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The Functional Relevance of the Area Postrema in Drug-Induced Aversion Learning

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GALLO, M., M. ARNEDO, A. AGÜERO AND A. PUERTO. *The functional relevance of the area postrema in drug-induced aversion learning*. PHARMACOL BIOCHEM BEHAV **35**(3) 543–551, 1990.—Research into the neural mechanisms involved in the acquisition of learned aversions induced by drug points toward the area postrema (AP) as one of the structures implicated in the detection of drug aversive consequences. The evidence suggest that although the AP is indeed involved in drug-induced learned aversions, its functional integrity is not always a necessary requisite for learning to take place. The aim in this study was to determine whether the AP is essentially or selectively involved in all learned aversions induced by scopolamine methyl nitrate (SMN) using different number of trials with the aversive stimulus. In Experiment 1, AP-lesioned rats were injected with SMN fifteen minutes after consuming a flavoured solution during three consecutive trials. A single-stimulus test failed to detect learned aversions, which were, however, evident in two subsequent choice-tests. In one-trial paradigms, however, choice-tests as well as single-stimulus tests failed to detect learned aversions in AP-lesioned rats, both when SMN was injected immediately after stimulus intake (Experiment 2) and when a fifteen-minute delay was introduced (Experiment 3). The results suggested that the AP is not essential for the acquisition of SMN-induced aversion learning with three consecutive trials if learning is detected with a choice-test, although effective single-trial learning does apparently require a functional AP.

Area postrema Aversion learning Scopolamine methyl nitrate Rats

RESEARCH into the neural mechanisms involved in the acquisition of drug-induced aversion learning points toward the area postrema (AP), a chemosensitive structure situated beyond the blood-brain barrier, as one of the zones implicated in the detection of aversive consequences caused by chemical substances such as histamine (21), 1,5-HTP (18), copper sulfate (6), amphetamines (24), lithium chloride (13, 21, 25) and scopolamine methyl nitrate (SMN) (3, 19, 16, 25, 29).

Lesioning of the AP, however, prevents the acquisition of learned aversions induced by intravenously administered copper sulfate, but has no effect on learning when this product is given intragastrically (6). Similarly, despite studies suggesting that the AP is not essential for amphetamine-induced learned aversions (3,25), more recent observations have shown that the effect appears, in fact, to be dose-dependent (24). At low doses of amphetamine, AP lesions result in a learning deficit, but simply raising the dose can reinstitute learned aversion. One possible conclusion to be drawn from these findings is that the participation of the AP in learned aversions depends on the drug injected, the route of administration and the dose used. The evidence, therefore, seems to suggest that although the AP is indeed involved in drug-induced learning, its functional integrity is not always a necessary requisite for learning to take place. Lesioning the AP thus appears to attenuate rather than obviate a number of drug-induced learning processes (21).

In order to more precisely delimit the functional relevance of the AP, scopolamine methyl nitrate was chosen to induce learned aversions in the present series of experiments. Deficits in SMN-induced aversions are the type of learning impairment most consistently observed following lesions to the AP (3,25), to the point where this test has been used in a number of studies to confirm behaviorally that the AP has been completely destroyed (16,29). By varying the number of acquisition trials, we have tried to determine whether the integrity of the AP was necessary and sufficient for this type of aversion learning to take place. The sequence of experiments is illustrated in Fig. 1.

EXPERIMENT 1

A review of the experiments in which lesioning the AP blocked learned aversions induced by SMN shows that single-trial paradigms were most commonly used, the aversive stimulus following immediately upon ingestion of the stimulus (3, 16, 25). Although administering the drug immediately after the ingestion does not

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	FLAVOR STIMULI	BRAIN LESION	NUMBER OF TRIALS	DELAY
EXP. 1	S C	AP	3	YES
EXP. 2a	S C	AP	1	NON
EXP. 2b	S C	SHAM AP	1	NON
EXP. 3a	S C	AP	1	YES
EXP. 3b	S C	SHAM AP	1	YES

FIG. 1. Flow chart showing the experimental sequence. S: strawberry; C: coconut; AP: area postrema.

entirely eliminate a possible delay (because a certain amount of time must be allowed for absorption), this variable was not explicitly manipulated in most studies. After acquisition, learning was generally quantified with single-stimulus tests (23,29).

Although a functional AP is undoubtedly necessary for learning to occur under these conditions, it is worth asking whether this structure is essential in all learning situations, particularly when the strength of learning is enhanced by increasing the number of trials while maintaining the delay, or, on the other hand, whether the AP is replaced functionally by other structures.

METHOD

Subjects

Eleven male Wistar rats weighing 280–320 g were used. Animals were housed individually in 30 × 15 × 30 cm cages which also served as training chambers during the experiment. A 12:12 light-dark cycle was in effect with lights on at 8.00 a.m. and off at 8.00 p.m. Food was available ad lib.

Apparatus

The front panel of the cages had two holes located at the same height and distance from the midline through which spouts of different textures were placed according to the requirements of the experimental paradigm. The spouts were attached to graduated burettes which contained the fluid stimulus.

The animals were operated on with a David Kopf stereotaxic instrument for rats (David Kopf Instruments, Tujunga, CA). Electrolytic lesions were made with a DCML-5 lesion generator (Grass Instruments Corp., Quincy, MA) which supplied direct negative current through a monopolar electrode approximately 200 micra in diameter which was insulated with INXL-X throughout its length except for the last 0.5 mm.

The stereotaxic coordinates (A-P: −6.8; L: 0; V: −1.7; from the interaural point of reference) of the AP were obtained from the stereotaxic atlas of Pellegrino *et al.* (20).

Surgical Procedure

Surgery was performed under general anesthesia with sodium thiobarbital (50 mg/kg). Animals were placed in the head holder, and after locating the bregma and lambda points, a hole was drilled in order to place a electrode over the AP. A 1 mA direct negative current was passed through the electrode for 15 seconds. At the end of the stereotaxic surgical procedure the electrode was removed and the wound sutured.

Behavioral Procedure

After surgery the subjects were allowed one week for recovery, after which they were adapted to a 23 hr 50 min water deprivation schedule, i.e., they were allowed to drink for ten minutes every day. Over a period of seven days the position of the burette and spout was varied in order to compensate for possible position preferences.

Following the week-long adaptation period, training was begun according to the procedure shown in Fig. 2 for training and testing except that Sessions 1 and 2 were carried out three times each.

The stimuli used were strawberry (S) and coconut (C) extracts (McCormick and Co., Inc., Baltimore, MD) diluted with tap water to a concentration of 2%. Flavoured solutions are characterized by their predominantly olfactory nature, but have, nevertheless, been used in earlier studies to verify the effects of lesioning the AP in SMN-induced aversion learning (25,29).

In each of the training sessions the subjects had access to one of the stimuli during ten minutes. In sessions in which the animals were given the aversive stimulus after a 15-min delay, the ingestion was followed by the IP administration of 1 mg/kg methyl nitrate scopolamine, i.e., a dose commonly used in previous research (5, 23, 29).

The same procedure was used in sessions in which the animals were given the neutral stimulus except that physiological saline was injected.

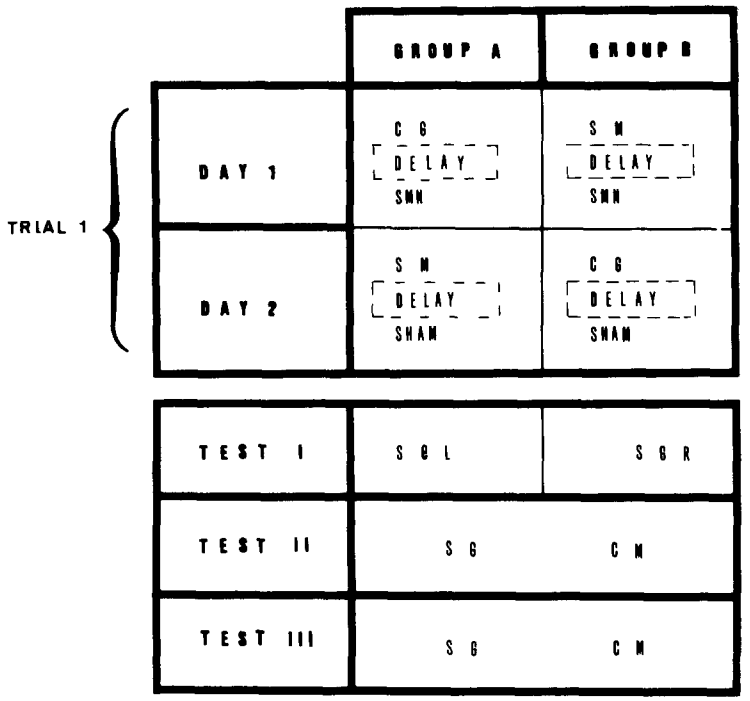

FIG. 2. Learning paradigm used in Experiments 2 (nondelay) and 3 (delay). The paradigm in Experiment 1 was the similar to Experiment 3 except that trial 1 was repeated three times (a total of 3 trials). Position and spout texture balancing is not shown. C: coconut; S: strawberry; G: glass spout; M: stainless steel spout; R: right opening; L: left opening; SMN: scopolamine methyl nitrate; SHAM: sham injection.

One session per day was carried out at approximately the same time of day. Hence, three acquisition trials alternated with neutral trials. The order of presentation, spout position and stimulus followed by SMN were balanced.

In order to test the specificity of association with the stimulus, the texture of the spouts was changed using either metal (M) or glass (G) as shown in Fig. 2. Because this variable had no effect on the results, it has been eliminated from the remainder of the description. Thus, after balancing all variables, two experimental groups were established. Rats in Group A received the SMN injection 15 min after drinking S, while in Group B, SMN administration was associated with stimulus C.

In both groups, Test I consisted of the simultaneous presentation of two burettes containing the same stimulus (S). This single-stimulus test, considered more demanding than the choice-test, predicts opposite behaviors in the two groups. If learned aversion occurs, Group A will consume smaller quantities of stimulus than Group B.

Three hours after Test I, a second test was presented in which subjects had access simultaneously to both stimuli. The position of each stimulus, maintained during training period, was inverted. The choice-test was presented in order to observe the behavior of animals that had previously had the opportunity to reduce their thirst three hours earlier. Because of the possibility that differences in the amounts consumed in Test I may have affected the results of Test II, a third test, identical to the second, was carried out 24 hr after Test II.

Histological Procedure

At the end of the experiment all animals were deeply anesthetized with sodium thiobarbital (80 mg/kg) and perfused intracardially. The brains were removed and stored in 10% formaldehyde for at least 48 hours.

Electrolytic lesions were located in sections prepared with a freezing microtome and examined under light microscope.

RESULTS

After analyzing the data with Student's t-test for independent samples, no significant differences were found between the amounts of stimulus drunk by the two groups in Test I, based on a single stimulus trial ($t=1.5227$, $p>0.1$). Positional effects were not noted ($t=0.679$, $p>0.5$).

In Test II ($t=4.674$, $p<0.01$) and Test III ($t=6.073$, $p<0.01$), however (choice tests), Student's t-test for paired samples showed that the subjects drank significantly less of the stimulus which was followed by an IP injection of SMN (Fig. 3).

The area postrema was lesioned in all cases, as histological verification showed (Fig. 4). The extent of damage to surrounding structures was variable, in four animals affecting the dorsal portion of the solitary nucleus and gracile nucleus and the gracile nuclei and in a fifth, more of the solitary nucleus and part of the dorsal motor nucleus (Fig. 5E). For the rest of the animals damage was limited to the AP. Individual analysis of the data showed no effect of different extent of damage.

EXPERIMENT 2

The results of the previous experiment suggested that the AP is not essential for SMN-induced learned aversions with three consecutive trials, even when delay was controlled. In the light of

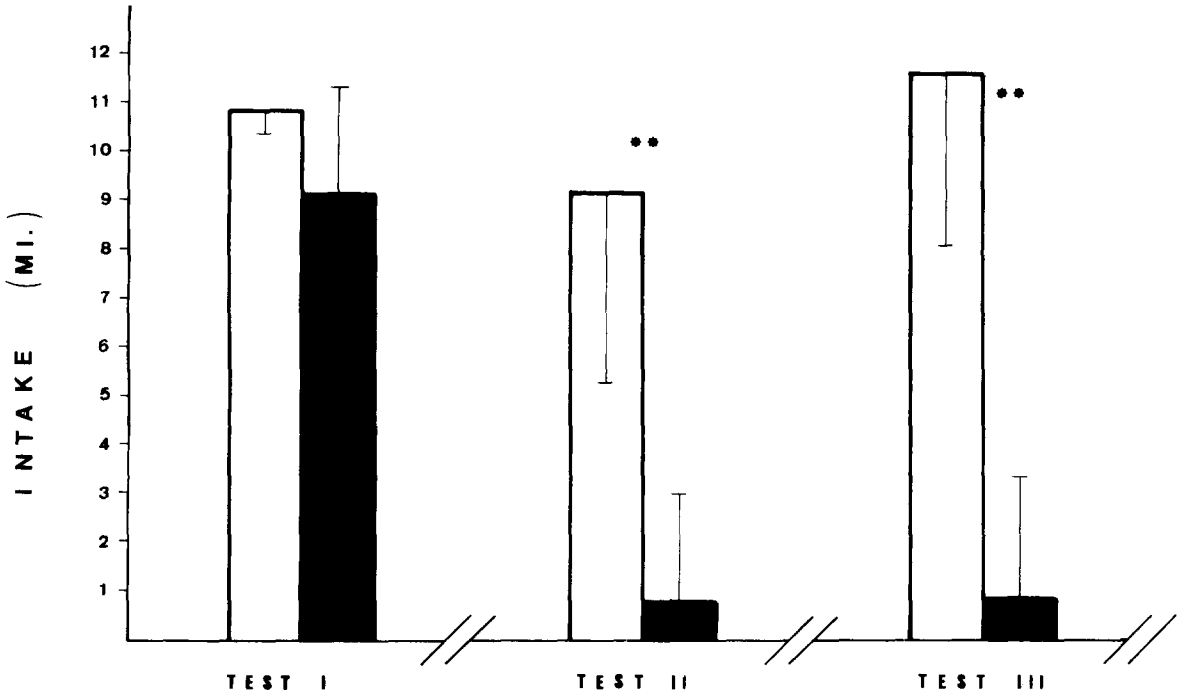

FIG. 3. Area postrema-lesioned rats' mean intake during testing in Experiment 1. Open bars: neutral fluid stimulus; filled bars: aversive fluid stimulus; vertical lines: S.D. $^{**}p<0.01$.

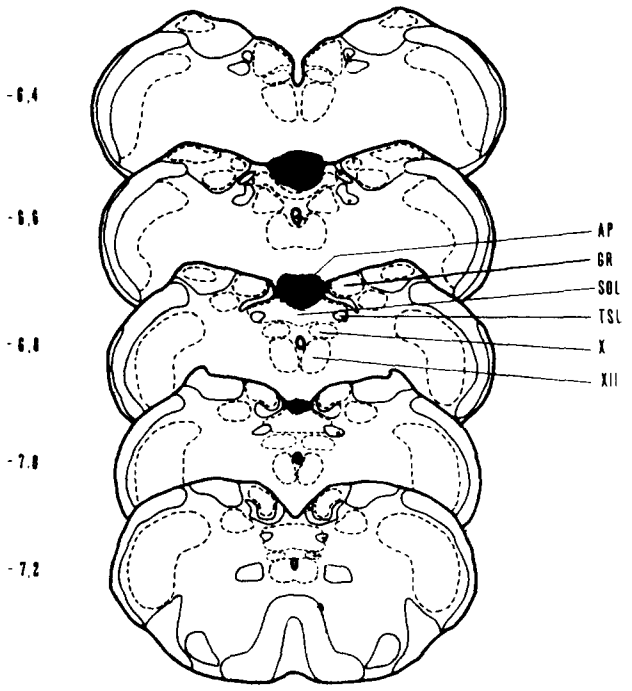

FIG. 4. Typical AP lesion in Experiment 1 (LAP1). Lesion based on coronal sections from the atlas of Pellegrino, Pellegrino and Cushman (20). Abbreviations: AP, area postrema; GR, nucleus gracilis; SOL, solitary nucleus; TSL, solitary tract; X, nucleus of cranial nerve X; XII, nucleus of cranial nerve XII.

the effects of AP lesions on learned aversions in single-trial paradigms (3,25), it appeared that the increase in the number of trials may have facilitated learning to the point where the deficit caused by the lesion was overcome. However, earlier studies (3,25) have used single-stimulus tests to confirm that the animal had, in fact, learned to avoid the aversive stimulus. Our findings confirm the previously demonstrated fact that such tests are less sensitive than choice-tests (9,23), especially in paradigms involving severe deprivation as was used in this case.

Thus, in order to rule out the possibility that the single-stimulus test may have failed to detect learning in previous experiments, or that some as yet unknown factor in the present procedure may have facilitated learning, Experiment 2 was designed around a paradigm similar to that described by other authors (number of trials and delay periods). The present experiment, however, employed more sensitive tests to detect learned aversions.

Although numerous studies have confirmed that SMN injections effectively induce learned aversions (3,25), it should be noted that previous authors used somewhat different procedures from the one described in Experiments 1 and 2 and above. We, therefore, included a sham-lesioned control group.

METHOD (A)

Subjects

Ten male Wistar rats weighing 280–320 g were used. Animals were housed individually in $30 \times 15 \times 30$ cm cages which also served as training chambers during the experiment. A 12:12 light-dark cycle was in effect with lights on at 8.00 a.m. and off at 8.00 p.m. Food was available ad lib.

Procedure

Surgical and histological procedures were performed as de-

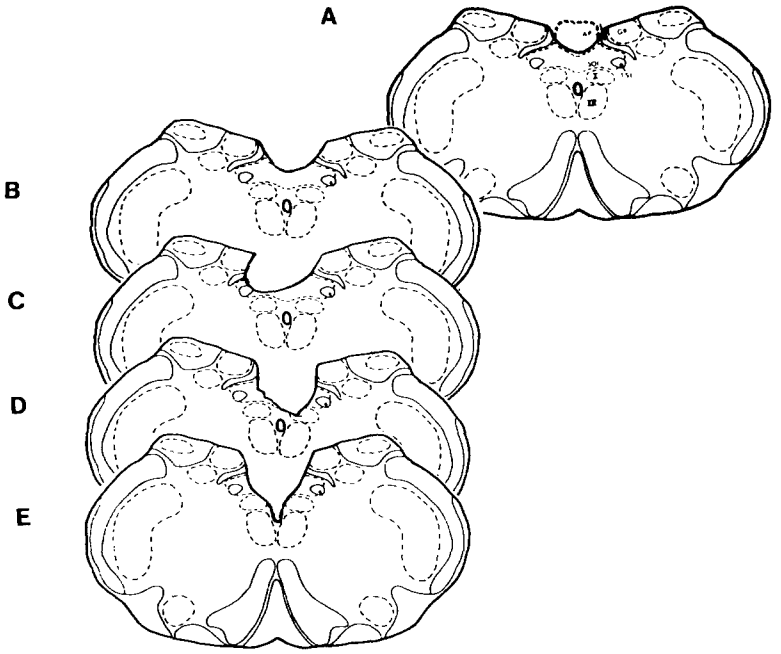

FIG. 5. Chartings of representative sections that illustrate relative size and variability of area postrema lesions. Drawing modified from Pellegrino, Pellegrino and Cushman (20). (A) Sham-lesioned control rat in section B of Experiment 2 (LAP2). (B) Lesion restricted to area postrema in section A of Experiment 2 (LAP4). (C) Lesioned rat in section A of Experiment 2 (LAP3). (D) Lesioned rat in section A of Experiment 2 (LAP8). (E) Lesioned rat in Experiment 1 (LAP9). Abbreviations: AP, area postrema; GR, nucleus gracilis; SOL, solitary nucleus; TSL, solitary tract; X, nucleus of cranial nerve X; XII, nucleus of cranial nerve XII.

scribed in Experiment 1.

The behavioral procedure was similar to that in Experiment 1 except that SMN and physiological saline were injected immediately after the subjects had drunk the stimuli and the number of training sessions was reduced in order to achieve one trial learning. Thus, animals were subjected to one acquisition trial. The procedure is shown in Fig. 2.

RESULTS

Statistical analyses of the data from Test I showed no significant differences between the groups ($t=0.941$, $p>0.3$) and intragroup comparisons of the amounts of each stimulus drunk in Test II ($t=1.653$, $p>0.1$) and Test III ($t=1.068$, $p>0.3$) likewise failed to turn up significant differences (Fig. 6).

Histological observations confirmed in all subjects that the AP had been destroyed. Most of the animals showed minimal damage to adjacent solitary nucleus (Fig. 5B). One of the subjects showed evidence of depth damage to the solitary nucleus and tract, extending unilaterally (Fig. 5C). Two animals sustained greater damage to the above structures (Fig. 5D). Individual analysis of the data showed no effect of different extent of damage.

METHOD (B)

Subjects

Twelve male Wistar rats weighing 280–320 g were used. Animals were housed individually in 30 × 15 × 30 cm cages which also served as training chambers during the experiment. A 12:12 light-dark cycle was in effect with lights on at 8.00 a.m. and off at 8.00 p.m. Food was available ad lib.

Procedure

Identical to that described in section A, except that no current was passed through the electrode.

RESULTS

The amounts of stimulus ingested by each group in Test I differed significantly in the expected direction ($t=2.446$, $p<0.05$). No positional effects were observed ($t=0.7239$, $p>0.3$).

Statistical analyses of the data from Test II ($t=4.0845$, $p<0.01$) and Test III ($t=3.2131$, $p<0.01$) also revealed significant differences in the amount of stimulus consumed (Fig. 7). Hence, in all three tests, the rats drank significantly less of the stimulus paired with SMN injection, providing additional proof that learned aversions had in fact taken place.

In all animals, histological studies showed the AP to be intact (Fig. 5A).

EXPERIMENT 3

The different procedures used in Experiment 1 and 2 above made it impossible at this stage to rule out delay between the drinking of the fluid stimulus and the injection of SMN as the crucial factor capable of explaining the results. Similar studies provided no further information in this regard (3, 16, 19, 25, 29), as in all cases SMN was administered immediately after the subjects had consumed the fluid stimulus. In Experiment 3, the

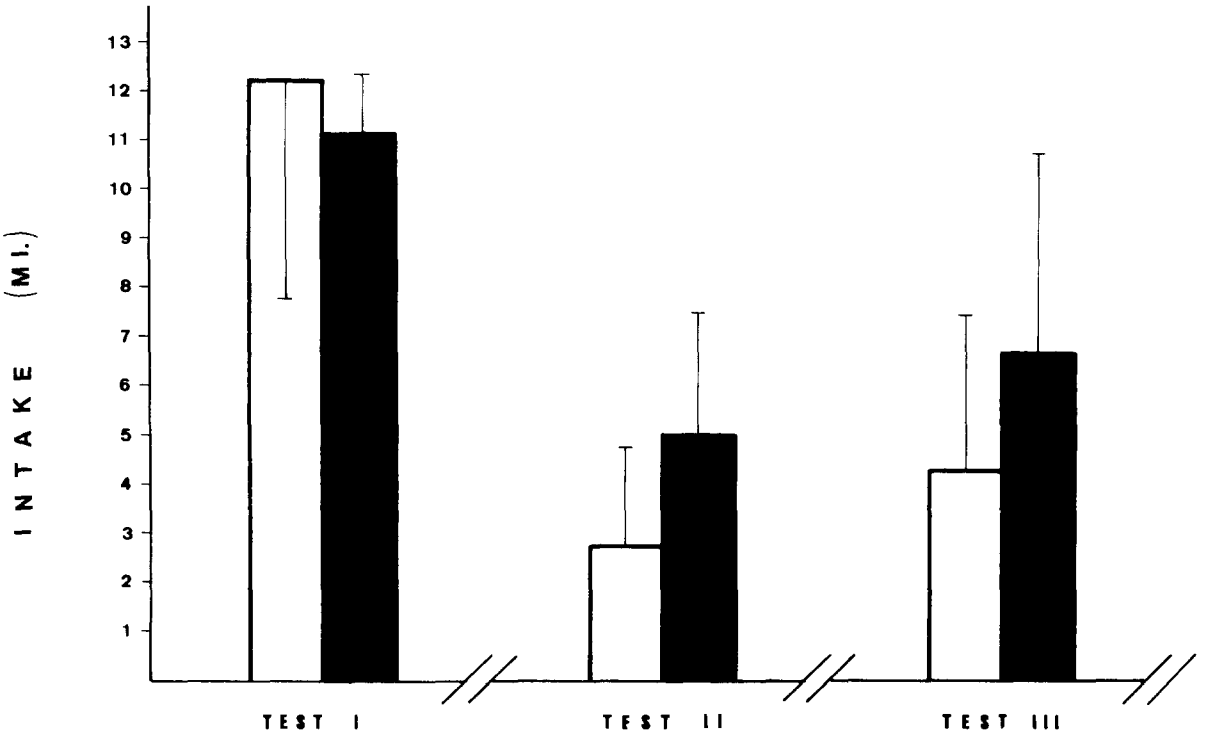

FIG. 6. Area postrema-lesioned rats' mean intake during testing in section A of the Experiment 2. Open bars: neutral fluid stimulus; filled bars: aversive fluid stimulus; vertical lines: S.D.

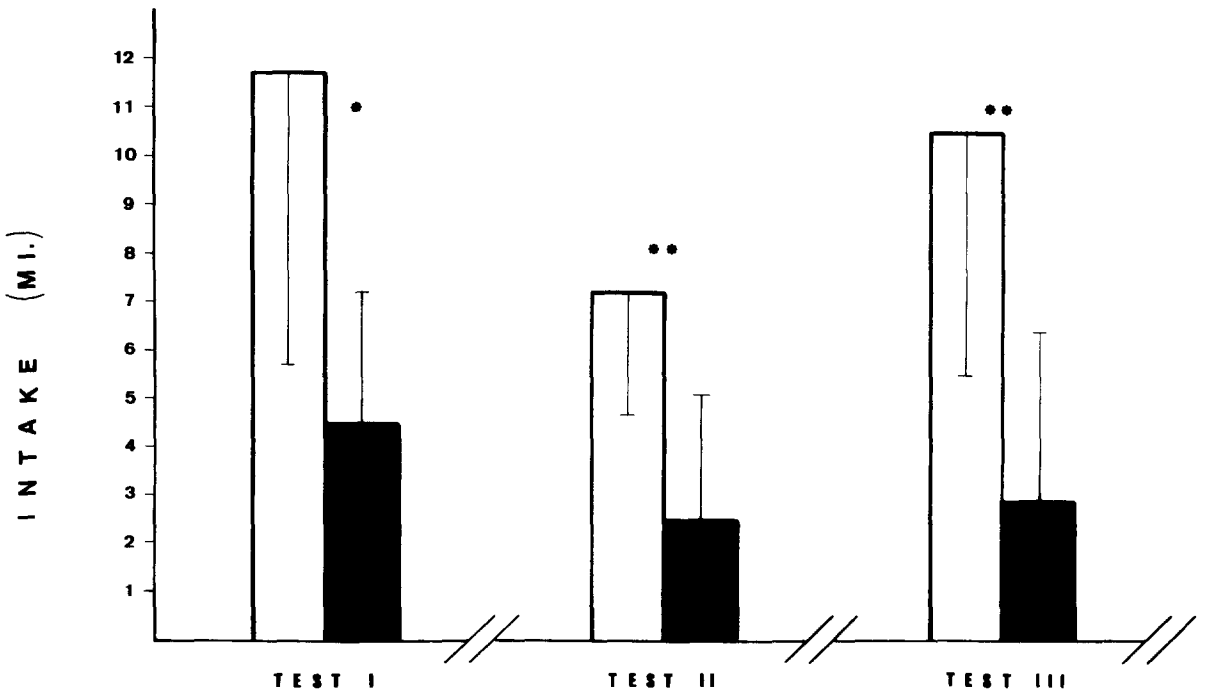

FIG. 7. Area postrema sham-lesioned rats' mean intake during testing in section B of the Experiment 2. Open bars: neutral fluid stimulus; filled bars: aversive fluid stimulus; vertical lines: S.D. $*p<0.05$; $**p<0.01$.

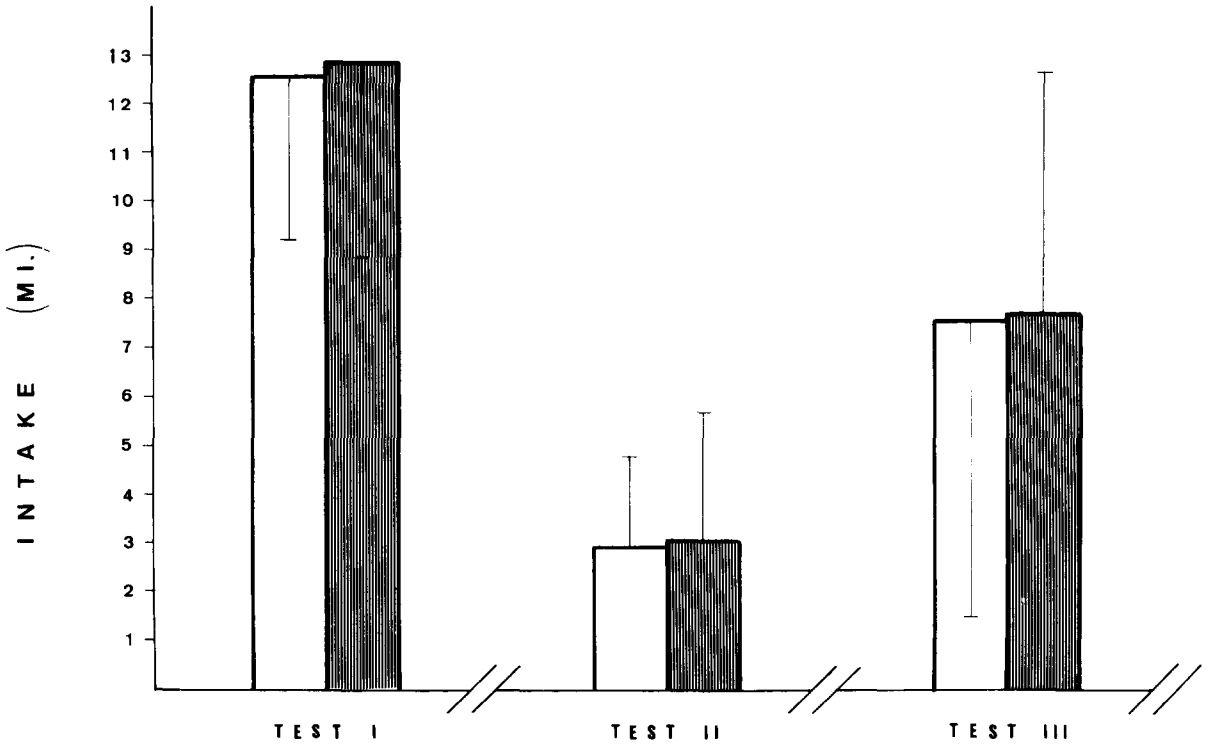

FIG. 8. Area postrema-lesioned rats' mean intake during testing in section A of the Experiment 3. Open bars: neutral fluid stimulus; filled bars: aversive fluid stimulus; vertical lines: S.D.

procedure employed in Experiment 2 was modified to include a 15-minute delay before injecting the aversive stimulus.

As in Experiment 2, a sham-lesioned control group was included.

METHOD (A)

Subjects

Nine male Wistar rats weighing 280–320 g were used. Animals were housed individually in $30 \times 15 \times 30$ cm cages which also served as training chambers during the experiment. A 12:12 light-dark cycle was in effect with lights on at 8.00 a.m. and off at 8.00 p.m. Food was available ad lib.

Procedure

Surgical and histological procedures were as described above in Experiment 1.

The behavioral procedure was similar to that described in Experiment 1 except that the number of training sessions was reduced in order to achieve one-trial learning.

RESULTS

No significant differences were seen in Test I ($t=0.1128$, $p<0.9$). Positional effects were not significant ($t=0.3395$, $p<0.7$).

Similar amounts of the two stimuli were consumed during the Choice-Tests II ($t=0.0975$, $p<0.9$) and III ($t=0.0322$, $p<0.9$) (Fig. 8). These findings show that learned aversion was disrupted upon delaying SMN injection by fifteen minutes.

In all animals the AP was completely destroyed, as verified histologically. The largest lesion impinged upon adjacent solitary nucleus, solitary tract and part of the dorsal motor nucleus of the X. Four lesions were restricted to the AP. The rest of the animals showed variable damage, but individual analysis of the results did not evidence any effect of the extent of the lesions.

METHOD (B)

Subjects

Ten male Wistar rats in the same conditions as described in section A.

Procedure

The procedure was the same as in section A above, except that sham lesions were performed as described in Experiment 2.

RESULTS

As shown by an analysis of the results of Test I ($t=3.4584$, $p<0.01$), significantly less stimulus was drunk when followed by SMN in the single-stimulus test. No significant preference was shown for any burette position ($t=2.1712$, $p>0.1$).

Choice-Tests II ($t=3.7036$; $p<0.01$) and III ($t=2.5022$, $p<0.01$) yielded similar results, i.e., the animals drank significantly lower amounts of the stimulus (Fig. 9), and can, therefore, be assumed to have acquired learned aversions.

A histological examination of the AP verified that it was intact in all subjects.

DISCUSSION

The results of Experiment 1 showed that lesioning the AP does not interfere with the acquisition of learned aversions induced by SMN in a three-trial protocol if learning is detected with a

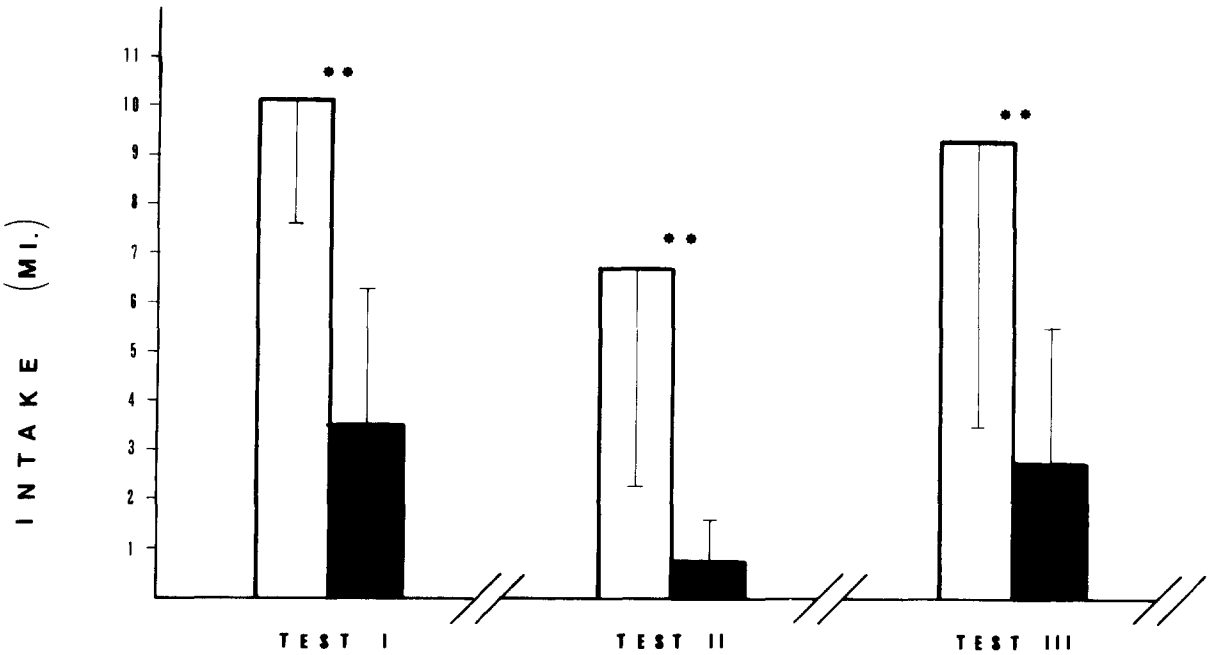

FIG. 9. Area postrema sham-lesioned rats' mean intake during testing in section B of the Experiment 3. Open bars: neutral fluid stimulus; filled bars: aversive fluid stimulus; vertical lines: S.D. $^{**}p<0.01$.

test-choice. Some attenuation in learning, however, may have been produced, since a one-stimulus test was unable to detect it. This test is well known to be less sensitive than the choice-test and more susceptible to the influence of strict deprivation (9,23). The results indicate, therefore, that it would seem important to use highly sensitive tests together with single-stimulus tests in experiments directed to determine the functional significance of the AP in learned aversions.

Although most studies of SMN-induced learned aversions have used single-trial tasks and single-stimulus tests, Ossenkopp alternated three acquisition trials with as many choice-tests (16,19), and found learning under these conditions to be disrupted by AP lesions. However, his procedure differed somewhat from ours. The tests performed between acquisition trials could rightly be considered extinction trials, because the subjects received no injection. The stimulus used by Ossenkopp (chocolate milk) also differs in gustatory qualities from our stimuli. Moreover, the use of palatable stimuli, preferred by AP-lesioned animals (8,28), versus water in the test-choice may explain the differences between his results and ours.

Experiment 2 was based on a paradigm identical (number of trials and nondelay) to that used by other authors (3,25), but with additional choice-tests. Lesioning the AP effectively prevented learning in a single-trial delayless procedure, thus, ruling out a weak learning process which the single-stimulus test might not have detected. As shown in Experiment 3, a single trial was sufficient for animals with an intact AP to acquire SMN-induced aversions, even with a fifteen-minute delay between the stimulus and the SMN injection. By contrast, lesioning the AP prevented learning in a single-trial and delay situation, demonstrating that the delay is not in itself responsible for the findings in Experiment 1 where the number of trials was shown to be the most crucial variable.

An intact AP, therefore, does not seem to be a necessary prerequisite for learned aversions induced by SMN in a paradigm where a greater number of acquisition trials is used to enhance learning, whereas effective single-trial learning, on the other hand, does apparently require a functional AP. Similar findings were recorded with amphetamine-induced learned aversions (24). With this agent the AP became relevant only at low doses, but had no effect on learning when given in large doses.

The structural characteristics of the AP, together with its well documented chemoreceptive sensitivity (1,11), its connections (2, 7, 12, 14, 15, 26) and its role in triggering vomiting (4, 5, 30), all suggest that the AP is able to detect subtle alterations in the humoral system such as would occur with low doses or short exposures to an aversive stimulus in a single-trial situation. Under such circumstances, the role of the AP may well be highly relevant. On the other hand, when the strength of learning is enhanced by raising the dose and/or the number of trials, other as yet unknown brain structures with higher activity thresholds may enter into action, playing a role analogous to that proposed for the AP.

Various structures may be involved in the acquisition of learned aversions. The AP could play a fundamental, highly specialized role in this process. This, of course, does not rule out the participation of other systems of humoral detection which very likely come to fore in the absence of the AP, as studies with other aversive agents suggest (17,22).

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