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Differential effects of morphine and LiCl on schedule-induced polydipsia

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Abstract

Lithium chloride (LiCl) and morphine both produce a conditioned taste avoidance response, while only LiCl is able to elicit a conditioned rejection response (taste reactivity), indicating that the effects of conditioning are drug and preparation dependent. The present experiments extend this assessment to another behavioral preparation, schedule-induced polydipsia (SIP), by examining the ability of LiCl and morphine to produce conditioned suppression of nonregulatory drinking. In Experiment 1, schedule-induced saccharin consumption was followed by LiCl or morphine (at doses comparably effective in conditioning taste avoidance under water deprivation) or by the distilled water vehicle. Although both LiCl and morphine suppressed SIP, morphine produced a significantly weaker suppression than did LiCl. Using a massed feeding design in which animals received all their food pellets in a single meal, Experiment 2 determined that LiCl and morphine were equally effective in suppressing consumption, indicating that the differential effects seen under SIP were due to the schedule of spaced food pellet deliveries. The basis for the differential effects of LiCl and morphine on SIP may be a function of an increase in the reinforcing properties of drugs of abuse (such as morphine) within this procedure that mask the acquisition and/or display of the conditioned suppression. If so, then this procedure may be useful in assessing the reinforcing properties of such drugs.

Keywords: Schedule-induced polydipsia; LiCl; Morphine; Models of drug abuse

1. Introduction

Animals injected with one of a number of drugs (e.g., LiCl, emetine, morphine, and amphetamine) following consumption of a novel solution avoid its consumption on subsequent exposures (see Garcia and Ervin, 1968; Revusky and Garcia, 1970; Rozin and Kalat, 1971; for a bibliography, see www.CTAlearning.com; see also Riley and Freeman, 2004). In a recent analysis of the basis of such conditioned taste avoidance learning, Parker (2003) argued that a taste paired with a drug is subsequently avoided because it is associated with the novel state induced by the compound. Thus, taste avoidance learning across a wide spectrum of drug classes (e.g., emetics and drugs of abuse) may be mediated by a common mechanism, specifically, drug novelty (see also Gamzu, 1977; Hunt and Amit, 1987). This is not to say that drugs from these two classes produce identical conditioned effects to the drug-associated taste. In fact, LiCl and apomorphine both can produce a conditioned disgust (or rejection) response in the taste reactivity preparation (see Grill and Norgren, 1978), in which a specific taste paired with a drug is infused directly into the animal's mouth. Such an effect is not seen with a taste paired with drugs of abuse, e.g., morphine, cocaine (Parker, 1993, 1995). These differences presumably reflect the fact that emetics, such as LiCl and apomorphine, produce nausea that mediates this conditioned disgust reaction. Drugs of abuse are without effect in this design, suggesting that they do not, as a class, produce nausea (Parker, 1995, 2003). Thus, depending upon the specific preparation examined (the conditioned taste avoidance design or taste reactivity test), drugs from different classes can condition similar or different reactions.

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Although the conditioned responses to emetics and drugs of abuse within these two preparations are well documented, it remains unknown the relationship of the conditioned responses produced by these drug classes in other behavioral preparations in which a taste is paired with a drug. One such preparation that may be useful in assessing the conditioned effects of emetic and abused drugs is schedule-induced polydipsia (SIP; see Falk, 1961, 1969, 1971). In this preparation, food-deprived rats given spaced food pellet deliveries (either contingent or noncontingent) drink voluminous amounts of water during the session. Typically, SIP follows an inverted U-shaped function such that drinking occurs immediately following the delivery of the food pellet, peaks shortly thereafter, and diminishes prior to the delivery of the next food pellet (Falk, 1969). SIP appears to be a very robust phenomenon in that it occurs with a variety of food delivery schedules, among several different species, and under a number of experimental conditions (see Falk, 1969; Wetherington, 1982). Like the conditioned taste avoidance and taste reactivity preparations, SIP involves the oral consumption of fluids. Unlike these two designs, however, consumption appears nonregulatory in nature, mediated more by the environmental contingencies of spaced food delivery than by physiological factors, such as thirst (Falk, 1969; Wetherington, 1982).

Interestingly, a number of manipulations known to condition taste avoidance and/or produce conditioned disgust have been examined for their effects on schedule-induced polydipsia. In one of the first assessments of the effects of such conditioning on SIP, Roll et al. (1969) reported that rats decreased the schedule-induced consumption of saccharin after it was paired with an exposure to radiation (which, independently, has been reported to produce conditioned taste avoidance; see Garcia and Koelling, 1967). Subsequently, Riley and his colleagues (Hyson et al., 1981; Riley et al., 1979, 1980; see also Clarke and Westbrook, 1978; for a review, see Riley and Wetherington, 1989) reported similar suppression of the schedule-induced consumption of saccharin by LiCl. This suppression of SIP was evident when the saccharin–LiCl pairings occurred during the SIP session (Riley et al., 1979) or under water deprivation prior to SIP training (Riley et al., 1979; see also Hyson et al., 1981). Although such suppression is robust, it is unknown to what extent, if any, drugs of abuse will affect the schedule-induced consumption of tastes with which they are paired. Accordingly, the purposes of the present experiments were to examine the effects of LiCl (a classical emetic) and morphine sulfate (a drug of abuse) on schedule-induced polydipsia (Experiment 1) and to assess the role of spaced food pellet deliveries in any reported differential effects (Experiment 2).

Specifically, in Experiment 1, different groups of rats were given spaced food pellet deliveries (once every 30 s, for a total of 60 food pellet deliveries), during which time a novel saccharin solution was made available. Immediately after the SIP session, subjects were injected with either LiCl, morphine sulfate, or the distilled water vehicle. The specific doses of morphine (10 mg/kg) and LiCl (0.6 mEq/kg) used in these assessments were chosen on the basis of their comparable ability to produce conditioned taste avoidance under traditional water-deprivation conditions (Randall-Thompson and Riley, 2003). That is, animals display a similar avoidance of a saccharin solution paired with either of the two drugs when trained and tested under water deprivation (see Randall-Thompson and Riley, 2003). This assured that any differences found with SIP would not reflect differences in the general strength of the two drugs in this conditioning preparation (Klosterhalfen and Klosterhalfen, 1985; Riley and Freeman, 2004). The effects of this treatment on the schedule-induced consumption of saccharin were monitored over five conditioning cycles. Data from this assessment were compared with those from animals given similar conditioning under comparable food deprivation but when the food pellets were delivered in a single massed meal (Experiment 2), providing an assessment of the role of the spaced food pellet deliveries in the effects of LiCl and morphine on SIP.

2. General methods

2.1. Subjects

The subjects were 60 experimentally naïve female rats of Sprague–Dawley descent (purchased from Harlan Sprague Dawley, Indianapolis, IN), weighing approximately 187±3 g at the outset of the study. All subjects were housed individually in stainless steel, wire-mesh cages and were maintained on a 12-h light/12-h dark cycle (lights on at 0800 h) and at an ambient temperature of 23 °C. They had restricted access to food (Harlan Tech Laboratory; see below), but ad libitum access to water in the home cages. All subjects were handled and weighed daily. Procedures recommended by the Guide for the Care and Use of Laboratory Animals (1996), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003), and the Institutional Animal Care and Use Committee at American University were followed at all times. If an animal fell below 85% of its baseline weight, it was removed from the study, given supplemental feeding, and allowed to recover prior to being placed back into the conditioning cycles.

2.2. Apparatus

Six identical chambers (27.7×19.8×20.0 cm) were used throughout the training. The chambers were constructed of 0.6-cm clear Plexiglas and a grid floor of 0.4-cm diameter stainless steel rods spaced approximately 2 cm center to center. A 1×1 cm food hopper was centered on the front wall 2 cm above the grid floor. A graduated Nalgene drinking tube, located outside the front wall of the chamber,

was attached in a manner such that the metal lick spout was flush with the outer wall of the chamber 2.5 cm above the grid floor and 7 cm to the right of the food hopper. Licking was detected by a drinkometer (Lafayette Model 58008). A continuously illuminated 28-V houselight was centered on the front wall of each chamber, 13.5 cm above the grid floor. All schedule events were programmed on a desktop IBM Aptiva and interfaced to the boxes via a Med Associates Interface that also recorded all lick responses.

2.3. Procedure

2.3.1. Phase I: adaptation

Following adaptation to ad libitum access to food and water, all subjects were deprived to 85% of their free-feeding weight and given free access to water in their home cages. At this point, training began. On Day 1 of this training, subjects were placed in the chambers for a 30-min session, during which time the subjects received a total of 60 standard formula 45-mg Noyes food pellets. Each subject received these food pellets either once every 30 s, independent of its behavior on a fixed-time 30 schedule (FT30; Experiment 1), or as a single massed meal (Experiment 2). Water was freely available during the session. Licks to the tube containing water were recorded throughout the session in 5-s intervals for the subsequent analysis of the postpellet temporal (Experiment 1) or within-session (Experiment 2) distribution of licking. Water intake was recorded at the termination of each session, and the amount consumed was calculated by subtracting the volume at the beginning of the session from the volume remaining at its end. The number of food pellets left in the hopper and/or found on the floor of the chamber (spillage) was noted and subtracted from 60 to determine the number of food pellets consumed during the session. At the end of the session, each subject was given supplemental food to maintain body weight at 85%. This daily procedure was repeated for 14 consecutive days.

2.3.2. Phase II: conditioning

Once fluid consumption stabilized (that is, water consumption was no longer increasing and was within 10% over three consecutive days), conditioning began. On the first day of this phase, subjects were treated as above, except that a novel saccharin solution (0.1% w/v Sodium Saccharin, Sigma Pharmaceuticals) replaced water as the available fluid. Immediately following this session, subjects in each experiment were assigned to one of three groups balanced for mean saccharin consumption. Subjects were then subcutaneously (sc) injected with 0.6 mEq/kg, 0.15 M LiCl (Group L; n=10), 10 mg/kg morphine (Group M; n=10), or distilled water equivolume to that administered with LiCl (Group W; n=10). Following the injection, each subject was returned to its home cage. This conditioning procedure was repeated every fourth day, for a total of five saccharin exposures. No injections were given on the final exposure to saccharin. On the three intervening recovery sessions between each saccharin exposure, subjects had access to water during the spaced feeding sessions.

2.4. Statistical analysis

For each experiment, differences in the amount of saccharin consumed and the number of pellets eaten were analyzed for the three groups using a 3×5 repeated measures analysis of variance (ANOVA) with the between-subjects variable of Drug (LiCl, morphine, and distilled water) and the within-subjects variable of Trial (1–5). For Experiment 1, differences in the postpellet temporal distribution of licking on the final saccharin exposure were analyzed for the three groups using a 3×6 repeated measures ANOVA, with the between-subjects variable of Drug (LiCl, morphine, and distilled water) and the within-subjects variable of 5-s Postpellet Interval (1–6). The repeated measures ANOVA was followed by one-way ANOVAs for each trial and pair-wise comparisons, using Tukey's post hoc tests. All determinations of statistical significance were made at $p<.05$. All statistical analyses were conducted using the Statistical Package for the Social Sciences, Version 10.0.

3. Experiment 1: spaced feeding

In Experiment 1, different groups of rats were given spaced food pellet deliveries and allowed access to saccharin during the session. Immediately following the session, they were injected with LiCl, morphine, or vehicle (distilled water) to assess the effects of such conditioning on schedule-induced saccharin consumption.

3.1. Results

3.1.1. Absolute consumption

Fig. 1 illustrates the mean (±S.E.M.) saccharin consumption for Groups L, M, and W on each of the five trials during taste avoidance conditioning on the spaced feeding baseline. There was a significant effect of Drug [$F(2,27)=59.379$, $p\leq.001$] and Trial [$F(4,108)=40.640$, $p\leq.001$] and a significant Drug×Trial interaction [$F(8,108)=31.090$, $p\leq.001$]. On the initial exposure to saccharin (Conditioning Trial 1), all subjects drank a mean of 18.72±1.06 ml of saccharin, with no significant differences in consumption among the three groups. On the following trial (the first exposure to saccharin following conditioning), subjects in the control group, Group W, drank significantly more saccharin than did the subjects in Groups L and M (all ps<.05), although these two groups did not differ from each other. On Conditioning Trial 3, Groups L and M continued to drink significantly less than did the controls ($p<.05$), and Group L drank significantly less than Group M did ($p<.05$). These relative differences were

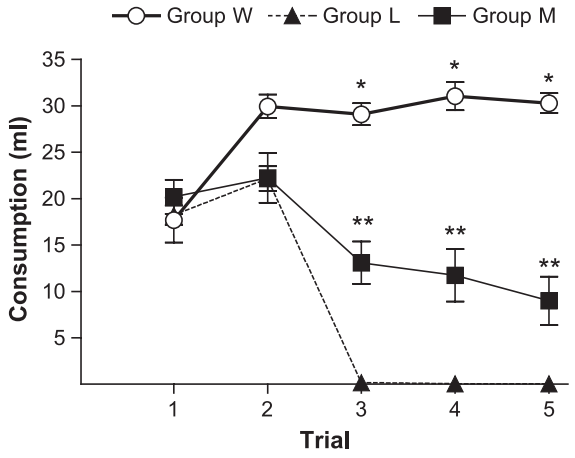

Fig. 1. Mean (±S.E.M.) saccharin consumption on each of the five conditioning trials for Groups W, L, and M under the spaced feeding preparation. *Significant difference between Group W and Groups M and L; **Significant difference between Group M and Group L.

maintained for the remainder of conditioning (all $ps<.05$). That is, subjects in Groups L and M continued to drink significantly less saccharin than did the controls, and Group L drank significantly less saccharin than Group M did. All subjects consumed all available pellets throughout all experimental sessions.

3.1.2. Temporal distribution

To determine the postpellet temporal distribution of licking on the final saccharin exposure, the average number of licks by the animals in each drug condition was noted for each 5-s period of the 30-s interpellet interval across all 60 pellets on this session. These mean (±S.E.M.) numbers of licks are represented in Fig. 2. There was a significant effect of Drug [$F(2,27)=8.832$, $p\leq.001$] and Interval [$F(5,135)=26.030$, $p\leq.0001$] and a significant Drug×Interval interaction [$F(10,135)=6.818$, $p\leq.001$]. In the first and second 5-s intervals following pellet delivery, subjects in Group L made significantly fewer licks than did the subjects in Groups M and W (all $ps<.027$). Groups M and W did not differ in the number of licks made in these 5-s periods. By the third 5-s postpellet interval, subjects in Group L licked significantly less than did the subjects in Group W ($p<.003$), but no longer differed from that of the subjects in Group M. Groups M and W still did not differ in licking (see also Interval 4). In the fifth postpellet interval, subjects in Group L did not differ from the subjects in Group W or M. In this period, subjects in Group M licked significantly less than did the subjects in Group W ($p<.006$). There were no significant differences in licking in the sixth postpellet interval.

3.2. Discussion

Experiment 1 demonstrated that LiCl and morphine had differential conditioned suppressive effects on the schedule-induced consumption of saccharin. As noted, although both groups drank significantly less than did the control subjects by Trial 3, subjects injected with LiCl drank less than did the morphine-injected subjects on Trials 3–5. These differential effects on consumption were also seen in the effects on the temporal distribution of postpellet licking on the final saccharin exposure (after four conditioning trials). As described, licking in the intervals immediately following food pellet delivery (first 10 s) was significantly suppressed in subjects injected with LiCl (compared with morphine- and vehicle-injected subjects). Although subjects injected with morphine drank significantly less saccharin than did the subjects injected with vehicle (Fig. 1), there were no significant differences in the overall temporal distribution of licking between these two groups (Fig. 2; although see the fifth 5-s postpellet period). The fact that fluid consumption was significantly reduced in Group M, without a significant decrease in licking over the 30-s postpellet interval, suggests that licking became less efficient in this group; that is, ml/lick decreased. Such a dissociation between licking and consumption is reminiscent of earlier reports of animals running faster than did the controls to the side of a chamber in which a morphine-associated solution was available, only to fail to drink the solution when reaching the chamber (see White et al., 1977; see also Wise et al., 1976); that is, approach behavior was evident, although consumatory behavior was reduced.

It is interesting that LiCl and morphine, at the doses used in the present assessment, condition a comparable taste avoidance response under identical conditioning parameters when animals are trained and tested under water deprivation (the procedure typically used in the assessment of conditioned taste avoidance; see Riley and Freeman, 2004). That is, animals injected with LiCl (0.6 mEq/kg) and morphine (10 mg/kg) following saccharin consumption under water deprivation decrease saccharin consumption but do not differ at any point over conditioning, indicating

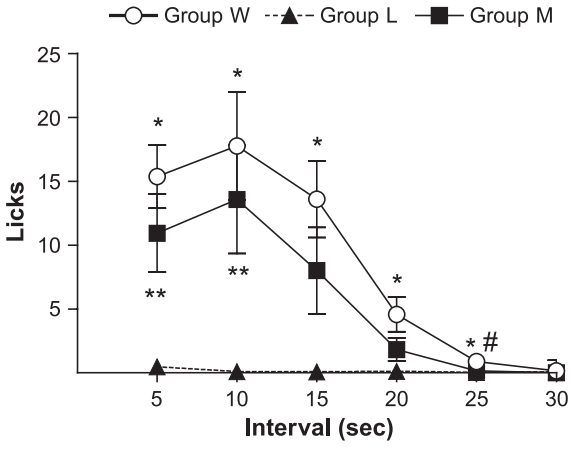

Fig. 2. Mean (±S.E.M.) number of licks for each 5-s period of the 30-s interpellet interval across all 60 food pellets on the final conditioning trial for Groups W, L, and M under spaced feeding. *Significant difference between Groups W and L; **Significant difference between Groups M and L. #Significant difference between Groups W and M.

that these compounds, at these specific doses, produce comparable conditioned avoidance (Randall-Thompson and Riley, 2003). The fact that, under the spaced feeding conditions of Experiment 1, the drugs were differentially effective in suppressing the consumption of the drug-associated taste and in suppressing its temporal patterning suggests that something about the schedule of spaced food pellet deliveries affects the conditioned response (its acquisition and/or display).

4. Experiment 2: massed feeding

If spaced feedings (in the case of Experiment 1 the delivery of food pellets on the FT30 schedule) is important to the differential ability of LiCl and morphine to suppress consumption, then such differential effects would not be expected if animals were given their food access in a single massed meal, i.e., not spaced. This was tested in Experiment 2, in which food-deprived animals were given 60 food pellets at the outset of a 30-min session, during which saccharin was available. Immediately following the session, subjects were injected with either LiCl, morphine, or vehicle to assess the effects of conditioning on saccharin consumption under massed feeding.

4.1. Results

Fig. 3 illustrates the mean (±S.E.M.) saccharin consumption for Groups M, L, and W on each of the five trials during conditioning on the massed feeding baseline. There was a significant effect of Drug [$F(2,27)=98.311$, $p<.01$] and Trial [$F(4,108)=33.045$, $p<.01$] and a significant Drug×Trial interaction [$F(8,108)=44.046$, $p<.01$]. On the initial exposure to saccharin (Conditioning Trial 1), all subjects drank a mean of 7.98±0.59 ml of saccharin, with no significant differences in consumption among the three groups. On the following trial, subjects in Groups L and M drank significantly less than did the subjects in Group W ($p<.05$), although Groups L and M did not differ from each other. Over conditioning, Groups L and M continued to drink less saccharin than did Group W (all ps$<.05$). With the exception of Trial 4, in which Group M drank significantly more than Group L did, these groups did not differ throughout conditioning.

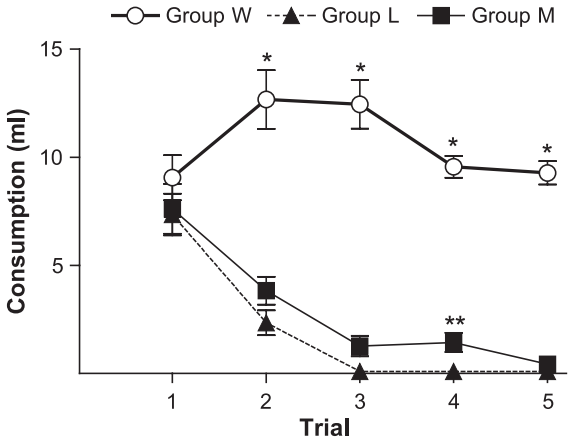

Fig. 3. Mean (±S.E.M.) saccharin consumption for all groups on each of the five conditioning trials for Groups W, L, and M under the massed feeding preparation. *Significant difference between Group W and Groups M and L; **Significant difference between Groups M and L.

4.2. Discussion

The fact that the schedule-induced consumption of saccharin was differentially affected by LiCl and morphine (Experiment 1), while the same doses of these drugs produce comparable taste avoidance under water deprivation (Randall-Thompson and Riley, 2003), suggests that some aspect of the spaced delivery of food pellets may be important in producing these differences. If so, then it might be expected that drinking under a massed feeding condition in which food deprived animals receive their food pellets in a single massed meal (i.e., without the spacing) would not be differentially affected by these two drugs. This was tested in Experiment 2. As reported, both LiCl and morphine significantly suppressed drinking under the massed feeding baseline. Interestingly, the rate of acquisition of the suppression, as well as its degree, was similar for both drugs. Although similar, there was at least one trial on which the effects of morphine were less than those of LiCl. One possible explanation for this difference is suggested by the work by Cohen and Looney (1984), who reported that, even under massed feeding, animals may space their meals in such a way that induces some degree of drinking. That is, animals do not eat all their pellets in a single prolonged meal, but intersperse eating with bouts of drinking. An analysis of the licking pattern under massed feeding in the present experiment (data not shown) revealed that subjects displayed multiple drinking bouts in the session, although the frequency and distribution of the bouts did vary among subjects. These patterns of licking suggest that the animals were eating the 60 pellets in multiple discrete meals separated by bouts of drinking. If this were the case, then there was some degree of spaced feeding even under the massed feeding baseline, a spacing that may have affected the acquisition of the avoidance response. However, given that the patterns of feeding and drinking were not evaluated in the present study, this explanation must be seen as speculative. The basis for the weak difference in the suppression induced by LiCl and morphine under massed feeding remains unknown. What is clear, however, is that while LiCl and morphine did differ, these differences were inconsistent (only on one trial) and to a much smaller degree than that seen under spaced feedings. It is, of course, possible that a more sensitive procedure might have detected more consistent and greater differences in the effects of the two drugs under the massed feeding baseline.

5. Final discussion

As described, animals avoid consumption of tastes paired with either LiCl or morphine, yet only display a disgust reaction to (and reject) tastes paired with LiCl (and not morphine). Parker (2003) has used such data to argue that different mechanisms (drug novelty and nausea, respectively) mediate the two behavioral expressions and that the differences among drugs are a function of the properties of the drugs used during conditioning. The present experiments attempted to extend this characterization of these two drug classes by assessing the ability of LiCl and morphine to suppress the schedule-induced consumption of drug-associated tastes. Although SIP is a consumatory response, it is nonregulatory in nature, allowing for an examination of drug conditioning on a different class of behavior (see Wetherington, 1982). As reported, LiCl and morphine differentially affected the schedule-induced consumption of the drug-associated saccharin solution (Experiment 1). Specifically, SIP was suppressed to a greater extent by LiCl than by morphine. This differential suppression was not a function of the relative strengths of these two compounds as conditioning agents, given that these compounds comparably suppress the consumption of the drug-associated solution when training and testing occurs under water deprivation (under identical parametric conditions as in Experiment 1 of the present paper; see Randall-Thompson and Riley, 2003). Furthermore, under the specific feeding condition of Experiment 2, in which food pellet deliveries were not spaced but were given in a single massed meal, consumption of saccharin was similarly suppressed by both LiCl and morphine, suggesting that something about the spaced food deliveries was important to the differential effects of the two drugs under the SIP procedure.

The basis of this effect of spaced feeding, however, remains unknown. One possibility concerns the actual nature of the SIP procedure itself, i.e., its induction of fluid consumption (Falk, 1969). Spaced delivery of food pellets does induce consumption, and it is possible that such an induction procedure is sufficiently strong to attenuate the effects of conditioning; that is, the solution is paired with drug administration, but spaced food pellet deliveries override any conditioning effects. Such an argument has been used to account for the relatively weaker effects that conditioning has under SIP than under water deprivation or massed feeding when LiCl is used as the conditioning agent (Riley and Wetherington, 1989). For example, Riley and his colleagues noted that, while LiCl immediately (after a single conditioning trial) suppressed the consumption of the drug-associated taste under water deprivation and massed feeding, this suppression was delayed under SIP, suggesting that the induction of fluid consumption by spaced feeding was sufficiently strong to affect the display of suppression (Hyson et al., 1981; Riley et al., 1980; for a review, see Riley and Wetherington, 1989). Furthermore, the extinction of the conditioned suppression was significantly accelerated under SIP (as compared with that under water deprivation and massed feeding), again indicating the effects of the induction schedule. Interestingly, when taste avoidance (established by LiCl) was acquired under water-deprivation conditions and tested in extinction under spaced and massed feeding, differential effects were again evident with greater suppression under massed versus spaced feeding (Hyson et al., 1981). Clearly, the spaced feeding condition induces fluid consumption to a degree that overrides the avoidance response. Although this induction to drink may impact behavioral suppression (compare the effects of LiCl on spaced vs. massed feeding in the present studies), it is important to note that, in Experiment 1, such an induction procedure was operating under both the LiCl and morphine conditions. That is, while the suppressive effects of both drugs may have been affected by the strong induction to drink, the same induction procedure was in effect for both drugs. Thus, this alone is unlikely the basis for the different effects of LiCl and morphine on SIP.

The differential effects of LiCl and morphine on SIP parallel differences with these drugs on the taste reactivity test where LiCl-associated tastes elicit a rejection response that is not seen with morphine-associated tastes. As noted, Parker (2003) ascribes this difference to the fact that only LiCl produces nausea, a condition apparently necessary for the conditioning of disgust reactions. This might suggest that only drugs with such a capability would suppress SIP, but as illustrated, morphine does suppress SIP, just not to the level as that produced by LiCl. That is, the differences between LiCl and morphine are more graded in nature as opposed to absolute (as in the taste reactivity test; Parker, 1995). The differences between LiCl and morphine on SIP may be mediated by yet another difference between the two drugs (as opposed to nausea).

Instead, the differential effects of LiCl and morphine on SIP may be related to their differential rewarding effects. That is, drugs with reinforcing effects (as assayed in conditioned place preference and self-administration preparations; see Bozarth, 1987) may have less of an effect on SIP than do emetics such as LiCl (with no known reinforcing effects). This position argues that the reinforcing effects of drugs of abuse may become more pronounced under the conditions of spaced feeding (see Falk, 1983, 1998; Falk and Tang, 1989) and that these effects may compete with or mask the effects of the drug that conditions taste avoidance, e.g., drug novelty (Gamzu, 1977; Parker, 2003) and toxicity (Riley and Tuck, 1985). Interestingly, a variety of drugs of abuse known to condition taste avoidance (but not conditioned disgust) under water deprivation are readily consumed under schedules of spaced food pellet deliveries (Falk and Tang, 1985; Falk et al., 1990; Leander et al., 1975; Lester, 1961; Meisch, 1975; Singer et al., 1982; Singer and Wallace, 1984; Tang and Falk, 1990), suggesting that the reinforcing effects of recreational compounds may become more pronounced or evident under spaced feedings and alter their ability to

suppress drinking. Furthermore, Falk and his colleagues have recently shown that not only will animals consume cocaine under a schedule of spaced food pellet deliveries, but also the cocaine self-administered under this procedure is effective in conditioning a place preference (Seidman et al., 1992). Clearly, drugs consumed within the SIP baseline can be reinforcing. It remains unknown if and to what extent these properties increase under conditions of spaced food pellet delivery, why these properties would increase (see Falk, 1983, 1998), or how such properties might interact or impact the ability of compounds to suppress consumption. Assessments with and comparisons among other emetic and recreational drugs might provide evidence for similarities and differences in their ability to affect SIP. It would be expected that compounds such as cocaine, alcohol, and amphetamine would be less effective in this suppression than classical emetics such as apomorphine and emetine. If so, then the spaced feeding preparation may be useful as an animal model to assess the reinforcing effects of drugs in general.

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