*Pharmacology Biochemistry & Behavior*, Vol. 23, pp. 37–42, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

# The Conditioned Place Preference Is Affected by Two Independent Reinforcement Processes

NORMAN M. WHITE AND GEOFFREY D. CARR

*Department of Psychology, McGill University, 1205 Dr. Penfield Ave., Montreal, Quebec, Canada H3A 1B1*

Received 20 August 1984

WHITE, N. M. AND G. D. CARR. *The conditioned place preference is affected by two independent reinforcement processes.* PHARMACOL BIOCHEM BEHAV **23**(1) 37–42, 1985.—The conditioned place preference method for measuring the affective properties of reinforcing events was studied using treatments of known affective value. The size of the place *aversion* observed increased with dose when the reinforcer was injections of lithium chloride. The size of the place *preference* observed increased with concentration when the reinforcer was drinking sucrose solutions. However, when the reinforcer was solutions of saccharin (that were consumed in the same amounts as the sucrose solutions) no place preferences were observed. This finding was explained in terms of the dual reinforcement hypothesis [20] which postulates that although sucrose and saccharin both have positive affective properties (based on their tastes) only sucrose has memory improving properties (based on its post-ingestive action). It was therefore proposed that conditioned place preferences depend on the activation of both affective and memory improving processes. This hypothesis was confirmed by the observation of place preferences with a saccharin solution as the reinforcer when the pairing trials were followed by non-contingent, post-pairing injections of glucose or amphetamine (both of which are known to improve memory). Therefore, behavior in the place preference method depends upon both the affective and the memory improving properties of the reinforcers under test.

Aversion Preference Memory Glucose Saccharin Conditioned place preference Amphetamine

VERSIONS of the conditioned place preference method have been used to measure the reinforcing properties of drugs by Beach [2], Kumar [17], Rossi and Reid [29] and Reicher and Holman [26]. More recently, the method has been used to detect rewarding effects of food [31] as well as those of morphine [22,23], apomorphine [37], cocaine [33] and amphetamine [32]. The method has also detected aversive effects of lithium chloride [11,23], naloxone [22,23], ethanol [30] and cholecystokinin [35].

As implied by its name, the rationale for the conditioned place preference method of measuring the effects of reinforcing events on behavior derives from associative learning theory. It has been suggested [38] that rewarding or aversive effects of reinforcers are expressed behaviorally as approach or withdrawal tendencies, respectively; and that these affective states and behaviors become associated with the constellation of neutral stimuli making up the distinctive pairing environments used with this method. On future occasions contact with the conditioned environmental stimuli evokes the approach or withdrawal behaviors, leading to increased or decreased contact with the environment containing the conditioned stimuli. The outcome of this process is a conditioned place preference or aversion.

This description implies that three stages precede the observation of a conditioned place preference. First, the reinforcing event under study must produce some affective arousal leading to approach or withdrawal. Second, the behavioral tendency produced must become associated with the environmental stimuli with which it is paired. Finally, this association must be remembered so that it can influence behavior on future occasions. The distinction between the affective process involved in the formation of associative memories and the memory improving process involved in their retention has been discussed in several previous papers describing the results of experiments with electrical self-stimulation of the brain [9,18], sucrose and glucose solutions [20], amphetamine [5] and morphine [39,40].

In the present study we set out to examine the ability of the conditioned place preference method to detect the affective properties of a variety of different pharmacological and non-pharmacological stimuli. Some of these data are presented in Experiment 1. In the course of this investigation we discovered that the detection of affective properties by this method depends on both of the processes described above: the formation and the retention of associative memories. The evidence for this conclusion is presented in Experiment 2.

## EXPERIMENT 1

### METHOD

*Subjects*

Subjects were 69 male hooded rats weighing 275–300 g at the start of the experiment. They were housed individually in hanging wire cages with standard food pellets and water continuously available except as described in the procedure.

*Apparatus*

The place preference apparatus consisted of two large pairing boxes (45×45×30 cm) made of wood with Plexiglas fronts. The two boxes were separated by a wood partition. In one large box the walls were painted white and the Plexiglas floor was covered with wood chips. In the other large box the walls were black with white masking tape stripes, there was a wire grid floor, and 1 cc of 2 percent acetic acid was dropped onto the floor before each training or test session. The two large boxes were joined by a tunnel (36×18×20 cm) made of unpainted wood, attached outside the pairing boxes at the rear. When a rat was in one of the large boxes it could not see the other one, but could move freely to it via the tunnel. To confine an animal to one of the large boxes the entrances from them to the tunnel were blocked with a moveable wood partition. A diagram of this apparatus has been published [6].

*Procedure*

The place preference procedure required 14 days. On day 1 each rat was exposed to the apparatus with free access to all boxes for 10 min. Over the next 12 days each rat was confined in one of the two large boxes for 30 min. The box in which each rat was confined alternated from day to day giving a total of 6 exposures to each box. Within each group half the rats received the experimental treatment in conjunction with exposure to one of the two boxes (the "paired" box), and the control treatment in conjunction with exposure to the other box (the "unpaired" box). The paired and unpaired boxes were reversed for the other half of the rats in each group. The assignment of rats to treatment boxes was random. On day 1 half of the rats were exposed to their paired boxes and the other half were exposed to their unpaired box.

On day 14 each rat was placed into the tunnel and allowed free access to all boxes for 20 min. The amount of time spent in each of the large boxes was recorded by observation. A rat was considered to be in one of the boxes if any part of its body (except its tail) was in that box. We have previously reported [6] that a group of 8 rats tested with the apparatus and procedure described, but with no experimental treatment associated with either large box, showed no significant preference (382 sec vs. 373 sec) on the test day.

Four groups of rats were used to test the effect of drinking four concentrations of sucrose with the place preference method: 1 percent (n=7), 4 percent (n=7), 20 percent (n=8) and 40 percent (n=8). The 1 percent solution was made by dissolving 1 g of sucrose in 100 ml water; for the other solutions sucrose was increased to the required amount. Food was removed from the rats' home cages and two Richter tubes, one containing the appropriate sucrose solution and the other containing water, were placed on the front of each cage. For the duration of the experiment food was placed in the cages for 2 hr per day; during the place preference procedure the rats were fed 30 min after their treatments for the day. On the third day of deprivation the sucrose tubes were removed from the cages (but water remained available ad lib) and the 14 day place preference procedure began. The sucrose solutions were presented in Richter tubes supported by a stand placed in the rear outside corner of each animal's paired box. No solutions were presented in the unpaired boxes.

Two groups of rats were used to test the effects of injections of lithium chloride with the place preference method: 32 mg/kg (0.75 mEq/kg) (n=8) and 64 mg/kg (n=8). The drug

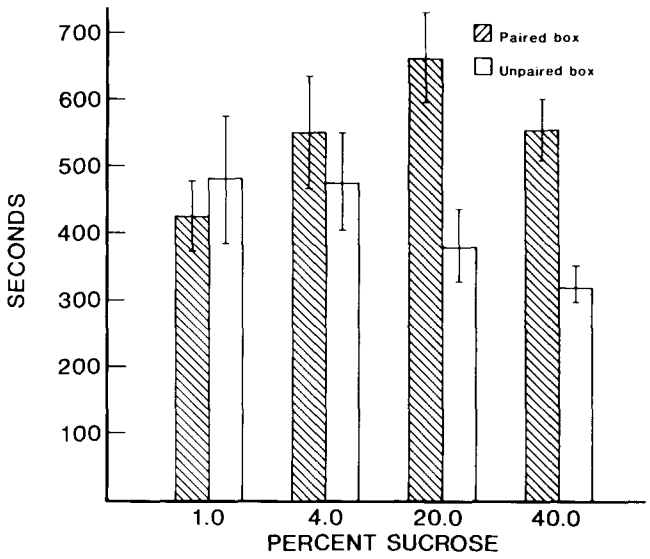


FIG. 1. Mean times spent in paired and unpaired boxes during 20 min test by rats in the groups that drank sucrose solutions in their paired boxes. The vertical lines are standard errors.

was prepared in a solution of 15 mg/ml of distilled water and injected intraperitoneally. During the 14 day place preference procedure these animals received injections of LiCl immediately before being placed into their paired boxes, and injections of equivalent volumes of normal saline solution before being placed into their unpaired boxes.

Two final groups of rats were used to test the effects of saccharin with the place preference method: 0.5 percent (n=8) and 0.8 percent (n=8). The solutions were made by adding 0.5 or 0.8 mg of sodium saccharin to 100 ml of water. These two concentrations were chosen on the basis of previous work from our laboratory [20] comparing 0.5 percent saccharin with 4 percent sucrose and 0.8 percent saccharin with 20 percent sucrose. In these experiments with satiated rats: (1) the animals consumed approximately equal amounts of the solutions within each pair when each was offered in a choice with water; and (2) the amplitude of the conditioned taste preferences produced by the solutions within each pair was approximately equal.

The procedure was similar to that described for the sucrose groups: the animals were on a food deprivation schedule and were pre-exposed to the appropriate saccharin solution in their home cages. During pairing the solutions were presented in the animals' paired boxes, and no solutions were presented in their unpaired boxes.

## RESULTS AND DISCUSSION

Figure 1 shows the effects of the 4 concentrations of sucrose tested with the place preference method. An increasing dose-concentration relationship, measured by preference for the paired side, is apparent between 1 and 20 percent. At 40 percent the preference is decreased. A two-way analysis of variance was computed for these data, with concentration of glucose as one factor and side (repeated measure) as the other. There was a significant effect of glucose concentration, $F(3,26)=3.47$, $p<0.03$, and a significant effect of side, $F(1,26)=4.89$, $p<0.04$. The amounts of time spent by the animals on their paired and unpaired sides were not signifi-

TABLE 1

MEAN TOTAL AMOUNTS [ml (sem)] OF SWEET SOLUTIONS CONSUMED ON 6 EXPOSURES TO PAIRED BOXES

| | | |
|---|---|---|
| Sucrose | | |
| 1 percent | 4.9 | (1.0) |
| 4 | 47.9 | (14.0) |
| 20 | 23.0 | (10.3) |
| 40 | 20.5 | (3.4) |
| Saccharin | | |
| 0.5 percent | 21.3 | (5.4) |
| 0.8 | 22.6 | (7.2) |

cantly different at 1 ($F=0.20$) or 4 ($F=0.34$) percent, but were significantly different at 20, $F=5.81$, $p<0.004$, and 40, $F=4.06$, $p<0.02$, percent (all $df$s=1,26). These data suggest that the version of the place preference method used in the present experiment can detect the positive affective properties associated with the ingestion of glucose solutions.

The correlation coefficient between the total amount of glucose solution consumed during each rat's 6 exposures to its paired box and the time spent in that box during the test, calculated for all 30 rats in the 4 glucose groups, was 0.31. This suggests that the amount consumed during pairing accounted for about 10 percent of the variance of the amount of time spent in the paired box on the test day. Table 1 shows the means of the total amounts of glucose drunk by the animals during their 6 exposures to their paired boxes. The conclusion that there is no consistent influence of amount consumed on time spent in the paired box is strengthened by the lack of relationship between these variables on a group basis.

The consumption data in Table 1 also suggest that for rats in the conditions of deprivation used in the present experiment the 1.0 percent sucrose solution was the least rewarding, the 4.0 percent solution was the most rewarding, and that the reward values of the 20 and 40 percent solutions were equal and about midway between the other two. (It is unlikely that feedback from the ingested sucrose inhibited intake [7,36] because the amounts consumed on each trial were too low.) The fact that the most rewarding solution—as judged by consumption—failed to cause a significant place preference while more concentrated but less rewarding solutions did cause preferences will be discussed further in the General Discussion.

Data for pairings with LiCl and saccharin are presented in Fig. 2. Exposure to the paired box while under the influence of LiCl caused an aversion to that box during the test session. A two-way analysis of variance computed on the lithium data showed a significant effect of side, $F(1,14)=13.67$, $p<0.003$, and a significant interaction between dose and side, $F(1,14)=4.78$, $p<0.05$. The difference between the amounts of time spent on the paired and unpaired sides was not significant at 32 mg/kg ($F(1,14)=1.14$), but was significant at 62 mg/kg, $F(1,14)=17.31$, $p<0.001$. These data suggest that the place preference method can detect the aversive affective properties that are generally assumed to be associated with an injection of lithium chloride [14, 27, 28]. However, it is of interest that a much higher dose of lithium was required to demonstrate aversion using the present method than is required with the taste aversion method. Conditioned taste aversions have been

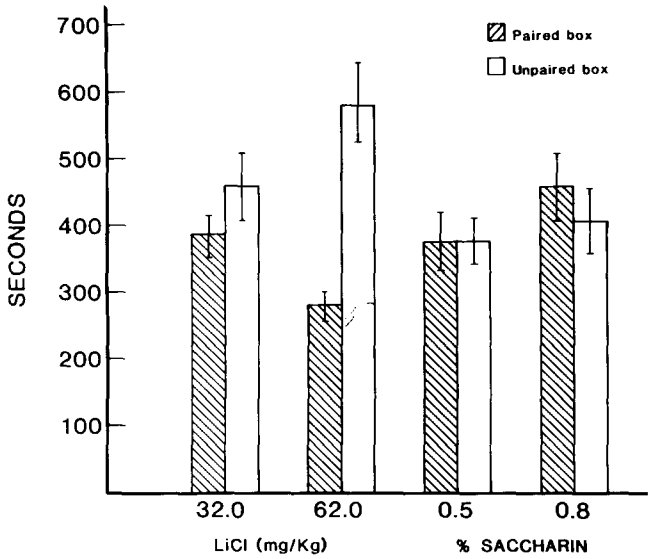


FIG. 2. Mean times spent in paired and unpaired boxes during 20 min test by rats that received injections of lithium chloride before being placed into their paired boxes (first two pairs of bars) and by rats that drank saccharin solutions in their paired boxes (last two pairs of bars). The vertical lines are standard errors.

demonstrated [24] with only a single pairing of doses equivalent to and even lower than the 32 mg/kg which failed to produce a significant place aversion after six pairings in the present study.

The data for the two groups of rats that experienced pairings with saccharin are also shown in Fig. 2. Neither concentration caused a place preference. The analysis of variance showed no significant effect of group ($F(1,14)=3.57$) or side ($F(1,14)=0.21$). The total amounts of saccharin solutions consumed by the rats in each group during their 6 exposures to their paired sides are shown in Table 1. The correlation coefficient between the total amounts of saccharin consumed during the 4 pairings and time spent in the paired box on the test day was 0.26.

The fact that these two concentrations of saccharin failed to cause a place preference is of particular interest in view of the fact that total consumption of the two solutions was about equal to that for the 20 and 40 percent sucrose solutions (Table 1) which did cause preferences. This fact, taken together with our previous data [20] described briefly in the Procedure section, as well as the data of other workers [8, 36, 42], all support the suggestion that the saccharin solutions used in the present experiment had substantial rewarding properties. The question is, therefore, why did the place preference method fail to detect rewarding effects of saccharin that are detected by direct consumption, by preference tests against water, and by conditioned taste preference methods? A possible explanation of this phenomenon, and of the fact that the place preference method also failed to detect the rewarding properties of the 4 percent glucose solution, is presented in Experiment 2.

## EXPERIMENT 2

A possible explanation of the fact that the place preference method detects the rewarding properties of glucose but not those of saccharin rests on the findings of a previous experiment [20] that examined the reinforcing properties of

these two substances. That experiment showed that although appropriately chosen concentrations of sucrose and saccharin have equal rewarding or positive affective properties based on their tastes, the differences in the post-ingestional effects of these two substances [3, 12, 34] lead to demonstrable differences in their reinforcing, or memory improving properties. The memory improving properties of sucrose and saccharin were measured by giving animals access to solutions of these substances after a training session on a conditioned emotional response task. Drinking sucrose solutions or subcutaneous injections of glucose improved retention of the CER in a retroactive, non-contingent manner. Drinking equally rewarding saccharin solutions had no such effect.

When applied to the data of Experiment 1, these findings suggest that drinking sucrose solutions caused place preferences because these solutions had positive affective consequences based on their taste and because they also had memory improving properties based on their post-ingestive consequences. On this hypothesis drinking saccharin solutions failed to cause place preferences because, although they probably have equivalent rewarding properties based on their taste, these solutions lack the post-ingestive consequences that produce the memory improvement effect.

This explanation of the data of Experiment 1 leads to an hypothesis about the place preference method. Although it seems clear from Experiment 1 and from the data of other workers cited in the introduction that the place preference method measures the affective properties of reinforcing events, it may be that these properties are not detected by this method unless a second process—memory improvement—is also activated. In the present experiment this hypothesis was tested by exposing rats to saccharin during the pairing phase of the place preference method and giving them post-training, non-contingent treatments with two known memory improving agents: glucose [20] or amphetamine [5, 10, 16, 19]. If it is true that saccharin solutions fail to cause a place preference because they lack the post-ingestional consequences that initiate a memory improving process then activating that process with post-training treatments should allow the affective consequences of these solutions to be expressed as preferences for the animals' paired boxes.

## METHOD

### *Subjects*

Subjects were 32 rats similar to those used in Experiment 1.

### *Apparatus*

The apparatus was the same as described in Experiment 1.

### *Procedure*

There were 4 groups with 8 subjects per group. The rats in the No Treatment group did not receive any post-training injections. The rats in the Saline group were injected with 2 ml/kg normal saline. The rats in the Glucose group were injected with 2 g/kg glucose prepared as 1 g/ml distilled water. The rats in the Amphetamine group were injected with 2 mg/kg d-amphetamine sulphate prepared as 2 mg/ml normal saline. All injections were given subcutaneously on the flank.

The procedure was similar to that described for Experiment 1. Food was removed from the animals' home cages and they were given access to 2 Richter tubes, one filled with water and the other with 0.5 percent sodium saccharin, for 48 hr. They were then pre-exposed to the place preference apparatus for 10 min, and pairings began on the following day. The pairing procedure differed from that for Experiment 1 in two ways. First, it lasted for 8 days, so that each rat received 4 exposures to each of the two boxes. Second, on each of the last two pairing days each rat in the three treatment groups received an injection immediately after it was removed from the apparatus. Thus, each animal received an injection after its last exposure to its paired box and after its last exposure to its unpaired box. The order of exposure to the paired and unpaired boxes was counterbalanced. All animals were returned to their home cages immediately after their injections. The test session was identical to that described for Experiment 1.

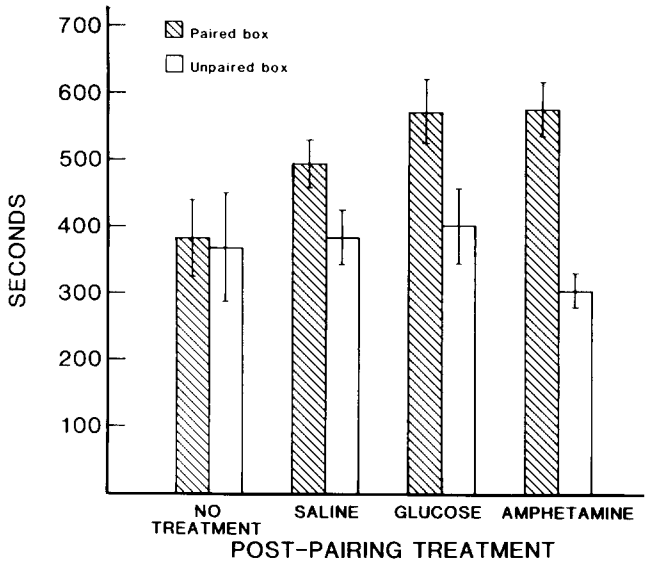


FIG. 3. Mean times spent in paired and unpaired boxes during 20 min test by rats that drank 0.5 percent saccharin solution in their paired boxes and received the injections indicated on the abscissa immediately after their last exposures to both their paired and unpaired boxes. The vertical lines are standard errors.

## RESULTS AND DISCUSSION

The place preference data are illustrated in Fig. 3. The lack of effect of saccharin alone contrasts with the place preferences observed in the rats that received the post-training memory improving treatments. The analysis of variance of these data showed a significant effect of treatment, $F(3,28)=3.52$, $p<0.03$, and a significant effect of side, $F(1,28)=15.51$, $p<0.005$. There was no significant difference between the amounts of time spent on the paired and unpaired sides by the animals in the No Treatment ($F=0.01$) or Saline groups ($F=2.52$). These two values were significantly different for the Glucose, $F=5.95$, $p<0.005$, and Amphetamine, $F=15.01$, $p<0.001$, groups (all $df$s $=1,28$).

The main hypothesis of this experiment, that drinking saccharin solutions would cause a place preference if the pairings were followed by a post-training, non-contingent memory improving treatment, is confirmed by these data. It is important to note that the post-training treatments could not have contributed directly to the place preferences observed because they were given after exposure to both the paired and unpaired boxes for each animal. Therefore, even

TABLE 2

MEAN TOTAL AMOUNTS [ml (sem)] OF 0.5 PERCENT SACCHARIN CONSUMED ON 4 EXPOSURES TO PAIRED BOXES

| | | |
|---|---|---|
| No treatment | 13.2 | (1.7) |
| Saline | 11.5 | (1.1) |
| Glucose | 10.3 | (1.4) |
| Amphetamine | 9.1 | (3.1) |

if these treatments had rewarding consequences and even if the animals were able to form an association between the experience of the boxes and these consequences, these putative associations had an equal chance of influencing behavior with respect to both boxes and could not therefore be the cause of the preferences observed. The only source of bias in the animals' experience of the two boxes was the presence of saccharin in one of them. Therefore, this must have been the cause of the observed preferences. However, the data of this experiment make it clear that in the absence of a memory improving event preferences are not expressed in this situation. The data suggest that in the absence of such an event animals do not remember the association between the paired box and the reward on the test day.

The fact that a noticeable (although non-significant) effect was observed in the Saline group is consistent with our previous data on the effect of post-training injections in experiments designed to test memory effects [5,20]. In those studies a significant difference between the effect of saline and treatment injections was observed. The fact that no such differences exist in the present data make it difficult to attribute the effects observed to specific actions of glucose or amphetamine on memory substrates. However, the place preference method was never intended to be used in the study of memory processes, and this was not the purpose of the present experiments. These data provide no new information about memory processes. They do however provide an important insight into the characteristics of the place preference method because they show that it depends on the operation of two independent and separable processes: affective arousal and memory improvement.

## GENERAL DISCUSSION

In agreement with data published by other workers the present experiments show that the place preference method is a measure of the affective arousal produced by certain types of rewarding stimuli. However, the lack of effect of saccharin alone, together with the fact that its rewarding effects were detected when post-training memory improving treatments were used, show that the place preference method is not a simple measure of affective arousal. These findings suggest that the behavior observed with this method is influenced by both the affective and the memory improving processes.

This conclusion has implications for the interpretation of the finding—in Experiment 1—that the 4 percent solution which was judged most preferred on the basis of consumption failed to cause a significant place preference, while the 20 and 40 percent solutions that were less preferred did cause place preferences. Unpublished experiments from our laboratory show that 2 g/kg, which is the equivalent of a 300 g rat drinking 3 ml of a 20 percent solution, is approximately the minimum dose of glucose that will produce an improvement in retention. Calculations based on the consumption data in Table 1 show that, on each of the 6 trials when glucose was presented, the rats in the 1 and 4 percent groups consumed an average of 0.03 and 1.06 g/kg respectively, while the rats in the 20 and 40 percent groups consumed an average of 2.55 and 4.55 g/kg respectively. The fact that the consumption of glucose was below threshold in the 1 and 4 percent groups but above threshold in the 20 and 40 percent groups may account for the fact that place preferences were observed in the latter but not in the former groups.

A second implication of the present findings is that the treatments that cause significant place preferences must have both affective and memory improving consequences. There is independent evidence that sucrose has memory improving properties [20]. There is also independent evidence for memory improving properties of amphetamine [5, 10, 16, 19], of morphine [39], of naloxone [15,21] and of ethanol [1,25] all of which cause conditioned place preferences or aversions. There is also some evidence that lithium has a memory improving effect [11], and clear evidence that aversive events in general can improve retention [41]. The conditioned place preference effects that have been observed for these substances are consistent with the suggestion that they initiate both types of processes. There do not appear to be any data on the post-training, non-contingent memory improving properties of apomorphine, cocaine or cholecystokinin, the other substances for which affective properties have been detected with the conditioned place preference method. However, if the present analysis of the factors influencing place preference is correct then the affective properties suggested by the place preference data for these substances can be taken at face value since the memory improving process affects only the expression but not the nature of the affective process. Moreover, it can be predicted that apomorphine, cocaine and CCK would exhibit memory improving properties if tested in the appropriate experiments.

As illustrated by the data for saccharin however, the absence of an effect for a particular treatment is problematical. In the general case it is not possible to know if a particular treatment fails to cause an effect because it lacks affective properties, or because it lacks memory-improving properties. One solution to this problem is to try the post-training, non-contingent memory improving method described here. Possibly a better solution is to try another method of measuring the affective properties of the treatment. As already discussed other methods such as simple consumption, preference tests and conditioned taste preference techniques detect the rewarding properties of saccharin quite well, and the same may prove to be true for other treatments that fail to cause conditioned place preferences.

Another illustration of the importance of studying the affective properties of drugs with several different methods is found in the present data for lithium chloride injections. A dose of lithium that gives unambiguous evidence of aversion with the taste aversion method [24] failed to exhibit aversive properties in the present experiment. A much higher dose and many more pairings were required to demonstrate these properties with the place preference method. This finding may suggest that taste aversion is a more appropriate measure than place aversion method for the particular affective properties of lithium. This is a case where the use of data from a single method would lead to erroneous conclusions about the affective properties of a treatment. A more striking instance of the power of using more than a single method to study the reinforcing properties of drugs is the fact that con-

ditioned place preferences—evidence of positive affective arousal—are observed with both amphetamine [32] and apomorphine [37] while these same substances both cause conditioned taste aversions [4,13]—evidence of negative affective arousal. Finally, the present data demonstrate the importance of examining the memory improving properties of drugs in separate experiments. A complete understanding of the effects of drugs on behavior will be possible only when data are available from a variety of measures of both the affective and the memory improving processes they initiate.

## REFERENCES


1. Alkana, R. L. and E. S. Parker. Memory facilitation by post-training injection of ethanol. *Psychopharmacology (Berlin)* **66:** 117–119, 1979.
2. Beach, H. D. Morphine addiction in rats. *Can J Psychol* **11:** 194–212, 1957.
3. Bunke, C. A. and R. W. Lachey. Failure of oral saccharin to influence blood sugar. *Proc Soc Exp Biol Med* **68:** 581, 1948.
4. Carey, R. J. Long-term aversion to saccharin solution induced by repeated amphetamine injections. *Pharmacol Biochem Behav* **1:** 265–270, 1973.
5. Carr, G. D. and N. M. White. The relationship between stereotypy and memory improvement produced by amphetamine. *Psychopharmacology (Berlin)* **82:** 203–209, 1984.
6. Carr, G. D. and N. M. White. Conditioned place preference from intra-accumbens but not intra-caudate amphetamine injections. *Life Sci* **33:** 2251–2257, 1983.
7. Collier, G. and R. Bolles. Some determinants of intake of sucrose solutions. *J Comp Physiol Psychol* **65:** 379–381, 1968.
8. Collier, G. H. and K. Novell. Saccharin as sugar surrogate. *J Comp Physiol Psychol* **64:** 404–408, 1967.
9. Coulombe, D. and N. M. White. The effect of post-training lateral hypothalamic self-stimulation on aversive and appetitive classical conditioning. *Physiol Behav* **25:** 267–272, 1980.
10. Doty, B. and L. Doty. Facilitating effects of amphetamine on avoidance conditioning in relation to age and problem difficulty. *Psychopharmacologia* **9:** 234–241, 1966.
11. Ettenberg, A., D. van der Kooy, M. le Moal, G. F. Koob and F. E. Bloom. Can aversive properties of (peripherally injected) vasopressin account for its putative role in memory? *Behav Brain Res* **7:** 331–350, 1983.
12. Fischor, F. and A. Schroter. Does saccharin orally administered influence blood sugar? *Deutsche Med Wehnschr* **61:** 1354, 1953.
13. Garcia, J., F. R. Ervin and R. A. Koelling. Learning with prolonged delay of reinforcement. *Psychonom Sci* **5:** 121–122, 1966.
14. Garcia, J., D. J. Kimeldorf and E. L. Hunt. The use of ionized radiation as a motivating stimulus. *Psychol Rev* **68:** 383–395, 1961.
15. Izquierdo, I. Effect of naloxone and morphine on various forms of memory in the rat: possible role of endogenous opiate mechanisms in memory consolidation. *Psychopharmacology (Berlin)* **66:** 199–203, 1979.
16. Krivanek, J. and J. L. McGaugh. Facilitating effects of pre- and post-training amphetamine administration on discrimination learning in mice. *Agents Act* **1:** 36–42, 1969.
17. Kumar, R. Morphine dependence in rats: secondary reinforcement from environmental stimuli. *Psychopharmacologia* **25:** 971–979, 1972.
18. Major, R. and N. M. White. Memory facilitation by self-stimulation reinforcement mediated by the nigro-neostriatal bundle. *Physiol Behav* **20:** 723–733, 1978.
19. Martinez, J. L., R. A. Jensen, R. B. Messing, B. J. Vasquez, B. Soumireu-Mourat, D. Geddes, K. C. Lian and J. L. McGaugh. Central and peripheral actions of amphetamine on memory storage. *Brain Res* **182:** 157–166, 1980.
20. Messier, C. and N. M. White. Contingent and non-contingent actions of sucrose and saccharin reinforcers: effects on taste preferences and memory. *Physiol Behav* **32:** 195–203, 1984.
21. Messing, R. B., R. A. Jensen, J. L. Martinez, V. R. Spiehler, B. J. Vasquez, B. Soumireu-Mourat, K. C. Liang and J. L. McGaugh. Naloxone enhancement of memory. *Behav Neural Biol* **27:** 266–275, 1979.
22. Mucha, R. F. and S. D. Iversen. Reinforcing properties of morphine and naloxone revealed by conditioned place preferences: a procedural examination. *Psychopharmacology (Berlin)* **82:** 241–247, 1984.
23. Mucha, R. F., D. van der Kooy, M. O'Shaughnessy and P. Bucenieks. Drug reinforcement studied by the use of place conditioning in rat. *Brain Res* **243:** 91–105, 1982.
24. Nachman, M. and J. H. Ashe. Learned taste aversions in rats as a function of dosage, concentration, and route of administration of LiCl. *Physiol Behav* **10:** 73–78, 1973.
25. Parker, E. S., I. M. Birnbaum, H. Weingartner, T. J. Hartley, R. C. Stillman and R. J. Wyatt. Retrograde enhancement of memory with alcohol. *Psychopharmacology (Berlin)* **69:** 219–222, 1980.
26. Reicher, M. A. and E. W. Holman. Location preference and flavor aversion reinforced by amphetamine in rats. *Anim Learn Behav* **5:** 343–346, 1977.
27. Revusky, S. H. and E. W. Bedarf. Association of illness with prior ingestion of novel foods. *Science* **155:** 219–220, 1967.
28. Richter, C. P. The development and use of alphanapthylthiourea (ANTU) as a rat poison. *J Am Med Assoc* **129:** 927, 1945.
29. Rossi, N. A. and L. Reid. Affective states associated with morphine injections. *Physiol Psychol* **4:** 269–274, 1976.
30. Sherman, J. E., C. F. Hickis, A. G. Rice, K. W. Rusiniak and J. Garcia. Preferences and aversions for stimuli paired with ethanol in hungry rats. *Anim Learn Behav* **11:** 101–106, 1983.
31. Spyraki, C., H. C. Fibiger and A. G. Phillips. Attenuation by haloperidol of place preference conditioning using food reinforcement. *Psychopharmacology (Berlin)* **77:** 379–382, 1982.
32. Spyraki, C., H. C. Fibiger and A. G. Phillips. Dopaminergic substrates of amphetamine-induced place preference conditioning. *Brain Res* **253:** 185–193, 1982.
33. Spyraki, C., H. C. Fibiger and A. G. Phillips. Cocaine-induced place preference conditioning: lack of effects of neuroleptics and 6-hydroxydopamine lesions. *Brain Res* **253:** 195–203, 1982.
34. Steffens, A. B. Rapid absorption of glucose in the intestinal tract of the rat after ingestion of a meal. *Physiol Behav* **4:** 829–832, 1969.
35. Swerdlow, N. R., D. van der Kooy, G. F. Koob and J. R. Wenger. Cholecystokinin produces conditioned place-aversions, not place preferences, in food deprived rats: evidence against involvement in satiety. *Life Sci* **32:** 2087–2093, 1983.
36. Valenstein, E. S. Selection of nutritive and non-nutritive solutions under different conditions of need. *J Comp Physiol Psychol* **63:** 429–433, 1967.
37. van der Kooy, D., N. R. Swerdlow and G. F. Koob. Paradoxical reinforcing properties of apomorphine: effects of nucleus accumbens and area postrema lesions. *Brain Res* **259:** 111–118, 1983.
38. White, N. M., C. Messier and G. D. Carr. Operationalizing and measuring the organizing influence of drugs on behavior. In: *Methods of Assessing the Reinforcing Properties of Abused Drugs*, edited by M. A. Bozarth. Brunswick, ME: Haer Institute, 1985.
39. White, N. M., R. Major and J. Siegal. Effects of morphine on one trial appetitive learning. *Life Sci* **23:** 1967–1972, 1978.
40. White, N. M., L. Sklar and Z. Amit. The reinforcing action of morphine and its paradoxical side effect. *Psychopharmacology (Berlin)* **52:** 63–66, 1977.
41. White, N. M. and P. Legree. Effect of post-training exposure to an aversive stimulus on retention. *Physiol Psychol* **12:** 233–236, 1984.
42. Young, P. T. and C. H. Masden. Individual isohedons in sucrose-sodium chloride and sucrose-saccharin gustatory areas. *J Comp Physiol Psychol* **56:** 903–909, 1963.