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Disruption of Tolerance to the Ataxic Effect of Ethanol by an Extraneous Stimulus

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SIEGEL, S. AND S. J. LARSON. *Disruption of tolerance to the ataxic effect of ethanol by an extraneous stimulus.* PHARMACOL BIOCHEM BEHAV **55**(1) 125–130, 1996.—According to a conditioning analysis, pharmacological conditional responses (CRs) contribute to tolerance. We previously reported (24) that, as expected on the basis of this model, tolerance to the hypothermic effect of ethanol is attenuated by "external inhibition," for instance, by presentation of a novel stimulus (a strobe). However, results of more recent research (2,12,13) indicate that novel stimuli augment the hypothermic effect of ethanol in rats receiving the drug for the first time. It is possible, therefore, that a novel stimulus apparently attenuates ethanol tolerance because it augments ethanol-hypothermia, rather than because it functions as an external inhibitor. Two experiments were designed to evaluate external inhibition of tolerance to another effect of ethanol—ataxia. Although the initial ataxic effect of the drug (unlike the hypothermic effect) is not enhanced by a novel stimulus, the stimulus reinstated ethanol-induced ataxia in tolerant rats. The results demonstrate external inhibition of ethanol tolerance in a preparation not confounded by the effects of the novel stimulus on initial responding to ethanol.

Alcohol tolerance Conditioning Ethanol tolerance External inhibition

RESULTS of many experiments indicate that drug tolerance is modulated by drug-associated cues present at the time of tolerance testing [reviewed in (20)]. The contribution of such cues has been incorporated in a Pavlovian conditioning analysis of tolerance (16,20). According to this analysis, tolerance is mediated not only by homeostatic corrections elicited by the presence of the drug, but also by homeostatic corrections made in response to cues that have signaled the drug in the past. These pharmacological conditional responses (CRs), elicited by predrug stimuli, attenuate the response to the drug.

The conditioning account of tolerance is supported by the results of experiments indicating that nonpharmacological manipulations of the hypothesized conditional stimulus (CS), drug-predictive cues, similarly affect both tolerance and conditioning. Thus tolerance, like conditioning, is subject to extinction, CS preexposure effects, partial reinforcement effects, sensory preconditioning, inhibitory learning, overshadowing, and blocking (20). Results of many experiments indicate that conditioning contributes to tolerance to a variety of drugs, including ethanol (6,19). Of special relevance to the present experiments is Siegel and Sdao-Jarvie's (24) demonstration that tolerance to the hypothermic effect of ethanol is attenuated by presentation of a novel extraneous stimulus (a strobe light). This would be expected, on the basis of the conditioning analysis, because established CRs are attenuated by presentation of a novel stimulus—a phenomenon Pavlov termed "external inhibition" (11).

Although Siegel and Sdao-Jarvie (24) explained their findings as evidence of Pavlovian external inhibition of the CR mediating tolerance to the hypothermic effect of ethanol, Cunningham and colleagues (2,12,13) suggested an alternative interpretation. They reported that a variety of stressful stimuli increase the hypothermic response to ethanol; rats receiving ethanol for the first time display a more pronounced hypothermia if they are stressed in conjunction with ethanol administration. [The mechanism of this effect is not yet clear, but an endorphinergic interpretation has been presented (2,12,13)]. It is possible, then, that a strobe may attenuate ethanol tolerance because of the hypothermia-augmenting effect of the stress induced by this novel stimulus, rather than to external inhibition of the CR hypothesized to mediate tolerance. In fact, Cunningham and Bischof (2) reported that a strobe presentation is one of the stressors that is effective in enhancing ethanol-induced hypothermia.

The present experiment was designed to evaluate further the disruption of ethanol tolerance by a novel stimulus. Inasmuch as the analysis of hypothermic tolerance may be complicated by the unconditional effect of a novel stimulus on the hypothermic effect of ethanol, a different measure of the effect of ethanol, ataxia, was used. As was the case in the Siegel and

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Sdao-Jarvie (24) experiment, the effect of a novel stimulus was evaluated in rats tolerant to ethanol. In addition, as was the case with Cunningham and colleagues, the effect of the extraneous stimulus was also evaluated in nontolerant rats to determine whether it unconditionally affects the response to the drug.

EXPERIMENT 1

Method

Subjects, Drugs, and Apparatus. Thirty-two, experimentally-naive, male, Sprague–Dawley-derived rats (weighing 250–275 g at the start of the experiment) were maintained in individual cages with food and water freely available.

The effect of ethanol was assessed with a tilting plane (1,5,7,28). The apparatus consists of an alley, 60 cm long × 18 cm wide, constructed of Plexiglas. It is enclosed by walls 30 cm high, and open at the top. The alley is hinged at one end. The other end can be elevated by the operation of crank (one complete revolution of the crank elevates the apparatus approximately 2°). A protractor built into the hinged end of the apparatus provides an indication of the angle of inclination. The ataxic effect of ethanol was measured by an experimenter who gradually turned the crank (elevating the alley approximately 4°/s) and noted the angle of inclination at which the rat started slipping down the alley (slip angle).

All injections were IP. Ethanol, injected at a dose of 2 g/kg, was prepared as a 20% solution (by volume) of 95% ethanol in physiological saline. This dose of ethanol is similar to that used by Cunningham and colleagues (1.8 g/kg) in their studies demonstrating that novel stimuli augment the hypothermic effect of ethanol (2), and is at the lower end of the range of parenterally administered ethanol doses previously used in evaluations of ataxic effect of ethanol using the tilting plane [e.g., (7), see review (28), pp. 367–371]. Physiological saline injections were equated volumetrically with ethanol injections.

The novel stimulus used during test consisted of simultaneous presentation of a strobe light and white noise. The strobe light was generated by a Grass PS2 photostimulator. This photostimulator uses a Xenon flash tube to generate 10 microsecond flashes. It was set at a flash rate of 4 Hz at maximum intensity (139,350 lx). Moderate intensity white noise, delivered through a ceiling speaker, was presented at the same time as the strobe stimulation. During periods of strobe/noise presentation overhead room lights were turned off.

Procedures. Two groups of subjects (n/group = 16) differed with respect to the substance injected on each daily session—either ethanol or saline. For each session, subjects were taken from their home cage in the colony room to the room containing the tilt apparatus. Within 2 min of transport, they received a preinjection slip-angle assessment. They then were injected, and slip angle was again determined at 2-min intervals for 14 min.

The experiment consisted of 24 daily sessions. Day 1 was the pretolerance test day. Half the rats injected with each substance were presented with the strobe/noise stimulus. The stimulus was initiated 90 s after injection and continued throughout the remainder of the session.

Days 2–23 consisted of tolerance development sessions. The single preinjection and the seven postinjection determinations of slip angle were made for each of the ethanol and saline subjects on each session. The strobe/noise stimulus was not presented on any of these 22 sessions.

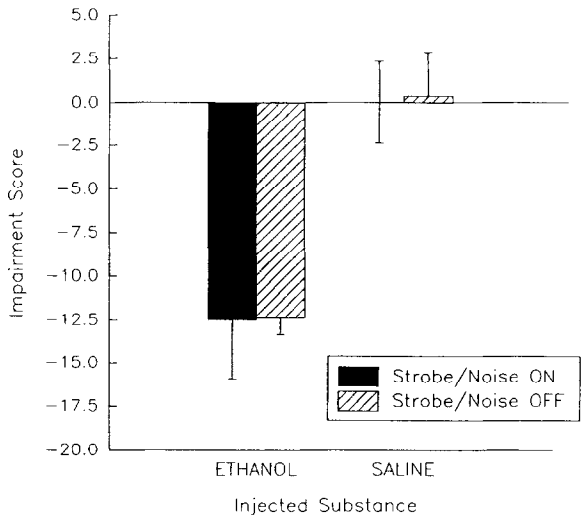

FIG. 1. Mean impairment scores (+ 1 SEM) displayed by ethanol- and saline-injected rats that were and were not presented with the strobe/noise on the pretolerance test (Experiment 1).

Day 24 was the posttolerance test session. As was the case with the pretolerance test session, half the rats injected with each substance were presented with the strobe/noise stimulus starting 90 s after injection, with the stimulus continuing until the final postinjection determination of slip angle. Half the ethanol- and saline-injected rats presented with this stimulus on the posttolerance test session were not presented with it on the pretolerance test session.

Data Treatment. A measure of impairment was computed for each subject for each session. This was the difference, in degrees, between the smallest slip angle noted during postinjection determinations and that subject's preinjection slip angle for that session [see (5,7)]. Thus, increasing ataxia is indexed by increasingly negative impairment scores.

Results and Discussion

The pretolerance test session was conducted on the first day of the experiment. As expected, the preinjection slip angles (obtained prior to differential treatment) were similar for ethanol- and saline-injected subjects that were and were not presented with the strobe/noise stimulus on this test session (mean preinjection slip angles: ethanol-strobe = 39°, ethanol-no strobe = 35°, saline-strobe = 36°, saline-no strobe = 37°). A 2 × 2 ANOVA of this preinjection data indicated no significant main effects or interactions, all Fs (1, 28) $\leq$ 1.7, all ps $\leq$ 0.20. Figure 1 depicts the mean impairment scores (± 1 SEM) displayed by ethanol- and saline-injected subjects that were and were not presented with the strobe/noise stimulus on this pretolerance test session. The ataxic effect of ethanol was apparent. Ethanol-injected rats showed greater impairment scores than saline-injected rats. The extraneous stimulus, however, did not augment impairment scores. That is, in contrast with the hypothermic effect of ethanol, the ataxic effect of ethanol is not augmented by a novel stimulus in nontolerant rats. These observations were supported by the results of an ANOVA of the data summarized in Fig. 1. The only significant effect was due to the injected substance, $F(1, 28) = 26.0$, $p < 0.001$.

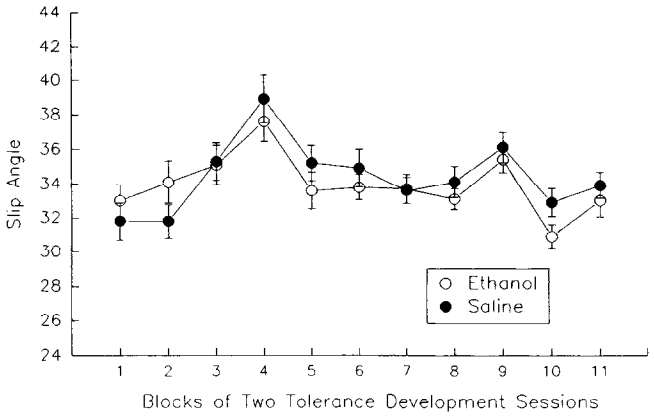

FIG. 2. Mean preinjection slip angles (± 1 SEM) for ethanol- and saline-injected rats over two-session blocks during tolerance development (Experiment 1).

Figure 2 depicts the mean preinjection slip angles (determined prior to injection) over two-session blocks during the tolerance development phase of the experiment (days 2–23). As can be seen in Fig. 2, these preinjection angles displayed session-to-session variability, but were similar for ethanol and saline rats. A mixed design ANOVA of the data summarized in Fig. 2 indicated that neither the drug injected subsequent to the preinjection determination, nor the interaction between drug and session, was significant, $F(1, 30) < 1$ and $F(10, 300) = 1.3$, respectively, $ps > 0.20$.

Figure 3 depicts the mean impairment scores (± 1 SEM) for ethanol- and saline-injected subjects, over two-session blocks, during the tolerance development phase of the experiment. Over the course of repeated injections there was little change in impairment scores for saline subjects, but the impairment initially displayed by ethanol subjects gradually decreased. A mixed-design ANOVA of the data summarized in Fig. 3 indicated a significant session block × group interaction, $F(10, 300) = 5.48$, $p < 0.001$. Subsequent one-way repeated measures ANOVAs indicated that the effect of session blocks was statistically significant for ethanol subjects, $F(10, 150) = 7.10$, $p < 0.001$, but not for saline subjects, $F(10, 150) = 1.67$, $p > 0.09$.

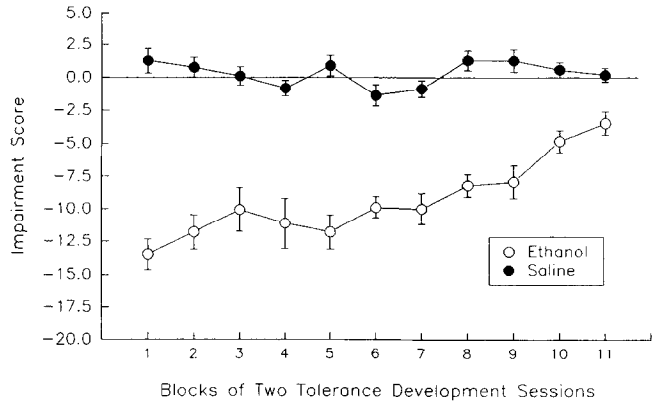

FIG. 3. Mean impairment scores (± 1 SEM) for ethanol- and saline-injected subjects, over two-session blocks, during tolerance development (Experiment 1).

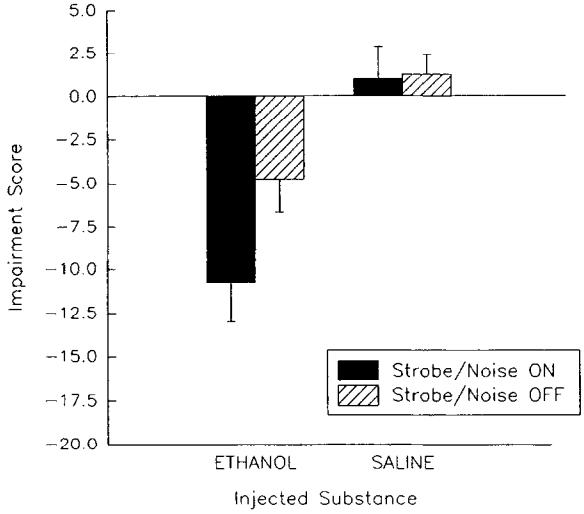

FIG. 4. Mean impairment scores (+ 1 SEM) displayed by ethanol- and saline-injected rats that were and were not presented with the strobe/noise on the posttolerance test (Experiment 1).

The results of the posttolerance test are summarized in Fig. 4, which depicts the mean impairment scores (± 1 SEM) of ethanol- and saline-group rats that were and were not presented with the strobe/noise stimulus. Again, these impairment scores were calculated as differences from preinjection tilt angles that were similar for the groups (mean preinjection slip angles for the four groups ranged from 32° to 34°, with differences not approaching statistical significance). An ANOVA of the data summarized in Fig. 4 indicated a significant drug (ethanol vs. saline) × strobe/noise status (on vs. off) interaction, $F(1, 28) = 5.91$, $p < 0.02$. Ethanol subjects presented with the strobe/noise displayed significantly greater impairment than ethanol subjects not presented with this stimulus, $t(14) = 2.90$, $p < 0.02$. No such effect of strobe/noise presentation was seen in saline rats, $t(14) < 1$.

The results of this experiment suggest that tolerance to the ataxic effect of ethanol is subject to external inhibition; a novel cue augmented the ataxic effect of ethanol in tolerant, but not nontolerant rats. However, rats displaying apparent external inhibition of ethanol tolerance had experience with both the drug and the tilting plane apparatus prior to the final test session. Although the noise/strobe augmented the hypothermic response to the final administration of ethanol, and not the initial administration, it is conceivable that the strobe would augment the response to an initial administration of the drug in rats that were experienced in the tilting-plane apparatus. This possibility was evaluated in Experiment 2.

EXPERIMENT 2

One group of rats was treated as the ethanol group in Experiment 1 (i.e., they were injected with ethanol on each of 24 days, with the effect of the strobe/noise assessed on pre- and posttolerance test sessions). A second group of rats was treated as the saline group in Experiment 1, except that they were injected with ethanol, for the first time, on the posttolerance test session. Thus, for the final test session, rats in both

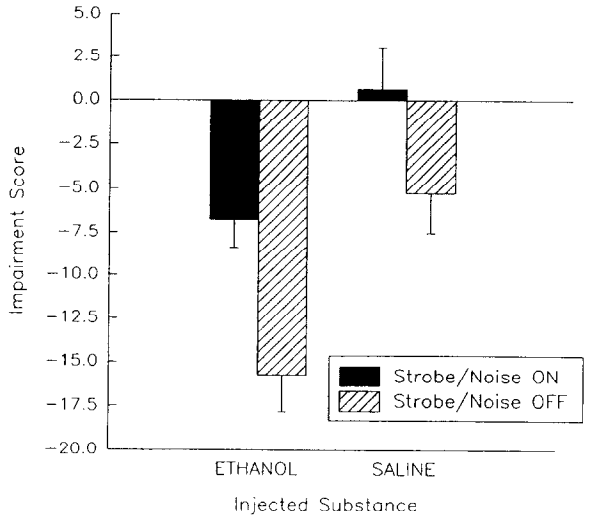

FIG. 5. Mean impairment scores (+ 1 SEM) displayed by ethanol- and saline-injected rats that were, and were not, presented with the strobe/noise on the pretolerance test (Experiment 2).

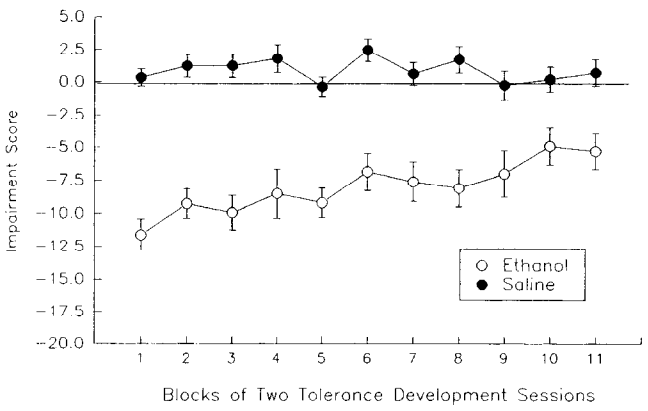

FIG. 6. Mean impairment scores (± 1 SEM) for ethanol- and saline-injected subjects, over two-session blocks, during tolerance development (Experiment 2).

groups were injected with ethanol, and both had extensive experience with the tilting-plane assessment.

Method

The subjects were 32 male rats of the same strain and weight range as those used in Experiment 1. The procedure was identical to Experiment 1, except for modifications during the posttolerance testing (day 24). Unlike Experiment 1, all animals were given ethanol during posttolerance test. Half of the saline and ethanol animals were given the strobe/noise stimulus during the posttolerance test (as in Experiment 1), and the other half were not.

Results and Discussion

Impairment scores in this experiment, as in the previous experiment, were calculated as differences from preinjection slip angles. Preinjection angles in this experiment were similar to those obtained in the previous experiment, and did not differ significantly between groups in any comparisons.

The pretolerance test session was conducted on the first day of the experiment. Figure 5 displays the mean impairment scores (± 1 SEM) displayed by ethanol- and saline-injected rats that were and were not presented with the strobe/noise during this test session. Again, the ataxic effect of ethanol was apparent; ethanol-injected rats displayed greater impairment scores than did saline-injected rats. There was no evidence that the novel stimulus enhanced the ataxic effect of ethanol. Indeed, as may be seen in Fig. 5, in this experiment the strobe/noise actually decreased ataxia; rats in both groups tested with the strobe/noise combination exhibited less impairment than those tested without the stimuli. These findings were confirmed by an ANOVA that revealed a significant effect of drug (ethanol vs. saline), $F(1, 28) = 17.3$, $p < 0.001$, and strobe/noise presentation (on vs. off), $F(1, 28) = 11.9$, $p < 0.002$. This contrasts with the results of the previous experiment in which the strobe had no significant effect on ethanol-induced ataxia. Although the reason for the difference is unclear, it should be emphasized that the direction of the effect in the present experiment (unconditional attenuation of the ataxic effect of ethanol) is opposite in direction to findings that would support a nonassociative interpretation of the external inhibition effect.

Figure 6 depicts the mean impairment scores (± 1 SEM) for ethanol- and saline-injected subjects, over two-session blocks, during the tolerance development phase of the experiment (days 2–23). The ataxic effect of ethanol and the development of tolerance to this effect is apparent. A mixed-design ANOVA of the data summarized in Fig. 6 indicated a significant session block × group interaction, $F(10, 300) = 2.80$, $p < 0.01$. Subsequent one-way repeated measures ANOVAs indicated that the effect of session blocks was statistically significant for ethanol subjects, $F(10, 150) = 3.63$, $p < 0.001$, but not for saline subjects, $F(10, 150) = 1.27$, $p > 0.20$.

For the posttolerance test, all rats were injected with ethanol. The results of this test are summarized in Fig. 7, which depicts the mean impairment scores (± 1 SEM) of ethanol- and saline-group rats that were and were not presented with the strobe/noise stimulus. The effect of the strobe/noise on ethanol-group rats, which received their 24th injection of the drug on this test day, was similar to that seen in the previous experiment. That is, the extraneous stimulus enhanced the ataxic effect of the drug in these ethanol-tolerant rats, $t(14) = 2.25$, $p < 0.05$. In contrast, there was no evidence that the strobe/noise affected ataxia in saline-group rats, which received their first injection of ethanol on this posttolerance test, $t(14) < 1$. Thus, in the present experiment, as in the prior experiment, the strobe/noise increased ethanol ataxia in ethanol-tolerant rats. It did not increase ataxia in rats receiving ethanol for the first time (even if they were experienced with the ataxia-assessment situation).

GENERAL DISCUSSION

The results of these experiments, demonstrating disruption of tolerance to the ataxic effect of ethanol by an extraneous stimulus, are similar to previous findings concerning disruption of tolerance to the hypothermic effect of ethanol by such a stimulus (24). The hypothermic tolerance findings, however, have been subjected to alternative interpretations. Siegel and Sdao-Jarvie suggested that their findings "are parallel to Pavlov's observation of external inhibition of an established CR," and thus, "are consistent with the conditioning account of

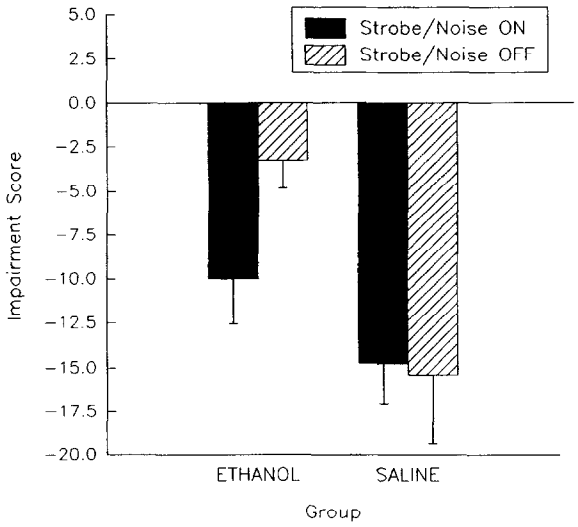

FIG. 7. Mean impairment scores (+ 1 SEM) displayed by ethanol-injected rats that were, and were not, presented with the strobe/noise on the posttolerance test (Experiment 2). Saline-group rats received ethanol for the first time on this test; ethanol-group rats received ethanol throughout the experiment.

ethanol tolerance" [(24), p. 261]. However, Cunningham and colleagues (2,12,13) reported that the novel stimulus (in common with a variety of stressors) augments the hypothermic effect of ethanol independently of whether or not the subject is tolerant to the drug; thus, Siegel and Sdao-Jarvie's results do not unambiguously demonstrate external inhibition of tolerance.

Although the nonassociative interpretation of the Siegel and Sdao-Jarvie (24) findings is relevant to putative demonstrations of external inhibition of tolerance to ethanol hypothermia, it is not readily applicable to the results of the present experiments. In these experiments we demonstrate that a novel stimulus that does not unconditionally augment a behavioral effect of ethanol, nevertheless, disrupts the display of tolerance to this effect. Thus, the results of these experiments demonstrate external inhibition of ethanol tolerance in a preparation not confounded by novel stimuli-induced enhancement of initial responding to ethanol.

In experiments concerning external inhibition of ethanol tolerance, extraneous environmental stimuli have been used to disrupt tolerance. Results of an experiment by Poulos et al. (15), concerning external inhibition of morphine tolerance, demonstrate that extraneous pharmacological stimuli may be used to disrupt tolerance. In this experiment, ethanol was used as a stimulus to disrupt tolerance to the opiate. During the tolerance acquisition phase of this experiment, two groups of rats were repeatedly injected with morphine and became tolerant to the drug's analgesic effect. One of these groups was additionally injected with ethanol 15-min after each morphine injection. Following tolerance acquisition, all rats were tested for morphine analgesic tolerance with a novel state being introduced following morphine administration, for instance, they experienced either the novel introduction, or the novel omission, of the alcohol cue. Both novel states attenuated tolerance.

Results of this Poulos et al. (15) experiment provide further evidence of external inhibition of tolerance in a preparation not subject to the nonassociative interpretation offered by Cunningham and colleagues. In the Poulos et al. (15) experiment, there was no evidence that postmorphine ethanol augmented the analgesic effect of the opioid in rats receiving the drugs for the first time. Nevertheless, ethanol was an effective external inhibitor of morphine-analgesic tolerance. Indeed, in the case of rats receiving ethanol following each tolerance-acquisition morphine administration, the absence of the usual ethanol disrupted tolerance. It would seem that the phenomenon of external-inhibition of tolerance is not dependent on the use of an external inhibitor that augments the effect of the drug, or that is stressful.

In the present experiments, ethanol was administered once per day, with distinctive environmental cues associated with each administration. These administration procedures favor both the development of ethanol-anticipatory CRs [see (6,19)], and associative tolerance [e.g., (25)]. Thus, in the present report [and elsewhere, (15,20,24)] disruption of tolerance by an extraneous stimulus has been seen as evidence of external inhibition of the CR that mediates tolerance. However, it is conceivable that the effect of the novel cue is unrelated to conditioning. That is, the cue may unconditionally interfere with nonassociative activities that mediate tolerance [(11), pp. 43–44]. Although there is nothing in the results of these experiments that rules out such an interpretation, there is reason to believe it implausible. Disruption of CRs by novel cues is a general phenomenon, and thus, on the basis of a conditioning interpretation, it is not surprising that a novel cue disrupts tolerance to several drugs (ethanol and morphine). In contrast, a nonassociative explanation would have to postulate that the cue [or the novel omission of a cue, (10)] interferes with a variety of different, unconditionally elicited homeostatic mechanisms to explain the effect of the cue on the display of tolerance to several pharmacologically distinct drugs.

The results of the present experiments are consistent with a Pavlovian conditioning analysis of tolerance. There are other ways in which learning may contribute to tolerance [see (6,19)]. For example, Dews (3) suggested that the frequently drugged subject may acquire a behavioral strategy that compensates for some drug-induced impairments. Dews' example clearly illustrates the operation of such an instrumentally acquired ability to cope with the effects of ethanol: the experienced drinker is more proficient in remaining erect than the inexperienced drinker because the experienced drinker has instrumentally acquired a behavioral strategy (a broad-based gait) that compensates for the effect of ethanol because he has practiced this behavior while intoxicated. In the present experiment, rats assessed on the tilting plane after ethanol administration may have learned to make postural adjustments that caused them to resist slipping as the assessment apparatus was tilted. The relationship between such instrumental conditioning and classical conditioning accounts of tolerance has been a matter of considerable discussion [e.g., (6,14,17)]. Instrumental conditioning, like Pavlovian conditioning, is disrupted by external inhibition [e.g., (4,29,30)]; thus, demonstrations that a novel stimulus disrupts tolerance to the ataxic effect of ethanol is consistent with an instrumental conditioning analysis of such tolerance, as well as a Pavlovian conditioning analysis.

Regardless of the mechanism by which external cues interfere with tolerance, the phenomenon has important implications. As suggested by Poulos et al. (15), external inhibition of tolerance may be relevant to some instances of exaggerated drug toxicity. That is, in the tolerant subject the effect of a drug may be unexpectedly large if it is presented in conjunction with an extraneous stimulus. It has been demonstrated that the

conditioning analysis of tolerance is relevant to understanding overdoses from a variety of drugs, including opiates (18,21–23), pentobarbital (27), and ethanol [(9,10); but see (26)]. It is possible that some instances of overdose may result because an extraneous stimulus intrudes into the usual drug administration ritual, thus disrupting the expression of tolerance. Indeed, Siegel (20) described such a scenario occurring in the case of an enigmatic overdose suffered by a heroin addict. It also is possible that external inhibition of tolerance has forensic implications. For example, the individual apparently tolerant to alcohol may suddenly fail to display such tolerance when a novel stimulus occurs, such as the arrival of police (8).

ACKNOWLEDGEMENTS

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