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Effects of Atropine on Conditioned Taste Aversion[1]

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DEUTSCH, R. *Effects of atropine on conditioned taste aversion.* PHARMAC. BIOCHEM. BEHAV. 8(6) 685–694, 1978. – Atropine sulfate, which has a deleterious effect on various learning tasks, was found to have a similar effect on the acquisition of conditioned taste aversion. Thus, intraperitoneal injection of atropine sulfate shortly before tasting was found to interfere with conditioning of the aversion, but injection of atropine after tasting did not. The interference effect was also obtained with intraventricular administration of atropine sulfate, but not with intraperitoneal injection of the peripherally-acting atropine methylnitrate. These results show that central rather than peripheral mechanisms are involved in this effect, and suggest that conditioned taste aversion, like other kinds of learning, involves cholinergic mediation.

Conditioned taste aversion Atropine sulfate Atropine methylnitrate

IF A RAT is exposed to a novel taste such as saccharin (conditioned stimulus; CS) and then malaise is induced through X-irradiation or injection of a drug such as LiCl (conditioned stimulus; US), it will develop an aversion to that taste. The conditioned taste aversion (CTA) can be acquired in a single trial, and even when the CS-US interval is several hours [19]. These and other properties of CTA are thought to have considerable importance for theories of learning [47] and for the understanding of biological adaptation [45].

One of the contentious issues is whether CTA has different neural mechanisms than other types of learning [20,48]. Approaches to this problem have included the use of lesioning techniques (e.g., [34]), cortical spreading depression (e.g., [8]), electroconvulsive shock (e.g., [31]), and Metrazol-induced seizures (e.g., [37]). Surprisingly, few attempts have been made to influence CTA by manipulation of the cholinergic system, a system which is widely believed to be involved in learning and memory [14,33]. This paper reports that atropine sulfate, an anticholinergic drug which has been shown to interfere with the acquisition of various conventional learning tasks, has a similar effect on CTA.

EXPERIMENT 1

The first experiment was designed to test whether atropine, injected before the taste-illness pairing, will interfere with the acquisition of the aversion. Since atropine is known to depress drinking [52,55], the taste of saccharin was presented using the intravascular taste method of Bradley and Mistretta [5]. In this method, taste receptors are stimulated by saccharin injected directly into the vascular system; thus, no drinking is involved.

METHOD

Animals

Forty male experimentally naive Wistar rats, weighing 250–340 g at the beginning of the experiment, were used. In both this and the subsequent experiments, rats were individually housed, with food available ad lib, and water on a 30 min/day schedule.

Conditioning Procedure

The animals were given three injections, in the following sequence: (1) Intraperitoneal (IP) injection of either (a) 1 ml 0.15 M NaCl, or (b) 100 mg/kg atropine sulfate in 1 ml distilled water. (2) After a delay of 5 min, all animals received an intravenous (IV) injection of 1 ml 4% sodium saccharin. The tail vein was used as the injection site. (3) Immediately after the IV injection, the animals were given a second IP injection, either (a) 8 ml/kg 0.15 M LiCl, or (b) 8 ml/kg 0.15 M NaCl.

Thus, four groups were formed (N = 10 in each group), all of them receiving the saccharin injection, differentiated by whether they were pretreated with atropine or saline, and by whether the post-saccharin injection was of LiCl or saline.

Testing Procedure

On each of four consecutive days following conditioning, all animals were given 30-min two-bottle preference tests, with 0.2% sodium saccharin and tap water as the choices. Bottle positions were alternated on successive days. Statistical analysis was performed on saccharin preference (saccharin/total intake) scores. All p values are based on two-tailed tests.

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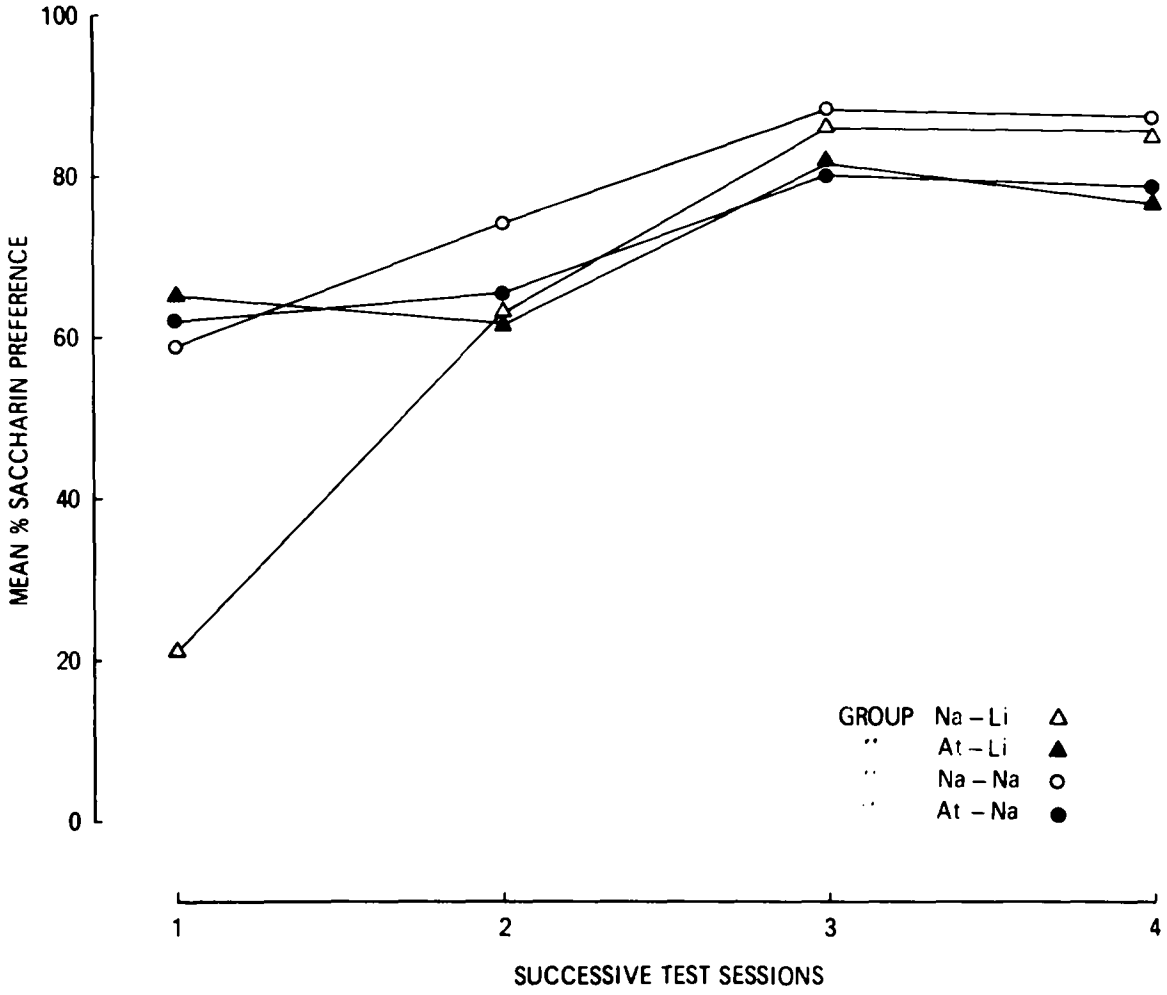

FIG. 1. Mean postconditioning saccharin preference scores in Experiment 1 for animals pretreated with atropine sulfate (At) or saline (Na) and later receiving lithium chloride (Li) or saline (Na).

RESULTS

Figure 1 shows the saccharin preferences in the four groups for each of the four test sessions. On Day 1, saccharin preferences in Group Na-Li were significantly lower than in Group Na-Na, $t(18) = 2.34$, $p<0.05$, showing that the procedure was effective in producing a conditioned aversion to saccharin. Group At-Li, which was pretreated with atropine sulfate, showed significantly less aversion than Group Na-Li, $t = 6.25$, $p<0.001$; in fact, saccharin preferences in Group At-Li were not significantly different from Group Na-Na or Group At-Na, and the latter two groups do not differ from each other ($ps>0.2$). On Days 2, 3, and 4, there were no significant differences among any of the groups. In this experiment, and in all the following experiments, total fluid consumption among the groups was comparable.

DISCUSSION

The results of this experiment, showing that intravascular injection of saccharin can be used in a CTA paradigm, replicate the results reported by Bradley and Mistretta [5]. However, it should be noted that, in comparison with conventional procedures, the degree of aversion is relatively weak, and it extinguishes very rapidly.

The most salient finding of this experiment is the dramatic blocking, by atropine, of the acquisition of CTA. Furthermore, the lack of elevated saccharin preference in Group At-Na (compared to Group Na-Na) shows that the elevation of saccharin preference observed in Group At-Li (compared to Group Na-Li) cannot be attributed to an effect of atropine on saccharin preference per se, but rather represents an effect on the conditioning of the aversion. These findings might be considered to be unexpected, in view of the apparent failure of a variety of procedures to block CTA [3, 38, 44].

The most immediately obvious interpretation of the effect of atropine on CTA is that, as has been suggested in the context of other learning tasks (e.g., [57]), atropine interferes with trace formation and/or short term memory (STM). While this interpretation is a plausible one, there are first alternative interpretations to be ruled out. One possible alternative interpretation is that the findings may reflect some artifact of the intravascular taste procedure. For example, since atropine blocks salivation and since saccharin is excreted, in part, through saliva [11], it is

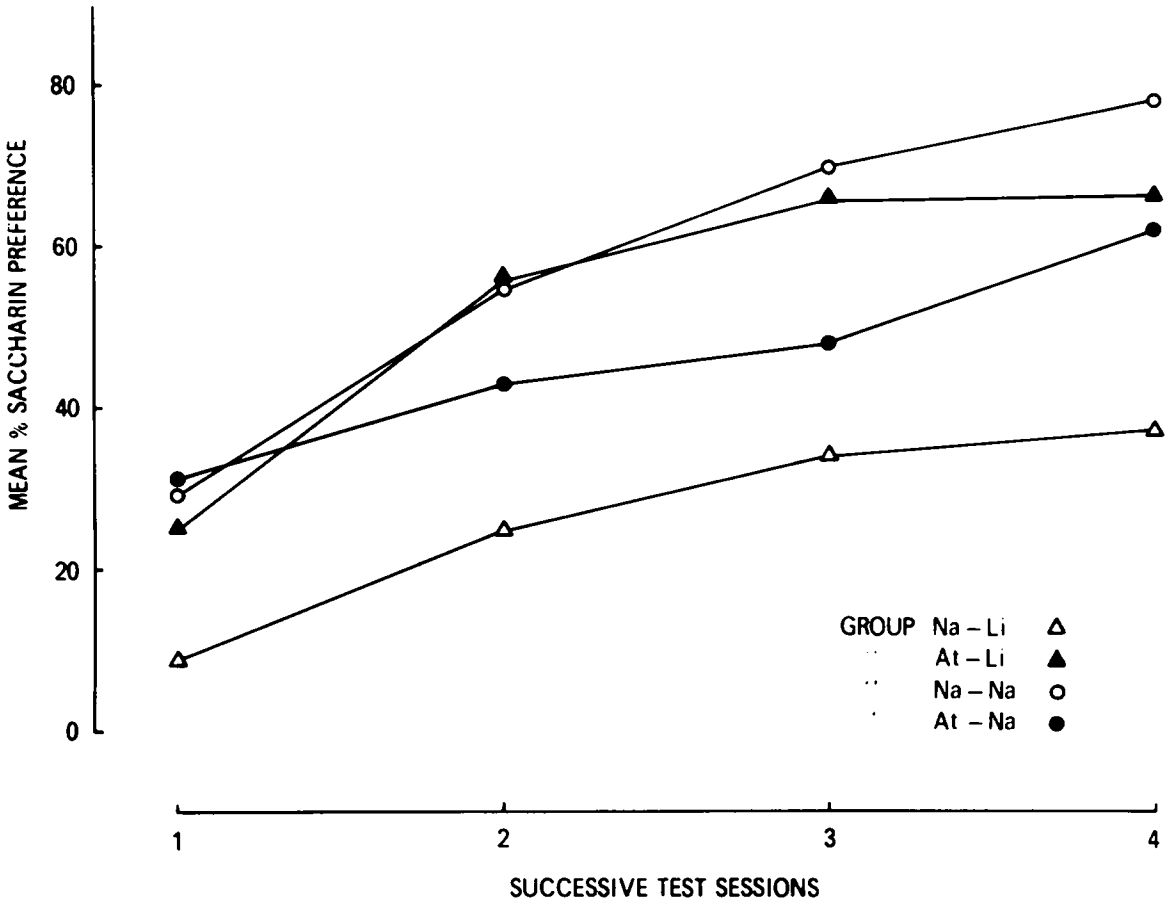

FIG. 2. Mean postconditioning saccharin preference scores in Experiment 2 for animals pretreated with atropine sulfate (At) or saline (Na) and later receiving lithium chloride (Li) or saline (Na).

possible that atropine is simply preventing the animal from tasting the saccharin in its own saliva. This problem is circumvented in the next experiment by the use of an intraoral infusion procedure. This procedure [15] allows for normal tasting of saccharin, yet still controls for possible atropine-induced suppression of drinking.

EXPERIMENT 2

The basic plan of this experiment was the same as that of Experiment 1, except that saccharin was introduced through the intraoral rather than IV route. This allows for tasting of saccharin even if salivation is blocked.

METHOD

Forty rats, of the same type as in Experiment 1, were used.

Each rat had a cheek cannula implanted under ether anesthesia (see [15] for details), and, following a five-day recovery period, was placed on a 30 min/day drinking schedule for four days.

Animals were then restrained in a blood pressure cuff (following Domjan and Wilson's procedure) for 10 min on each of the next three days, and 2 ml water, at the rate of 1 ml per min, was introduced into the oral cavity through the cheek cannula. The purpose of this procedure was to produce habituation to the restraint and to the method of drinking. This was followed by a single conditioning day on which each animal was randomly assigned to one of four groups: Na-Li, At-Li, Na-Na, At-Na. Each group was treated exactly as the corresponding group in Experiment 1, except that saccharin (0.2%) was introduced into the oral cavity (2 ml, 1 ml/min) rather than injected into the tail vein. Saccharin preference tests (30 min, 0.2% sodium saccharin vs tap water) were given on four consecutive days.

RESULTS

As Fig. 2 demonstrates, the saccharin aversion shown by Group Na-Li on Day 1 was essentially absent in Group At-Li, $t(18) = 2.75$, $p<0.02$. The difference between the two groups continued to be significant on Days 2 and 3; Day 2, $t(18) = 3.32$, $p<0.01$; Day 3, $t(18) = 2.30$, $p<0.05$, and bordered on significance on Day 4; $t(18) = 2.09$, $0.05<p<0.10$. Group At-Na started off at approximately the same point as Group Na-Na on Day 1, but saccharin preference in Group At-Na did not increase at as rapid a rate, and the difference between these groups reached significance on Day 3; $t(18) = 2.11$, $p<0.05$.

The major finding, as in Experiment 1, is that pretreatment with atropine blocked the acquisition of the taste aversion. As in the previous experiment, comparison of Group At-Na with Group Na-Na shows that atropine, by itself, does not increase saccharin preference. Furthermore,

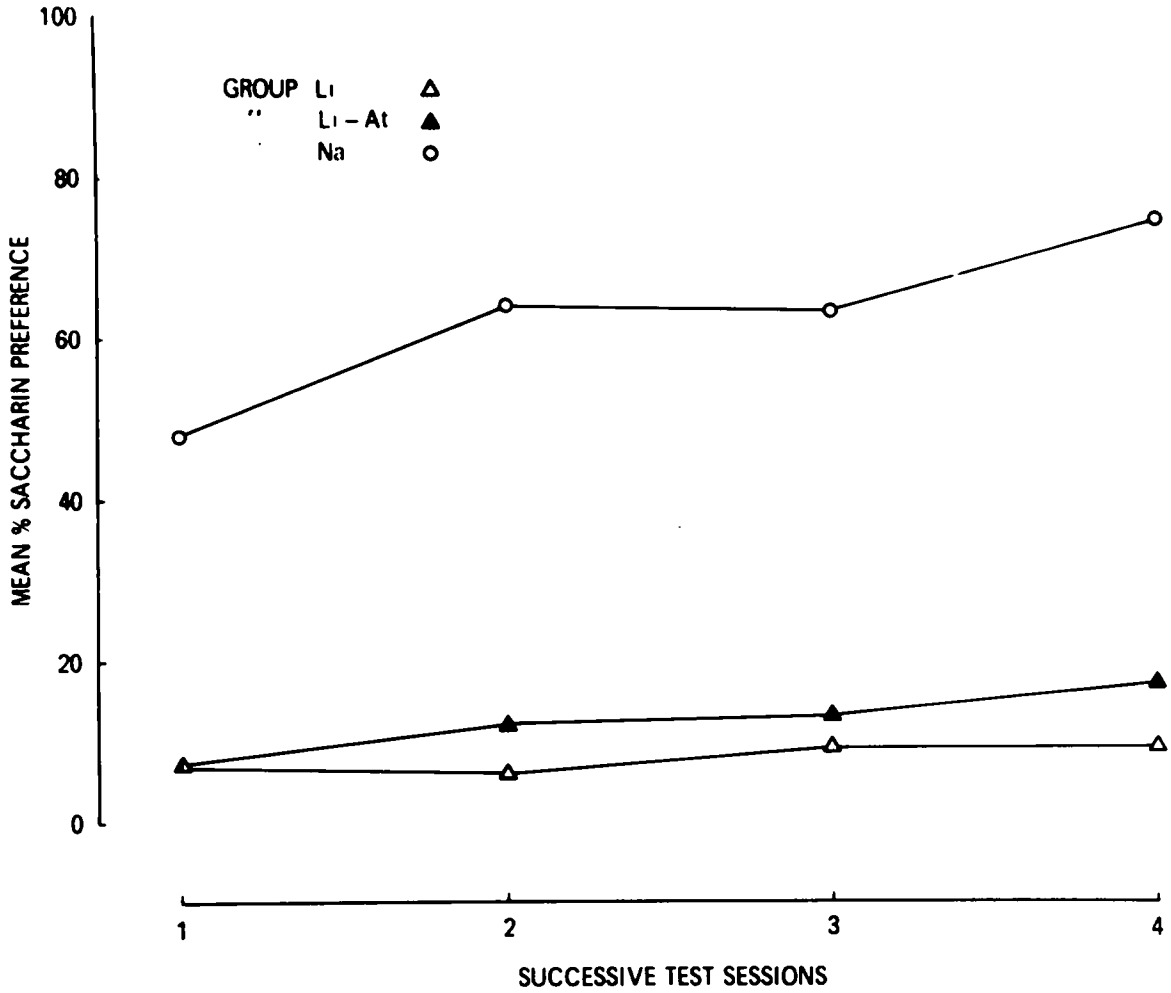

FIG. 3. Mean postconditioning saccharin preference scores in Experiment 3 for animals injected with lithium chloride (Li), lithium chloride and atropine sulfate (Li-At), or saline (Na).

this experiment shows that the effect of atropine on CTA is not due to some artifact of the tail vein injection procedure (such as interference with the excretion of saccharin through saliva).

EXPERIMENT 3

Although the results of the first two experiments may indeed be attributable to the effect of atropine on trace formation and/or STM, another alternative interpretation is that atropine may attenuate the effects of LiCl, the US in these experiments. The attenuation may be a specific antidote effect, or it may be a function of an anticholinergic interference with punishment [53], fear [43], or nociception [42]. This interpretation was tested in the following experiment by including atropine in the same injection with LiCl. If this interpretation is correct, atropine, which is distributed very rapidly in the body [25], should attenuate the effect of LiCl and thus the formation of the CTA.

METHOD

Twenty-seven rats, of the same type as in Experiment 1, were used.

The procedure was similar to Experiment 2, in that saccharin was introduced through the intraoral route, but in this experiment the animals did not receive any injection prior to the oral infusion of saccharin. Rather, they received a single injection after tasting saccharin. Depending on the experimental condition, this injection contained either LiCl (Group Li, N = 9), LiCl and atropine sulfate (Group Li-At, N = 9), or NaCl (Group Na, N = 9). Pre-experimental conditions, drug doses, and temporal parameters were the same as in Experiment 2. Two-bottle saccharin preference tests were run following conditioning, using the same procedure as in Experiment 1.

RESULTS

The results of this experiment, shown in Fig. 3, are in striking contrast to the results of Experiments 1 and 2. While the animals in Group Li did show the expected aversion to saccharin, this aversion was not significantly attenuated by atropine (Group Li vs Group Li-At, *t*-tests for all four days ns). Thus, atropine injected simultaneously with LiCl clearly does not block the acquisition of the CTA. This finding argues strongly against the view that the

interfering effect of atropine pretreatment on conditioning is attributable to a diminution of the effects of the US.

DISCUSSION

Experiments reported here up to this point have shown that atropine sulfate, injected shortly before tasting in a CTA paradigm, interferes with the acquisition of the aversion. The interference effect does not depend on a particular way of stimulating taste receptors (intravascular or intraoral), but does depend on whether atropine is injected before or after tasting.

Two major hypotheses may be offered to explain the above findings. One hypothesis is that the effect is due to some peripheral effect of atropine sulfate (a drug with both central and peripheral effects). Thus, atropine may interfere with the stimulation of taste receptors or with visceral afferents. A second hypothesis is that the observed results are due to central rather than peripheral effects of atropine. Thus, atropine may interfere with some aspect of the associative process, e.g., the formation and/or maintenance of the taste memory trace.

In order to decide whether these results are attributable to central or peripheral effects of atropine, two kinds of evidence would be useful: (a) examination of the central effects of atropine on CTA, without the confounding peripheral effects, (b) examination of the peripheral effects, unconfounded by central effects. The next two experiments provide both kinds of evidence. Experiment 4 considers the effect of a minute amount of atropine sulfate, injected into the cerebral ventricules. The dose of atropine used in this study (10 μg/rat) is in the lower part of the range typically employed in studies of intraventricular atropine (e.g., Khavari [28] used 5–50 μg/rat), and is unlikely to have significant peripheral effects. Experiment 5 tests the effect of atropine methylnitrate, the quaternary form of atropine, which has peripheral effects comparable to atropine sulfate, but which shows very little penetration of the blood-brain barrier [24].

EXPERIMENT 4

METHOD

Animals

Forty-four rats, of the same type as in Experiment 1, were used. The experiment was carried out in two independent replications: 21 rats were used in Replication 1, 23 in Replication 2.

Surgery

A double-walled stainless steel cannula (outer cannula: 21 ga, inner cannula: 30 ga) was implanted in the lateral cerebral ventricle of each rat, half the animals having the cannula on the right and half on the left side. The anesthetic was sodium pentobarbital (60 mg/kg, IP), with ether serving as supplemental anesthetic. Twenty-one of the animals (Replication 1) were also implanted with cheek cannulas [15] at the same time. At least one week was allowed as a recovery period.

Procedure

Following the period of recovery from surgery, the animals were placed on a 30 min/day drinking schedule for four days, and, in Replication 1, were habituated to the blood pressure cuff restraint for three additional days. In Replication 2, cheek cannulas were not implanted, and the animals were not restrained in the blood pressure cuff. Instead, for three days, animals were lightly restrained by hand, and were trained to drink from an eye dropper. Pilot research indicated that dropper trained animals will drink in this situation even if they are pretreated with atropine. On the conditioning day, which was the day immediately following the habituation days, each animal was assigned to one of four groups: Na-Li, At-Li, Na-Na, At-Na. Each group was treated as the corresponding group in Experiment 2, except that atropine sulfate (10 μg in 10 μl distilled water), or an equivalent volume of physiological saline, was injected into the lateral ventricle. In Replication 1, animals were given saccharin through the cheek cannula, whereas in Replication 2 the dropper technique was used. The conditioning day was followed by four saccharin preference tests, using the same procedure as in Experiment 1. Two-way (2 × 2) ANOVA were carried out on the preference data for each test session. These analyses were designed to assess the effect of atropine (Group At-Li vs Group Na-Li, Group At-Na vs Group Na-Na) as well as the effect of replications (Replication 1 vs Replication 2).

RESULTS

Figure 4 shows saccharin preference in the four groups in each of the four test sessions. (This figure combines the results from Replication 1 and Replication 2, since, although there were significant differences between replications, these differences did not interact with the atropine vs control differences that were of interest.)

As in the previous experiments, atropine significantly attenuated the amount of aversion acquired: Group At-Li vs Group Na-Li, Day 1, $F(1,18) = 5.74$, $p<0.05$; Day 2, $F(1,18) = 4.61$, $p<0.05$; Days 3 and 4 ns. Differences between replications were also significant: Day 1, $F(1,18) = 7.89$, $p<0.05$; Day 2, $F(1,18) = 6.00$, $p<0.05$; Days 3 and 4 ns, but, as noted above, the Group × Replication interactions did not approach significance (all $ps>0.3$).

Examination of the Group At-Na vs Group Na-Na data in Fig. 4 shows, again, that atropine does not by itself elevate saccharin preference; in fact, the trend (ns) is in the opposite direction. For Groups At-Na and Na-Na, as well, there were significant differences between replications: Day 1, $F(1,18) = 4.43$, $p<0.05$; Day 2, ns; Day 3, $F(1,18) = 14.46$, $p = 0.001$; Day 4, $F(1,18) = 13.77$, $p<0.01$, but all the Group × Replication interactions were nonsignificant, $ps>0.2$.

EXPERIMENT 5

The previous experiments have shown that an IP injection of atropine sulfate (which has both central and peripheral effects) and an intraventricular injection of the same drug (in a small enough dose to prevent the possibility of significant peripheral effects) both interfere with CTA acquisition. These results argue for a central interpretation of the effects of atropine on CTA. The fact that a very small dose of atropine can have a powerful interfering effect (Experiment 4) also argues against the view that the effects observed in Experiments 1 and 2 are in artifact of the magnitude of the atropine dose used in those studies.

Another sort of evidence that relates to the central vs peripheral issue deals with the effects of a form of atropine

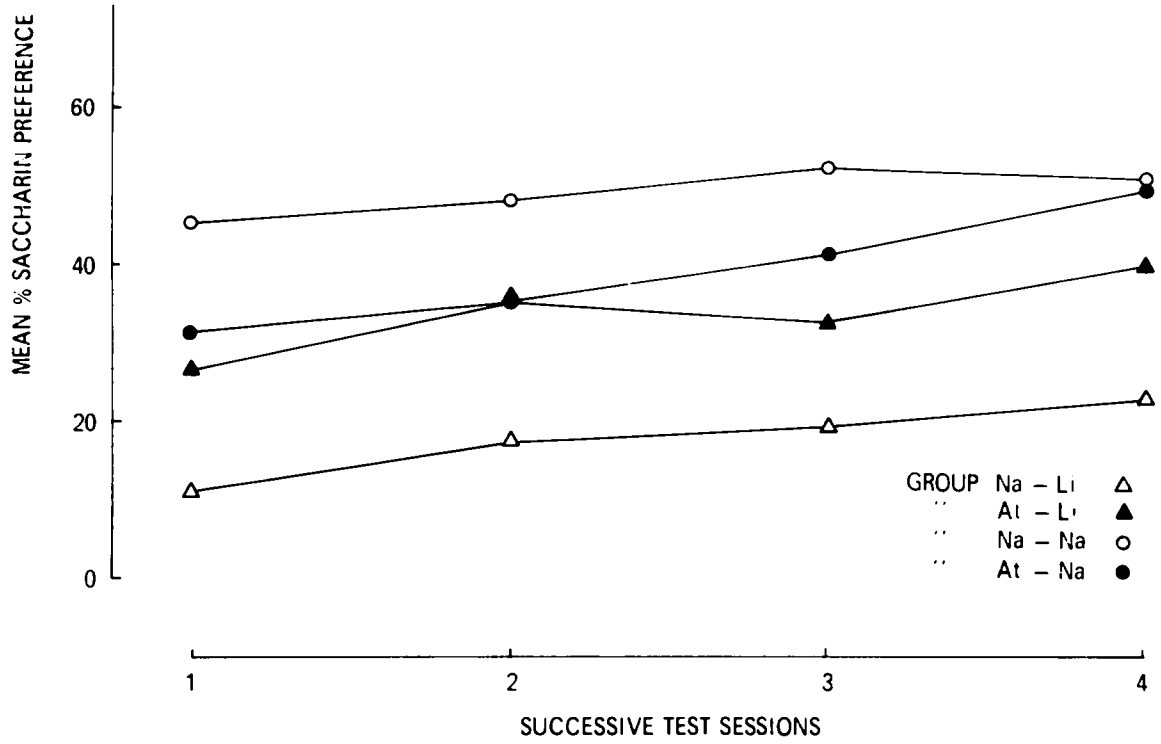

FIG. 4. Mean postconditioning saccharin preference scores in Experiment 4 for animals pretreated with intraventricular atropine (At) or saline (Na) and later receiving lithium chloride (Li) or saline (Na).

which is chiefly peripheral in its locus of action, i.e., atropine methylnitrate. This is examined in the present experiment.

METHOD

Sixty-eight rats, of the same type as in Experiment 1, were used.

The procedure of this experiment was substantially the same as Experiment 2, except that (a) saccharin was presented through the dropper method (see Experiment 4), (b) atropine methylnitrate rather than atropine sulfate was used, and (c) the experiment comprised two independent subexperiments; one subexperiment (28 rats) was conducted with the atropine methylnitrate dose set at 100 mg/kg (same as the atropine sulfate dose in Experiments 1, 2 and 3), whereas in the other subexperiment (40 rats) the atropine methylnitrate dose was 50 mg/kg. The lower-dose subexperiment was carried out because it was thought that at 100 mg/kg some atropine methylnitrate might have reached the brain.

RESULTS AND DISCUSSION

Figures 5 and 6 show the results of Subexperiment A (100 mg/kg) and Subexperiment B (50 mg/kg), respectively. In both subexperiments, atropine methylnitrate, unlike atropine sulfate in the previous experiments, generally did not interfere with CTA acquisition. Thus, in Subexperiment A, saccharin preferences in Group Amn-Li were not significantly different from Group Na–Li on Days, 1, 3, and 4, and just reached significance on Day 2, $t = 2.27$, $p<0.05$. In Subexperiment B, none of the Group Amn-Li vs Group Na-Li differences approached significance.

In some of the previous experiments, Group At-Na tended to show aversion compared to Group Na-Na. This was confirmed in the present experiment, using atropine methylnitrate. Thus, in both subexperiments, and in all four test sessions, the Group Amn-Na vs Group Na-Na comparisons are significant (all $ps<0.05$). The aversion seen in Group Amn-Na is not unexpected, in view of the close temporal contiguity between the atropine injection and saccharin tasting. While this contiguity technically represents backward conditioning, others (e.g., [4]) have reported that this can be effective in a CTA paradigm.

The results of this experiment, showing that atropine in its quaternary form does not interfere with CTA acquisition, support the view that the previously-observed interfering effect of atropine sulfate is due to a central rather than a peripheral mechanism.

GENERAL DISCUSSION

There have been at least six published attempts to influence CTAs using anticholinergic drugs [17, 23, 24, 30, 50, 51]. Kral [30] injected scopolamine during the CS-US interval, and found that it did not interfere with the acquisition of the aversion. These findings are consistent with the results of Experiment 3 in the present study. Gadusek and Kalat [17] injected scopolamine just before the test sessions, and found that it did not influence the degree of conditioned aversion. Their experiment, which looks at retention rather than at acquisition, does not relate directly to the present study. Smith and Morris [51] did examine the effects of atropine sulfate on CTA acquisition

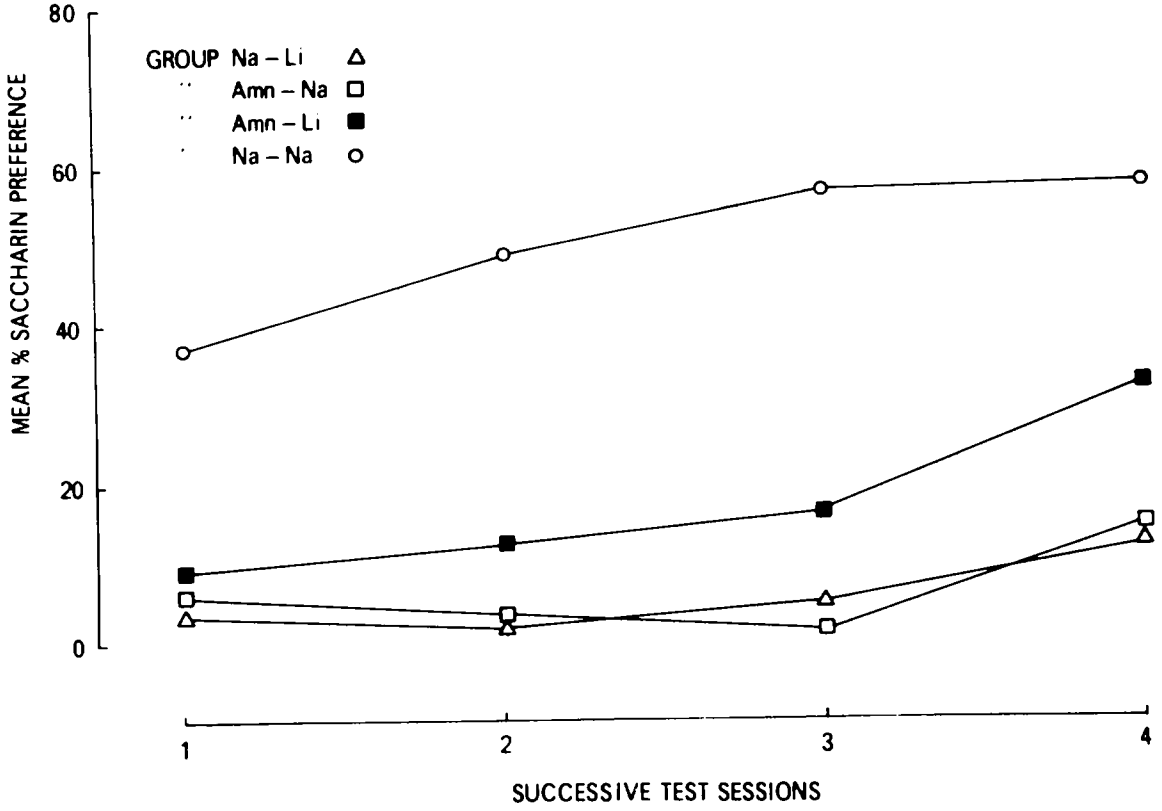

FIG. 5. Mean postconditioning saccharin preference scores in Experiment 5, Subexperiment A, for animals pretreated with atropine methylnitrate (100 mg/kg; Amn) or saline (Na) and later receiving lithium chloride (Li) or saline.

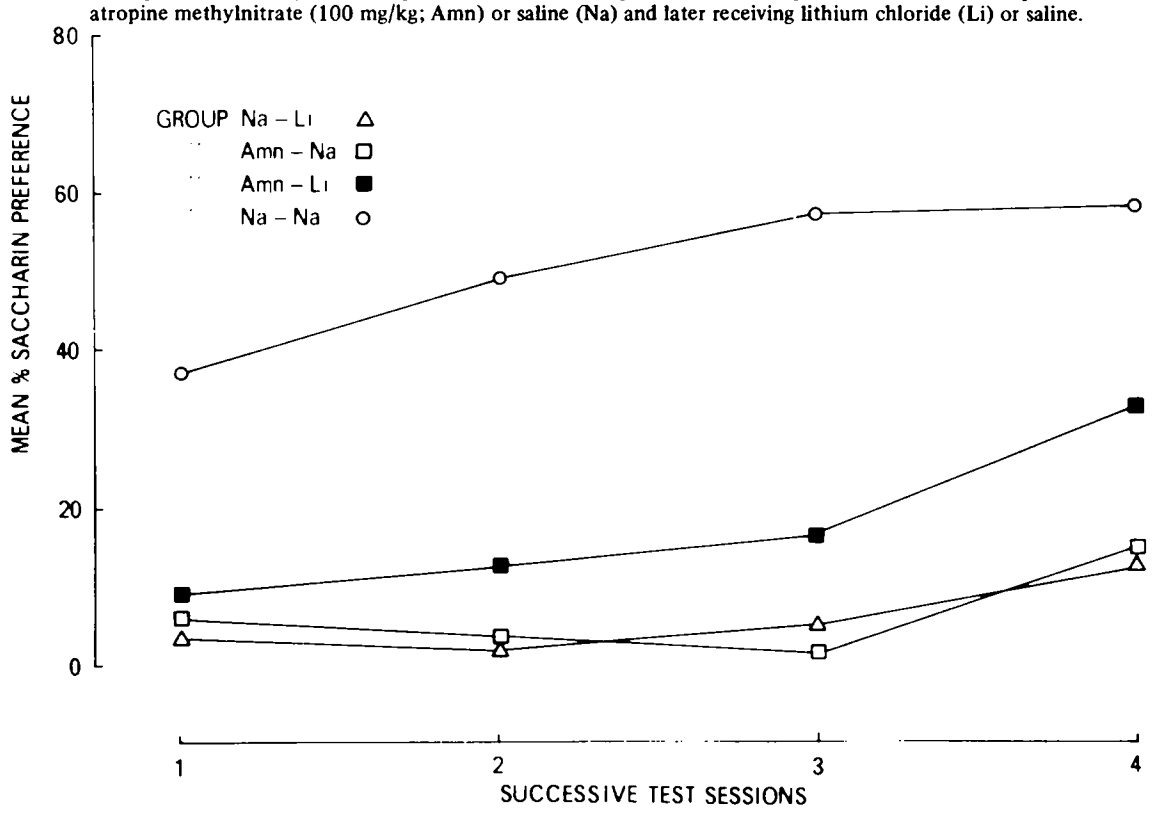

FIG. 6. Mean postconditioning saccharin preference scores in Experiment 5, Subexperiment B, for animals pretreated with atropine methylnitrate (50 mg/kg; Amn) or saline (Na) and later receiving lithium chloride (Li) or saline.

and found no significant effect. The present study research differs from their study in a number of methodological aspects (use of LiCl injection rather than X-irradiation, repeated 30-min saccharin preference tests rather than a single 48-hr one, different doses of atropine), and perhaps most significantly, in the use of a larger number of animals. The most interesting of the previous attempts to assess the effects of anticholinergics on CTA are a pair of studies by Gould and Yatvin [23,24]. Using X-irradiation as the US, they found that atropine sulfate (but not various other drugs, including atropine methylnitrate) blocked the acquisition of conditioned aversion to saccharin. They also found that atropine sulfate injected just before testing had a similar blocking effect, suggesting, in contrast to Gadusek and Kalat's findings [17], that anticholinergics may affect retrieval processes as well.

Experiments reported here have shown that atropine sulfate injected before tasting in a CTA paradigm does interfere with the acquisition of the aversion, thus confirming the findings of Gould and Yatvin [23,24]. This interference effect is not limited to a particular taste presentation method (Experiments 1 and 2) and does not represent attenuation of the effects of the US (Experiment 3). Further experiments have shown that this effect can be obtained with atropine administration that is restricted to the CNS (Experiment 4), but not with a form of atropine that is primarily peripheral in its locus of action (Experiment 5).

Before considering the hypothesis that the results are due to interference with cholinergic associative mechanisms, two alternative hypotheses should be considered. The first hypothesis is that the results reflect state-dependent or dissociated learning [21,39]. To the extent that Group At-Li animals in this study were conditioned under the influence of a drug and were tested in a no-drug state, whereas Group Na-Li animals were not under drug influence either in conditioning or testing, the design of the present study incorporates two of the cells of the classic 2 × 2 state-dependent learning design.

It is difficult to assess the validity of the state-dependent learning hypothesis in the present context. In addition to the methodological problems involved in any test of state-dependent learning, [40,46], a special problem derives from the effect of atropine on drinking. Saccharin preference tests would have to be given while the animals are under the influence of atropine, and atropine administration would probably depress all drinking to a very low level [52,55]. It should be noted, however, that although the data presented here cannot lead to outright rejection of this hypothesis, anticholinergics generally produce only moderate or inconsistent dissociative effects [13,40], and thus the viability of the dissociation hypothesis in this context is at least questionable.

A second attempt to account for these results is the hypothesis that they represent the effects of drug preexposure per se. A considerable amount of evidence (e.g., [7, 10, 36]) now exists showing that previous experience with the drug which is to be the US (or, in some cases, with other drugs [18]) results in impaired CTA acquisition. A number of hypotheses (physiological, pharmacological, and psychological) have in turn been advanced to account for these findings. The question is whether the results reported here represent another instance of this more general phenomenon. A comparison of the methods used in the drug-preexposure studies with those used in the present study, as well as a closer examination of the present results, suggests that the two phenomena are, in fact, different. The drug preexposure studies have typically used the same drug for preexposure as for conditioning (e.g., [32], but see [6]), repeated drug administration (e.g., [2]), and, furthermore, studies which varied the number of drug preexposures (e.g., [22]) have found that the attenuation of the aversion varies as a direct function of the number of preexposures. These studies also involve a considerable interval (24 hr or more) between preexposure and conditioning. The present research, in contrast, used very different drugs for pretreatment and conditioning, a single pretreatment, and the pretreatment – conditioning interval was 5 min. More importantly, the failure of atropine methylnitrate to interfere with the formation of the aversion is difficult to account for by the hypothesis that previous drug experience is the crucial factor. A further possible test of this hypothesis would be to inject atropine sulfate or atropine methylnitrate 24 hr before conditioning.

The most intriguing interpretation of the results reported here is that they represent interference with cholinergic mechanisms for learning. There is now a great deal of evidence that suggests involvement of the cholinergic system in various phases and in various kinds of learning [14,33]. Atropine sulfate has been found to interfere with the acquisition of simple habituation (e.g., [41]), classical eyeblink conditioning (e.g., [16]), passive avoidance (e.g., [9]), active avoidance (e.g., [35]), and maze learning (e.g., [58]). Comparison of the effects of atropine sulfate and atropine methylnitrate [16] has shown that central rather than peripheral mechanisms are involved. There is a striking similarity between this set of results and the results of the present research. A potentially useful working hypothesis is that CTA, like many other types of learning, involves a cholinergic mechanism.

In addition to accounting for the present results, this hypothesis allows us to interpret the recent report by Danguir and Nicolaidis [12], showing that paradoxical sleep deprivation interferes with CTA acquisition. There is much evidence [27] showing paradoxical sleep is cholinergically mediated; in fact, atropine has been shown to suppress paradoxical sleep [29]. It is possible, then, that the results of Danguir and Nicolaidis, like those of the present study, represent interference with cholinergic mechanisms for CTA.

Although the present research has yielded evidence suggesting cholinergic mediation of CTA, this hypothesis cannot, at this stage, be regarded as more than a tentative one. Each drug has a variety of effects; specifically, atropine, in addition to its anticholinergic effect, is known to influence other neurochemical systems, e.g., dopamine [1]. Thus, further research on neurochemical mechanisms of CTA might consider the use of a variety of drugs that affect the cholinergic system, and application of these drugs to specific brain loci (e.g., the hippocampus) that are thought to be involved in cholinergic modulation of learning [49, 54, 56].

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