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BRIEF COMMUNICATION

Latent Inhibition in the Aversion to Oral Methadone

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LYNCH, M. R., J. H. PORTER AND J. A. ROSECRANS. *Latent inhibition in the aversion to oral methadone.* PHARMACOL BIOCHEM BEHAV **20**(3) 467–472, 1984.—Fourteen adult Sprague-Dawley rats received daily 3 mg/kg naltrexone (Group One, n=7) or saline (Group Two, n=7) injections for 24 days. During this time they underwent forced choice testing with 0.125 mg/ml methadone (the unconditioned stimulus, UCS) versus taste-balanced 0.04 mg/ml quinine placebo solutions. The handling, injection ritual, and taste cues served as a conditioned stimulus (CS)-complex. While Group Two (CS-UCS paired) animals showed pronounced pharmacological methadone aversions, those in Group One (CS pre-exposed rats in which the effects of methadone were blocked by the naltrexone) maintained a moderate intake of the opiate solution. When the injection conditions were reversed for 10 days, no change in percent methadone solution occurred for either group; thus, Group One displayed a latent inhibition effect after the CS pre-exposure, while Group Two maintained its previously acquired aversion. Testing after a 3-month drug free period, however, revealed the acquisition of a comparable methadone aversion by Group One (hence, recovery from the latent inhibition observed in the first reversal phase). Parallels with latent inhibition and retention in conditioned taste aversion studies were drawn, and further support for generality in the laws of learning, suggested.

Methadone aversion Latent inhibition CS pre-exposure Conditioned taste aversion Aversion retention

THE conditioned taste aversion (CTA) paradigm, developed by Garcia, Kimeldorf and Koelling in 1955 [18], has been successfully employed to demonstrate aversive properties of many psychoactive substances. Even the opiates, which are readily self-administered [21], are capable of conditioning aversions to novel-tasting solutions in the same doses that reinforce behavior in operant situations [8, 9, 11].

Similarities between this CTA paradigm and more traditional classical conditioning procedures include the conditioned stimulus (CS) pre-exposure effect. That is, pre-exposure to the CS makes it more difficult to establish a conditioned aversion in CTA studies [5, 14, 15, 16, 25]. This effect has also been observed in the classical conditioning of involuntary reflexes [31]. This phenomenon, known as latent inhibition [31], is proportional to the number of CS-alone presentations prior to introduction of the UCS in both paradigms [14, 16, 30]. Recent evidence indicates that in addition to the usual CS of taste, exteroceptive features of the conditioning environment (such as odor, sound, light, and physical properties of the apparatus) also play a role in the strength of CTAs [1,4]. This being the case, it is possible that an entire "CS-complex" which includes both the intended taste-CS and temporally contiguous environmental stimuli may take on latent inhibitory properties with pre-exposure to an experimental situation, prior to the actual experiencing of drug effects (the UCS). In experiments on the aversive properties of orally ingested drugs, this complex could include taste cues and associated drug administration rituals such as handling and injection. The subsequent establishment of an association between such a pre-exposed stimulus complex and a drug-induced aversive state would thus be rendered more difficult.

The present experiment was conducted to extend the study of latent inhibition with a similar CS-complex situation, employing a drug aversion paradigm developed by Chipkin and Rosecrans [10]. In this procedure, rats given 24-hr choice tests between methadone and equibitter quinine solutions (devoid of pharmacological effects) display pronounced aversions to 0.125 mg/ml methadone solutions by the fifth day of testing. Thus, the examination of CS-complex (handling, injection ritual and taste cues) pre-exposure effects on subsequent aversions is possible by blocking the pharmacological actions of methadone (the UCS) with the long-acting narcotic antagonist naltrexone, and then presenting the drug UCS (methadone) paired with this set of cues (i.e., the CS-complex) under saline treatment (instead of nal-

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trexone) so that the pharmacological actions of methadone are no longer blocked.

METHOD

Fourteen adult drug-naive Sprague-Dawley rats (Flow Laboratories, Dublin, VA), seven males and seven females, served as subjects. Their body weights at initiation of the experiment ranged from 274 to 603 g with a mean weight of 405 g. Animals were housed individually in 19.7×24.1×18.4 cm stainless steel cages in the animal colony room throughout the experiment. They were kept on a 12-hr light/dark cycle under controlled temperature conditions. Unlimited Purina laboratory chow was available on the floor of the cages and drinking solutions were provided ad lib throughout the experiment.

Cage fronts were outfitted with two wire bottle-hangers, allowing bottles to be mounted so that drinking tubes entered equidistant from the cage sides and bottom, and at equal angles. Solutions were provided in 250 ml glass drinking bottles, fitted with rubber stoppers and identical curved stainless steel drinking tubes.

Drugs

Racemic preparations of methadone hydrochloride (Mallinckrodt, St. Louis, MO) and quinine sulfate (Pure-Pac, Elizabeth, NC) were dissolved in tap water to yield 0.125 mg/ml and 0.04 mg/ml solutions respectively. Concentrations refer to the salt. The quinine dose was chosen based on previous parametric testing in our laboratory to equate the bitterness of the two solutions as closely as possible, thereby controlling for influences of palatability in fluid selection. (Specifically, methadone and quinine solutions at these concentrations were chosen with similar frequency by animals receiving naltrexone injections to block the pharmacological effect of methadone.) At this low concentration, the quinine offers the additional advantage of serving as a taste-balanced placebo, due to its lack of pharmacological effects.

Naltrexone HCl (NIDA) was dissolved in distilled water and injected in a volume of 1 ml/kg. This particular drug was chosen because it is a long acting (24 to 72 hr) and "pure" opiate antagonist [20, 32, 38, 51].

Procedure

Initial conditioning was conducted to replicate the findings of Chipkin and Rosecrans [10], with choice testing extended from 14 to 24 days in order to examine any tolerance which might develop to the aversive properties of methadone. The following reversal of injection procedures was designed to reveal effects of pre-exposure to the conditioning stimulus-complex on the development of methadone aversions (in a pre-exposed group of animals), and examine the retention of established aversions (in CS-UCS paired rats).

Phase one: initial conditioning. Animals were rank ordered into pairs on the basis of body weight. Seven rats (one from each pair) were assigned to a CS pre-exposed group (Group One) and seven to a CS-UCS paired group (Group Two). Animals in Group One were removed from the home cage each day between 1200 and 1400 hr and injected intraperitoneally (IP) with 3 mg/kg naltrexone to block opiate effects of the methadone solution (UCS), while CS-UCS paired rats (Group Two) received 1 ml/kg of 0.9% saline solution (IP) at the same time.

Forced choice testing with the methadone (UCS) and quinine solutions was conducted in home cages for all rats over 24 consecutive days with daily IP injections as above. Both solutions were available for each entire 24 hr period, except when they were removed for measurement between 1200 and 1400 hr. At this time bottles were weighed and weights recorded to the nearest tenth of a g, with 1 g assumed to be equivalent to 1 ml of solution. Bottle positions were alternated daily to control for position preferences. Preference scores for methadone were calculated by dividing the ml methadone consumed by the total daily ml intake (methadone plus quinine) and multiplying this ratio by 100 to yield a percent. Thus, during Phase One of the experiment, Group One (naltrexone-injected rats) was exposed to all aspects of the experimental situation and the taste of methadone (CS-complex), while the pharmacological effects of the methadone were blocked; they were therefore pre-exposed to this CS-complex which consisted of the injection ritual, handling and taste properties of the solutions, in the absence of UCS drug effects. Group Two (saline-injected rats), however, were allowed to experience the pharmacological effects of the methadone in the presence of the CS-complex, and, therefore, had the CS explicitly paired with the UCS during initial conditioning.

Phase two: reversal of daily injection conditions. The choice testing procedure employed in initial conditioning was continued for an additional ten consecutive days. During this testing, however, previously naltrexone-injected animals (Group One) received IP saline at a volume of 1 ml/kg, and the previously saline-injected rats (Group Two) were instead injected with 3 mg/kg naltrexone. Thus, animals previously pre-exposed to the CS-complex (Group One) now experienced the unblocked effects of methadone paired with this complex (i.e., a test for latent inhibition), while the previously CS-UCS paired group (Group Two) now had UCS effects blocked with daily IP naltrexone administration and experienced the CS-complex alone (i.e., an extinction test procedure). All other aspects of choice testing remained the same as during initial conditioning (Phase One).

Phase three: repeated reversal of injection conditions. Following the 10 days of choice testing under reversed injection conditions during Phase Two, animals were placed on ad lib water and allowed to remain in the home cages undisturbed for three months. At the end of this period, the conditions (reversed injections) of Phase Two were reinstated for 20 consecutive days of choice testing. Due to deaths during this three-month drug free period, only five animals remained in each group.

RESULTS

Preference scores for the two groups are presented in Fig. 1 for each phase of the experiment, with means of the daily percent methadone consumed computed for two-day blocks. Figure 2 displays the mean absolute ml intakes of quinine plus methadone solutions, also in two-day blocks, for these same three phases. As is apparent from Fig. 1, a strong aversion to the methadone solution was displayed by Group Two (CS-UCS paired animals) by the third block and was maintained over the next 18 days of choice testing, while Group One (CS pre-exposed group) maintained a steady drug intake of 30 to 40% over these 24 days in Phase One. A two-way ANOVA with repeated measures across blocks was performed on data from all 12 blocks of Phase One. Both the main effects of blocks, $F(11,132)=3.79$, $p<0.001$, and the

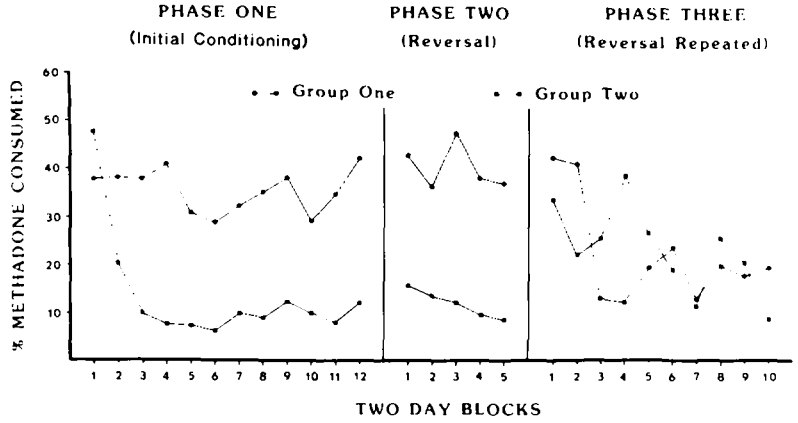

FIG. 1. The mean percent methadone (ml methadone/ml methadone + quinine × 100) consumed by Group One (CS pre-exposed, naltrexone injections), and Group Two (CS-UCS paired, saline injections) during initial conditioning (Phase One) and subsequent reversals of daily injection conditions (Phases Two and Three).

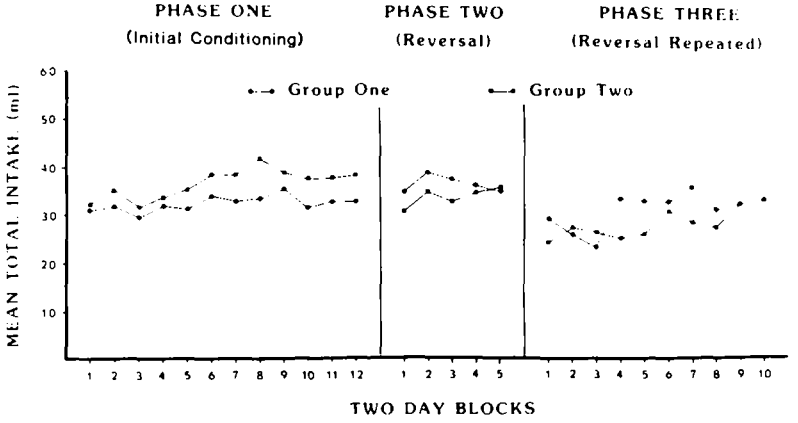

FIG. 2. The mean total ml intake of quinine plus methadone for Group One (CS pre-exposed, naltrexone injections) and Group Two (CS-UCS paired, saline injections) during initial conditioning (Phase One) and subsequent reversals of daily injection conditions (Phases Two and Three).

injection × blocks interaction, $F(11,132)=2.25$, $p<0.05$, were significant, while the injection factor, $F(1,12)=4.37$, $p>0.05$, was not. Subsequent post-hoc comparisons with the Tukey hsd test indicated that while the percent methadone consumed by the two groups did not differ on block one, mean intakes were significantly different ($p<0.01$) by block 3 and persisted through block 12. The total ml data for this same phase of initial conditioning (Fig. 2), however, showed no differential change for the two groups, as a similar ANOVA yielded a significant main effect for blocks only, $F(11,132)=3.74$, $p<0.001$. The main effect for groups, $F(1,12)=1.61$, $p>0.05$, and the groups × blocks interaction, $F(11,132)=0.69$, $p>0.05$, were not significant.

When Group One was switched to daily saline injections (therefore CS-UCS pairings) and Group Two to naltrexone (extinction) in Phase Two, no changes in mean percent methadone were observed (Fig. 1). A two-way ANOVA with repeated measures performed on these data, incorporating data from block 12 of initial conditioning, revealed that only the main effect for groups was significant, $F(1,12)=5.09$, $p<0.05$. A two-way ANOVA on the ml data from this phase of the experiment yielded a significant groups × blocks interaction only, $F(5,60)=4.77$, $p<0.001$. Subsequent post-hoc tests revealed that the absolute ml intake was significantly different between groups on block 1 of this phase ($p<0.05$), but not on block 5.

Significant changes in the percent methadone consumed were observed, however, when the reversed injection conditions were repeated in Phase Three, after a three-month drug free period. While Group One (the original CS pre-exposed animals) retained their previous level of methadone intake over the first two blocks (an overall mean of 41.5%), this percent fell to 13.2 by block 3 and remained low throughout the daily saline injections of this phase. Group Two (now receiving naltrexone injections), which had maintained its methadone aversion through 10 days of extinction in Phase Two, showed an initial increase in methadone intake during this repeated reversal. This increase above the previously low intakes of the first two phases was not maintained over the course of choice testing in Phase Three, but instead fell gradually over this period. A two-way ANOVA with repeated measures conducted on these blocked data also in-

corporated block 12 of the initial conditioning phase (i.e., Phase One). While overall effects of the injection condition were no longer significant after the three-month drug free period, $F(1,8)=0.25$, $p>0.05$, a significant effect of blocks, $F(10,80)=2.90$, $p<0.01$, and a significant injection × blocks interaction, $F(10,80)=4.47$, $p<0.001$, were obtained. Within group post-hoc comparisons indicated no significant change in intake on block 1 for Group One (now saline-injected) but a significant ($p<0.01$) drop from previously moderate intakes on block 12 of Phase One by the third block of Phase Three. This significant decrease in percent methadone consumed was maintained throughout this reversal phase and was not significantly different from the percent methadone consumed by CS-UCS paired animals (Group Two) in the initial conditioning. Methadone intakes by Group Two (now naltrexone-injected, and therefore undergoing extinction), were significantly greater ($p<0.01$) than block 12 of Phase One only on block 4, indicating a transient dissipation of the previous aversion. This maintenance of low methadone intake and the subsequent return to low levels again after block 4 of this phase indicates a retention of the drug aversion which was originally acquired during initial condition (Phase One) and maintained over 10 days of extinction in Phase Two. Comparisons with the Tukey test indicated that the means of the two groups were not significantly different during any block of Phase Three. The ANOVA on ml data for this phase revealed no significant main effects or interactions.

DISCUSSION

The significant methadone aversion displayed by Group Two (CS-UCS paired animals) during the initial conditioning (Phase One) replicated the earlier findings of Chipkin and Rosecrans [10]. While they too reported a decrease in percent methadone intake which was maintained over 14 days of testing, the demonstrated aversion in the present study persisted over 24 days, indicating a lack of tolerance development to the aversive properties of this narcotic. Further, effective blockade of the methadone aversion in Group One by the naltrexone injections indicated that the aversion was attributable to the opiate actions of methadone, rather than to other properties of the solution (such as its bitter taste). The fact that no differential changes in overall fluid intakes were observed during this period of initial conditioning indicated that the aversion was not an artifact of disruptions in drinking per se by the opiate solution. The observed general increase in total fluid intakes over the two-day blocks of Phase One probably reflected on acclimation to the bitter taste of the solutions by both groups.

A number of responses to psychotropic drugs have been demonstrated to operate in accordance with Pavlovian principles of reinforcement, and are influenced by the stimulus conditions of the drug administration procedure. Siegel [45, 46, 47] and Siegel, Hinson and Krank [48] have demonstrated such "CS-complex" effects on morphine analgesia, as have others on hyperthermic responses [3]. In addition, exteroceptive cues have been found to enter into association with drug UCSs in CTA paradigms [1, 2, 3, 4] and these associations can be modified with CS pre-exposure, extinction procedures, [1,27] and UCS (drug) pretreatment [37]. The results of the injection reversal in Phase Two extends the application of such generality in the laws of learning to the aversion paradigm of Chipkin and Rosecrans [10], with the demonstration of a latent inhibition effect in Group One. These animals received 24 days of exposure to the CS-complex (drug administration procedures and taste of methadone), with opiate actions of the UCS blocked by daily antagonist injections of naltrexone; therefore, they were pre-exposed to this CS-complex in the absence of UCS drug effects. Their lack of an aversion to the drug solution during daily saline injections in Phase Two (in contrast to the strong aversion demonstrated by Group One (CS-UCS paired animals over the first 24 days), parallels the difficulty Elkins [14] and others [16] report in establishing CTAs with similar CS pre-exposure durations. A parallel with latent inhibition effects in traditional classical conditioning studies of involuntary reflexes [23,30], is also apparent.

Another explanation for the failure of Group One to develop a methadone aversion during Phase Two is the possibility of a sustained opiate blockade or alterations in endogenous opioid systems. Specifically, the opiate effects may have continued to be antagonized by such an alteration, or the methadone may have been rendered less effective in these animals on subsequent UCS (drug) exposure. These "after-effects" of naltrexone treatment could then have dissipated over the 3-month drug free period between Phases Two and Three. Reports on peak plasma levels after effects of chronic versus acute antagonist treatment [51], first pass metabolism, metabolic clearance and volume of distribution [26], however, render this an unlikely interpretation. There in fact appears to be no build-up of the antagonist in physiological systems; therefore, after-effects of treatment during the initial conditioning phase probably do not contribute to the lack of aversion development seen in subsequent aversion testing. Considering alterations in endogenous systems, the literature does indicate an increase in the number of opiate receptor sites in rats following chronic naloxone exposure [22,43], with concomitant supersensitivity to agonist analgesia ([35, 43, 50] and in mice, [36]). If this increase in available receptor sites allows opiate agonists to have more profound effects (as is true of analgesia), then the opposite result would have been expected in the present study. Rats given daily naltrexone injections in the initial conditioning (Group One) should have more easily acquired a methadone aversion when exposed to this UCS in Phase Two. In conclusion, therefore, the results of the present study indicated that the lack of aversion was probably due to learning about the lack of CS-complex associated consequences.

The injection reversal situation for Group Two during Phase Two involved CS-complex presentations in the absence of the drug UCS for 10 days, and thus, is analagous to extinction procedures employed in CTA studies. The failure of this original CS-UCS paired group to show recovery from the drug aversion when injected with naltrexone in Phase Two is similar to CTA retention during extinction, where aversions to a flavor CS have persisted for as long as 90 days [7,12]. The results of continued extinction procedures for this group during Phase Three indicate recovery only during the fourth block of testing, with methadone aversions before and after this block, not significantly different from those seen on block 12 of Phase One. Although extinction with CS-alone presentation in CTA studies typically results in loss of the aversion in the form of a monotonic function, Biederman, Milgram, Heighington, Stockman, and O'Neil [6] have observed CTA memory and found it to follow an inverted "U" function, similar to the curvilinear pattern displayed in Phase Three by this group.

In summary, findings of the present study indicate that laboratory rats will avoid methadone solutions when provided with a taste-balanced placebo solution as an alterna-

tive. This result is not surprising given the difficulty others have encountered in demonstrating methadone self-administration [33,34]. Further, the aversion demonstrated in the present study was directed toward the opiate effects of the methadone solution, as this aversion was blocked by a narcotic antagonist in naltrexone treated animals (Group One). Acquisition of this aversion was retarded with pre-exposure to the CS-complex, resulting in a latent inhibition effect which dissipated over a period of 90 days. Finally, the methadone aversion demonstrated in this paradigm was a robust phenomenon which persisted over 10 days of extinction, and showed an inverted "U" retention function three months following the initial conditioning procedures.

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