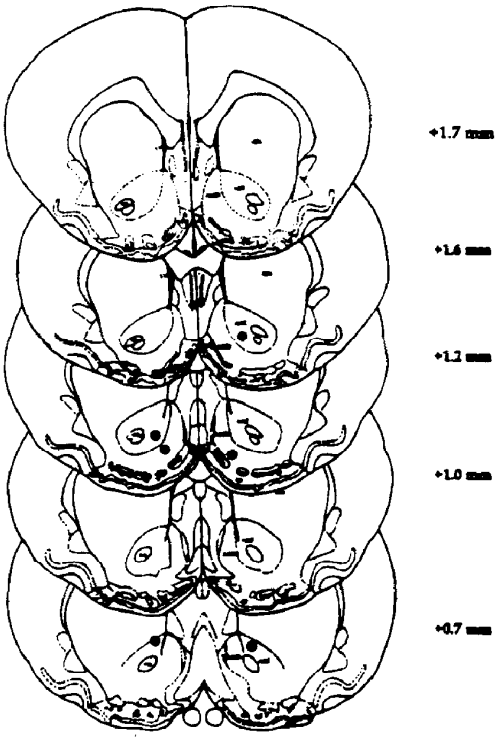
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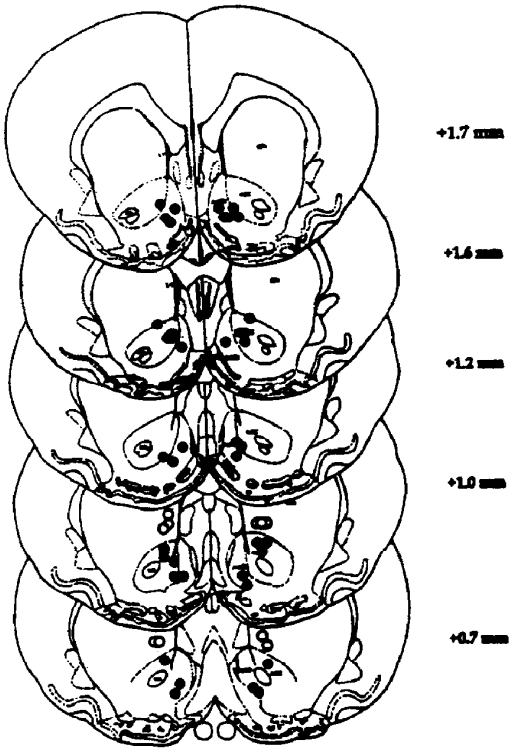
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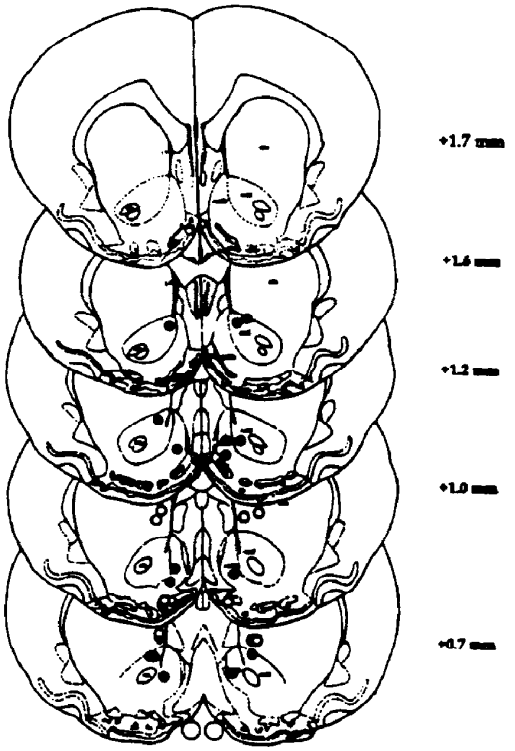
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Test Phase. The test session was 40 min in length and all animals were drug free. For the first time, the two levers were available to the rats. Depression of the CR lever (the left lever for all animals) resulted in the presentation of the CS according to a random ratio (RR2) schedule, while depression of the NCR lever (the right lever) had no programmed response. Responding on the NCR lever therefore provided a measure of nonspecific motor activity. Acquisition of the conditioned reward task was demonstrated by a selective increase in the number of responses on the CR lever.

Histology

Upon completion of the experiment, confirmation of cannulae placements was verified through histologic analysis. Brains were removed from rats, frozen, and sliced in 40-μm sections that were mounted and stained.

Statistics

The total number of depressions on each lever during the test session was subjected to square-root transformation to maintain homogeneity of variance [as suggested by Winer (34)]. The untransformed data were also analyzed and the results were generally in agreement with the statistical interpretation of the transformed data. An analysis of variance (ANOVA) was conducted using the Statistica software package (StatSoft, Inc., Tulsa, OK) with between-factor dose of drug administered in the conditioning phase (0, 1.0, 10.0, and 20.0 μg of PD-140548) and a within-factor lever (CR vs. NCR lever). The data obtained from improperly cannulated animals were analyzed separately.

RESULTS

Histologic analysis revealed that the cannulae tips were most often situated in, or just dorsal to, the NAC and that a line of gliosis extended ventrally, indicating that most of the drugs were infused bilaterally into the NAC, as can be seen in Fig. 1. A "hit" was defined as a placement anywhere within the NAC, whereas a "miss" constituted those placements outside the boundaries of the NAC as defined by Paxinos and Watson (23). In several animals, the misses were positioned in more dorsal areas of the striatum. The vehicle group was composed of seven hits and two misses; the PD-140548 1.0-μg dose contained three hits; and the PD-140548 10.0- and 20.0-μg doses contained 21 hits, five misses, and eight hits and five misses, respectively.

Figure 2A shows the mean (±SEM) square-root responses on the CR and NCR levers during the drug-free test day, when food was no longer available in the operant cages, for animals with hit placements. As can be seen, animals receiving vehicle treatment in the conditioning phase responded more often on the lever that produced the stimuli previously associated with food presentation (the CR lever) in the test phase. PD-140548 administration into the NAC, before the food–CS pairings, decreased the preference for the CR over the NCR lever in the test session. The ANOVA showed a significant Dose × Lever interaction [$F(3, 35) = 5.10, p < 0.05$] as well as significant effects of Dose [$F(3, 35) = 11.13, p < 0.05$] and Lever [$F(1, 35) = 7.37, p < 0.05$]. Analysis of the simple main effects revealed that in the vehicle group, rats pressed the CR lever significantly more often than the NCR lever [$F(1, 35) = 19.90, p < 0.001$]. For rats receiving the 1.0-, 10.0-, or 20.0-μg dose of PD-140548, there were no significant difference between the number of responses on the CR vs. NCR levers

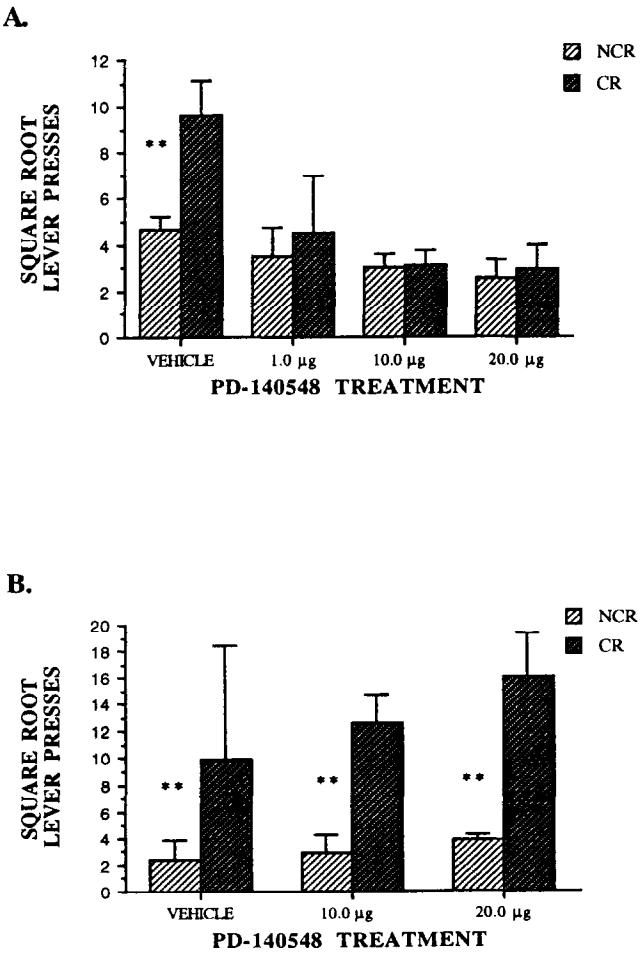

FIG. 2. The effects of microinjecting PD-140548 into the NAC or surrounding regions on the acquisition of conditioned reward. Animals received PD-140548 (1, 1.0, 10.0, or 20.0 μg in 0.5 μl) before 4 conditioning days during which initially neutral CS was paired with food delivery. On a drug-free test day, animals were presented with two levers: depression of the CR lever resulted in presentation of the CS, while depression of the NCR lever resulted in no programmed consequence. **CR lever was pressed significantly more often than the NCR lever ($p < 0.001$). (A) Cannulae placements within the NAC. (B) Cannulae placements outside the NAC.

[$F(1, 35) = 0.38, p > 0.05$]; [$F(1, 35) = 0.001, p > 0.05$]; and [$F(1, 35) = 0.14, p > 0.05$], respectively. Thus, animals receiving vehicle into the NAC during the food–CS pairing phase acquired the conditioned reward response, while animals receiving PD-140548 into the NAC did not.

Figure 2B shows the mean square-root lever responses (±SEM) on the CR and NCR levers for animals with cannulae placements outside the boundaries of the NAC, the miss category. As all animals receiving the 1.0-μg dose of the drug were hits, there were three levels of the dose variable for the ANOVA (0-, 10.0-, and 20.0-μg PD-140548). As can be seen, animals seemed to show a strong preference for the CR over the NCR lever in the test session, regardless of dose of PD-140548 microinjected into brain tissue surrounding the NAC. The results of an ANOVA support this observation. There was a significant effect of Lever [$F(1, 9) = 26.91, p < 0.001$] but no significant effects of Dose [$F(2, 9) = 0.64, p > 0.05$]

or Dose × Lever interaction [$F(2, 9) = 0.52, p > 0.05$]. Posthoc Newman–Keul comparisons on the significant lever effect show that the CR lever was pressed significantly more often than the NCR lever ($p < 0.001$). Thus, vehicle or PD-140548 microinjected into brain regions near the NAC did not block the acquisition of conditioned reward.

DISCUSSION

Stimuli possessing motivationally neutral properties that gain incentive properties from their predictive association with primary rewards are termed *conditioned rewards* [see (5)]. In the present experiment, a light-tone CS was paired with food delivery, and in a subsequent test session, drug-free animals were given access to two novel levers. Animals pressed more often on the lever that produced the CR rather than a control lever, demonstrating the acquisition of conditioned reward.

The association between the CS and food presentation resulted in the CS becoming a conditioned reward. Thus, animals learned a novel lever-press response to obtain presentation of the CS alone. The acquisition of a new response procedure used here provides a stringent test of conditioned reward (20). The importance of the contingency between the CS and the primary reward has been demonstrated in previous experiments, as stimuli randomly (19,28) or negatively (14) correlated with the presentation of the primary reward during the conditioning phase of these do not support the acquisition of conditioned reward.

In this experiment, microinjection of PD-140548 into the NAC during the CS–food delivery conditioning phase blocked the selective increase in responding on the CR lever in a subsequent test. Thus, acquisition of conditioned reward was blocked by antagonism of CCK_A receptors in the NAC. However, similar administration of this drug into regions surrounding the NAC, such as more dorsal areas of the striatum that also contain substantial concentrations of CCK-like immunoreactivity (11), did not block the acquisition of conditioned reward. Thus, the blockade of conditioned reward produced by the CCK_A antagonist shows some neuroanatomic specificity, although other brain regions were not systematically examined.

The hypothesis that CCK_A receptor–mediated events are involved in the acquisition of reward-related learning derives mainly from the observation that systemic administration of the CCK_A antagonist devazepide, but not the CCK_B antagonist L-365,260, during the conditioning phase of a conditioned place preference experiment impaired the acquisition of morphine-induced conditioned place preference, as measured on a drug-free test day (12,13). Previously we have reported that systemic administration of devazepide blocked the acquisition of conditioned reward and conditioned activity induced by amphetamine (19). Similar injection of L-365,260, however, did not block acquisition of conditioned reward (19). The present results extend the analysis of the role of CCK_A mechanisms in the acquisition of reward-related learning by determining a possible neuroanatomic site of action.

The present experiment is the first of which we are aware to use a central manipulation during the conditioning phase to block the acquisition of conditioned reward in this type of paradigm. However, other experiments have shown that intra-NAC microinjections of DA antagonists impair other forms of reward-related learning, such as acquisition of a conditioned place preference. Thus, Josselyn and Beninger (18) found that the place preference induced by neuropeptide Y (NPY) was blocked by microinjection of the DA antagonist, *cis*-flupenthixol into the NAC. Similarly, administration of *cis*-flupenthixol into the NAC decreased the place preference induced by amphetamine (1).

Phillips and colleagues (24) reported that there is an interaction between CCK_A receptor–mediated mechanisms and amphetamine within the NAC in the expression of conditioned rewarded behavior, as measured in a slightly different paradigm. Intra-NAC microinjection of CCK-8S increased the already high levels of responding on the CR lever produced by amphetamine. Systemic administration of devazepide reversed the effects of CCK-8S but had no effect on its own. The crucial difference between this experiment and the present is that in the present experiment, the CCK_A receptor antagonist was administered in the CS–primary reward pairing (conditioning) phase of the experiment, and the study of Phillips et al. administered the CCK antagonist in the test phase. Thus, the present study examined the acquisition of reward-related learning whereas the study of Phillips et al. investigated the expression of reward-related learning.

It is not surprising that a drug treatment was shown to impair the acquisition, but not expression, of reward-related learning. For instance, the DA antagonists pimozide and SCH 23390 block the acquisition but not expression of amphetamine-induced conditioned activity (4) or cocaine-induced conditioned place preference (6). Thus, both DA and CCK_A receptor antagonists seem to block the acquisition but not expression of reward-related learning.

We have shown previously that systemic administration of the CCK_A antagonist devazepide impairs the development of conditioned reward and conditioned activity produced by amphetamine (19). In the present experiment, microinjection of the structurally unrelated CCK_A antagonist PD-1450548 into the NAC blocked the development of conditioned reward. Neuroanatomic specificity was demonstrated in that injections of PD-140548 outside the NAC did not impair the development of conditioned reward. Previous control experiments ruled out the possible interpretations that devazepide produced a blockade of conditioned reward due to a nonspecific effect on food consumption or by inducing a conditioned taste aversion. Together with previous findings, the present results support the conclusion that reward-related learning, as measured by various behavioral paradigms, depends on intact functioning of CCK_A receptors in the NAC. Furthermore, these findings shows pharmacologic, neuroanatomic, and behavioral specificity.

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