Radiation produced avoidance to morphine

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The effects of two concentrations of morphine solution (CS) upon a conditioned avoidance response were investigated with X-radiation as the UCS. The effects of avoidance conditioning were measured by changes in preference for morphine solution and tapwater. Both groups displayed an immediate and statistically significant drop in morphine preference. The results indicated that a physiological dependency could be modified by avoidance conditioning techniques in the rat.

Radiation has been demonstrated to function as an unconditioned aversive stimulus (UCS) for avoidance conditioning (Garcia et al, 1955). Although saccharin solution has been used as the conditioned stimulus (CS) in many studies, avoidance conditioning has been obtained utilizing chocolate milk (Kimeldorf et al, 1960) and alcohol (Peacock & Watson, 1964).

The above studies produced conditioned avoidance behavior to "naturally" preferred solutions. Given a choice between tap water and morphine solutions, tap water will be the "natural" choice displayed by rats. A technique has been developed (Nichols et al, 1956) which will train rats to choose morphine solution. The rat then displays opiate directed behavior in a two choice situation. The "trained" preference (morphine solution) gradually reverts to the natural choice of tap water as a function of time; this phenomenon is represented by gradual decrease in morphine consumption over a period of weeks (Nichols et al, 1956; Nichols, 1965). It appeared to be of interest to investigate the modification of opiate directed behavior (which represents a physiological dependency) by avoidance conditioning techniques.

Method and Procedure

The Ss were 18 male Sprague-Dawley rats from the Western Michigan University colony, approximately six months old, with a mean weight of 305 g at the beginning of experimentation.

Pre-Irradiation. Morphine dosage began at 9 mg/kg/day and was increased by 1/2 of the dose of the previous day until 40 mg/kg/day was reached. Increases of 10 mg/kg/day were made until Ss were receiving 110 mg/kg/day, then by 20 mg/kg/day until a level of 210 mg/kg/day was reached. Subcutaneous injections of morphine sulphate were scheduled at 12 h intervals, 9:00 AM and 9:00 PM. The site of injections was alternated between the left and right sides. During the injection series, Ss received tap water for 1 h during every 24 h period, 6 h after the morning injection to avoid association of water availability with the injection of morphine. Wayne Lab Blocks were available at all times. Following cessation of injections, Ss were offered morphine in tap water (0.5 mg/cc) for oral intake in a forced

choice presentation for 20 days, involving 10 presentations (schedule: 24 h presentation, 24 h deprivation). Morphine preferences of Ss were next determined by invoking the following conditions: a choice between tap water and morphine solution (c); a 24 h fluid deprivation (o); and a 24 h morphine only (m), in a sequence of c-o-m-o-c-o-m-o-c-o. Positions of the fluid containers were randomly varied during the (c) conditions.

At the completion of the injection schedule, when only morphine solution (0.5 mg/cc) was presented, 14 Ss did not drink this concentration of morphine. Four of these Ss did drink a 0.25 mg/cc solution. Ten Ss continued to refuse to drink. When no measurable amount of morphine solution had been ingested for seven days, tap water was made continually available, but the Ss still did not drink. Using pre-injection weight as a base, these Ss had lost 42-45% of their body weight at the time of death. Group 1 was composed of those four Ss which drank a 0.5 mg/cc morphine solution, Group 2 of those four Ss which drank a 0.25 mg/kg concentration.

Irradiation. In keeping with the deprivation schedule, Ss were irradiated on the day when morphine only was presented.² The radiation (X-radiation) source was a Mathison 140 PKV mobile therapy unit drawing 8 milliamperes and having an 8 in. cone. Exposure was checked by a CD V 746 dosimeter which gave readings in Roentgen (R) units. The radiation chamber was a circular wooden Sprague-Dawley shipping cage 16 in. in diameter and 6 in. high, divided by plywood into four equal sections. A water bottle was attached to the outside of each section with the stem available to S. The chamber was placed directly under the cone, 30 in. from the exposure source. Both groups received a summated dose of 1000 R (10 R/min).

Post-Irradiation. Test for preference changes were made over 18 days (nine sessions) by presenting a choice between tap water and morphine solution on a schedule of 24 h presentation and 24 h deprivation. The first test occurred 24 h after irradiation. The positions of the fluid containers were randomly varied to avoid stereotyped position responses.

Results and Discussion

During irradiation, the mean morphine intake for Group 1 was 9 ml and for Group 2 was 10 ml. All Ss drank during irradiation. Changes in fluid preferences were measured by utilizing a Morphine Index score (MI): morphine intake divided by total fluid intake multiplied by 100. Each S's MI was calculated after each session and was utilized for statistical analysis. Due to the small samples, a Walsh test (Siegel, 1956) was used to determine group differ-

Table 1. The MI scores of individual Ss on the last pre-irradiation day and the first post-irradiation day.

Group 1 (0.5 mg/cc)			Group 2 (0.25 mg/cc)		
S	Pre-	Post-	S	Pre-	Post-
1	29.8	10.8	1	40.0	5.9
2	41.3	13.8	2	35.0	18.3
3	51.4	19.1	3	44.0	6.2
4	24.2	8.8	4	31.2	7.1

ences. Both Group 1 and Group 2 showed a significant decrease in morphine preference ($p < .062$). A sham irradiated control group was not utilized since the effects of radiation have been conclusively demonstrated. A Mann-Whitney U test (Siegel, 1956) indicated no significant differences in morphine preference between the groups prior to irradiation. Following irradiation, the difference in morphine preference between the groups was significant at the .10 level of confidence. Table 1 presents the scores of individual Ss. Inspection of Table 1 indicated a severe and immediate drop in morphine intake for both groups. This immediate drop is quite different from the gradual decrease in morphine consumption which is generally reported (Nichols et al, 1956; Nichols, 1965). During the pre-irradiation period, the absolute mg/kg morphine intake was twice as great for Group 1 as that for Group 2, although the MI scores for both groups are quite similar. Following irradiation, the absolute morphine intake was four times as great for Group 1 as that for Group 2, but neither group approached their pre-irradiation levels. It appeared

that Group 2 was more affected by the treatment than Group 1.

Early in the injection series, at a very low dose (20 mg/kg), it was observed that some Ss bit their forepaws and vigorously licked their genital area. As the morphine dose was increased, more Ss exhibited this behavior, and the biting became more severe. At 50 mg/kg/day, three Ss had severed the bones on the dorsal surface of both their forepaws, and had amputated some of their phalanges. At 70 mg/kg/day, all Ss were displaying self injurious behavior. Biting behavior was exhibited during a 1 to 4 h interval after each daily injection. There is no report in the literature concerning this self destructive phenomenon being observed in connection with morphine injection.

References

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Notes

1. Now at University of Tennessee
2. Radiation was conducted by Dr. Imy V. Holt Department of Biology, Western Michigan University.