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Anatomical disassociation of amphetamine's rewarding and aversive effects: An intracranial microinjection study

Geoffrey D. Carr and Norman M. White
Department of Psychology, McGill University, 1205 Dr. Penfield Avenue, Montreal, Quebec, Canada H3A 1B1

Abstract. Amphetamine has rewarding properties in some behavioral paradigms, such as self-administration and conditioned place preference (CPP), but an aversive component is also apparent when the drug is tested with the conditioned taste aversion (CTA) paradigm. The persent study was an attempt to determine the neuroanatomical substrates of the drug's rewarding and aversive effects. Previous evidence suggested that amphetamine's stimulation of activity in dopaminergic synapses is critical for both effects. Amphetamine was therefore micro-injected bilaterally (10 μg/0.5 μl per side) into six different dopaminergic sites, each in a different group of animals: the medial prefrontal cortex, nucleus accumbens, anteromedial caudate nucleus, lateroventral caudate nucleus, amygdala, and the region subjacent to the area postrema (AP region). The effects of these injections in both the taste and place conditioning paradigms were examined in separate experiments. Of the six sites, a significant CPP was observed only with accumbens injections and a significant CTA was observed only with AP region injections. It was concluded that the accumbens plays a primary role in mediating the rewarding effects of amphetamine and that the AP region plays a primary role in mediating the CTA. This constitutes an anatomical disassociation of amphetamine's rewarding and aversive effects. The differential associative bias of place-reward and taste-aversion learning apparent in the results is discussed.

Key words: Amphetamine – Reward – Conditioned place preference – Conditioned taste aversion – Nucleus accumbens – Dopamine

Amphetamine's rewarding properties have been demonstrated in a variety of ways. Humans and other species self-administer the drug (Kliner and Pickens 1982; Pickens and Harris 1968; Schuster and Thompson 1969; Kalant 1966), humans report euphoria from the drug and prefer it over other drugs of abuse (Kliner and Pickens 1982), and experimental animals prefer a place that has been previously paired with the drug (conditioned place preference; CCP) (Reicher and Holman 1977; Spyraki et al. 1982).

In contrast to this evidence for amphetamine's rewarding effects, experimental animals avoid novel tastes that have previously been paired with the drug, suggesting that it also has an aversive effect (conditioned taste aversion; CTA) (Le Magnen 1969) This paradox of obtaining a CTA from a rewarding drug has also been observed with a variety of other rewarding drugs, such as morphine, cocaine, ethanol, mescaline, cannabis, several benzodiazepines, and several barbiturates (see Goudie 1979, for a review).

The paradox of both rewarding and aversive effects with the same drug was made pointedly clear by Reicher and Holman (1977), who observed both a CPP and a CTA from the same amphetamine injections. These apparently opposing effects have been the subjects of a considerable amount of theorizing and research (see Goudie 1979). Thus far, no explanation for the paradox has held up to experimental scrutiny.

The neuropharmacological substrates of the two effects have been examined. Although amphetamine exerts its effects primarily by stimulating activity in both dopaminergic and noradrenergic synapses, it appears that both its rewarding and aversive effects depend critically on dopamine. Dopamine antagonists disrupt amphetamine self-administration in rats (Yokel and Wise 1975), antagonize the conditioned place preference to amphetamine (Spyraki et al. 1982), and result in a reduction of reported euphoria in humans (Gunne et al. 1972). Neurotoxin lesions (6-hydroxydopamine) of the dopamine terminals in the nucleus accumbens also block amphetamine self-administration and conditioned place preference (Lyness et al. 1979; Spyraki et al. 1982). The prominent role of dopamine in mediating the CTA to amphetamine was demonstrated by antagonizing the effect using the dopamine receptor blocker pimozide (Grupp 1977) and by using selective 6-hydroxydopamine lesions of the central dopamine neurons (Wagner et al. 1981).

Given this evidence of the importance of amphetamine's dopaminergic agonist activity in both the reward and conditioned taste aversion, the present study examined the contributions of several dopaminergic brain site to these effects. Amphetamine was microinjected into one of six discrete brain sites and the tendency of the injections to produce either a conditioned place preference or a conditioned taste aversion was examined. Our preliminary work (Carr and White 1983) demonstrated that unilateral injections of amphetamine into the nucleus accumbens produced a CPP. Hoebel et al. (1983) have also reported self-administration of the drug directly into this area. It therefore appears that the nucleus accumbens play a role in amphetamine's rewarding effects and the present study examines possible

Offprint requests to: N.M. White

contributions of several other dopaminergic sites to this phenomenon.

There is no clear evidence about which brain sites mediate the CTA. The amygdala has been implicated by Grupp et al. (1976) who found that bilateral lesions of this area produced a partial attenuation of CTA learning with both amphetamine and the toxin lithium chloride. However, it is not clear if amphetamine actually acts in the amygdala to produce a CTA or if the structure is instead necessary for the later expression of CTA learning. It is known that toxins such as lithium chloride act on the chemoreceptive area postreme to produce CTAs. Lesions of this structure abolished CTAs to toxins but did not block the CTA to amphetamine (Berger et al. 1972).

Subjacent to the area postrema lie the nucleus of the solitary tract (NST) and the dorsal motor nucleus of the vagus (DMNV). The caudal portion of the NST receives input from the area postrema (Morest 1967) in addition to input from the sensory vagus (Sumal et al. 1983), which has been shown to be critical for producing some types of CTA (Coil et al. 1978). The rostral NST receives the primary taste input from the tongue (Morest 1967). The convergence of visceral and chemoreceptive input with taste input in the same structure is suggestive of a possible role in mediating taste aversion learning. A role for the DMNV in CTA learning has not yet been examined, but its location in this region, the fact that it contains dopaminergic neurons (Kalai et al. 1984), and that it receives input from the NST (Morest 1967), make it a candidate for a possible role in mediating the CTA to amphetamine. The region subjacent to the area postrema was therefore chosen as a site for amphetamine microinjetion.

In addition to nucleus accumbens and area postrema, four other forebrain dopamine terminal areas were selected for study: the medial frontal cortex, anteromedial caudate nucleus, lateroventral caudate nucleus, and the amygdala. These sites include the major dopamine terminal regions in the brain (see Fallon and Moore 1978a, b, and Fallon et al. 1978 for an examination of dopamine terminal areas).

Experiment 1: Conditioned place preference

Methods

Subjects. Fifty-nine male hooded rats (Canadian Breeding Farms and Laboratories) weighing 300–325 g at the time of surgery were used. They were housed individually in suspended metal cages in a room with the lights on between 7 a.m. and 7 p.m. Water and rat chow pellets were continuously available.

Apparatus and procedures. Stereotaxic surgery was performed to implant stainless steel guide cannulae (0.7 mm outer diameter; Plastic Products Co.). Surgery was performed under 60 mg/kg sodium pentobarbital anesthesia and the implanted cannulae were anchored to the skull using screws and dental cement. The cannulae were aimed at one of six sites for each animal. Coordinates (below) were modifications (based on experience), of the atlas of Pellegrino et al. (1979) and measured from bregma (anterior-posterior and lateral) with the depth determined by lowering a pre-cut cannula until the plastic sleeve touched the skull. Each rat was implanted bilaterally except for those in the midline area postrema region group which received a single cannula. The brain sites, their abbreviations used here, and the stereotaxic coordinates are:

1. Medial frontal cortex (MFC) – anterior (A): 4.5, lateral (L): 0.7, rotated 20° laterally from the midline to avoid the superior sagittal sinus and lowered to the depth of a 4 mm cannula.

2. Nucleus accumbens (accumbens) – A: 3.6, L: 1.5, rotated 20° to avoid the ventricles, and lowered to the depth of an 8 mm cannula.

3. Antero-medial caudate nucleus (medial caudate) – A: 3.4, L: 1.9, rotated 15° to avoid the ventricles, and lowered to the depth of a 5.5 mm cannula.

4. Latero-ventral caudate nucleus (lateral caudate) – A: 2.0, L: 4.0, and lowered to the depth of a 7 mm cannula.

5. Amygdaloid complex (aimed at the central nucleus) (amygdala) – A: 0.0, L: 4.0, lowered to the depth of an 8.5 mm cannula.

6. Area postrema/nucleus of the solitary tract region (AP region) (aimed for the region just below the area postrema in the surrounding NST) – 11.6 posterior to bregma, L: 0.0, and lowered to the depth of a 10 mm cannula, with the posterior edge of the sleeve 2 mm from the skull (note that this placement is 1 mm anterior to where the atlas of Pellegrino et al. (1979) places the area postrema).

Following surgery, a screw-on wire stylet was inserted into the guide cannula. This stylet, and the internal cannulae used for the injections (0.4 mm outer diameter), were cut so as to extend 0.5 mm from the tip of the guide cannula. An exception to this was the area postrema region placement, which was previously found to be sensitive to mechanical stimulation. This was avoided here by cutting the stylet to be flush with the tip of the guide cannula and recessing the internal injection cannula by 0.5 mm. Following surgery, the rats were given one to three injections of penicillin (Derapen) and were given a minimum of 1 week to recover before the experiment was started.

Intracranial injections. Injections were made via internal cannulae which were connected to 5 µl Hamilton syringes by polyethylene tubing. For the bilateral injections, two syringes were attached together and two separate lengths of tubing connected them to the left and right internal cannulae. The injections were done simultaneously, infusing the fluid over a one minute period (50 s for injection plus 10 s for diffusion). Each injection consisted of 10 µg *d*-amphetamine sulphate (Smith, Kline & French, Canada) dissolved in 0.5 µl physiological saline solution, or the saline vehicle alone, injected bilaterally. For the one-cannula area postrema region injections, 20 µg was dissolved in 0.5 µl of distilled water. The concentration of this solution is approximately iso-osmotic with serum and the saline control injections (Pharmaceutical Society of Britain, 1977). The AP region injections were done over 1 min with 30 additional seconds of diffusion time to compensate for the recessed injection cannula.

CPP procedure. The place preference apparatus (Carr and White 1983) consisted of two main "conditioning compart-

ments" (45 × 45 cm × 30 cm high), separated by a wood partition and connected by a third offset shuttle-box compartment (36 × 18 cm × 20 cm high). The apparatus was constructed of wood with a hinged, clear Plexiglas front. The conditioning compartments had the following distinguishing stimulus characteristics. Compartment A was painted white and a handful of laboratory bedding wood chips were spread on the floor. Compartment B was painted black with vertical white 2 cm masking tape stripes (three per wall). The floor was 12 mm wire mesh suspended over a black base. Vinegar (1 ml 2% acetic acid) was dropped onto the floor before each rat was placed into the apparatus. The apparutus was cleaned between rats by removing feces and urine-soaked wood chips and by wiping the floor under the wire grid with a damp cloth. The third compartment (made of unpainted wood) served as a "tunnel" connecting the conditioning compartments. A removable partition sealed off the conditioning compartments from the shuttle compartments.

The 1st day of the procedure consisted of a pre-exposure period with the shuttle compartment open, to allow free movement among the three compartments. Each rat was placed separately into the apparatus for 10 min.

The pairing trials began on the following day. The shuttle-compartment was closed off by the partition, thereby confining the rat to one of the two main compartments. Rats representing each of the brain sites were randomly assigned to receive amphetamine injections paired with either compartment A or compartment B. The rats in each compartment group were then again randomly assigned so that half received amphetamine on days 1, 3, 5, 7, 9, 11 and the others on days 2, 4, 6, 8, 10, 12. On alternate days, each rat was confined in the opposite compartment and received saline control injections. The daily procedure involved removing the rat from its home cage, administering its assigned injection for that day, placing it into its assigned compartment for 35 min and then returning it to its home cage.

On the day following the 12 pairing trials, the rats were tested for their relative preferences for the compartments. The shuttle compartment partition was removed, allowing the rat to move freely among the three compartments. Each animal was placed into the shuttle compartment and its movements were observed through the Plexiglas front on the box. Its position in the apparatus was recorded over a 20-min period. The rat was recorded as being in one of the main compartments if any part of its body (except its tail) was in that compartment.

At the end of the experiment, the animals were anesthetized with an overdose of chloral hydrate and perfused intra-cardially with physiological saline, followed by 10% formalin. Their brains were removed and frozen sections were cut at 100 micron intervals for histological examination.

Results and discussion

The results of the histological examination are presented in Fig. 1. Of the animals that completed the experiment, four were excluded from the data analysis on the basis of this examination. One medial caudate animal had a cannula in the ventricle. Two nucleus accumbens group animals had placements in the anterior caudate (both had shown slight place preferences). One amygdala rat had infections around its cannulae and was anterior to the other placements. All other rats were included.

The results of the place preference test are presented in Fig. 2. A two-way (site × treatment) analysis of variance with one repeated measure (treatment) revealed significant effects of site [$F(5,53)=4.34$, $P<0.01$] and treatment [$F(1,53)=8.11$, $P<0.01$], and a significant site × treatment interaction [$F(5,53)=4.65$, $P<0.01$]. Simple main effects tests showed that the nucleus accumbens group spent significantly more time on the amphetamine-paired side than on the saline-paired side ($P<0.001$). No effect approaching significance was observed for any other site.

All of the accumbens-injected rats showed a preference for their amphetamine-paired sides, spending an average of over twice as much time on that side. This conditioned place preference indicates that the stimuli that were paired with intra-accumbens amphetamine injections acquired rewarding properties. The failure of amphetamine injections into other sites to produce CPPs is more difficult to interpret. The failure to observe a place preference (or aversion) does not rule out the possibility that injections into other sites may have had rewarding or aversive effects. We have previously found cases where treatments that could be shown to be rewarding or aversite in other paradigms produced no effect in place preference conditioning (White et al. 1985; White and Carr 1985). Although it is possible that the amphetamine injections into these other sites were rewarding (or aversive), any such effects were clearly quite different from the effects of the intra-accumbens injections.

This finding extends our previous finding (Carr and White 1983) of a CPP with unilateral intra-accumbens amphetamine injections, demonstrating a considerably stronger effect of bilateral injections and isolating the effect within the accumbens. Combined with the findings of Spyraki et al. (1982) of an attenuated CPP to systemic amphetamine following 6-hydroxydopamine lesions of the accumbens dopamine neurons, it indicates that the nucleus accumbens is a primary site of action of systemically injected amphetamine for producing a CPP. This suggests that dopamine activity in the accumbens plays a key role in mediating the rewarding effect of amphetamine.

Experiment 2: Conditioned taste aversion

Methods

Subjects. The subjects were 70 male hooded rats whose characteristics and treatment were the same as described in the previous experiment except for a water deprivation schedule.

Apparatus and procedures. The surgical and injection procedures were the same as in the previous experiment. Following 1 week of recovery from surgery, water was removed from the home cages of all subjects. Over the next 6 days, water was presented for restricted periods in tubes with stainless-steel ball-bearing spouts. For the first 3 days, water was presented twice a day for 15-min periods, separated by a minimum of three hours. For the next 3 days (4–6) water was presented once a day for 15 min. The 7th day was the pairing day, on which a novel maple-sucrose solution was substituted for water during the 15-min drinking period. Amphetamine or saline injections were given

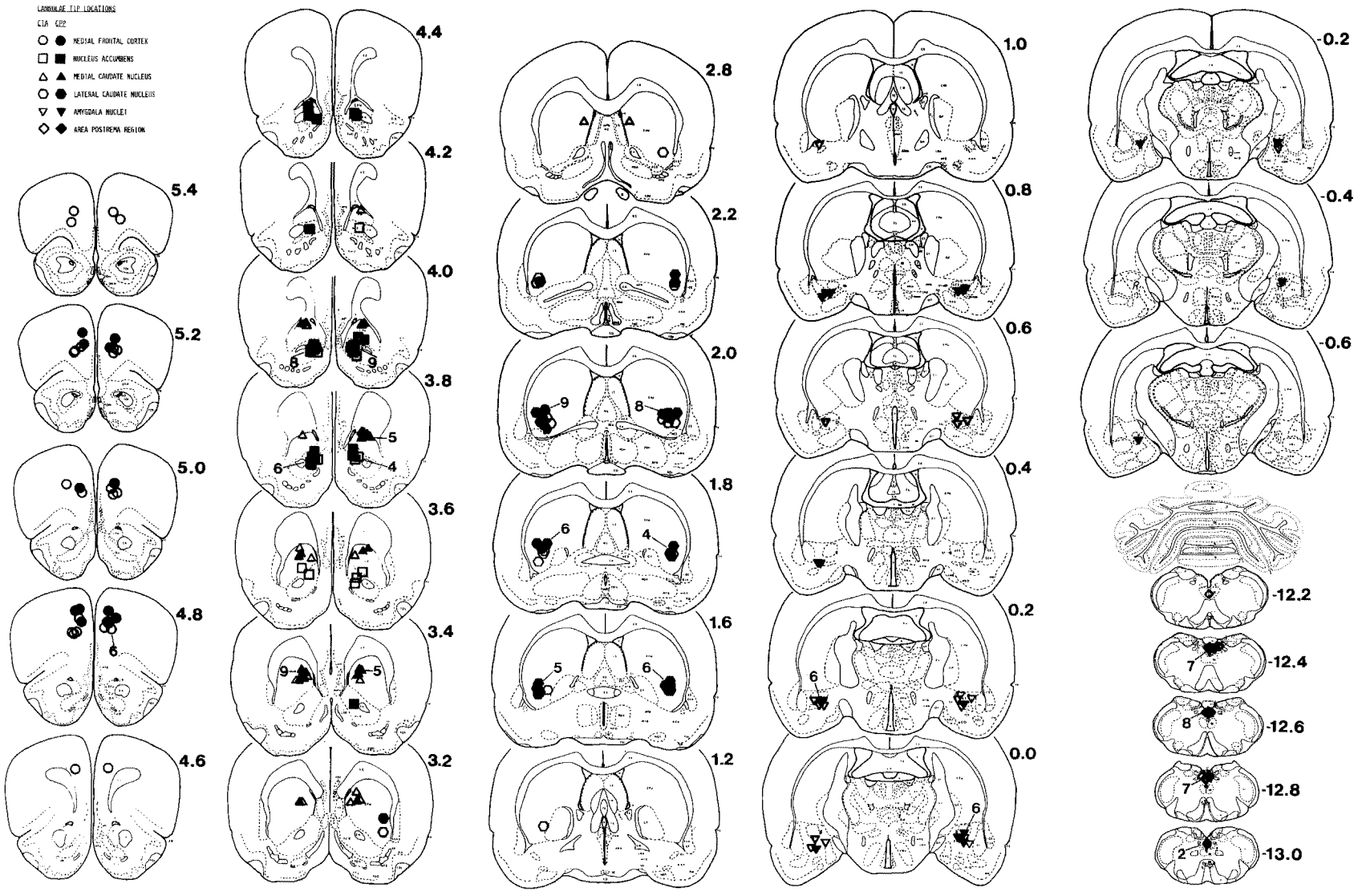

Fig. 1. Locations of cannula tips for all animals included in the data analysis. The cross sections are from the atlas of Pellegrino et al. (1979) and the anterior-posterior reference plane is measured from bregma. The six different sites are represented by the different symbols shown in the legend. *Open symbols* indicate that a subject was tested in the CTA experiment and *filled symbols* indicate that it was tested in the CPP experiment. In cases where several placements overlapped, an adjoining number indicates how many symbols are in the cluster

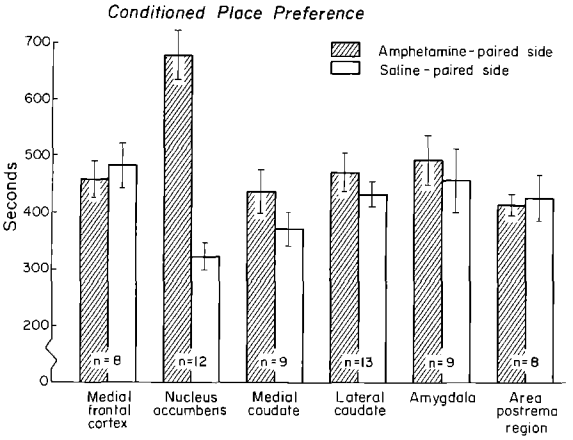

Fig. 2. Mean amounts of time spent by rats in each brain site group in the amphetamine- and saline-paired compartments of the place preference apparatus. The *vertical lines* on each bar are the standard errors of the mean

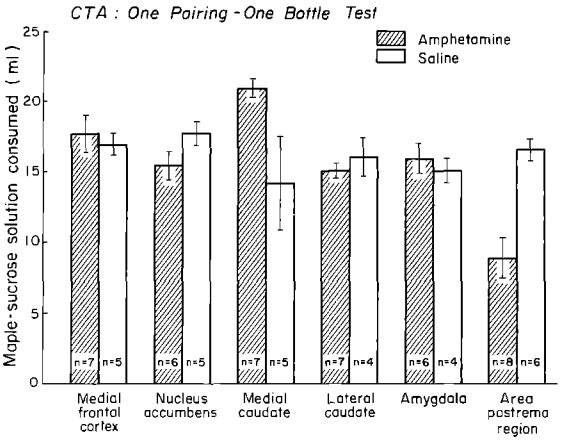

Fig. 3. Mean amounts of the maple-sucrose solution consumed by rats in each brain site group after one pairing with either amphetamine or saline microinjections. The *vertical lines* on each bar are the standard errors of the mean

immediately following the drinking period. The novel solution was made of 10 ml maple extract (French's) and 20 g sucrose (Fisher) in 1 l of tap water. The following day the animals were presented with the maple-sucrose solution for 15 min. All liquids were presented at room temperature.

Results and discussion

The results of the histological examination are presented in Fig. 1. Of the animals that completed the experiment, six were excluded from the data analysis on the basis of this examination. In the medial caudate group, one rat was dropped because of a cannula in the ventricle, and a second because of an infection around a cannula tip. In the AP region group one rat was dropped because its placement was in the opening of the spinal canal. Three others were dropped because cerebrospinal fluid was seen at the top of a guide cannula before the injections, suggesting that the tip of the cannula was in the fourth ventricle.

The results of the consumption test are presented in Fig. 3. The analysis of variance revealed a significant effect of site [$F(5,58)=3.96$, $P<0.01$] and a significant site $\times$ treatment interaction [$F(5,58)=6.87$, $P<0.001$] but no significant overall effect of treatment [$F(1,58)=0.30$, $P>0.1$]. Simple main effects tests showed that the amphetamine-injected AP region group consumed significantly less of the paired flavor than did the saline group ($P<0.001$). The preference of the medial caudate amphetamine group for the paired solution can be accounted for by an unconditioned preference for the maple solution. This group consumed significantly more of the solution than the saline group did on the pairing day presentation [$t(10)=3.72$, P 0.01]. Since this occurred before any amphetamine injection, conditioning was not the cause of the increased consumption. To control for pairing day consumption an analysis of covariance was done for all groups, using pairing day consumption as the covariate and test day consumption as the dependent variable. With the test day scores adjusted for the pairing day scores, there was still a significant effect of site [$F(5,57)=4.29$, $P<0.01$], a significant site $\times$ treatment interaction [$F(5,57)=4.78$, $P<0.001$], and no significant overall effect of treatment [$F(1,57)=1.07$, $P>0.1$]. Post-hoc analysis, using Newman-Keuls test, confirmed a significant effect of intra-AP region injection ($P<0.05$), but no other comparisons were significant ($P>0.05$).

In addition to the procedure described here, these rats were also tested for CTA after three maple-amphetamine pairings using a two-bottle choice test with water and were tested again (one bottle) in a water-sated state after the three pairings. Both of these tests resulted in the same basic pattern of consumption as the one described here, with the AP region being the only group to show a significant CTA to the amphetamine-paired solution. Since these findings corroborate the main finding, they are not presented in detail, but serve to indicate that the results are replicable using different measurement methods.

In addition to the sites presented here, pilot studies failed to find any evidence of CTAs from the medial or basolateral nuclei of the amygdala.

The results demonstrate that injections of amphetamine into the region around the area postrema result in a CTA. Since the cannulae entering the area postrema region must pass through the fourth ventricle, it is important to exclude the possibility that the drug may have flowed up the cannula shaft to the ventricle and then moved through the cerebrospinal fluid (CSF) to act at another site. There is evidence that this did not occur in the present experiment. First, in earlier studies, some of the rats had cannula tips in the fourth ventricle or just caudal to it in the cisterna magna, but these placements almost never produced a CTA. Second, injecting amphetamine through cannulae aimed at a site 1 mm antero-ventral to the present site failed to produce a CTA in a group of eight rats. Since this cannula placement also passed through the fourth ventricle, if diffusion of the drug up into the CSF mediated the effect, then a CTA should also have been seen from this site. Finally, in this study, and in a large number of animals tested in earlier experiments (e.g. White et al. 1985), the pattern of the CTAs observed consistently indicated that proximity to the area postrema was a prerequisite for producing a CTA. In the present study, the rats with the two placements that were furthest from the area postrema failed to show CTAs. One rat's cannula tip was in the opening of the spinal canal and was excluded from the data analysis and the other was the most postero-ventral placement, but its data were still included in the results presented.

For these reasons, it appears that the injected amphetamine acted locally in a fairly circumscribed area to produce the taste aversion. This area also appears to correspond closely to the part of the NST that receives input from the area postrema itself and from the vagus nerve (Morest 1967), both known contributors to CTA learning. However, the present data do not permit conclusions about the exact substrate of the CTA caused by amphetamine, which will have to be determined using another method.

General discussion

Intra-accumbens amphetamine injections resulted in a strong conditioned place preference, but no effect on this measure was observed from any other site. Spyraki et al. (1982) found that 6-hydroxydopamine lesions of the accumbens attenuated the CPP produced by subcutaneous amphetamine injections. Together, these findings indicate that the nucleus accumbens is a primary site of action for mediating the CPP to amphetamine and that the other sites tested do not contribute significantly. It is possible that the other sites studied contribute in some way to the overall rewarding effects of systemic amphetamine injections but none were capable of producing the robust effects observed here from the accumbens.

The observation of a CPP indicates that the intra-accumbens injections were rewarding. This suggestion is supported by the finding that rats self-administer amphetamine into the accumbens (Hoebel et al. 1983). The critical role of dopamine in mediating this rewarding effect was demonstrated by Aulisi and Hoebel (1983), who found that the CPP produced by intra-accumbens amphetamine was attenuated by adding the dopamine receptor blocker *cis*-flupenthixol to the injection fluid. Dopaminergic involvement is also implicated by the block of amphetamine CPP using selective 6-hydroxydopamine lesions of the accumbens dopamine neurons (Spyraki et al. 1982). These findings suggest that dopaminergic synapses in the nucleus accumbens play a primary role in mediating amphetamine's rewarding effects.

In contrast to these findings, injections into the region around the area postrema resulted in a CTA to the paired flavour. The exact site of action of the drug cannot be identified from the data, but it can be localized to the region immediately surrounding the area postrema. Evidence cited in the introduction suggests a role for this region in mediating CTA learning and the present findings are consistent with this. This region includes some possible structures for mediating the CTA. The NST is implicated by the convergence of primary taste afferents and visceral input from the vagus nerve (Morest 1967). It also receives input from the area postrema itself (Morest 1967). Both the vagal input and the AP input synapse in the caudal part of the NST, which corresponds closely with the site that produced the CTA in the present study. The vagal input synapses on noradrenergic neurons in the NST (Sumal et al. 1983) and the NST also receives a dense noradrenergic input from the lateral tegmental system (Levitt and Moore 1979). While dopaminergic neurons have been shown to be critical for the amphetamine CTA (Wagner et al. 1981), Lorden et al. (1980) have also demonstrated a noradrenergic contribution using selective neurotoxin lesions. It is therefore possible that amphetamine's stimulation of these brainstem noradrenergic neurons contributes to the amphetamine-induced CTA.

Another possible site of action is the DMNV. This structure receives a dense noradrenergic projection from the lateral tegmental system and contains the highest concentration of dopamine in the brainstem (Levitt and Moore 1979). It has recently been demonstrated to contain dopaminergic neurons (Kalai et al. 1984). Since dopamine has been shown to be critical for the amphetamine CTA (Wagner et al. 1981), perhaps this is the relevant area.

Lesions of the area postrema itself do not block the CTA to systemic amphetamine (Berger et al. 1972), which rules out this structure as a critical site. However, this finding does not exclude the possibility of some contribution to the amphetamine CTA by the area postrema, and this idea is consistent with the demonstration of dopamine receptors in this structure (Stefanini and Clement-Cormier 1981).

Any or all of these sites could have contributed to the observed amphetamine-induced CTA. The observed CTA suggests that the sub-area postrema region is a primary site of action for systemic amphetamine, but the involvement of other sites cannot be ruled out. Lesion studies would be the most likely way to answer this question. We have attempted to produce such lesions using thermal, electrolytic, neurotoxin and aspiration techniques but found that a small lesion was not sufficient to block the CTA to systemic amphetamine and a larger lesion killed the animals because of the region's important role in autonomic function. However, it may be possible to perform a more specific neurotoxin lesion or to localize a specific area that could be lesioned to block the amphetamine CTA without killing the animal. A temporary interference of function in the region might also be achieved using receptor blockers which would further serve to localize the effect.

The amphetamine reward and CTA paradox

The demonstration that a systemic injection of amphetamine can result in a CTA is a paradox when contrasted with the evidence of its rewarding effects. Aside from the CTA, there is no evidence to suggest that there is an aversive component to amphetamine's actions. This has led some theorists to try to account for the CTA by a non-aversive effect of the drug, such as conditioned anorexia (e.g., Carey 1978). Evidence has been presented against the conditioned anorexia hypothesis (Stolerman and D'Mello 1978), and we have found that intra-area postrema region amphetamine injections, which resulted in clear CTAs, failed to produce anorexia or adipsia in the same rats (Carr and White, submitted). Although it remains conceivable that the amphetamine-induced CTA could be produced without a noxious effect of the drug, it is still likely that the amphetamine CTA reflects a genuinely aversive effect.

The present findings provide some insight into this paradox. The data indicate that injections of amphetamine into the nucleus accumbens result in a conditioned preference for the place with which they were paired. Injections of the drug into the region subjacent to the area postrema result in a conditioned aversion towards the taste with which they were paired. Together, these findings suggest that perhaps the rewarding and the aversive effects of amphetamine result from the drug's actions on different anatomical sites. However, this anatomical disassociation does

not explain why the reward becomes associated with the stimulus characteristics of the place preference apparatus but fails to become associated with taste stimuli. Nor does it explain why the aversion becomes associated with the taste stimuli but fails to become associated with place-related stimuli. This associative bias parallels findings for natural reinforcers (White et al. 1985). Ingestion of glucose, a naturally rewarding event, can cause a place preference, but it is difficult to produce a taste preference with this stimulus (Holman 1975). Conversely, although a low dose of lithium chloride causes robust CTAs with a single pairing, six pairings with the same dose failed to produce a conditioned place aversion (White et al. 1985).

The present findings therefore offer additional evidence of the associative bias that Garcia and Ervin (1968) reported for CTA learning. The present demonstration of anatomical disassociation of the sites mediating the learning of CPP and CTA to amphetamine suggests that perhaps associative bias reflect learning of different kinds of associations by different parts of the brain.

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