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Postinjection suppression of drinking is modified by the presence of conditioned contextual cues: Implications for both anticipatory and posttreatment nausea in humans

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In three experiments, we set out to determine whether the response of rats to an injection of LiCl would be modified by the presence of an environmental context that had previously been paired with LiCl. Experiment 1 confirmed that one feature of the malaise produced by LiCl is a reduced tendency to consume an otherwise palatable flavor. Experiment 2 showed that the size of this response was enhanced if it was measured in the presence of a conditioned context. In Experiment 3, we investigated the possibility that the postinjection response could be modified by an overshadowing treatment given during the conditioning phase. The significance of these findings for the understanding of chemotherapy-induced nausea in the clinical population is discussed.

Patients undergoing a regime of chemotherapy for the treatment of cancer often experience a range of unpleasant side effects, perhaps most notably nausea and vomiting (Morrow & Dobkin, 1987). Of particular interest is the observation that these side effects can occur in anticipation of the treatment: The sights, sounds, and smells of the clinic can become sufficient to induce nausea and vomiting. It has been suggested that this phenomenon, referred to as *anticipatory nausea and vomiting* (ANV), has its origins in a classical conditioning process (see, e.g., Nesse, Carli, Curtis, & Kleinman, 1980). In terms of this account, the complex of stimuli that are present in the clinical setting constitutes the conditioned stimulus (CS), and the cytotoxic drug treatment is regarded as the unconditioned stimulus (US). Following a number of treatments, experience of the CS alone is sufficient to produce the responses (nausea and vomiting) that are reminiscent of those produced by the drug itself.

In spite of the advent of modern antiemetics, ANV still remains a considerable problem. For instance, in a study conducted by Tyc, Mulhern, Barclay, Smith, and Bieberich (1997), 59% of the patients complained of ANV in spite of receiving ondansetron antiemetic therapy. Moreover, it has been asserted that once the symptoms of ANV have developed, they cannot be controlled by antiemetic agents (Morrow & Rosenthal, 1996). It may therefore be worthwhile to look for other procedures that can be used to supplement antiemetic medication (particularly in those cases in which such medication is inappropriate) in order to alleviate the severity of ANV.

The conditioning model of ANV has led to the proposal that laboratory studies of the conditioning process in animals may provide a tool with which to develop possible intervention strategies for reducing the occurrence of ANV in the clinic. Using rat subjects, it has been established that an environmental context can serve as a CS for illness. In particular, rats given an injection of LiCl before being placed in a distinctive environment will subsequently show a conditioned aversion to that context, as is revealed by a test in which the subjects decline to drink a flavored solution that is offered in that context. This result is taken to suggest that the context has come to acquire aversive properties as a consequence of this training procedure (Rodriguez, Lopez, Symonds, & Hall, 2000). The parallel between the training given to rats in the latter study and the regime given to patients that develop ANV is straightforward; in both cases, a conditioned response (CR) to the contextual cues develops as a consequence of the subjects' having experienced, it is supposed, some degree of illness in the presence of these cues.

Some investigators have already begun to explore the potential of procedures derived from the conditioning model for the relief of ANV in the clinical population. For example, it has been well established in studies of animal conditioning that conditioning to a target cue can be restricted by the presentation of a salient additional cue in compound with the target cue during conditioning trials. This *overshadowing effect* has been confirmed for nausea-based context conditioning in rats by Symonds and Hall (1999), who showed that the magnitude of the context aversion could be reduced if the rats were allowed to consume a novel flavored drink on the conditioning trials. A

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study by Stockhorst et al. (1998) provides evidence of a similar effect in the clinic. In their study, patients receiving chemotherapy who were given a novel juice drink prior to each treatment session complained less of ANV than did a group of patients that had received plain water in the treatment sessions. These overshadowing effects, obtained in both animals (Symonds & Hall, 1999) and humans (Stockhorst et al., 1998), are uniquely anticipated by a conditioning model of ANV.

A further finding of Stockhorst et al. (1998) (and the one that will form the focus of the present paper) is also of interest. They found that subjects for whom ANV had been reduced by the overshadowing treatment showed a tendency to suffer less from posttreatment nausea and vomiting (PNV). In other words, the overshadowing treatment appeared to be capable of attenuating not only the conditioned effects of the drug treatment (ANV), but also the direct effects of the drug treatment (PNV). The interpretation offered by Stockhorst et al. was that ANV may contribute to PNV. Given that administration of the drug takes place in the presence of cues that can evoke ANV, it is possible that the latter will summate with the direct responses induced by the chemotherapy treatment. One implication is that ANV, when it develops, would also have the potential to make PNV worse; a further implication is that an overshadowing treatment that reduces the severity of ANV would also reduce the observed magnitude of PNV.

The notion that PNV may involve a contribution from ANV amounts, in terms of the conditioning model, to the proposal that the CR (i.e., ANV) will summate with the unconditioned response (UR) directly produced by the drug infusion. Experimental studies of conditioning provide only limited support for the proposal that CRs and URs summate. The summation effect has been obtained with some training procedures (see, e.g., Donegan, 1981), but in others the presence of a CS prior to the occurrence of a US has been found to be without effect on the size of the UR (Donegan, 1981) or even to produce a reduction in its magnitude (Donegan, 1981; Kimble & Ost, 1961). Wagner (1981; see also Canli, Detmar, & Donegan, 1992; Donegan, 1981) has developed a coherent account of this varied pattern of results. One important factor, according to this account, is the intensity of the US: Summation is more likely to be observed when the vigor of the UR elicited by the US is not substantially greater than the vigor of the CR. More obviously critical is the nature of the CR. According to Wagner, some response systems operate according to opponent-process principles, and in these evocation of the CR will restrict the size of the UR. Only in systems in which the conditioned change in behavior is in the same direction as that evoked by the US can summation be expected to occur.

Clearly, it will require experimental study to determine whether the particular parameters used in our studies of nausea-based context conditioning will generate summation between CR and UR. Our first step, therefore (in Experiment 1), was to establish the nature of the UR produced by an injection of LiCl using the response measure (fluid consumption) that served as the CR in the context conditioning procedure of Rodriguez et al. (2000). As we have noted, the CR in this situation is a suppression of consumption; we hoped to confirm, for our training situation, the previous observation (Domjan, 1977) that such a suppression also characterizes the UR. In Experiment 2, we investigated the interaction of the CR and the UR by observing the reaction of rats to an injection of LiCl in a context that had previously been paired with the US. Evidence for summation would be consistent with the hypothesis of Stockhorst et al. (1998) that the magnitude of PNV may be enhanced by a contribution from ANV. Finally, in Experiment 3, we explored the effects of an overshadowing manipulation on the response of rats given the LiCl injection in the presence of conditioned contextual cues.

EXPERIMENT 1

Our aim in Experiment 1 was to determine the UR to an injection of LiCl using the measure (willingness to consume an otherwise palatable flavored solution) that had previously been used as the CR in studies of nausea-induced context conditioning. Previous work (Domjan, 1977) suggests that this UR is likely to be a suppression of consumption. In order to confirm this finding with our experimental procedures, two groups of subjects received an injection of either LiCl (Group LiCl) or physiological saline (Group Sal) before being placed into an experimental context for 30 min. During the 30-min session, the consumption of a novel sucrose solution was measured during each of six 5-min periods. This particular session length (30 min) was chosen so as to match the time scale that is routinely used in our standard context conditioning procedure (see Rodriguez et al., 2000). The test was divided into 5-min sections because pilot work carried out in our laboratory has revealed that, although rats given LiCl consume less than animals given saline do, the former animals show an initial tendency (during the first 15 min of testing) to consume *more* fluid than do those given saline. It therefore seemed worthwhile to establish a more precise profile of the UR over a 30-min test period. Nonetheless, our expectation was that, overall, Group LiCl would consume less of the sucrose than would Group Sal.

Method

Subjects and Apparatus. The subjects were 16 experimentally naive male hooded (Lister) rats with a mean free-feeding weight of 445 g (range: 420–480 g). Throughout the duration of the experiment, the subjects were housed in pairs in their home cages, where they were allowed continuous access to food. The cages were made of opaque plastic, and each measured 35 × 22 × 19 cm. These had wire mesh roofs that held food and (when available) a water bottle; a layer of wood shavings covered the floors. The cages were situated in a large colony room that was brightly lit from 0800 h to 2000 h each day.

Two types of cage, each distinct from the home cage, served as the experimental contexts. In this experiment, each subject experienced only one of these contexts, but we thought it necessary to establish the effectiveness of each, given that the design of a subse-

quent experiment (Experiment 3) required the use of both. The first set of cages was located in a separate small room dimly lit by a single 60-W red lamp and containing a speaker supplying constant background white noise, with an intensity of 75 dB, close to the cages. In addition, a commercially obtained pine fragrance (Magic Tree) air freshener was hung over the lamp during each experimental session. The walls and floors of these cages were made of transparent plastic, and each cage measured 33 × 20 × 19 cm, and the roofs were made of wire mesh, each containing a hole, through which a drinking spout could be inserted. The floors were covered with commercially obtained cat litter. The cages in the second set were larger, each measuring 42 × 35 × 16 cm, and were located in a brightly lit colony room in a separate part of the laboratory. The floors and walls of these cages were made of translucent white plastic, and the wire mesh roofs included a section through which a drinking spout could be inserted. Inverted 50-ml centrifuge tubes equipped with stainless steel ball-bearing-tipped spouts were used to present measured quantities of a solution of 3.4% sucrose (w/v). The US used for the experimental sessions was an intraperitoneal injection of 0.15 M LiCl administered at 10 ml per kg of body weight.

Procedure. The initial stages of water deprivation were carried out with the subjects housed in pairs in their home cages. The standard water bottles were first removed overnight, and on the next 2 days access to water was restricted to two daily 30-min sessions, initiated at 1100 h and at 1700 h. The experimental session was given on the next day. During this session, the subjects in Group LiCl received an injection of LiCl before being transferred immediately to one of the contexts. Half of the subjects experienced the small dark cages, and half the larger cages. The subjects in Group Sal were treated similarly, except for receiving an injection of physiological saline (10 ml/kg of body weight) prior to being transferred to one of the contexts. Immediately after being placed in the context, they were given access to a bottle containing the sucrose solution, and consumption was measured at intervals of 5 min over the next 30 min. This was achieved by removing the bottle and weighing it at the end of each 5-min period. It should be noted that the process of transferring the injected animals from the preparation area of the laboratory to the experimental cages took a small amount of time; the estimated interval between the administration of the injection and the onset of the first test period was approximately 5 min.

Results and Discussion

Group mean scores for consumption of sucrose during each of the six 5-min intervals are shown in Figure 1. Inspection of the data showed no differences between the subgroups that experienced the small cages as the experimental context and those given the larger cages, and their results are pooled in the figure. The figure shows that Group LiCl consumed more of the sucrose than did Group Sal during the first 5-min period, but over the next five test intervals the pattern was reversed, Group LiCl drinking less of the sucrose on these trials than Group Sal. As a result, the overall level of drinking during the 30-min testing period was lower for Group LiCl (5.8 ml) than for Group Sal (9.5 ml), similar to the effect reported by Domjan (1977). Statistical analysis confirmed this impression of the data. The rejection level adopted for this and for subsequent analyses was $p < .05$. An analysis of variance (ANOVA) with group and trial as the variables revealed there to be a significant effect of group [$F(1,14) = 7.33$] and of trial [$F(5,70) = 12.64$], and a significant interaction between these two variables [$F(5,70) = 11.19$]. This interaction was explored using an analysis of simple effects, which confirmed that sucrose consumption differed significantly between the groups on Trial 1 ($F = 7.02$), Trial 2 ($F = 20.67$), Trial 3 ($F = 14.18$), Trial 4 ($F = 9.30$), Trial 5 ($F = 9.69$), and Trial 6 ($F = 5.60$).

The results of Experiment 1 are broadly similar to those of Domjan (1977), in which rats showed a tendency to suppress their consumption of a novel flavor in direct response to an injection of LiCl. Our results further revealed, however, that this response is of a biphasic nature; although the animals injected with LiCl showed an overall suppression of consumption over the 30-min testing period, they also showed an increased level of consumption during the first 5-min test period. The reason for this initial elevation of sucrose intake in Group LiCl is unclear; one possibility is that the initial discomfort induced by the injection of a toxin such as LiCl induces a need for fluid consumption. Our primary concern, however, is with the possibility that the pattern of responding that constitutes the UR can be enhanced if it is measured in the presence of conditioned contextual cues. This possibility was explored in Experiment 2.

EXPERIMENT 2

Previous work (e.g., Rodriguez et al., 2000) has confirmed that one CR that is observed when animals are placed in an illness-paired context is, like the overall UR observed in Experiment 1, a suppression of consumption of a novel flavor. Our aim in Experiment 2 was not only to confirm this context conditioning effect over a time course comparable to that used in Experiment 1, but also to examine whether the postinjection response to LiCl would be modified if it were measured in the presence of conditioned contextual cues.

Experiment 2 employed four groups. Group Paired received injections of LiCl prior to exposure to an experimental context. Group Unpaired experienced the LiCl injection and the context on separate occasions. Both groups then received a test phase, in which they were given access to a sucrose solution in the target context. On the basis of the results reported by Rodriguez et al. (2000), it was anticipated that Group Paired would drink less of the test flavor than would Group Unpaired. A further pair of groups—Group Paired–LiCl and Group Unpaired–LiCl—were treated identically, except that they received an injection of LiCl immediately prior to the test session with the sucrose. The purpose of measuring this postinjection response was to assess whether the UR evoked by the LiCl would summate with the CR evoked by the conditioned context. If this is the case, then the subjects tested in the conditioned context (Group Paired–LiCl) might be expected to show a greater tendency to suppress consumption of the test flavor than subjects in Group Unpaired–LiCl do.

Method

Subjects and Apparatus. The subjects were 32 experimentally naive male hooded (Lister) rats with a mean free-feeding weight of 462 g (range: 430–500 g). They were housed and maintained in the same way as the subjects in the previous experiment.

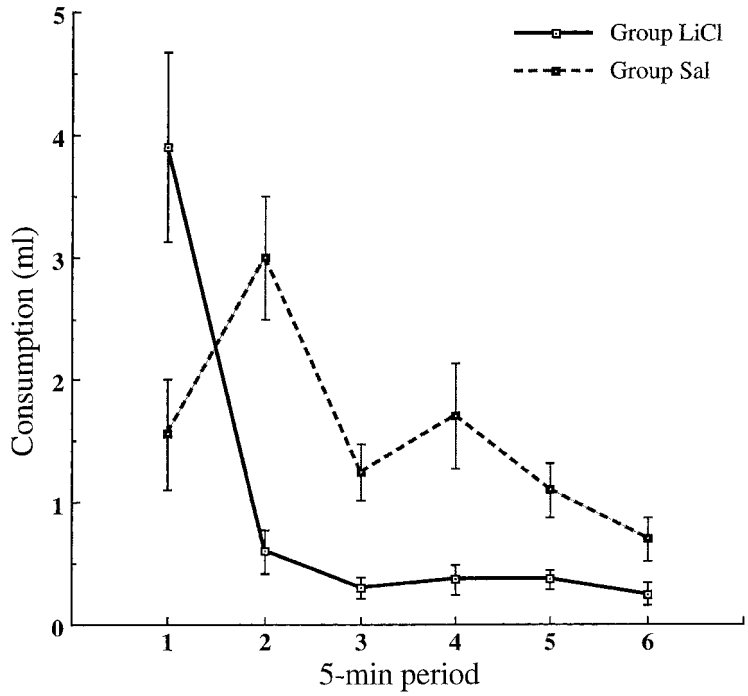

Figure 1. Group mean scores (with standard errors) for sucrose consumption in each 5-min test period in Experiment 1. For the subjects in Group LiCl, this test immediately followed an injection of LiCl. For those in Group Sal, this test followed an injection of physiological saline.

Procedure. A schedule of water deprivation was initiated as in the previous experiment. The subjects were divided into four groups, and the next 4 days constituted the conditioning phase of the experiment. On Day 1 of this phase, Group Paired and Group Paired–LiCl received an injection of LiCl at 1100 h, after which they were placed in an experimental context for 30 min. Group Unpaired and Group Unpaired–LiCl were treated identically, except that they were returned to the home cage immediately after being given the injection of LiCl; their exposure to the context was then given 5 h later, at 1600 h. At 1700 h, all of the subjects received supplementary water in the home cage for 30 min. The next day was a recovery day, on which the subjects received two 30-min sessions of free access to water in the home cage, initiated at 1000 h and at 1700 h, respectively. This 2-day cycle was then repeated. On Day 5, the subjects received a single test trial, on which they were placed in the experimental context for 30 min. For the subjects in Group Paired–LiCl and Group Unpaired–LiCl, this test was preceded by an injection of LiCl. During the test, all of the subjects had access to the sucrose solution, and consumption of this flavor was recorded every 5 min. As before, for half of the subjects in each group the small cages served as the experimental context, and for the remainder the large cages were used.

Results and Discussion

Group mean scores for each of the 5-min test periods are presented in Figure 2. It is first of all evident that the groups given an injection of LiCl immediately prior to the test drank less overall than did those not given the injection, confirming the finding of Experiment 1. Also in line with the results of that experiment is the finding that Group Unpaired–LiCl (the condition that most closely approximates that of Group LiCl of Experiment 1) consumed the sucrose solution perfectly readily during the first test period, suppressed consumption becoming evident only in later test periods. This effect was not seen, however, in the group (Group Paired–LiCl) that experienced the effects of the injection in the conditioned context; for these subjects, consumption was suppressed throughout the test. An analogous effect was also obtained in the groups that did not receive the injection prior to the test: Animals in Group Paired drank less than did those in Group Unpaired, but only in the initial stages of the test.

Statistical analysis confirmed these impressions. An ANOVA was conducted on the data summarized in Figure 2, the variables being conditioning treatment (paired or unpaired), test condition (LiCl or no LiCl on test), and test period. This analysis revealed that there was an effect of test condition [$F(1,28) = 51.65$] and an interaction between conditioning treatment and trial [$F(5,140) = 2.42$; all other Fs < 1]. The source of this interaction was explored using an analysis of simple main effects, which revealed an effect of conditioning treatment (paired vs. unpaired) on the first trial of the test [$F(1,28) = 8.08$]. The evidence for the summation of the CR and UR critically depends on there being a difference between the two groups given LiCl on the test. Accordingly, a further analysis was conducted on the data from Groups Unpaired–LiCl and Paired–LiCl for the first test trial, which confirmed that these two groups did indeed differ [$F(1,14) = 7.45$].

The results of Experiment 2 are clear-cut. First, the difference in consumption of the test flavor between Group Paired and Group Unpaired is broadly consistent with the results of the study reported by Rodriguez et al. (2000), in which subjects given prior context–LiCl pairings were found to consume less of the test flavor than unpaired controls did. In that study, however, the difference was found for data pooled over the entire 30-min test period, whereas in the present study the conditioning effect was found only during the first 5 min of testing. One possible reason for this discrepancy is that only two conditioning trials were given in the present study, in comparison with four trials in the Rodriguez et al. study. The context–illness association is therefore likely to have been weaker in the present study, perhaps resulting in a CR that prevails only over a shorter period of testing.

Our primary concern, however, is that the present results are consistent with the notion that the severity of postinjection responding to LiCl can be enhanced if measured in a context that has previously been paired with illness. The profile of this response, when measured in an unconditioned context (Group Unpaired–LiCl), was comparable to the UR that was demonstrated in Experiment 1. In this case, the subjects showed a substantial decline in responding after the first 5-min test trial. The pattern of responding to the LiCl was different, however, in those subjects for whom the test context had been previously paired with illness (Group Paired–LiCl). This group showed consistently low levels of consumption throughout the six test trials. Our explanation for this difference rests on the assumption that, for the subjects in Group Paired–LiCl, the postinjection response to LiCl will be composed of both the UR and, by virtue of the presence of the conditioned context, the CR, which produces suppression of consumption in the early stages of testing. The summation of these two responses will thus result in a greater suppression of consumption relative to that of the subjects in Group Unpaired–LiCl; in the latter group, the postinjection response will presumably consist only of the UR evoked by the LiCl. Further evidence of the summation effect might also be derived from a comparison of the test intakes between Group Paired and Group Paired–LiCl; the greater suppression of consumption in the latter group indicates that the UR is indeed present (although this comparison should be treated with caution, given that Group Paired and Group Paired–LiCl were treated differently on the test: The latter group received an injection prior to the test, whereas the former did not).

Given the parallel between the procedures used here to measure contextual conditioning and those that produce ANV in the clinical population, the results of Experiment 2 could be of clinical significance. In particular, our present results lend support to the suggestion that ANV, when it develops, could also enhance the direct effects of anticancer drugs (e.g., PNV). Our analysis implies that any procedure that is capable of reducing the strength of context–illness associations should also be able to reduce the severity of the postinjection response when it is measured in the presence of the contextual cues. If this is the case, then such an intervention could potentially be used as a treatment for both ANV and PNV. One possibility, suggested by the animal learning model, is taken up in Experiment 3.

EXPERIMENT 3

A robust feature of classical conditioning is that the associative strength acquired by a CS will be reduced if conditioning occurs in the presence of a second, nontarget CS. This *overshadowing phenomenon* (Kamin, 1969) has been documented for a variety of conditioning procedures, including procedures similar to those used in the present series of experiments. Symonds and Hall (1999) have found that rats given a novel flavor prior to exposure to context–illness pairings showed less evidence of contextual conditioning than did those given equivalent training in the absence of the novel flavor. The conditions of training and testing used by Symonds and Hall were, however, not exactly the same as those used in the present experiments. In particular, Symonds and Hall used a training procedure in which the subjects received experience of the target context *prior* to the injections of LiCl, and a test that made use of the blocking procedure rather than the consumption measure used in the present experiments. Given that it might be argued that the procedure used by Symonds and Hall provides a less valid parallel to the conditions that give rise to ANV in the clinic, it seemed worthwhile to establish whether an overshadowing effect could be obtained with our present procedure for producing contextual conditioning. Furthermore, in order to assess the potential therapeutic value of an overshadowing intervention as a treatment for PNV as well as for ANV, an injection of LiCl was given prior to the test, allowing us to determine if the overshadowing procedure is effective when the behavior recorded includes a component from direct postinjection effects.

There were two groups of subjects in Experiment 3. All received a single conditioning trial with each of two contexts, A and B. As in Experiment 2, the conditioning session consisted of the subjects' receiving an injection of LiCl before being placed in the context for 30 min. On the conditioning trial with Context A, the subjects in Group H were allowed to consume a solution containing HCl before receiving the LiCl injection, whereas for subjects in Group W only plain water was made available on this trial. On the conditioning trial with Context B, this arrangement was reversed. For all of the subjects, there followed a single test trial in which they were given an injection of LiCl before being placed into Target Context A. On the basis of previous findings (Symonds & Hall, 1999), it was anticipated that the presence of the HCl would overshadow conditioning to Context A; therefore, subjects for whom this flavor had been made available on this conditioning trial (Group H) would have lesser grounds for displaying a CR than would those for whom only water had been given on the conditioning trial (Group W). Critically, we expected

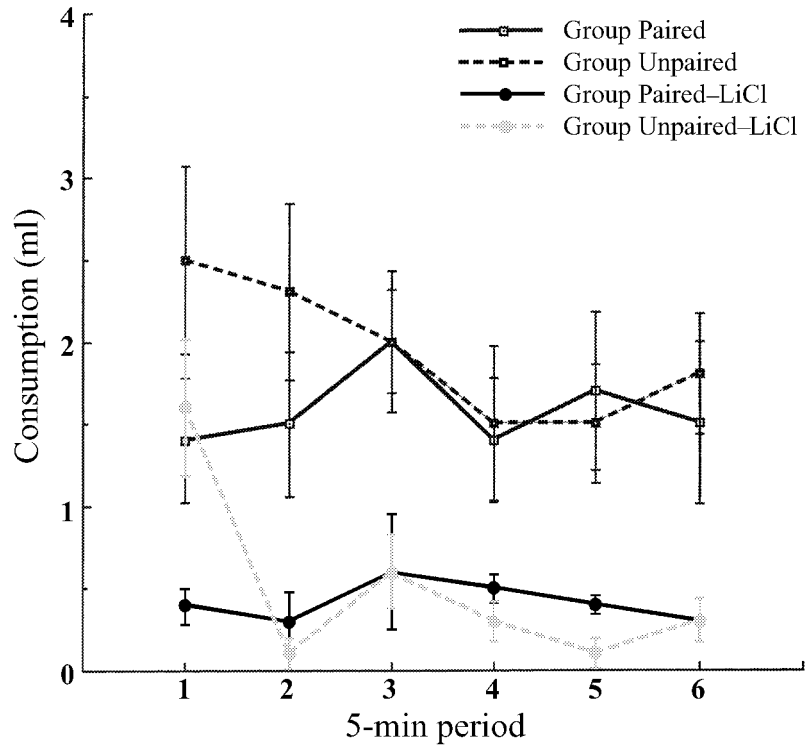

Figure 2. Group mean scores (with standard errors) for sucrose consumption (in each 5-min test period) in the target context in Experiment 2. Half of the subjects (Group Paired and Group Paired–LiCl) had previously received trials in which the test context had been paired with LiCl; for the remaining subjects (Group Unpaired and Group Unpaired–LiCl), the test context and LiCl had been experienced separately. Immediately prior to the test, the subjects in Group Paired–LiCl and Group Unpaired–LiCl received an injection of LiCl, whereas those in Group Paired and Group Unpaired did not.

that evidence for this effect might be revealed by fact that the subjects in Group H showed a less severe response to the injection of LiCl than did those in Group W.

Method

Subjects and Apparatus. The subjects were 16 experimentally naive male hooded Lister rats with a mean free-feeding weight of 408 g (range: 360–440 g). They were housed and maintained in the same way as the subjects in the previous experiments. The fluids presented in this experiment were a solution of .01 M hydrochloric acid, plain tap water, and 3.4% sucrose. All other details of the experimental apparatus were identical to those described for the previous experiments.

Procedure. A schedule of water deprivation was established as in the previous experiments. The next 4 days constituted the conditioning phase of the experiment. On Day 1 of this phase, all of the subjects received, at 1200 h, a 20-min presentation of 12 ml of a fluid in the home cage before receiving an injection of LiCl. They were then immediately transferred to Target Context A for 30 min. For the subjects in Group H, the fluid was HCl; for those in Group W, it was plain tap water. At 1700 h, all of the subjects had access to water for 30 min in the home cage. The next day (Day 2) was a recovery day, on which the rats remained in their home cages and received 30-min sessions of water in the standard bottles, initiated at 1200 h and 1700 h. On Day 3, the subjects received a conditioning session with Nontarget Context B. For the subjects in Group H, this session was preceded by a 12-ml, 20-min presentation of water, and for the subjects in Group W, the conditioning trial was preceded by a presentation of HCl. Again, the subjects received supplementary water in the home cage at 1700 h, followed on Day 4 by a recovery day. On Day 5, all of the subjects received a test trial, in which they were given an injection of LiCl before being placed in Context A for 30 min, where they received free access to sucrose. Consumption of the test flavor was recorded at 5-min intervals as in the previous experiments. For half of the animals in each group, Context A consisted of the large cages and Context B of the smaller cages; for the other animals, this arrangement was reversed.

Results and Discussion

Group means for the test session in which the sucrose was presented in Context A are shown in Figure 3. It is clear that both groups showed a tendency to reduce their consumption of the test fluid over the course of the test session. The subjects in Group H, however, consumed more of the test flavor than did those in Group W. An ANOVA conducted with group and trial as the factors confirmed this impression of the data. This analysis confirmed that there was a significant effect of group [$F(1,14) = 4.78$] and of trial [$F(4,56) = 5.00$], but no significant interaction between these two factors ($F < 1$).

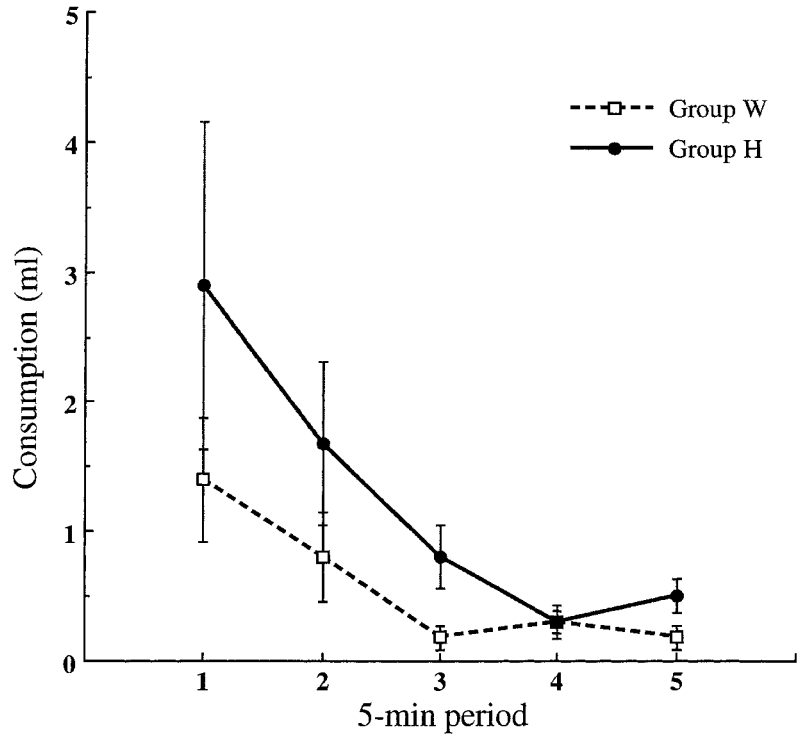

Figure 3. Group mean scores (with standard errors) for sucrose consumption in each 5-min test period in the target context in Experiment 3. For the subjects in Group H, the target context had previously been paired with LiCl in the presence of a novel flavor (HCl); for those in Group W, only plain water had been present on the conditioning trials.

These results show that the rats for which a novel flavor (HCl) was presented prior to conditioning with a target context showed less evidence of an aversion to that context than did those for which only plain water had been made available prior to the conditioning trial. This finding is best interpreted as an instance of the overshadowing effect, in which conditioning (in this case to a context) is restricted by the presence of a second, salient cue. This result accords with that reported by Symonds and Hall (1999). It differs from that of the previous study, however, in that we were able to reveal the overshadowing effect when measuring the subjects' postinjection response to LiCl in the target context. In particular, those subjects that had received the overshadowing treatment showed a rather less severe response to the injection of LiCl than did those that had not. Our interpretation of this effect accords with the assumption, supported by the results of Experiment 2, that postinjection responding in a previously conditioned context is composed of both the UR evoked by the drug and the CR evoked by the context. For the subjects given the overshadowing treatment (Group H), the CR evoked by the context will be weaker, and therefore will contribute less to the responding seen on the test. For the subjects in Group W, however, the postinjection response will reflect the UR and a (presumably stronger) CR, with the result that suppression of consumption will be more profound.

GENERAL DISCUSSION

One reported direct consequence of LiCl-induced illness in the rat is a tendency to reject an otherwise palatable flavor (Domjan, 1977). The results of Experiment 1 in general supported this conclusion; although an injection of LiCl produced an initial elevation of consumption, the effect was short-lived and, thereafter, consumption was suppressed, with the result that, over the course of the entire test, the animals given the LiCl injection drank less than did the controls not given the injection. To this extent, the UR evoked by LiCl matches the CR that is generated by contextual cues that have been associated with an injection of LiCl; in the presence of such cues, rats drink less than control subjects do, for whom the context has not been paired with nausea (see, e.g., Rodriguez et al., 2000; see also Best, Brown, & Sowell, 1984; Boakes, Westbrook, & Barnes, 1992).

The similarity of the CR and the UR in this training procedure (see also Meachum & Bernstein, 1992) has encouraged the view that conditioned contexts are capable of evoking a state of nausea comparable to that produced by the drug itself. It follows that direct responses to LiCl might be augmented by the presence of a previously conditioned context. We examined this possibility in Experiment 2. In this experiment, we were able to confirm the

finding of Rodriguez et al. (2000) that the conditioned response produced by an illness-paired context is a decline in consumption of a novel flavor, and to demonstrate further that the presence of these conditioned cues would increase the severity of the postinjection response. It should be acknowledged that such a summation effect is not a necessary outcome of presenting the US in the presence of the CS (Donegan, 1981; Wagner, 1981), and it is possible that a change in the details of the procedure (e.g., a change in US intensity) might have led to a different result. It remains the case, however, that for our experimental paradigm the US intensity that is successful in establishing a context aversion also yields the summation effect when that US is presented along with the contextual cues.

In Experiment 3, we sought to determine whether a treatment designed to reduce contextual conditioning would have the corresponding effect of reducing the severity of the response to LiCl when said response was measured in the presence of these cues. In accord with the preceding analysis, Experiment 3 demonstrated that presentation of a novel flavor at the time of the conditioning sessions served to reduce the severity of the response to LiCl when it was presented in the target context. This finding was interpreted as an instance of overshadowing, in which the presence of the flavor reduced conditioning to the target context. As a consequence, the extent to which the CR could contribute to the postinjection response was correspondingly reduced.

The latter finding is of potential clinical significance. Recall that Stockhorst et al. (1998) found signs that the overshadowing treatment they employed might reduce the severity of PNV. The present findings confirm the validity of the interpretation they offered: that conditioning-produced ANV might be able to summate with the direct effects of the drug. The general notion that an overshadowing treatment may have the potential to be of considerable therapeutic value has already received support from a study carried out by Broberg and Bernstein (1987). They found that children given a novel "candy scapegoat" flavor in between a normal meal and chemotherapy were less likely to develop an aversion to the target meal, a result that was taken to be an instance of overshadowing by the novel taste. Although the Broberg and Bernstein study was concerned with reducing chemotherapy-induced aversions to taste, rather than to context, their findings at least encourage the view that an overshadowing treatment might also be capable of reducing the contextual aversion that contributes to both ANV and PNV in the clinic.

It should be noted, however, that the effect of overshadowing on PNV in the Stockhorst et al. (1998) study was very small. A next step, therefore, might be to make use of the animal model provided by the experiments described here, to refine parameters so as to increase the effectiveness of overshadowing in this respect. The need to do this is made more acute by the fact that, in some circumstances, the presence of a novel flavor during context conditioning has been found to produce quite the reverse of overshadowing—to *potentiate* learning about the context (see Symonds & Hall, 1999, for a review). According to the present analysis, a treatment that produced potentiation by context conditioning would make both ANV and PNV worse.

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