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Motor Activity Changes and Conditioned Taste Aversions Induced by Administration of Scopolamine in Rats: Role of the Area Postrema

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OSSENKOPP, K.-P., C. SUTHERLAND AND R. L. LADOWSKY. *Motor activity changes and conditioned taste aversions induced by administration of scopolamine in rats: Role of the area postrema.* PHARMACOL BIOCHEM BEHAV **25**(1) 269–276, 1986.—Three experiments examined the effects of centrally and peripherally acting scopolamine (scopolamine hydrochloride-SHC) or only peripherally acting scopolamine (scopolamine methyl nitrate-SMN), on motor activity levels and the ability of these agents to induce taste aversions. In Experiment 1 rats were injected with isotonic saline, 1 mg/kg SHC, or 1 mg/kg SMN. SHC produced significant increases in stabilimeter activity ($p<0.025$) and in rearing response frequency ($p<0.01$), whereas SMN resulted in significantly less activity ($p<0.025$). Both agents induced strong conditioned taste aversions to saccharin ($p<0.01$). Experiment 2 examined the role of the area postrema in mediating these drug induced behavioral changes. Sham lesioned and area postrema lesioned rats were given saline, SHC or SMN (1 mg/kg for both drugs) and examined for changes in activity, rearing response frequency and induction of taste aversions to saccharin. SHC again produced significant increases in activity ($p<0.01$) and in rearing responses ($p<0.01$), whereas SMN produced decrements in activity ($p<0.05$). However, the brain lesion did not consistently alter the effects of these drugs on activity but it did reduce the amount of the decrement observed in rearing responses in SMN treated rats. The brain lesion also altered the ability of the drugs to induce taste aversions. Both SMN and SHC produced strong taste aversions in the sham lesioned rats ($p<0.01$) but no significant aversions were observed in the area postrema lesioned rats. Experiment 3 examined the ability of the brain lesion to alter the effects of SMN by using a within groups design. Area postrema lesions were found to attenuate but not abolish, the inhibitory effects of SMN on both activity levels and rearing responses ($p<0.03$). The results of these experiments suggest that in the absence of the chemically-sensitive area postrema both SMN and SHC fail to induce taste aversions and the inhibitory effect of SMN on spontaneous activity is attenuated.

Area postrema Conditioned taste aversions Scopolamine hydrochloride Scopolamine methyl nitrate
Brain lesions Hyperactivity Behavioral depression Rats

IN rodents anticholinergics such as scopolamine and atropine increase locomotor activity when they act on the central nervous system [1, 16–18, 30, 32, 34], however, quaternary anticholinergics, which do not cross the blood-brain-barrier are reported to have either no significant effect on motor activity (e.g., [13, 16, 32]) or to inhibit activity levels [17]. Scopolamine is also a highly effective agent for induction of conditioned taste aversions (CTA). Strong avoidance conditioning of a novel taste can be produced in rats by pairing ingestion of the novel tasting substance with exposure to a toxic agent such as lithium [14,19] or to ionizing radiation [31], and the suggestion has been made that it is the illness-inducing properties of these treatments which make them such effective agents in producing CTA [9,10]. Both centrally and peripherally acting scopolamine can produce robust CTA in rats [2,3] and several experiments have shown that the peripherally acting scopolamine acts on the area postrema (AP) in the fourth ventricle to induce this type of avoidance behavior [3,20].

The AP is a circumventricular structure containing central chemoreceptors, which when stimulated, can initiate an emetic response in animals capable of vomiting [4–6]. An analagous role for the AP in detection of toxic agents in non-emetic mammals, such as rats, has been shown in experiments on rats with AP lesions. Destruction of the AP results in the absence of CTA normally induced by scopolamine methyl nitrate [3,20], lithium [14, 26, 29] or exposure to ionizing radiation [21, 23, 26, 27]. The AP also seems to mediate the depression in activity seen in rats treated with lithium chloride [14]. Rats with AP lesions no longer displayed the reductions in activity shown by the sham lesioned animals after administration of the lithium. Ladowsky and Ossenkopp [14] suggested that the depression in activity normally seen after acute administration of lithium may result at least partially from malaise or nausea and that stimulation of the AP by the lithium may be a sufficient condition to induce such malaise. If both the CTA and the depression in activity resulted from activation of the AP by the lithium,

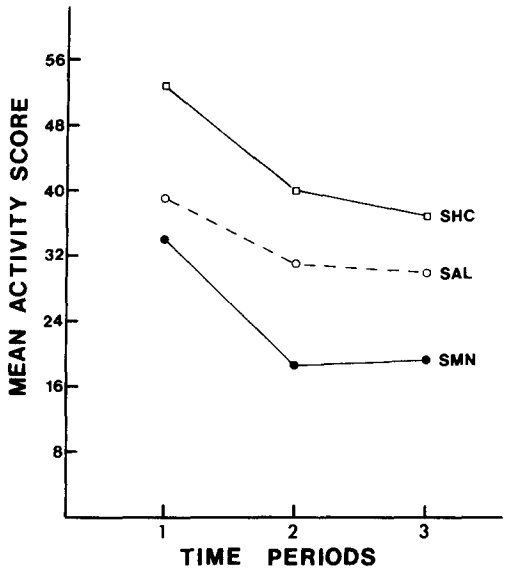

FIG. 1. Mean activity scores for rats injected with isotonic saline (SAL), 1 mg/kg, scopolamine hydrochloride (SHC), or 1 mg/kg scopolamine methyl nitrate (SMN). The time periods represent 20 minute periods on 2 consecutive days.

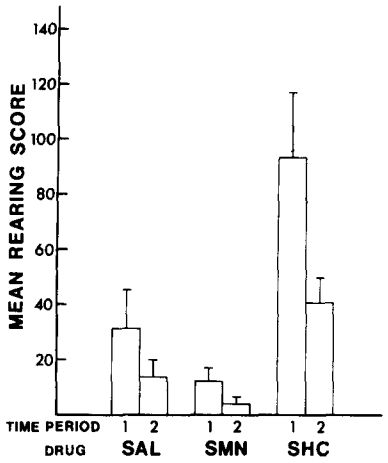

FIG. 2. Mean rearing response scores for rats injected with isotonic saline (SAL), 1 mg/kg scopolamine hydrochloride (SHC), or 1 mg/kg scopolamine methyl nitrate (SMN). The time periods represent 30 minute periods on 2 consecutive days.

TABLE 1

BASELINE WATER INTAKE LEVELS AND SACCHARIN INTAKE LEVELS ON THE TWO CONDITIONING DAYS FOR THE THREE DRUG TREATED GROUPS

		Fluid Intake	
Drug Group	Baseline (water)	Conditioning Day 1 (saccharin)	Conditioning Day 2 (saccharin)
Isotonic	15.13	16.88	16.63
Saline	(1.71)	(1.14)	(1.43)
Scopolamine methyl	16.13	16.13	4.50 *
nitrate	(1.52)	(2.43)	(1.54)
Scopolamine	16.20	20.60	8.90 *
hydrochloride	(1.25)	(2.60)	(2.52)

The injections (1 mg/kg) were given after the drinking period had terminated (numbers in the brackets are standard errors).

*$p<0.05$ relative to conditioning Day 1.

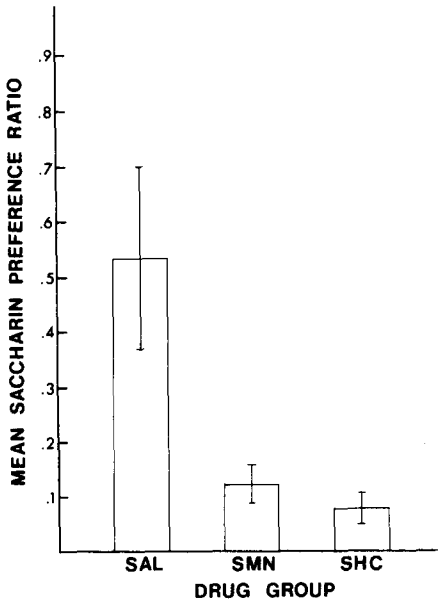

FIG. 3. Mean saccharin preference ratio scores for rats conditioned with 2 pairings of a saccharin taste and injections of isotonic saline (SAL), 1 mg/kg scopolamine hydrochloride (SHC), or 1 mg/kg scopolamine methyl nitrate (SMN). The error bars are standard errors.

then destruction of the AP should protect against both of these lithium induced behavioral changes; findings in fact obtained [14,29].

In the present experiments we observed the effects of centrally acting and peripherally acting scopolamine or only peripherally acting scopolamine on motor activity levels and the ability of these agents to induce CTA. We then examined the necessity for integrity of the AP in producing these drug-induced CTA and motor activity changes.

EXPERIMENT 1

The first experiment investigated the effects of administering scopolamine hydrochloride (SHC) or scopolamine methyl nitrate (SMN) on spontaneous activity levels and the ability of these two agents to produce a CTA to a novel saccharin solution. Of special interest was the possibility that the peripherally acting SMN might have effects similar to lithium and produce both a strong CTA along with depression in activity. In contrast, the centrally acting SHC was expected to increase activity levels but also produce a CTA.

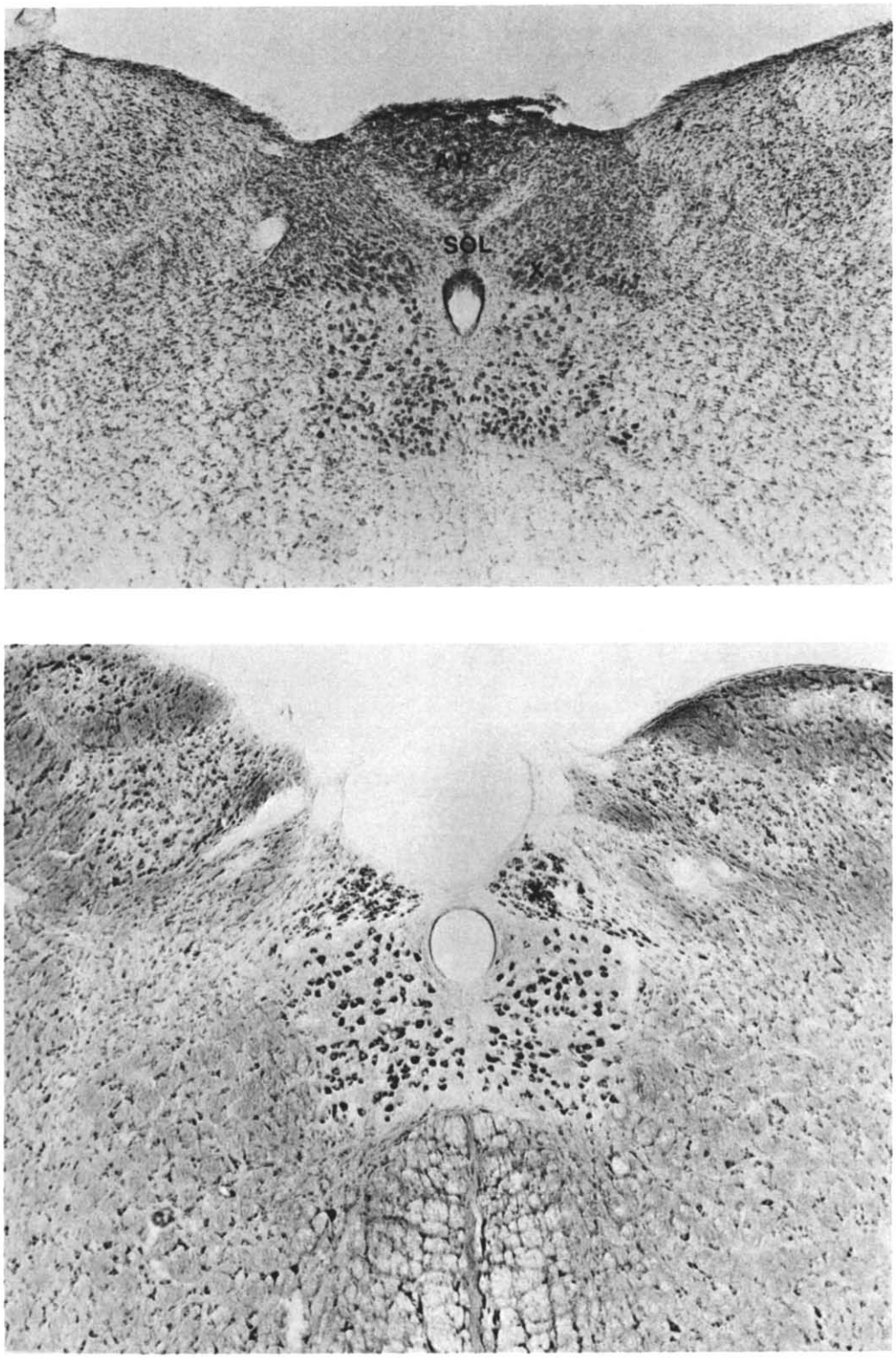

FIG. 4. Photomicrographs of coronal sections of the rat's brainstem showing the area postrema (AP) in the top section and a representative lesion of the AP in the bottom section. Abbreviations: AP—area postrema, SOL—solitary nucleus, X—nucleus of the vagus nerve (taken from Pellegrino, Pellegrino and Cushman [25]).

METHOD

Subjects

Thirteen adult male hooded rats (Long-Evans strain) were individually housed in stainless-steel cages and kept in a colony room maintained at about 20°C and on a 12:12 hr light-dark cycle with lights on from 8:00 to 20:00 hr. The animals had free access to Purina lab chow and tap water and weighed 400 to 500 g at the start of the experiment.

Procedure

All animals were adjusted to a 23 hr/day water deprivation schedule over 7 days. On Day 8 all rats were given 1 hr access to a 0.1% sodium saccharin solution and then injected intraperitoneally (IP) with 1 mg/kg of scopolamine hydrochloride (Group SHC, n=5), 1 mg/kg of scopolamine methyl nitrate (Group SMN, n=4), or 1 ml/kg of isotonic saline (Group SAL, n=4). Immediately after the injection all animals were placed in a stabilimeter apparatus (Lafayette, Model A-501) and their motor activity was monitored for 1 hr. The stabilimeter employed a magnet and coil transduction mechanisms connected to a voltage sensitive relay to quantify motor activity. During this time period the animals' behavior was also recorded on videotape via a Sony video camera positioned in front of the stabilimeter apparatus and connected to a videotape recorder and television monitor. At the end of the test period the rats were returned to their home cages. On Day 9 all animals were treated exactly the same as on the previous day and on Days 10 to 12 the rats were given tap water for 1 hr but not otherwise disturbed. On Day 13 all animals were given a two bottle choice test [7,12]. One bottle containing tap water and the other containing saccharin solution were presented to each animal for 1 hr. A saccharin preference ratio was calculated for each animal by dividing the amount of saccharin solution consumed by the total fluid intake on the test day (water plus saccharin).

RESULTS

Activity Levels

Stabilimeter scores for each of the 3 groups are shown in Fig. 1 and rearing response frequencies for the 3 groups are presented in Fig. 2. Analysis of variance of these data revealed significant group differences in activity scores, $F(2,10)=39.09$, $p<0.001$, and in rearing response frequencies, $F(2,10)=11.40$, $p<0.003$. Post-hoc comparisons indicated that the SHC group had significantly greater activity levels than the SAL group ($p<0.025$) whereas the SMN group had significantly lower levels of activity than Group SAL ($p<0.025$). Similarly, Group SHC reared significantly more often than the saline group ($p<0.01$) and Group SMN reared less often, but not significantly so.

Taste Aversion Conditioning

Table 1 presents the baseline water intake levels for all 3 groups on Day 7 together with the saccharin solution intake levels on Days 8 and 9. Both scopolamine groups exhibited significant ($p<0.05$) decrements in saccharin intake on Day 9 relative to Day 8, whereas, Group SAL maintained comparable saccharin intake on both these days. Group mean saccharin preference ratios are shown in Fig. 3 and analysis of variance of these data indicated a significant groups main effect, $F(2,10)=7.50$, $p=0.01$, with the two scopolamine groups exhibiting significantly lower preference ratios ($p<0.01$) than the saline group.

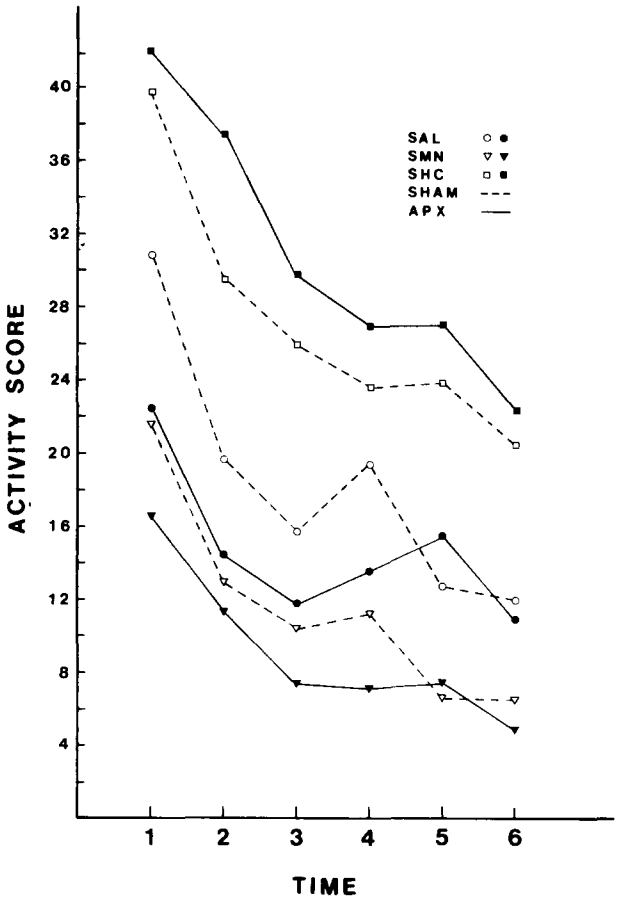

FIG. 5. Group mean activity scores for sham lesioned (SHAM) and AP lesioned rats (APX) given isotonic saline (SAL), 1 mg/kg scopolamine hydrochloride (SHC), or 1 mg/kg scopolamine methyl nitrate (SMN). The time intervals represent 10 minute intervals on 2 consecutive days.

DISCUSSION

The data from Experiment 1 clearly show robust CTA induced by both centrally and peripherally acting scopolamine. These findings are consistent with previous reports of similar scopolamine induced CTA [2,3]. In contrast, centrally active scopolamine increased motor activity levels, whereas, peripherally active scopolamine inhibited activity levels. Increased motor activity has been reported previously with the SHC dose levels used in the present study (e.g. [16]). However, the depression in activity after SMN is less well known and clearly represents a peripheral effect of scopolamine which may include its action on the area postrema. Previous research has demonstrated the presence of muscarinic receptors in AP [24] which could have been activated by SMN in the present experiment since AP is known to have a reduced blood-brain-barrier [4].

EXPERIMENT 2

Since Experiment 1 established that SMN and SHC have similar abilities to induce CTA in rats but opposite effects on their spontaneous motor activity levels, the second experiment examined the role of the area postrema in the production of CTA and changes in activity levels after administra-

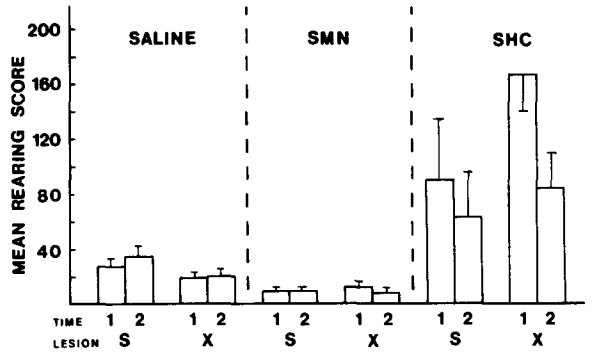

FIG. 6. Group mean rearing frequency scores for sham lesioned (S) or AP lesioned (X) rats given isotonic saline (SAL), 1 mg/kg scopolamine hydrochloride (SHC), or 1 mg/kg scopolamine methyl nitrate (SMN). The time periods represent the first and second test days.

tion of the two types of scopolamine. It was hypothesized that the AP would mediate the CTA induced with SMN as well as the depression in activity produced by this drug. In contrast SHC was expected to produce both a CTA and increased levels in activity after SHC administration even in rats lacking an AP. The "drug-novelty" hypothesis proposed by Gamzu [8] suggests that all novel drug states may be perceived as aversive and therefore capable of inducing CTA. Thus, it was expected that the central actions of SHC would produce both a CTA and hyperactivity.

METHOD

Subjects

Thirty-five adult male hooded rats were maintained as in Experiment 1. The animals weighed 250 to 350 g at the start of the experiment.

Surgical Procedure

Animals receiving lesions of the area postrema (n=18) were anesthetized with sodium pentobarbital (Sommotal, 65 mg/kg) and then placed in a head-holder which kept the head in a ventroflexed position. The dorsal surface of the medulla was exposed by retracting the overlying muscles and the atlanto-occipital membrane joining the cranium and the spinal column, and enlarging the foramen magnum. The floor of the fourth ventricle was viewed through an operating microscope (Zeiss OPMI 99) and lesions of AP were made by touching the structure with the tip of a small cautery. The neck muscles and scalp were then sutured and the animals were allowed to recover from the operation for at least 7 days. Animals receiving sham lesions were treated in an identical manner except that the AP was not lesioned.

Behavioral Procedure

All animals were adjusted to a 23 hr/day water deprivation schedule over a 7 day period. On Day 8 all rats were given 1 hr access to a 0.1% sodium saccharin solution and then some sham lesioned (S) and AP lesioned (X) rats were injected IP with 1 ml/kg of isotonic saline (Group SAL-S, n=6 and Group SAL-X, n=7, respectively), 1 mg/kg SMN (Group SMN-S, n=7 and Group SMN-X, n=7, respectively), or 1 mg/kg SHC (Group SHC-S, n=4 and Group SHC-X, n=4, respectively). The rest of the procedure for these 6 groups was then identical to the procedure outlined in Experiment 1.

Histological Procedure

At the conclusion of the experiment all rats were deeply anesthetized and then perfused intracardially with isotonic saline followed by a 10% solution of formalin. The brains were removed and stored in formalin for at least 2 days and then coronal sections 50 μm thick were cut on a freezing microtome at the level of the brain stem containing the AP. These sections were mounted and stained with cresyl violet.

RESULTS

Histology

Figure 4 presents representative sections from a rat with a sham lesion procedure and a rat with an AP lesion. Histological analyses of all the rats indicated complete lesions of the AP with additional damage to the adjacent caudo-medial solitary nucleus. Several rats also sustained damage to the dorsal efferent nucleus of the vagus. There were no apparent correlations between individual variations in lesion size and the behavioral data recorded. None of the sham lesioned rats exhibited any signs of damage to the AP.

Activity Measures

Figure 5 presents group mean activity levels over the test period. Analysis of variance of these data revealed a significant drug main effect, $F(2,29)=21.26$, $p<0.001$, with no significant lesion main effect or drug by lesion interaction. Post-hoc analysis revealed that SHC produced greater activity levels in both the sham lesioned and the AP lesioned groups relative to the two saline groups ($p<0.01$) whereas the SMN treatment significantly reduced activity levels in rats with and without an AP ($p<0.05$). In Fig. 6 the group means for rearing response frequency are depicted. Statistical analysis of these data also revealed a significant drug main effect, $F(2,29)=23.23$, $p<0.001$, with the SHC treated rats showing enhanced rearing rates relative to the saline groups ($p<0.01$) and the SMN treated rats rearing less often than the saline treated animals, but not significantly so. The drug × lesion × days × time interaction was also significant, $F(2,29)=9.20$, $p<0.001$, and post-hoc tests indicated that during the initial half of the test session the SMN treatment significantly reduced rearing levels in the sham lesioned rats relative to the saline treated rats ($p<0.05$) but not in the AP lesioned rats given SMN relative to the saline treated AP lesioned rats ($p>0.10$). SHC greatly increased rearing frequency levels in both sham lesioned and AP lesioned animals ($p<0.01$).

Conditioned Taste Aversions

Figure 7 shows the baseline water intake and saccharin solution intake on both conditioning days for all 6 groups. Baseline water intake levels did not differ significantly among the 6 groups ($F<1$). It is quite clear from Fig. 7 that both SMN and SHC reduced saccharin intake on the second conditioning day, in the two sham lesioned groups, relative to the first conditioning day and this was confirmed statistically ($p<0.01$). However, no such significant reduction in saccharin was evident in the two AP lesioned groups given scopolamine ($p>0.10$). Likewise no significant decrement in saccharin consumption was found in the saline treated rats.

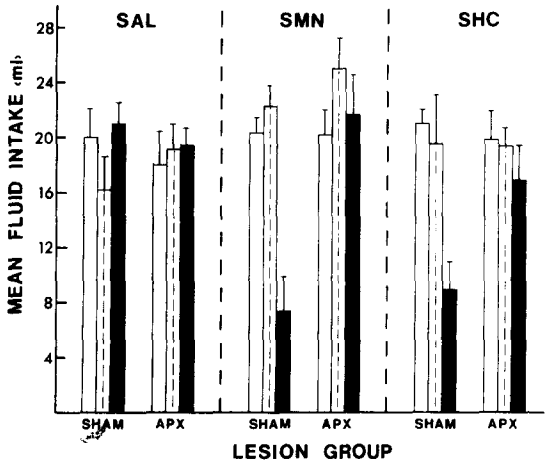

FIG. 7. Group mean fluid intake by sham lesioned (SHAM) and AP lesioned (APX) rats during baseline water access (open bars), saccharin fluid access on the first conditioning day (bars with broken line) and on the second conditioning day (black bars). On the conditioning days the animals were injected with isotonic saline (SAL), scopolamine methyl nitrate (SMN), or scopolamine hydrochloride (SHC). Error bars are standard errors.

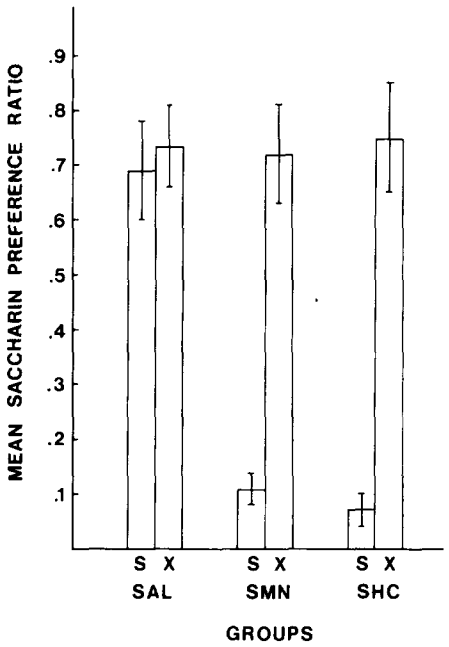

FIG. 8. Group mean saccharin preference ratios for sham lesioned (S) or AP lesioned rats (X) conditioned with isotonic saline (SAL), scopolamine methyl nitrate (SMN), or scopolamine hydrochloride (SHC). Error bars are ±standard errors of the mean.

The saccharin preference ratio means shown in Fig. 8 confirm these findings. Both SMN and SHC resulted in strong conditioned taste aversions in the sham lesioned groups but not in the AP lesioned animals. Statistical analysis of these data support this visual impression. The drug by lesion interaction was highly significant, $F(2,29)=9.74$, $p<0.001$, and post-hoc tests showed that the two saline treated groups and the two AP lesioned groups given scopolamine exhibited comparable levels of saccharin preference ($p>0.10$). However, the two sham lesioned groups given scopolamine exhibited significantly lower saccharin preference ratios relative to the other 4 groups ($p<0.01$).

DISCUSSION

The results of Experiment 2 show that integrity of the AP is necessary for induction of a CTA with both the peripherally active SMN and the centrally and peripherally active SHC. In addition, the rearing data suggest that the inhibitory effects of SMN are at least partially mediated by the AP.

The observation that the AP mediates the induction of CTA with SMN is consistent with previous reports [3,20]. The finding that the AP also mediates the induction of a CTA with SHC is somewhat surprising. Previous research had suggested that drugs with a central action produce CTA as a result of their perceived aversive central effects [8]. The present experiment shows that the central actions of SHC are not sufficient to induce a CTA when the AP is absent. However, the present results are consistent with the suggestion that stimulation of the AP may be a sufficient, although not a necessary condition for the induction of a CTA [28]. In any case, the present data do not support the hypothesis that any novel central change in state can act as a US to produce a CTA.

The findings in this experiment that at least some of the inhibitory effects of SMN are mediated by the AP are consistent with similar observations for the effects of lithium chloride [14]. The inhibitory effect of both lithium and SMN may be a result of induced malaise produced by activation of the AP. In the absence of the AP much less or no malaise may be present after administration of these agents. Previous work [15] has shown that cats with lesions of AP and treated with cisplatin, a chemotherapeutic agent which normally causes retching and vomiting in cats, failed to show an emetic response. Not only did these cats not vomit in response to the cisplatin, they also failed to show any sign of malaise which is normally quite evident. Thus, the lesions of AP seemed to protect the cats against the effects of cisplatin, in inducing malaise. A similar process may underlie the mediating role of AP in the inhibitory effects of lithium and SMN on motor activity levels in rats. If depression in activity after administration of SMN reflects the development of malaise, then lesions of AP clearly attenuate the effects of SMN in inducing illness. A similar explanation may also hold for the mediating role of the AP in scopolamine induced CTA.

EXPERIMENT 3

Since the mediating role of the AP in the inhibitory effects of SMN on activity and rearing frequency was not completely clear in Experiment 2, this issue was re-examined in Experiment 3. A confound in the data from Experiment 2 was the consistent finding that AP lesioned rats exhibit less spontaneous activity than sham lesioned rats. Other unpublished data from our laboratory [22] have confirmed this difference in activity in untreated AP lesioned rats. The differential in basal levels of activity between sham lesioned and AP lesioned rats make interpretation of the activity data in Experiment 2 problematic. Experiment 3 avoided this

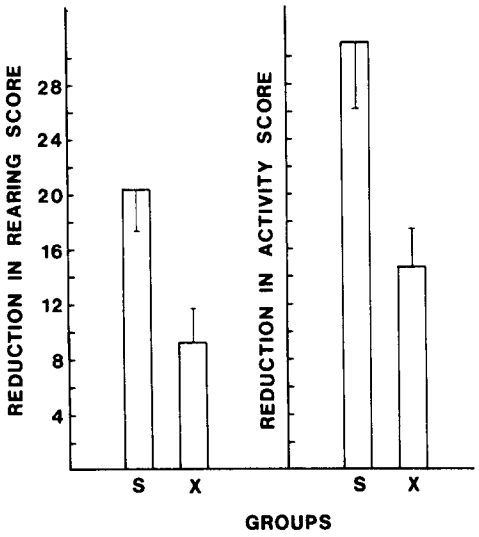

FIG. 9. Group mean reductions in rearing frequency scores (left panel) and activity scores (right panel) in sham lesioned (S) or AP lesioned (X) rats given isotonic saline during baseline testing and 1 mg/kg scopolamine methyl nitrate during drug testing 1 week later. Error bars are standard errors.

problem by using a within groups design such that each animal served as its own control in examining the inhibitory effects of SMN on spontaneous activity.

METHOD

Subjects

Eleven adult male hooded rats were maintained as in Experiment 1. The animals weighed 300 to 400 g at the start of the experiment.

Surgical Procedure

Five rats received lesions of AP (Group APX) as described in Experiment 2 and 6 rats were given sham lesions (Group APS). All animals were allowed to recover from the operation for at least 7 days.

Behavioral Procedure

All rats were first given a baseline activity test session. Each animal was injected with isotonic saline and then placed in the stabilimeter apparatus for 1 hr. During this time period activity levels were automatically recorded and the rat's behavior was videotaped. One week later all rats were injected with 1 mg/kg of SMN and again placed in the stabilimeter for 1 hr. Behavior was again videotaped during the test session.

Histological Procedure

At the conclusion of the experiment all rats were treated in the same way as in Experiment 2 and the brains were histologically examined for size and placements of the lesions.

RESULTS

Histology

Histological examination indicated that all 5 APX rats had complete lesions of AP with additional damage to the adjacent caudo-medial solitary nucleus. None of the sham lesioned rats showed any damage to the AP.

Activity Measures

Figure 9 depicts the decrements in activity level and rearing frequency induced by SMN administration in Groups APS and APX. Both activity levels and rearing response frequency showed less of a decrement in the AP lesioned rats than in the sham lesioned animals. Statistical analysis confirmed this impression. There was a significant lesion effect on both the activity ($p=0.027$) and on the rearing ($p=0.021$) measure. Clearly the AP only partially mediated the inhibitory effect of SMN since this lesion did not totally abolish the depressant effect of the peripherally active scopolamine.

DISCUSSION

The results of this last experiment confirm the findings of the second experiment by showing that the AP is involved in the inhibitory effects of SMN on activity. Although the destruction of AP did not completely protect against the inhibitory effects of SMN, a significant partial reduction was obtained in the AP lesioned rats. These data are thus consistent with the hypothesis that SMN may be producing at least part of its inhibitory action on spontaneous activity by acting on the muscarinic receptors in AP and inducing malaise.

GENERAL DISCUSSION

The major findings of the present series of experiments are: (1) centrally and peripherally acting scopolamine increases activity levels, whereas peripherally acting scopolamine inhibits spontaneous motor activity levels in rats, (2) both peripherally and centrally acting scopolamine can induce strong CTA in rats, (3) the AP mediates the CTA inducing effects of both peripherally and centrally acting scopolamine and also partially mediates the inhibitory effects of SMN on activity.

In general the results of these experiments are not inconsistent with the hypothesis that scopolamine induces CTA by producing malaise and that, unless the scopolamine has central actions, this malaise will result in inhibition of spontaneous motor activity. Activation of the AP seems to be a sufficient condition to produce both a CTA and inhibition of activity levels (unless it is masked by the central effects of the scopolamine) and this suggests that perhaps activation of the AP leads to malaise. Several previous reports are in agreement with this type of analysis [14,15]. However, given the difficulty of measuring malaise in an animal (except through operational definition, such as inhibition of activity levels) we must be cautious about interpretation of the present data since other effects of the SMN could possibly account for the present findings. Nevertheless, when compared to human reports of malaise, nausea, and vomiting after administration of peripherally active anticholinergics [11], the present hypothetical analysis is intriguing.

The demonstration that the AP mediates the CTA inducing effects of SHC even though this drug exerted strong central action by enhancing activity levels, clearly indicates that simply having some novel central change in state is not a

sufficient condition for production of a CTA. If this were indeed the case, then the AP lesioned rats should have exhibited a strong CTA when treated with SHC. Of special interest in this regard is a recent report [13] which examined the effects of scopolamine and methyl scopolamine on novelty preferences in exploration boxes. Both drugs were found to decrease preference for the novel environment and it was suggested that the reductions were due to the aversive peripheral actions of the anticholinergics. This type of analysis is consistent with the present data and suggests that the area postrema may be the peripheral site of action of these drugs. The present results also suggest that agents which do not require the AP in order to induce a CTA (such as amphetamine, apomorphine, and motion sickness [3, 20, 33]) probably act on other specific CNS structures to produce the taste aversions.

ACKNOWLEDGEMENTS

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