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BEHAVIORAL DISINHIBITION BY MESCALINE*

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Rats were exposed to a CER procedure in which sucrose drinking was suppressed by a tone previously paired with shock. Suppression of drinking during the tone was reduced by mescaline (50 mg/kg) independently of whether training took place under mescaline or placebo. Additional data on the effect of mescaline on sucrose drinking indicated that the result could not be attributed to an increased drive to drink sucrose. It was proposed that mescaline releases behavior from inhibitory control. A number of studies from the literature were cited which supported this hypothesis.

We have recently carried out a series of studies in our laboratory demonstrating a powerful facilitation of shock-induced aggression by mescaline. In the first study (1) a 15 mg/kg dose of mescaline produced an increased frequency of fighting while a 50 mg/kg dose produced prolonged bouts with severe biting and considerable injury. A second study (Carder & Sbordone, in press) demonstrated that rats treated with 50 mg/kg of mescaline would attack a variety of targets, including a dead rat, which were not capable of eliciting shock-induced aggression from normal subjects.

On the basis of these data we proposed that mescaline might facilitate aggression by removing aggressive behavior from inhibitory control. Thus the behavior would be directed at a wider variety of targets and would be more severe than aggressive behavior of untreated subjects.

Other behavioral studies of mescaline can be cited in support of a hypothesis that mescaline removes a variety of behaviors from inhibition. For example, Tilson & Sparber (2) found that mescaline (1-12 mg/kg) increased the lever pressing of rats during the early period of a fixed interval schedule. Responding is normally

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inhibited during this period, so that the effect of mescaline was to release the behavior from inhibition. Mescaline did not increase the terminal rate, at which point inhibitory control was not expected to be present.

In a series of studies, Bridger and his colleagues have shown that mescaline facilitates the potentiated startle response (3) and facilitates shuttle avoidance (4) (5). These authors have argued that the effects of mescaline on avoidance are accounted for by an enhancement of the acquisition of Pavlovian conditioned responses (CR's), a process that is deemed essential to the acquisition of instrumental avoidance (6).

The data of Bridger and his colleagues can also be explained by the disinhibition hypothesis. In the presence of aversive stimuli, rats are likely to freeze (7). Freezing is a state in which all active behaviors are inhibited, and thus freezing frequently competes with instrumental avoidance, especially shuttle avoidance (8) (9). Thus, mescaline may facilitate active behavior in the presence of aversive stimulation by interfering with the inhibitory competing response of freezing.

A potential contradiction to the disinhibtion hypothesis is represented by the data of Smythies et al (10) who examined the effect of mescaline (8.5 - 12.5 mg/kg) on CER baseline performance. They found that mescaline increased disruption of baseline performance, which might indicate that the drug increased inhibitory effects of the shock. However, the baseline was maintained on a DRL, limited-hold schedule, a relatively difficult problem for the subjects. The disruption of such performance by mescaline could result from disruption of timing behavior or other complex processes necessary for its maintenance.

Experiment I

This experiment represents an attempt to arrange a comparison between the disinhibition hypothesis and the conditioning facilitation hypothesis of Bridger. Rats were tested for the effect of mescaline in a conditioned emotional response (CER) procedure devised by Leaf and Muller (11) in which the Pavlovian CR was measured by the inhibition of drinking in the presence of a CS previously paired with shock. If the Bridger hypothesis that mescaline enhances aversive Pavlovian conditioning is correct, then mescaline should enhance the CR and cause a greater inhibition of drinking. If the disinhibition hypothesis is correct, then drinking should be increased under mescaline and the CR reduced.

Methods

Subjects. Subjects were 40 experimentally naive female Sprague-Dawley rats over 90 days old, obtained from the Simonsen Breeding Laboratory in Gilroy, California. Subjects were housed in individual cages with food and water available until the final 48 hours of the experiment.

Apparatus. Training and testing were carried out in a modified Gerbrands operant conditioning chamber (Ralph Gerbrands Co., Cambridge, Mass.), 29 x 24 x 20 cm. The front and rear walls

were of metal, the top and sides were of plexiglass, and the floor was a shock grid. In the rear wall about 3 cm. above the floor a stainless steel drinking tube protruded into the test chamber. A small loud speaker for CS presentations was in the center of the front wall just below the grid floor. The shocks, of .4mA intensity, could be delivered to the grid floor via a Davis (Davis Scientific Instruments, Studio City, California) grid scrambler. All experimental events were controlled by a series of timers and relays. Licks at the drinking tube were detected by a drinkometer circuit which activated a digital counter.

Procedure. Subjects were randomly divided into 4 groups of 10. Two of these groups received their initial training under mescaline and two under saline. Then when testing was carried out, one of the groups trained under mescaline and one of the groups trained under saline were tested under mescaline while the other two groups were tested under saline.

Subjects were dosed with the appropriate drug intraperitoneally 20 min. prior to each session. Mescaline was administered in a dose of 50 mg/kg in a solution of 50 mg of mescaline/ml of distilled water. Placebo injections were of .9% saline solution.

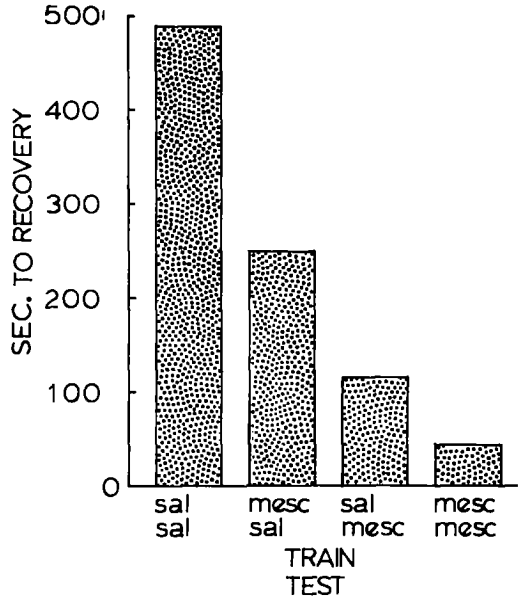
Each subject received one training session followed 48 hours later by one testing session. During the training session an 80 db, 300 HZ tone was presented for 10 seconds. During the final second a .4 mA shock was also presented with the tone and shock terminating together. Four trials were presented during the initial training session with an intertrial interval of 1 minute.

In the interval between the training session and the test session subjects were deprived completely of food and water. For this session only, the drinking tube was filled with a solution of 16% sucrose and tap water. When S made 100 licks at the drinking tube the CS was turned on and allowed to remain present for 15 minutes. (Two Ss from the mescaline-mescaline group and 1 from each of the other three failed to drink in the test session. Since it was impossible to test the effect of the CS in these Ss, they were replaced by new Ss that were run through the entire experimental procedure.) No further shocks were presented. The time between the onset of the CS and the recovery of drinking was recorded. The criterion for the recovery of drinking was when S made 100 licks. Usually this indicated the resumption of steady licking. According to Leaf and Leaf (12), time to recovery is the most sensitive measure of the CR. The test session ended when the CS had been on for 15 minutes (900 sec.).

Results and Discussions

Figure 1 presents the mean time to recovery for Ss in each of the four groups. It is immediately apparent that Ss tested under mescaline resume drinking more rapidly than Ss tested under saline. An analysis of variance revealed this effect to be statistically reliable ($F=11.2$, $df=1/36$, $p<.002$). Thus, the conditioned suppression of drinking is less in subjects treated with mescaline than in controls.

FIG. 1



Mean seconds to perform 100 licks in the presence of the CS as a function of training and testing conditions.

A second effect that is suggested by the data is that independent of testing conditions, subjects trained under mescaline show a more rapid recovery of drinking than subjects trained under saline. This effect did not quite reach the usual criteria of statistical reliability ($F=3.25$, $df=1/36$, $p<.1$).

The interaction between training and testing conditions did not approach statistical reliability ($F=.93$, $df=1/36$, $p<.98$). Thus the effects of mescaline on the conditioned response were independent of what drug was given during training and therefore the mescaline effect could not be attributed to state dependent learning. Mescaline attenuated the conditioned response whether Ss were trained under saline or under mescaline.

Experiment II

There are two attractive explanations for the attenuation of the CER by mescaline in the first experiment. One is that the hypothesis we initially set out to test is true, namely that

mescaline interferes with the inhibitory control of behavior. Thus the CER failed to inhibit drinking in mescaline treated subjects. A second explanation is that mescaline enhances drinking. Thus subjects tested under mescaline drink more than subjects tested under saline because they are essentially operating on a higher baseline, not because there is a failure of the suppressive mechanism. In order to test this second alternative we examined the effects of mescaline on sucrose drinking.

Methods

Ten female Sprague-Dawley rats about 70 days old and weighing from 150 to 200 grams were housed in individual cages. Following a period of unlimited access to food, they were deprived of all food and water for 48 hours. Ss were then randomly divided into two groups of five. Subjects in one group received 50 mg/kg of mescaline intraperitoneally in a solution of 50 mg/ml. Subjects in the second group received equal volumes of distilled water. Twenty minutes after the injections were carried out the water bottles were placed on the cages. These bottles were filled with 16% sucrose solution. The Ss were given a 15 minute period of exposure to the bottles. The amount drunk was recorded by weighing the bottles before and after the test. Since no spillage was noted in these experiments, it is assumed that number of licks and amount of fluid removed from the bottles are accurate reflections of actual consumption.

Results and Discussion

Subjects treated with 50 mg/kg of mescaline drank a mean of 5.6 ml (S.D. = 2.07) while Ss treated with distilled water drank a mean of 4.6 ml (S.D. = 2.41). It is quite obvious that there is considerable overlap between the groups and no large increase in sucrose drinking produced by mescaline. The alteration of drinking by mescaline does not remotely approach statistical reliability ($t=0.70$, $df=8$, $p<.50$). Thus it is unlikely that the large differences reported in the first experiment could have resulted solely from an increase in drinking by mescaline treated subjects.

Experiment III

It is possible that mescaline failed to enhance sucrose drinking in the absence of shock, in experiment II, because of a ceiling effect; controls were drinking so much that further enhancement by mescaline was impossible. To examine this possibility we observed the effects of mescaline on water drinking under conditions which were more likely to provide room for enhancement.

Methods

Twelve female Sprague-Dawley rats, about 90 days old, were deprived of food and water for 48 hrs. They were randomly divided into groups of 6. One group received 50 mg mescaline/kg, i.p., from a 50 mg/ml solution, while the second received an equal volume of distilled water. Twenty minutes later the water bottles were returned to their cages and the amount drunk recorded for the

next 60 minutes.

Results and Discussion

Ss treated with mescaline drank a mean of 4.65 ml in the 60 minutes while Ss treated with distilled water drank 10.87 ml. This difference is nearly statistically reliable ($t=2.15$, $df=10$, $p < .06$). Thus if anything mescaline decreases drinking. This further argues against the possibility that the increased drinking during the CS under mescaline was a result of increased thirst and supports the argument that mescaline disinhibits responding previously suppressed by a CER procedure.

General Discussion

The data clearly demonstrate that mescaline attenuates a CER, when the measure of the CR is suppression of sucrose drinking. The data cannot be explained by the hypothesis that mescaline enhances the drinking of sucrose thereby leading to less conditioned suppression, since additional data indicate that in fact mescaline does not increase sucrose drinking. Thus mescaline must act on the inhibition of drinking by a CS previously paired with a noxious US. This is consistent with our hypothesis that mescaline blocks the inhibitory effects of aversive stimuli on behavior. Thus mescaline may enhance both aggressive behavior and conditioned shuttle avoidance responding by interfering with inhibitory competing behaviors.

Of course, our findings must be tempered by the fact that our observations relate to a single rather high dose of mescaline and a single shock intensity. It is possible that Symthies et al (10) found inhibitory effects of mescaline because they employed lower doses of mescaline and a slightly higher shock level than the present study.

Our data contradict the hypothesis that mescaline facilitates avoidance behavior by enhancing the acquisition of Pavlovian CR's. In the present study the effect of mescaline on conditioned suppression seems to be mainly a performance effect. Subjects trained under saline showed a smaller CR when tested under mescaline than when tested under saline. In addition, however, there is some weak evidence for an impairment of the learning process by mescaline. Independently of testing conditions subjects trained under mescaline showed a smaller CER than subjects trained under saline, though the effect was not statistically reliable.

The effects reported here cannot be ascribed to state dependent learning. Subjects tested under mescaline show a reduced CER when compared to subjects tested under saline independently of whether they were trained under mescaline or saline.

It would appear fruitful at this point to explore the biochemical mechanisms by which mescaline attenuates the CER. Since it seems that mescaline interferes with inhibitory control of behavior in a variety of situations, the study of the biochemical mechanism of this interference would promise to give some insight into the neural and biochemical mechanisms of inhibitory behavioral control.

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