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Interactions Between Radiation and Amphetamine in Taste Aversion Learning and the Role of the Area Postrema in Amphetamine-Induced Conditioned Taste Aversions

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RABIN, B. M., W. A. HUNT AND J. LEE. *Interactions between radiation and amphetamine in taste aversion learning and the role of the area postrema in amphetamine-induced conditioned taste aversions.* PHARMACOL BIOCHEM BEHAV 27(4) 677–683, 1987.—Three experiments were run to assess the role of the area postrema in taste aversion learning resulting from combined treatment with subthreshold unconditioned stimuli and in the acquisition of an amphetamine-induced taste aversion. In the first experiment, it was shown that combined treatment with subthreshold radiation (15 rad) and subthreshold amphetamine (0.5 mg/kg, IP) resulted in the acquisition of a taste aversion. The second experiment showed that lesions of the area postrema blocked taste aversion learning produced by two subthreshold doses of amphetamine. In the third experiment, which looked at the dose-response curve for amphetamine-induced taste aversion learning in intact rats and rats with area postrema lesions, it was shown that both groups of rats acquired taste aversions following injection of amphetamine, although the rats with lesions showed a less severe aversion than the intact rats. The results are interpreted as indicating that amphetamine-induced taste aversion learning may involve area postrema-mediated mechanisms, particularly at the lower doses, but that an intact area postrema is not a necessary condition for the acquisition of an amphetamine-induced taste aversion.

Conditioned taste aversion Amphetamine Area postrema Dose-dependent Radiation Combined treatment

A conditioned taste aversion (CTA) is produced when a novel tasting solution is paired with an unconditioned stimulus (UCS), such that the organism will avoid ingestion of that solution at a subsequent presentation. In addition to toxic unconditioned stimuli, such as ionizing radiation and lithium chloride (LiCl), taste aversions can also be produced by pairing the novel stimulus with a variety of compounds that an organism will self-administer, such as amphetamine [4,12].

Taste aversions produced by toxic stimuli such as ionizing radiation or LiCl depend upon the integrity of the area postrema (AP) [7, 9, 14, 17], the brainstem chemoreceptive trigger zone for emesis [2]. In contrast, lesions of the AP have been reported to have no effect on the acquisition of an amphetamine-induced CTA [1,17]. The results of the lesion studies seem to be in accord with the results of the more behaviorally-oriented studies which have shown that the behavioral responses of rats to flavors paired with LiCl differ from the responses to flavors paired with amphetamine [10,11]. Thus, the acquisition of taste aversions following treatment with toxic unconditioned stimuli may involve different mechanisms than those produced by nontoxic stimuli [12].

In the preceding report [16], it was shown that subthreshold doses of radiation could be combined with subthreshold doses of LiCl to produce a CTA. This finding was interpreted as being consistent with the hypothesis that similar mechanisms underlie the acquisition of taste aversions produced by both radiation and LiCl. Since both radiation and LiCl unconditioned stimuli require that the AP be intact

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TABLE 1

FLUID INTAKE (ml) FOLLOWING COMBINED TREATMENT WITH SUBTHRESHOLD RADIATION AND AMPHETAMINE

Delay Interval (hr)	Conditioning Day		Test Day	
	Water	Sucrose	Water	Sucrose
Control	4.20±1.70*	24.20±1.85	3.20±0.83	20.20±2.02
0.25	3.42±0.96	18.83±1.43	11.25±2.14	9.75±1.72
0.50	4.30±1.27	18.50±1.25	11.90±1.64	9.00±1.67
1.00	4.50±0.92	16.40±1.18	4.50±1.21	15.20±1.41
1.50	4.58±0.78	16.00±1.59	11.42±1.51	13.25±1.61
2.00	7.64±1.52	21.18±1.51	9.27±2.04	15.36±2.23

*Mean±standard error.

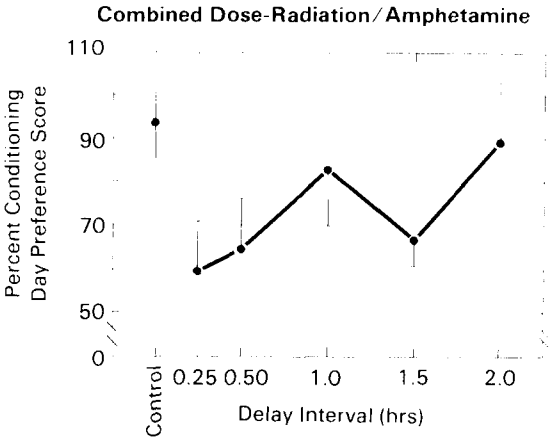


FIG. 1. Effects of combined treatment with subthreshold radiation (15 rad) and subthreshold amphetamine (0.5 mg/kg, IP) as a function of the delay interval between treatments. Control was given a single injection of amphetamine. Test day sucrose preference is expressed as the percentage of the conditioning day preference. Error bars indicate the standard error of the mean.

for CTA learning to occur [7, 9, 12, 17] it seems reasonable to assume that this brainstem structure may be involved in the observed interaction. If the common reliance of both radiation and LiCl on the AP provides the basis for the interactions observed in the preceding experiment, then combining radiation or LiCl with a UCS that does not require the mediation of the area postrema for CTA learning should not result in the acquisition of a CTA.

GENERAL METHOD

Subjects

The subjects were male Sprague Dawley rats weighing 300–375 g at the start of the experiment. The rats were housed in individual cages in a room with a 12:12, light:dark cycle. Food and water were continually available, except as required by the experimental protocol.

Taste Aversion Training

Taste aversions were produced using a two-bottle design in which the animal was given a choice between tap water and a 10% sucrose solution on both conditioning and test days. The rats were first placed on a 23.5 hr water deprivation schedule for 10 days. On the conditioning day (day 10) all rats were presented with two calibrated drinking tubes containing tap water and 10% sucrose solution for 30 min. Immediately following the drinking period, the rats were given the appropriate treatment and returned to their home cages for 24 hr. On the test day (day 11), the rats were again given a choice between tap water and sucrose solution and intake of each solution recorded. Relative intake of tap water and 10% sucrose solution were transformed into preference scores; sucrose intake divided by total fluid intake.

EXPERIMENT 1

The first experiment of this series was designed to determine whether or not subthreshold doses of ionizing radiation could be combined with subthreshold doses of amphetamine to produce a CTA. As indicated above, since the AP has been reported not to mediate the acquisition of an amphetamine-induced CTA [1,17], it should not be possible to combine subthreshold amphetamine with subthreshold radiation, in contrast to combinations of radiation and LiCl [16], to produce a CTA if the AP serves to integrate the combined treatments.

Method

The subjects were 63 male albino rats divided into 6 groups of 7–12 subjects/group. Immediately after ingestion of a 10% sucrose solution, the experimental rats were placed in a plastic restraining box and exposed to 15 rad at a dose rate of 20 rad/min using a ^{60}Co source. Dosimetry was performed using thermoluminescent detectors (LiF TLD 100's) and a 3.3 ml Victoreen chamber. Following delay intervals of 0.25, 0.5, 1.0, 1.5 or 2.0 hr, independent groups of rats were given an IP injection of 0.5 mg/kg d-amphetamine. The control animals were given a single IP injection of 0.5 mg/kg amphetamine. Preliminary experiments had indicated that this dose of amphetamine was just below threshold for producing CTA learning.

Results and Discussion

The effects of combined amphetamine and radiation treatment are presented in Table 1. These data are summarized in Fig. 1, which presents the test day sucrose preference as a percentage of the conditioning day preference for the sucrose solution. The data from the control group confirms that a single dose of 0.5 mg/kg amphetamine does not produce a CTA. The results from the groups given combined treatment with radiation (15 rad) and amphetamine (0.5 mg/kg, IP) show that treatment with subthreshold doses of ionizing radiation and amphetamine can be combined to produce a CTA. Statistical analysis of the data using a one-way analysis of variance followed by planned comparisons [6] showed that significant differences from the controls were observed at delay intervals of 0.25 hr, $F(1,57)=4.94$, $p<0.01$, 0.5 hr, $F(1,57)=3.95$, $p<0.01$, and 1.5 hr, $F(1,57)=3.06$, $p<0.05$. The other delay intervals, 1.0 and 2.0 hr, did not differ significantly from control.

These results show that a subthreshold dose of radiation can be combined with a subthreshold dose of amphetamine to produce a CTA. This observation means that amphetamine is similar to LiCl because subthreshold doses of both drug stimuli can be combined with irradiation to produce a CTA. For both sets of drug unconditioned stimuli,

the effective delay intervals were relatively short, lasting for only 1.0 to 1.5 hr [16].

As such, these results are not consistent with the hypothesis proposed above that, because of presumed differences in the role of the AP in the acquisition of taste aversions produced by these unconditioned stimuli, subthreshold radiation exposure would not combine with subthreshold amphetamine to lead to the acquisition of a CTA. The observation that combined radiation and amphetamine treatment does produce a CTA would suggest either that the basis for the interaction of combined subthreshold unconditioned stimuli involves brain structures other than the AP, or that amphetamine, like radiation and LiCl, may also have effects on the AP.

EXPERIMENT 2

Although the lesion studies cited above [1,17] indicate that destruction of the AP does not prevent the acquisition of an amphetamine-induced CTA, the preceding results, which show an interaction between radiation and amphetamine, suggest that radiation and amphetamine may be producing similar effects within the organism. Otherwise, it should not be possible for the two unconditioned stimuli to combine to produce an effect on behavior. The basis for this interaction between radiation and amphetamine is not certain. Garcia *et al.* [5] have proposed that a treatment-produced malaise or illness experienced by the organism is the proximal UCS leading to the acquisition of a CTA. Because amphetamine can produce a CTA, it must produce an experienced illness within the organism which would form the basis for the observed interaction between radiation and amphetamine. Rabin and Rabin [13], on the contrary, have shown that CTA learning can occur in anesthetized animals which cannot experience a treatment-induced illness. They have proposed that the proximal UCS for CTA learning is the activation of specific neural circuits, independently of any experiential effects resulting from the treatment. According to this theory, the basis for the observed interaction between radiation and amphetamine would be in the capacity of these stimuli to excite similar neural circuits. Because a radiation-induced CTA requires the mediation of the AP, there is the possibility that treatment with amphetamine may also produce effects in the AP.

This experiment was designed to determine whether or not the AP may be involved in mediating the acquisition of a CTA produced by combined treatment with subthreshold doses of a UCS. Because it is already well-established that the radiation-induced CTA depends upon the integrity of the AP, this experiment utilized combined treatment with subthreshold doses of amphetamine in rats with lesions of the AP and in intact rats.

Method

The subjects were 28 rats divided into 3 groups. In the first group were 8 rats with AP lesions and treated with two combined injections of amphetamine (0.5 mg/kg, IP) separated by a delay interval of 30 min. The second group consisted of 10 intact control rats treated with the combined amphetamine injections. The third group of 10 intact rats, who were administered a single injection of amphetamine (0.5 mg/kg, IP) followed by an equivolume injection of isotonic saline 30 min later, served as a comparison group for the combined treatment groups.

Lesions were made in the AP of 8 rats using procedures detailed previously [14]. Briefly, all rats were anesthetized with sodium pentobarbital (35 mg/kg, IP). The AP was exposed and thermal lesions were made using a cautery probe under direct visual control. After surgery, the rats were given a prophylactic injection of bicillin (60,000 units) and allowed to recover in their home cages for a period of 2–4 weeks before beginning behavioral testing.

The general procedure was similar to that detailed in Experiment 1. Immediately following ingestion of the 10% sucrose solution on the conditioning day, all rats were given a single injection of amphetamine (0.5 mg/kg, IP). Thirty min later, without further access to the sucrose solution, the two amphetamine combined groups were given a second injection of amphetamine (0.5 mg/kg, IP), while the comparison group was given an injection of isotonic saline. All rats were tested for a CTA 24 hr later.

At the conclusion of the testing, all operated rats were anesthetized with sodium pentobarbital (50 mg) and perfused intracardially with isotonic saline followed by 10% formalin saline. Sections were cut through the brainstem at the level of the AP at 50 μm and stained with thionin. Representative sections of an intact animal and an animal with AP lesions are presented in Fig. 2. Examination of the histological material indicated that for the most part the lesions were restricted to the AP, although they did occasionally affect the dorsal parts of the nucleus of the solitary tract.

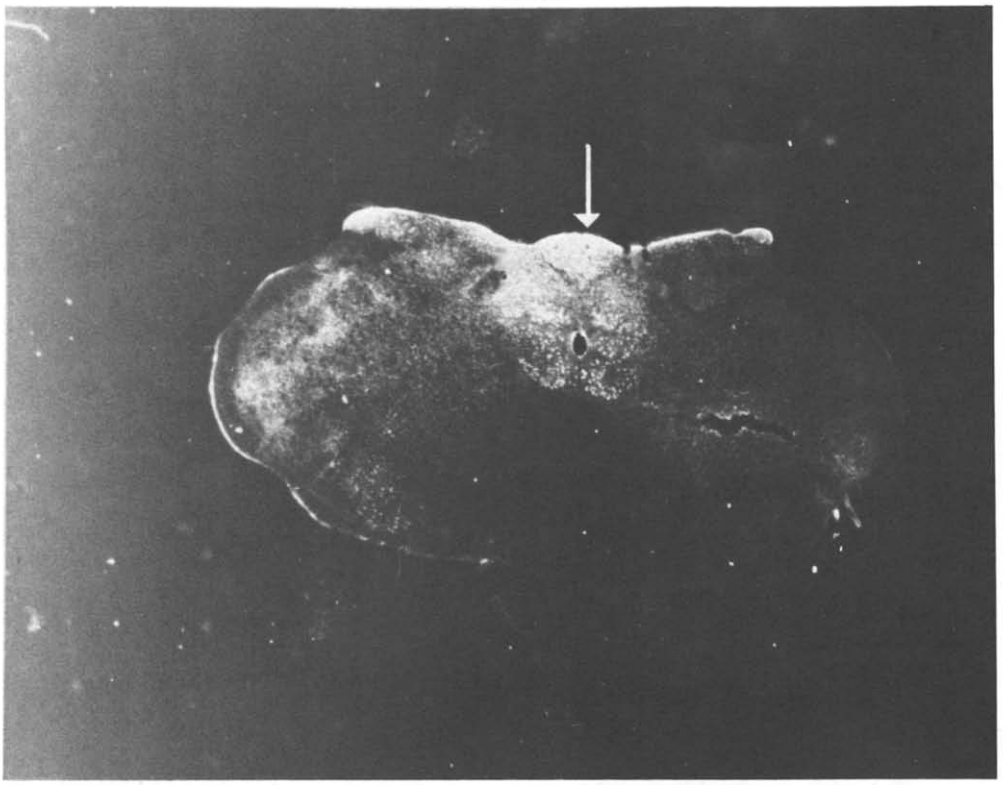
Results and Discussion

Mean conditioning day water intake showed a range of 4.30 to 9.40 ml and sucrose intake ranged from 14.40 to 22.60 ml. For both water and sucrose intake, the largest amounts were consumed by the rats with AP lesions.

As shown in Fig. 3, treatment with either a single injection of amphetamine followed by isotonic saline in intact rats, or treatment with combined injections of amphetamine in rats with AP lesions, did not produce a CTA. In contrast, a CTA was observed in the intact rats given the combined injections of amphetamine. A mixed analysis of variance for the groups receiving the combined amphetamine injections indicated that the main effect for condition for the comparison between the intact rats and rats with AP lesions was significant, $F(1,16)=11.92$, $p<0.01$, while the main effect for day was not significant, $F(1,16)=0.01$, $p>0.10$. The condition-by-day interaction, $F(1,16)=5.70$, $p<0.05$, was significant, thereby indicating that the test day preference scores of the two groups were significantly different, with the intact rats showing a reduction in sucrose preference, while the rats with AP lesions showed an increase in preference.

The implication of the present results, which show that lesions of the AP can block the acquisition of a CTA produced by combined treatment with two subthreshold doses of amphetamine, is that the AP is somehow involved in the acquisition of a CTA following treatment with amphetamine. As such, these results would support the hypothesis that the AP serves to integrate the combined effects of treatment with radiation and amphetamine. However, this finding would run counter to the results of previous research [1,17] which suggests that the AP is not involved in the acquisition of an amphetamine-induced CTA. These apparently discrepant findings regarding the possible role of the AP in amphetamine-induced CTA learning may derive from the fact that the studies which reported that AP lesions did not disrupt the acquisition of an amphetamine-induced CTA

A



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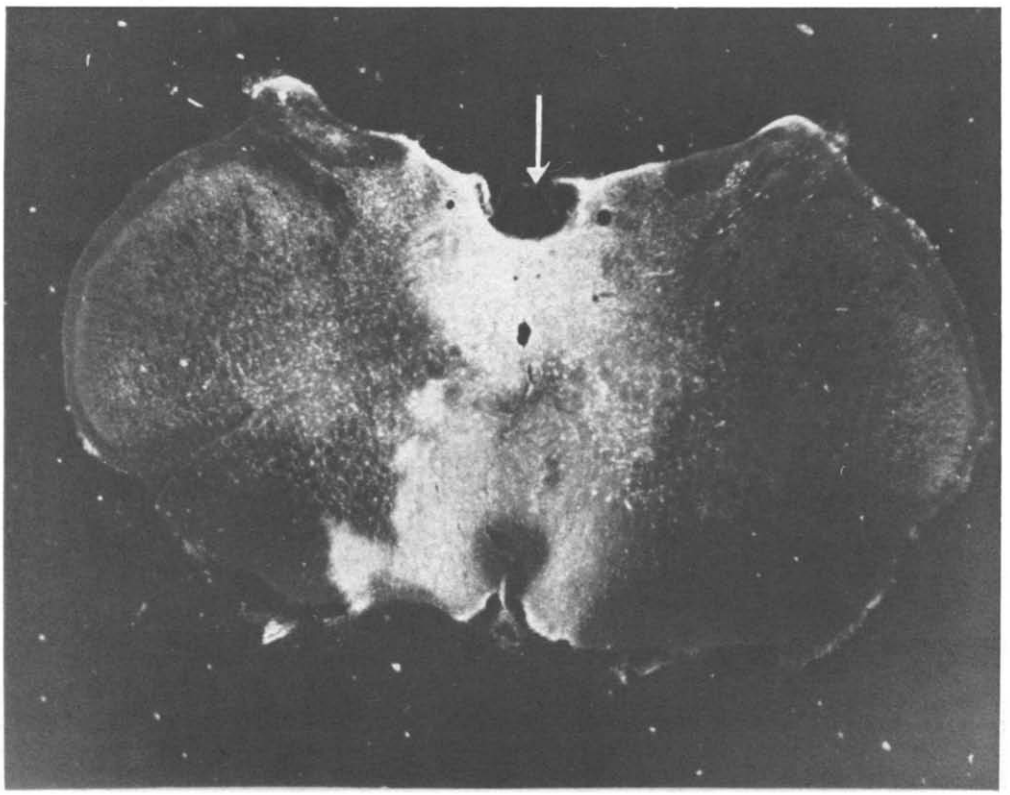

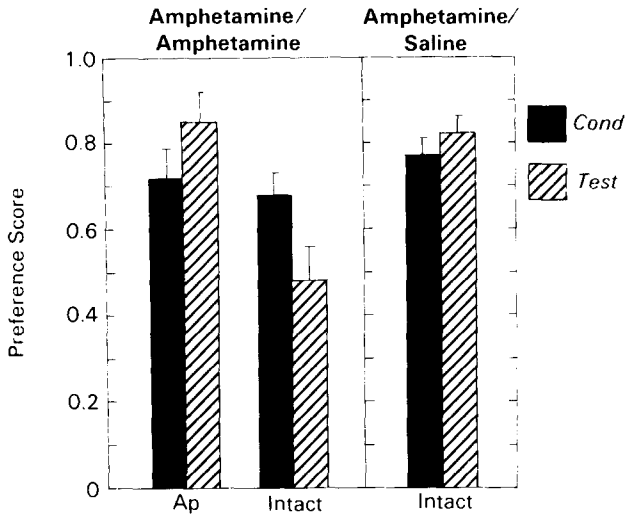

FIG. 3. Effects of area postrema lesions on the acquisition of a conditioned taste aversion produced by two subthreshold amphetamine injections separated by 30 min. Error bars indicate the standard error of the mean.

used a suprathreshold dose of amphetamine together with a single-bottle test in contrast to the subthreshold dose utilized in the present experiment which was combined with the more sensitive two-bottle procedure.

EXPERIMENT 3

Although the research cited above strongly indicates that lesions of the AP do not prevent the acquisition of an amphetamine-induced CTA [1,17], there are some findings that are difficult to reconcile with such an hypothesis. First, since dopaminergic terminals have been reported in the AP [8], it seems reasonable to assume that treatment with amphetamine would affect these terminals and, consequently, AP activity and taste aversion learning. Second, it has been reported that microinjection of amphetamine into the vicinity of the AP will produce a CTA [3]. This finding raises the question of why peripherally-administered amphetamine would not affect the AP to produce a CTA. These findings, in combination with the results of the preceding two experiments, would seem to be consistent with the hypothesis that the AP is, in some way, involved in CTA learning following combined treatment with amphetamine and ionizing radiation.

There is, therefore, evidence to suggest both that the AP is not involved in the acquisition of an amphetamine-induced CTA and that it is. It may be possible that the importance of the role of the AP in amphetamine-induced taste aversion learning is a function of the dose of amphetamine that is used to produce the CTA. Such a dose-related role for the AP in mediating CTA learning has been reported in studies of taste aversions produced by the toxic compound WR-2721 [15]. The present study was designed to examine the role of dose and AP lesions in the acquisition of an amphetamine-induced CTA.

Method

The subjects were 117 male Sprague Dawley-derived rats weighing 300–375 g at the start of the experiment. Lesions were made in the AP of 54 rats, while the remaining rats served as intact controls. The lesion and histological procedures were identical to those described in the preceding experiment. Examination of the histological material at the conclusion of the experiment indicated that most rats had lesions restricted to the AP, although the extent of tissue damage did include the dorsal parts of the nucleus of the solitary tract in some of the animals (see Fig. 2).

After a 2–3 week period to allow for recovery from the surgery, the behavioral testing was begun as detailed above. Immediately after the drinking period on the conditioning day, independent groups of control rats and rats with AP lesions were given IP injections of a single dose of amphetamine. The doses of amphetamine were 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 mg/kg. With the exception of the AP group receiving the lowest dose of amphetamine (n=5), there were between 9–11 subjects in each group. The rats were then returned to their home cages for 24 hr before testing for the acquisition of a CTA.

Results and Discussion

For the intact animals, conditioning day water intake averaged 5.28±0.41 ml and sucrose intake averaged 17.79±7.26 ml across all dose levels. For the rats with AP lesions, the corresponding intakes were 5.66±0.70 ml for water intake and 25.17±0.85 ml for sucrose intake. Although the development of a CTA in the intact rats was reflected as an increase in water intake which was paired with a corresponding decrease in sucrose intake such that total fluid intake remained relatively constant across all tested doses, the rats with AP lesions given the three highest doses of amphetamine showed a decrease in sucrose intake that was not completely balanced by the corresponding increase in water intake. As a result, these three groups of rats showed an average decrease in total fluid intake of approximately 10 ml.

The results are summarized in Fig. 4, which presents test day sucrose preference as the percentage of the conditioning day preference score. An analysis of variance showed that both the main effect for dose, $F(5,105)=7.48$, $p<0.001$, and the main effect for condition for the comparison between control and lesion rats, $F(1,105)=11.77$, $p<0.001$, were highly significant. The significant main effects would indicate that test day sucrose preference was a function both of the dose of amphetamine and of the presence of an AP lesion. The dose by condition interaction, $F(5,105)=0.81$, $p>0.10$, was not significant, indicating that both lesion and intact rats showed a reduction in sucrose preference in response to treatment with amphetamine across the various doses. These data indicate, therefore, that AP lesions attenuate an amphetamine-induced taste aversion, particularly at the lower doses, but do not prevent CTA learning following treatment with higher doses of amphetamine. As such, the present results would be concordant with previous research using the higher amphetamine doses which reported that lesions of the AP do not disrupt the acquisition of an amphetamine-induced CTA [1,17].

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FIG. 2. Photomicrographs of the brainstem of the rat showing an intact area postrema (A, arrow) and a representative lesion (B).

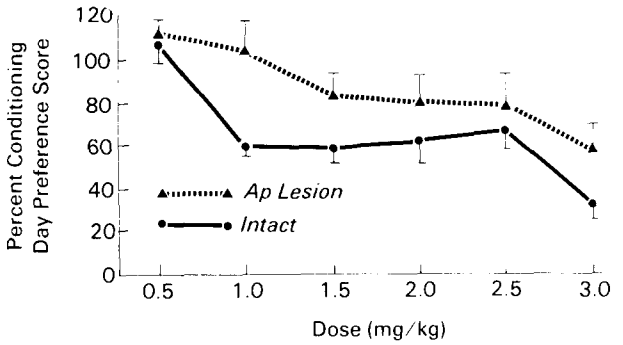

FIG. 4. Effect of dose and area postrema lesions on the acquisition of an amphetamine-induced taste aversion. Test day sucrose preference is expressed as the percentage of the conditioning day preference. Error bars indicate the standard error of the mean.

These data indicate that the major effect of AP lesions on the amphetamine-induced CTA is at the lowest effective doses, 1.0 and 1.5 mg/kg, although the intact animals seem to show a generally reduced preference compared to the animals with AP lesions at all tested doses. This finding is consistent with the observation of a dose-dependent effect of AP lesions on the CTA produced by treatment with WR-2721 [15].

The data presented in Fig. 4 seem to suggest a two-stage process underlying the acquisition of an amphetamine-induced CTA. In intact animals, there is an initial sharp decrease in sucrose preference between a dose of 0.5 and 1.0 mg/kg. Sucrose preference then seems to stabilize until a dose of 2.5 to 3.0 mg/kg, at which point there is another sharp decrease in sucrose preference. The responses of the rats with AP lesions generally parallel those of the intact animals. Given that the major effect of AP lesions seems to be at the lowest doses of amphetamine, at 1.0 and 1.5 mg/kg, it may be that the CTA produced by lower doses of amphetamine may involve some AP-mediated mechanisms, but as the dose of amphetamine increases, there is an increasing involvement of other mechanisms such that the AP becomes relatively less important for CTA learning at the higher doses.

GENERAL DISCUSSION

The results of these experiments indicate that the AP is involved in the acquisition of an amphetamine-induced CTA in a dose-dependent manner, such that the importance of the AP-mediated mechanisms decrease as the dose of amphetamine is increased. In contrast to taste aversions produced by LiCl or ionizing radiation [7, 9, 14, 17], an intact area postrema is not, therefore, a necessary condition for the acquisition of an amphetamine-induced CTA. Since lesions of the dorsal tegmentum disrupt the acquisition of an amphetamine-induced CTA in animals with an intact AP [18], an intact AP may not even be a sufficient condition for such learning. However, when an intact AP is present, it does contribute to the acquisition of a CTA produced by amphetamine. The present results indicate, therefore, that the role of the AP in amphetamine-induced taste aversion learning is a relatively complex one, which varies as a function of the dose of amphetamine.

As such, the results of the present studies are generally consistent with the results of previous research [1,17] in showing that destruction of the AP does not prevent the acquisition of an amphetamine-induced CTA following treatment with high doses of amphetamine. However, the observation that the AP can contribute to the development of a CTA following treatment with low doses of amphetamine is consistent with the observation that microinjection of amphetamine in the vicinity of the AP produces a CTA [3]. Similarly, the present observation that lesions of the AP can modulate the intensity of an amphetamine-induced taste aversion provides a potential physiological basis for the previous finding that a subthreshold dose of amphetamine can be combined with a subthreshold exposure to ionizing radiation to produce CTA learning [16].

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