Postconditioning scopolamine administration selectively influences generalized auditory-cue fear conditioning

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Under some conditions, a postconditioning injection of scopolamine hydrobromide reduces contextual fear conditioning but has no effect on auditory-cue fear conditioning. This finding is consistent with the idea that contextual fear conditioning and auditory-cue fear conditioning are mediated by different processes. Recently, however, we (Rudy & Pugh, in press) have reported that generalized auditory-cue fear conditioning is sensitive to many of the same manipulations that affect contextual fear conditioning. We now report that a posttrial injection of scopolamine has no effect on conditioned fear to the auditory cue paired with shock but does result in rats' showing more generalized auditory-cue fear. The effect of scopolamine on generalized auditory-cue fear, however, was eliminated by preexposing the rats to the auditory cue prior to conditioning. These results suggest that central cholinergic systems contribute to consolidation of a specific memory representation of an auditory experience. They also support the view that auditory-cue fear conditioning depends on two independent processes—one that constructs a representation of the stimulus, and another that associates the representation with the aversive outcome.

Rats that experience an auditory cue paired with shock subsequently display a conditioned defensive freezing response to both the auditory cue and to the static context in which the shock has occurred. Several variables, however, have been found to differentially affect these two forms of fear conditioning: (1) damage to the hippocampal formation impairs contextual but not auditory-cue fear conditioning (see, e.g., Kim & Fanselow, 1992; Phillips & LeDoux, 1992, 1994; Selden, Everitt, Jarrard, & Robbins, 1991), (2) contextual fear conditioning develops later in development than does auditory-cue fear conditioning (Rudy, 1993, 1994; Rudy & Morledge, 1994), (3) DBA and C57 mice display equivalent levels of auditory-cue fear conditioning, but DBAs show less contextual fear conditioning than do C57s (Paylor, Tracy, Wehner, & Rudy, 1994), and (4) postconditioning isolation impairs contextual fear conditioning but has no effect on auditory-cue fear conditioning (Rudy, 1996a). These observations suggest that contextual and auditory-cue fear conditioning may involve different memory systems. For example, it has been suggested that contextual but not auditory-cue fear conditioning depends on the hippocampal formation (Kim & Fanselow, 1992; Phillips & LeDoux, 1992, 1994).

Recently, however, we (Rudy & Pugh, in press) have found that whether or not a difference between contextual and auditory-cue fear conditioning is observed depends on

how auditory-cue fear conditioning is measured. In most comparisons of contextual and auditory-cue fear conditioning, fear to the auditory cue is assessed by measuring freezing to the auditory cue that was paired with shock, what we term *direct* auditory-cue fear conditioning. However, one can also compare contextual fear conditioning with both direct and *generalized* auditory-cue fear conditioning. In a generalization test, the rat is tested for fear of the tone frequency (e.g., 2976 Hz) that was paired with shock versus other similar tone frequencies (e.g., 988 Hz or 741 Hz). Such a generalization test is valuable, because it provides a tool with which to assess the specificity of the stimulus representation that is controlling behavior. Thus, when the rat responds less to a 741-Hz test tone than to a 2976-Hz training tone, one can infer that the rat has acquired a relatively specific representation of the training stimulus in comparison with when it responds equivalently to both stimuli.

We have found that variables such as age, retention interval, and postconditioning isolation had no effect on direct auditory-cue fear conditioning but did influence both contextual and generalized auditory-cue fear conditioning. For example, isolating rats immediately after the conditioning episode disrupted contextual but not direct auditory-cue fear conditioning (Rudy & Pugh, in press). This treatment also increased the rats' generalized auditory-cue fear (i.e., produced a flatter generalization gradient). Control rats displayed more freezing to the training stimulus than to the test stimulus, but isolated rats responded equally to both the training and the test stimulus. In general, Rudy and Pugh (in press) found that variables that reduced contextual fear conditioning increased generalized auditory-cue fear conditioning.

This research was supported by National Institute of Mental Health Grant RO1-MH49407. Correspondence concerning this article should be addressed to J. W. Rudy, Department of Psychology, CB 345, University of Colorado, Boulder, CO 80309-0345 (e-mail: jrudy@clipr.colorado.edu).

It has been suggested that both contextual (Young, Boheneck, & Fanselow, 1994; Rudy, 1996a) and auditory-cue fear conditioning (Rudy & Pugh, in press) depend on a set of dissociable processes. One set constructs a representation of the stimulus, and another associates this representation with the aversive event. We suggested that the variables that affect both contextual and generalized auditory-cue fear conditioning exert their influence on the processes that construct a representation of the stimulus (Rudy & Pugh, in press). Strong support for this hypothesis comes from the effect of stimulus preexposure on fear conditioning. It is well established that context preexposure can facilitate contextual fear conditioning in a variety of situations in which it would otherwise be depressed (Fanselow, 1990; Paylor et al., 1994; Rudy, 1996a; Rudy & Morledge, 1994; Young et al., 1994). For example, impaired contextual fear conditioning produced by damage to the hippocampus (Young et al., 1994) or by postconditioning isolation (Rudy, 1994) can be prevented by preexposing the rat to the conditioning context before hippocampal formation damage or isolation. Rudy and Pugh (in press) found that preexposure to the auditory cue also prevented the flattening of the generalization gradient produced by isolation. Presumably, preexposure eliminates the effects of hippocampal formation damage and isolation because it allows the rat to construct a representation of the stimulus that can later be activated and associated with shock.

Recently, it has been shown that under some circumstances, a posttrial injection of scopolamine hydrobromide, a muscarinic cholinergic receptor antagonist, impairs contextual fear conditioning but has no effect on auditory-cue fear conditioning (Rudy, 1996b, Experiment 5). For example, Rudy reported this result when rats were given three conditioning trials. The effect of scopolamine on generalized auditory-cue fear conditioning, however, has not been examined. Thus, the purpose of the present experiments was to determine whether central cholinergic systems contribute to the processes that construct a specific representation of the auditory CS.

GENERAL METHOD

Subjects

Subjects were male and female Long-Evans-derived hooded rat pups born to animals obtained from Charles Rivers Breeders and bred at the University of Colorado. They had free access to food and water and were maintained on a 12:12-h light:dark cycle. Checks for births were made each morning before 10 a.m., and litters were culled to 9 pups 1 day after birth. Pups were weaned when 21 days old.

Apparatus

Training took place in two identical Igloo ice chests (54 × 30 × 27 cm) with white interiors. A speaker and a 24-V dc light bulb were mounted on the ceiling of each chest. A clear plastic window (30 × 18 cm) was cut in the door of each chest so that the subjects could be observed. The conditioning chambers (26 × 21 × 24 cm) placed inside the chests had clear plastic sides and window screen tops. A 1-sec, .4-mA shock US was delivered through a removable floor of stainless steel rods 1.5 mm in diameter and spaced 10 cm center to center. Each rod was wired to a shock generator and

scrambler (Lafayette Model 82404SS), and the conditioning chambers rested on the steel rods. The rods and floor of each chest were cleaned with water before each rat was trained or tested. Auditory tone frequencies of 2976 Hz and 741 Hz were presented at 74 dB as measured in the test chamber by a Triplet sound level meter (Model 370) set on the C scale.

Procedure

In all experiments, rats were given a single conditioning session consisting of four trials. On each trial a 20-sec presentation of the 2976-Hz auditory cue terminated with the onset of the shock. The first trial occurred 120 sec after the rat was placed into the conditioning chamber. The intertrial interval was 120 sec, and the rat was removed from the conditioning chamber 30 sec after the final shock presentation. Thus, a conditioning session lasted approximately 590 sec. Immediately after being removed from the conditioning chambers, the rats were given a subcutaneous injection of saline, scopolamine hydrobromide (1.0 mg/kg), or methylscopolamine (1.0 mg/kg). The rats receiving saline and those receiving scopolamine were separated into two different cages after injection. Both cages contained soiled bedding from their home cages.

Thirty minutes before conditioned freezing to the auditory cue was assessed, the rats were tested for contextual fear conditioning. During the contextual fear test, the rats were placed into the original training context and observed for 5 min. According to a time sampling procedure, every 10 sec each rat was judged as either freezing or active at the instant the sample was taken. Freezing was defined as the absence of visible movement except for respiration. For these experiments, the correlation between trained observers with one blind to the experimental treatment was .997.

Conditioned freezing to the auditory cue was assessed by placing the rats into novel conditioning chambers. Rectangular conditioning chambers (26 × 21 × 10 cm) were altered by connecting two diagonal corners with a clear plastic panel (34 × 10 cm) creating a triangular chamber. The rod floors were removed so that the conditioning chambers rested on a clear plastic floor, and a 7-W 120-V ac clear red light bulb illuminated the chests. During the auditory cue test, the rats were scored for 6 min. The auditory CS was absent for the first 3 min (pre-CS) and was presented during the second 3 min (CS period). To obtain a score for each rat, the level of responding during the pre-CS period was subtracted from their responding during the CS period. This treatment of the data helped to ensure that each rat's score reflected the amount of freezing elicited by the auditory cue and was uncontaminated by any generalized contextual fear.

EXPERIMENTS 1A–1B

Our previous work (Rudy & Pugh, in press) revealed that normal rats show more conditioned freezing to the 2976-Hz training tone paired with shock than to a 741-Hz test tone. We expected to replicate this result in rats injected with saline. If central cholinergic systems contribute to the construction of the detailed representation of the auditory stimulus, the rats that received a posttrial injection of scopolamine hydrobromide, which penetrates into the central nervous system, should display more generalized fear to the 741-Hz test tone than should the rats injected with saline. However, the generalization gradient for rats that received a posttrial injection of methylscopolamine, which is not thought to penetrate into the CNS (Feldman & Quinzer, 1984) should not differ from saline-treated controls. In Experiment 1A, saline-injected control rats were compared with rats injected with scopolamine hydrobromide. In Experiment 1B, saline-injected

control rats were compared with rats injected with methylscopolamine.

Method

In Experiment 1A, eight litters of rats were conditioned to a 2976-Hz tone by pairing it with a shock unconditioned stimulus (US). Immediately following conditioning, half of the rats received an injection of scopolamine hydrobromide and half received an injection of a saline vehicle. The scopolamine- and saline-treated rats were separated into two different cages after conditioning. Twenty-four hours later, all animals were tested for contextual fear conditioning. Thirty minutes later, half of the rats in each condition were tested with the 2976-Hz tone, and the other half were tested with the 741-Hz tone.

Experiment 1B was conducted exactly as Experiment 1A, with the exception that rats were injected with either methylscopolamine (1.0 mg/kg) or saline after conditioning rather than scopolamine hydrobromide or saline.

Results

Experiment 1A: The effects of scopolamine hydrobromide. The top panel of Figure 1A shows that there was no difference between saline- and scopolamine-treated rats during the context test ($F < 1$). The results of the auditory-cue test are presented in the bottom panel. Note that rats injected with saline displayed more freezing to the 2976-Hz training tone than to the 741-Hz test tone. In contrast, rats treated with scopolamine hydrobromide showed more generalized conditioned fear than did rats treated with saline; scopolamine-treated rats displayed as much freezing to the 741-Hz test tone as they did to

the 2976-Hz training tone. They also displayed more freezing to the 741-Hz test tone than the saline treated rats did. This description of the data was confirmed by an analysis of variance (ANOVA) that revealed a significant drug $\times$ frequency interaction [$F(1,28) = 4.4, p < .05$]. An analysis of the simple effects showed that drug treatment was significant at 741-Hz [$F(1,28) = 5.6, p < .05$], but not at 2976 Hz ($F < 1$), and that frequency was significant for saline-treated rats [$F(1,28) = 6.9, p < .01$], but not for scopolamine-treated rats.

Experiment 1B: The effects of methylscopolamine. The top panel of Figure 1B shows that methylscopolamine had no effect on contextual fear conditioning. It also had no effect on generalized auditory-cue fear conditioning (Figure 1B, bottom panel). Both saline-injected control rats and rats injected with methylscopolamine displayed more freezing to the 2976-Hz training tone than they did to the 741-Hz test tone. An ANOVA indicated that there was a significant effect of tone frequency [$F(1,23) = 6.1, p < .02$], with rats tested to the 2976-Hz tone showing significantly more auditory-cue fear conditioning than rats tested to the 741-Hz test tone. There was no effect of drug on auditory-cue fear conditioning ($F < 1$) and no drug $\times$ test frequency interaction ($F < 1$).

Discussion

Blocking the cholinergic system with a central muscarinic receptor antagonist flattened the relatively steep generalization gradient observed in normal rats. In contrast,

Figure 1. (A) Mean percentage of freezing during the context test (top panel) and auditory-cue test (bottom panel) of Experiment 1A. (B) Mean percentage of freezing during the context test (top panel) and auditory-cue test (bottom panel) of Experiment 1B. Bars represent standard errors.

blocking cholinergic systems with an antagonist that does not directly influence central cholinergic function had no effect on generalized auditory-cue fear conditioning. These results support the hypothesis that central cholinergic systems contribute to the construction of the specific representation of the auditory stimulus that controls behavior.

EXPERIMENT 2

The results of the first experiments are consistent with the hypothesis that cholinergic systems contribute to the processes that construct a representation of the auditory cue paired with shock. If this hypothesis is true, one should be able to eliminate the effect of scopolamine by *preexposing* the rats to the auditory cue 24 h prior to the conditioning trials. Since preexposed rats would presumably have a representation of the tone available at the time of conditioning, the stimulus construction process should not be vulnerable to the effects of scopolamine. This hypothesis was evaluated in Experiment 2.

Method

Seven litters of 35-day-old rats were used as subjects. Twenty-four hours before conditioning, 4 rats from each litter were preexposed to the 2976-Hz tone in the training context, and 4 rats from each litter were preexposed to the training context without the tone. During tone preexposure, the rats were placed into the conditioning chamber where they received four 20-sec presentations of the tone. The first presentation occurred 120 sec after the rat was placed into the chamber, and the intertrial interval was 120 sec. The rats were removed 30 sec after the last tone presentation. Thus, the preexposure session lasted approximately 590 sec. The rats that were preexposed only to the context were placed into the conditioning chamber for 590 sec. The next day, all animals were conditioned to the 2976-Hz tone and then immediately injected with scopolamine hydrobromide (1 mg/kg) before being divided and returned to the home cages. The context and auditory-cue fear conditioning tests were administered 24 h after the conditioning session. Half of the rats that were preexposed to the tone were tested to the 2976-Hz tone, and the other half were tested to the 741-Hz tone. Likewise, half of the rats preexposed only to the context were tested to the 2976-Hz tone, and the other half were tested to the 741-Hz tone.

Results

As can be seen in Figure 2 (top), the two preexposure groups did not differ in the amount of contextual fear conditioning ($F < 1$). Figure 2 (bottom) shows that the rats preexposed to only the context showed more generalized auditory-cue fear conditioning than did the rats preexposed to the context and the tone. While the two groups did not differ in the amount of freezing to the 2976-Hz training tone, the rats that were preexposed to the tone showed less freezing to the 741-Hz test tone than to the 2976-Hz training tone. They also showed less auditory-cue fear conditioning to the 741-Hz tone than did the rats preexposed to only the context. The rats that were only preexposed to the context showed equivalent amounts of auditory-cue fear conditioning to both the 2976-Hz training tone and the 741-Hz test tone. A preexposure $\times$ tone frequency ANOVA revealed a significant main effect of

Figure 2. Mean percentage of freezing during the context test (top panel) and auditory-cue test (bottom panel) of Experiment 2. Bars represent standard errors.

frequency [$F(1,24) = 58.5, p < .05$] and a significant main effect of preexposure [$F(1,24) = 56.2, p < .05$]. More importantly, however, the ANOVA revealed a significant tone frequency $\times$ preexposure interaction [$F(1,24) = 4.6, p < .05$]. An analysis of the simple effects indicated that frequency was significant for rats preexposed to the tone, with these rats showing more freezing to the 2976-Hz tone than to the 741-Hz tone [$F(1,24) = 8.5, p < .01$]. However, frequency was not significant for rats preexposed only to the context ($F < 1$). The simple effects also showed that preexposure was associated with a significant difference in responding to the 741-Hz tone. Rats preexposed to the tone showed significantly less responding to the 741-Hz tone than did the rats preexposed only to the context [$F(1,24) = 8.5, p < .01$].

Discussion

These results support the hypothesis that scopolamine has its effect on the auditory generalization gradient by disrupting the posttrial processes that establish a specific representation of the auditory cue.

Stimulus preexposure often produces an effect called latent inhibition; it reduces the rate at which the preexposed stimulus acquires conditioned properties (see Lubow, 1973, for a review). However, no evidence of this effect was observed in the present experiment, probably because only a few (4) presentations of the stimulus were administered during the preexposure phase. Using similar fear conditioning procedures, Rudy (1994) did find a latent inhibition effect, but in those experiments, 20 presentations of the acoustic stimulus were given during the

preexposure phase, and the rats were tested after only a single conditioning trial. It is also worth noting that, using a taste aversion paradigm, Bennett, Wills, Wells, and Mackintosh (1994) found that preexposure can reduce generalized conditioning in normal rats.

GENERAL DISCUSSION

We have proposed that auditory-cue fear conditioning depends on two dissociable learning processes (Rudy & Pugh, in press). One process constructs a representation of the auditory cue, while the other associates this representation with the aversive event. These experiments provide evidence that support this view. First, scopolamine had no effect on direct auditory-cue fear conditioning, implying that the basic associative mechanisms were not affected by the drug. Second, scopolamine flattened the generalization gradient, implying that the stimulus construction processes are sensitive to scopolamine. Third, preexposure to the auditory-cue eliminated the effects of scopolamine on generalized auditory-cue fear conditioning, confirming that scopolamine influences the stimulus construction process.

Another implication of these results is that the construction of a representation of the auditory stimulus requires a consolidation period that lasts for several minutes at least. One can make this inference because scopolamine was not administered until after the conditioning session was over, and it is likely that the scopolamine required several minutes to exert its effect.

The conclusions above have considerable generality. Recall that Rudy and Pugh (in press) found that a postconditioning isolation treatment did not affect direct auditory-cue fear conditioning but did flatten the generalization gradient associated with the auditory cue. This effect of isolation was eliminated by preexposure to the auditory cue. Thus, two very different postconditioning treatments, scopolamine and isolation, produced the same pattern of results.

Previously, we (Rudy & Pugh, in press) had found that several variables (e.g., postconditioning isolation and retention interval) that increased the rat's generalized fear to the auditory cue also impaired contextual fear conditioning, suggesting that similar processes contribute to contextual fear conditioning and to generalized auditory-cue conditioning. In the present experiments, however, the postconditioning effect of scopolamine only increased generalized auditory-cue fear conditioning. It had no effect on contextual fear conditioning. This result was unexpected, because Rudy (1996b) previously reported that a posttrial injection of scopolamine impaired contextual fear conditioning. We have no definitive explanation of this failure to replicate Rudy's (1996b) result. The only procedural difference was that in the present experiments rats received four pairings of the tone and shock, whereas Rudy administered only three pairings in his experiments. We might speculate that the effect of scopolamine on contextual fear conditioning is more sensitive to the number of

trials than is its effect on generalized auditory-cue fear conditioning. Admittedly, one would not expect that a difference of one trial would make such a difference. Yet, Anagnostaras, Maren, and Fanselow (1995) also failed to find an effect of the posttrial scopolamine procedure when their rats received 5 trials. In addition, several researchers have found that the impairing effects of a cholinergic blockade can be overcome by increasing the number of conditioning trials (e.g., Prado-Alcala & Cobos-Zapiain, 1977; Prado-Alcala, Kaufmann, & Moscona, 1980). So our speculation may have some merit.

Nevertheless, one could argue that the present result that scopolamine affected generalized auditory-cue fear but not contextual fear is evidence against the hypothesis that these two phenomena depend on similar processes. However, given our previous results (Rudy & Pugh, in press), it would be premature to reject this idea.

One reason that generalized auditory-cue fear conditioning is more sensitive to the effects of scopolamine than direct auditory-cue fear conditioning may reside in the organization of the neural pathways that mediate auditory-cue fear conditioning. Romanski and LeDoux (1992) have identified two neural pathways that can support auditory-cue fear conditioning. Both pathways are assumed to produce conditioned fear by their associative connections with the lateral nucleus of the amygdala (Fanselow, 1994; LeDoux, 1994, 1995). One pathway, however, makes associative contact by a *subcortical* thalamo-amygdala projection from the magnocellular medial geniculate nucleus, whereas the other pathway involves a thalamo-cortico-amygdala projection from the ventral medial geniculate nucleus.

One way in which the two auditory pathways may differ has to do with the specific features of the auditory stimulus that they can represent. LeDoux (1994, 1995) has suggested that the subcortical auditory pathway presents a nonspecific representation of auditory stimulation to the amygdala, whereas the cortical pathway provides a more specific, detailed representation of the stimulus. Support for this hypothesis comes from the finding that damage to the auditory cortex impairs a rabbit's ability to display differential bradycardiac conditioning to auditory stimulation of different frequencies, but does not affect its overall level of conditioned responding (Jarrell, Gentile, Romanski, McCabe, & Schneiderman, 1987). One might speculate that scopolamine affected generalized, but not direct, auditory-cue fear conditioning, because it affected processing carried out in the cortical auditory pathway but had little or no effect on processing in the subcortical pathway.

In summary, the present experiments support the hypothesis that auditory-cue fear conditioning depends on two dissociable processes: a stimulus construction process and an associative process that links the representation of the stimulus with the aversive event. They also establish a role for central cholinergic systems in the construction of a specific representation of auditory stimulation.

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(Manuscript received April 18, 1996;
revision accepted for publication July 24, 1996.)