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Preexposure to the Unconditioned Stimulus in Nausea-Based Aversion Learning

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Learned flavor aversion is a familiar and widespread phenomenon. Every year I conduct an informal poll of my undergraduate students, asking how many have, at some time, developed an aversion to a particular food (or drink). They respond readily (they apparently have the concept of an acquired aversion prior to any formal teaching on the topic), and each year about 50% of the class report an aversion—usually to a specific alcoholic drink, and often with a vivid report of the specific episode of overindulgence and its immediate consequence.

Evidently flavor–nausea associations are readily established. From one point of view this is not surprising. The flavor that acts as the conditioned stimulus (CS) in the conditioning trials that my students inflict on themselves is usually quite novel—that is, the student in question is usually trying brandy (or whisky or champagne) for the first time. Novel flavors are highly associable; it is well established that prior exposure to a given flavor will dramatically reduce the ease with which it forms a conditioned aversion (the well-known phenomenon of *latent inhibition*, e.g., Lubow, 1989). Nausea (the putative unconditioned stimulus, US), on the other hand, is a state that my students will undoubtedly have experienced a number of times before. Nonetheless, it is still clearly able to operate as a powerful reinforcer. Is it perhaps immune from the effects of preexposure that CSs are susceptible to? Introspection suggests that, as years go by, later episodes (however produced) seem no less unpleasant than earlier ones. Indeed, there is some evidence to suggest that they might become more so—patients undergoing chemotherapy for cancer sometimes report that the nausea induced by a given drug infusion grows increasingly worse over the course of treatment (Stockhorst et al., 1998).

However this may be (and we will return to this last observation later), there is clear experimental evidence from the study of flavor aversion learning in the rat that the effectiveness of nausea as a reinforcer can be diminished by prior exposure. Figure 4.1 shows the results of one such experiment (Aguado, De Brugada, & Hall, 1997, Experiment 1). It shows the amount of a saccharin solution consumed by two groups of rats on a test trial given 2 days after a conditioning trial on which consumption of saccharin had been followed by an intraperitoneal injection of lithium chloride (LiCl). (LiCl acts on the area postrema of the hindbrain, a structure associated with distress in the upper gastrointestinal tract, Tsukamoto & Adachi, 1994.) Control subjects showed a marked aversion to saccharin, drinking very little on test. Preexposed subjects differed from controls in that they had been given three previous injections of LiCl, the last of these 2 days before the conditioning trial. These subjects showed much less of an aversion to saccharin. This effect, the retardation of conditioning produced by prior exposure to the US, has been labeled (unimaginatively) as the *US-preexposure effect* (there is no equivalent to the term latent inhibition, used for the CS-preexposure effect). The effect is robust and widespread, being found with almost all the procedures and drugs capable of establishing flavor aversion (as is fully documented in the review by Riley & Simpson, 2001). My analysis of the nature of the effect will, however, concentrate on the effect as it is shown by rats that are given LiCl as the US, a procedure for which a substantial body of, theoretically relevant, experimental work is now available.

In an early review of the US-preexposure effect, Randich and LoLordo (1979) identified two general classes of explanation for the effect—nonassociative and associative—and examples of each of these remain the central concern for this chapter. In the first category, Randich and LoLordo concentrated on *habituation*, suggesting that the effectiveness of a US as a reinforcer might decline simply as a consequence of repeated presentations of that US. The categorization of this proposed explanation as being necessarily nonassociative was rendered inappropriate by the development of accounts of habituation that relied on associative mechanisms (e.g., Wagner, 1981), but the process involved may still be distinguished from that postulated by the most widely considered associative explanation. This account, often called *context blocking* (although blocking by context would be a better term), takes as its starting point the observation that presenting a US without an explicit CS (as in the US-preexposure procedure) does not preclude the occurrence of conditioning. Each presentation of the US occurs in the presence of a distinctive set of cues, including those associated with handling and the injection procedure, and those that characterize the place in which the illness is experienced. These contextual cues could come to function as CSs, and since they will be present during the formal conditioning stage of the procedure, when a flavor CS is presented prior to the US, they could therefore act to *block* (Kamin, 1969) conditioning of the flavor, with the result that acquisition of an aversion is attenuated.

In what follows I will assess recent experimental evidence that bears on each of these proposals. It should be noted that these interpretations are not mutually exclusive; both could be operating and contribute to most instances of the US-preexposure effect. Equally, of course, there could be examples of the effect that are not explained by either.

Group	Pre	Cond	Test
Pre	3 Li	Sac → Li	Sac
Control	3 Sal	Sac → Li	Sac

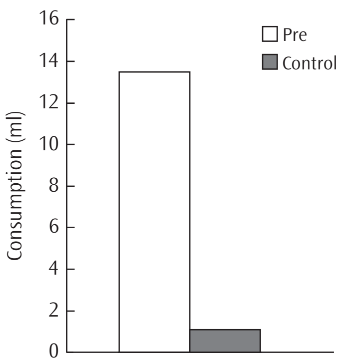

Figure 4.1. Design and results of an experiment by Aguado et al. (1997, Experiment 1). Group Pre (preexposed) had experienced three daily intraperitoneal injections of lithium chloride (Li) followed by a conditioning (Cond) trial in which consumption of a saccharin (Sac) solution was followed by an injection. The control group received injections of isotonic saline (Sal) in the preexposure phase. On the test, which followed conditioning after 2 days, consumption of saccharin was measured.

HABITUATION: AN INITIAL CONSIDERATION

At the level of behavioral observation, habituation refers to the waning in the magnitude or probability of an unconditioned response (UR) as a result of repeated presentations of the US. (When the stimulus in question is the administration of a given dose of a drug, the phenomenon may also be referred to as the development of *tolerance*; Riley & Simpson, 2001). If the suggestion that the US-preexposure effect is a consequence of US habituation is to be anything more than a redescription of the observed results, it seems necessary to show that the learning process that is responsible for the loss of the UR is also responsible for the reduced ability of nausea to act as a reinforcer. A first step, then, would be to show that the UR evoked by an injection of lithium is attenuated by a preexposure procedure of the sort that generates

Group	Pre	UR test	CR test
Pre	3 Li	Li → Sac	Sac
Cont-Hab	3 Sal	Li → Sac	Sac
Cont-Cond	3 Sal	Sal → Sac	Sac

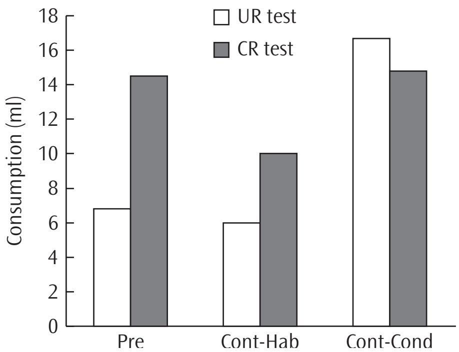

Figure 4.2. Design and results of the experiment by De Brugada et al. (2003a). Group Pre (preexposed) received three intraperitoneal injections of lithium chloride (Li); control groups (Cont) received saline injections. On the UR test, all groups drank saccharin (Sac) after an injection of Li or of Sal. The CR test assessed consumption of saccharin.

a US-preexposure effect. The available results are not encouraging.

An injection of LiCl produces a range of observable reactions. For the sort of dose used in flavor aversion conditioning, it produces a lowering of body temperature and a reduction in activity level. Batson (1983) examined these URs in rats that were given a series of eight injections of LiCl, but found no sign of habituation in them. Nonetheless, rats given this preexposure showed poor conditioning when LiCl was used as the US for conditioning. A similar dissociation was obtained in a study by De Brugada, González, and Cándido (2003a), the results of which are illustrated in Figure 4.2. An immediate effect of an injection of LiCl is that rats will refuse to consume an otherwise palatable substance (Domjan, 1977; Symonds & Hall, 2002). This was the UR measured by De Brugada et al. (the UR test in Figure 4.2). As the figure shows, control rats (the Cont-Cond group) drank a saccharin solution readily, but rats given an injection of LiCl just before the saccharin was offered showed a suppression of consumption. This was true both for rats that experienced LiCl for the first time (group Cont-Hab) and for rats that had had three previous injections (group Pre); that is, there was no indication of habituation. But preexposure did produce an attenuation of conditioning. The procedure that was used for testing the UR means that animals in the Pre and Cont-Hab groups drank some saccharin while under the effects of the LiCl injection, allowing the possibility that an association might be formed between the taste and nausea. The aversion that was conditioned on the UR test trial was assessed in a subsequent test on which saccharin was made available, and given a day later when the immediate effects of the injection had worn off (the CR test of Figure 4.2). On this test the Cont-Hab group showed a marked aversion to saccharin, whereas the Pre group drank the saccharin as readily as animals (group Cont-Cond) that had received no injection of LiCl.

This preliminary survey of the implications of the habituation hypothesis yields a clear outcome. The effects of an injection of LiCl appear not to habituate, within the parameters investigated, and yet the US-preexposure effect is still obtained. Some other process must be responsible for the effect seen in these conditions. We turn, therefore, to a consideration of the context-blocking hypothesis.

CONTEXT AVERSION CONDITIONING

A first requirement, if the context-blocking hypothesis is to be supported, is that it should be possible to demonstrate that injections of LiCl are capable of establishing a context as a CS for nausea. And this is precisely what has been denied by some. Thus, for example, Garcia and his colleagues (e.g., Garcia, 1989; Garcia, Brett, & Rusiniak, 1989), have asserted that nausea activates a special "gut-defense" system that specifically allows learning about tastes but which will not normally support learning about exteroceptive cues (such as contextual cues). The only exception allowed was to accommodate the phenomenon of *potentiation*—the discovery that the presence of a taste might foster learning about other cues. It was thus allowed that exteroceptive cues might be capable of acquiring aversive properties if they were presented in conjunction with taste cues. (According to the analysis offered by Garcia et al., the presence of the taste cues opens a "gate" that allows the exteroceptive cues to sneak into a learning system to which otherwise they would be denied access.)

Potentiation and the Consumption Test

The experimental evidence lends support to this suggestion. Several studies (e.g., Best, Brown, & Sowell, 1984; Boakes, Westbrook, & Barnes, 1992; Mitchell & Heyes, 1996) have shown that context conditioning occurs more readily when rats are permitted to drink a solution with a novel flavor during the conditioning phase. And although this effect is most apparent when the flavor is novel, simply giving access to unflavored water can generate the same outcome. Symonds et al. (1998, Experiment 1) conducted trials on two groups of rats in two different contexts (distinctive cages, different from each other, and both different from the home cage). Exposure to context A was followed by an injection of LiCl, exposure to context B was not. Contextual conditioning was assessed by means of a consumption test in which the rats were offered a sucrose solution in each of the contexts—we know that the state induced by an injection of LiCl suppresses consumption; if contextual cues, by way of conditioning, acquire the power to evoke some properties of this state then they too might be capable of suppressing consumption.[1] The two groups differed only in that one was allowed to drink (water) during the context conditioning trials whereas the other was not. The results (Figure 4.3) show that the rats that drank water during training showed a suppression of consumption when tested in context A, consistent with the notion that this context had acquired aversive properties. Rats that were not allowed to drink during conditioning did not show this effect.

Group	Pre	Test
Water	4 A(W) $\rightarrow$ Li and 4 B(W) $\rightarrow$ 0	Suc in A and Suc in B
No water	4 A $\rightarrow$ Li and 4 B $\rightarrow$ 0	Suc in A and Suc in B

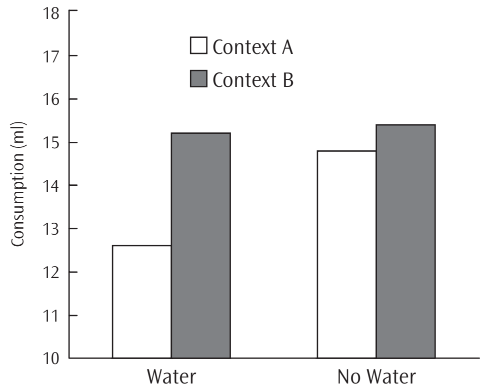

Figure 4.3. Design and results of an experiment by Symonds et al. (1998, Experiment 1). During preexposure (Pre), all subjects experienced context A followed by an injection of lithium chloride (Li); no injection followed exposure to context B. The water group (W) was permitted to drink during this phase. On the test, consumption of a sucrose solution was assessed in both contexts.

This result immediately raises doubts about the context-blocking hypothesis. There is no reason to think that the US-preexposure effect will be found only when the rats are allowed to drink during preexposure trials, and yet this appears to be necessary for context conditioning to occur. Worse, although this pattern of results has been taken as demonstrating potentiation of context conditioning, an alternative interpretation is available that denies that context conditioning has occurred at all. The problem is that allowing the animal to ingest something prior to the injection allows the possibility that what is ingested will acquire aversive properties. This can occur even when what is consumed is just plain water (Boakes, Westbrook, Elliott, & Swinbourne, 1997). Suppression of consumption of a different substance on the test might thus be a consequence of direct generalization from one flavored substance to another, rather than an indication that the contextual cues have acquired associative strength. It is true that suppressed consumption is seen only when the test is given in the trained context and not when it is given elsewhere (Mitchell & Heyes, 1996), but this observation does not require us to assume that the context has acquired aversive properties. It is known that flavor aversions can become context dependent so that they will be fully expressed only in the presence of the context used in training (Bonardi, Honey, & Hall, 1990). This phenomenon appears to be an instance of *occasion setting*, in which the context fosters the retrieval of associative information (Boakes et al., 1997; Puente, Cannon, Best, & Carrell, 1988). The context specificity demonstrated by Mitchell and Heyes (1996) could thus have occurred because their context acted as an occasion setter allowing a generalized aversion to the test fluid to show itself.

Other Procedures

To show that a context has indeed come to function as a Pavlovian CS requires a different procedure. I will describe two that have been used with some success. The first uses a different test procedure, the second a modified training procedure.

One strategy is to use a measure other than the suppression of consumption, and this has been arranged by making use of *blocking* as a test. It is well established that when one element of a compound stimulus has been pretrained as a signal for a given US, its presence in the compound will block conditioning to the other. Thus it should be possible to assess the aversive properties of a context previously paired with nausea in terms of its ability to block the acquisition of an aversion to a novel flavor, when this flavor and the contextual cues are conditioned as a compound. With this procedure, evidence for a context aversion would be provided by a failure of conditioning to the novel flavor (i.e., by a high level of consumption). Direct generalization from any flavor aversion formed during training could not generate such a result.

This strategy has been used a number of times (e.g., Best et al., 1984; Symonds et al., 1998; Symonds & Hall, 1997; Westbrook & Brookes, 1988; Willner, 1978). The design and results of one of these experiments (Symonds & Hall, 1997, Experiment 2) are shown in Figure 4.4. The initial training procedure, given to two groups of rats, was identical to that used for the water group of Figure 4.3, with one context (A) being paired with LiCl and another (B) not. In the next phase (compound conditioning), the rats were allowed to drink a sucrose solution in the home cage, and were then exposed to context A (the blocking group) or context B (the control group) prior to a further injection of LiCl. The aversion to sucrose was assessed in a final test given in the home cage. As the figure shows, the control group showed a strong aversion and drank rather little. Subjects in the blocking group drank rather more, an outcome consistent with the notion that the pretrained context (context A) had been able to block the acquisition of the aversion to sucrose.

Group	Pre	Cond	Test
Blocking	4 A(W) → Li and 4 B(W) → 0	Suc → A → Li	Suc
Control	4 A(W) → Li and 4 B(W) → 0	Suc → B → Li	Suc

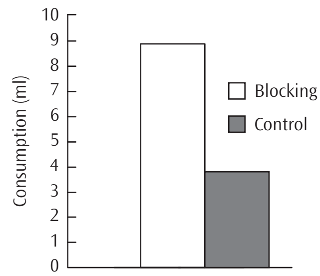

Figure 4.4. Design and results of an experiment by Symonds and Hall (1997, Experiment 2). During preexposure (Pre), all subjects experienced context A followed by an injection of lithium chloride (Li); no injection followed exposure to context B. In the conditioning (Cond) phase, consumption of sucrose (Suc) was followed by exposure to context A (the blocking group) or to context B (the control group) and an injection of Li. Consumption of sucrose in the home cage was measured in the test phase.

The blocking test appears to be a rather sensitive procedure for detecting context conditioning. In a study otherwise identical to that just described, Symonds et al. (1998) gave no access to water for any of the rats during the context conditioning phase. Recall that in these conditions the suppression-of-consumption test revealed no evidence of context conditioning (Figure 4.3). But Symonds et al. were able to detect clear evidence of context conditioning using the blocking test. A possible interpretation of this finding is that pairing a context with nausea *can* produce conditioning, even in the absence of a flavor, but the effect is small and difficult to detect. This brings us to the second strategy, which is simply to find a way of enhancing conditioning in these situations, to make it evident on the consumption test. This was achieved by Rodriguez, Lopez, Symonds, and Hall (2000) who introduced the technique of injecting the rat with LiCl shortly before it was put into the training context. Previous work had routinely used the procedure of exposing the rat to the context prior to the injection (in line with many other conditioning procedures in which the CS precedes the US). It turns out, however, that giving the injection first, so that the rat experiences the illness in the presence of the contextual cues, produces a context that is very effective at suppressing consumption of an otherwise palatable substance. This effect is seen in rats that are not permitted to eat or drink in the context, and thus cannot be the consequence of a generalized flavor aversion.

Nature of the CR

It remains to establish the nature of the CR established by this context conditioning procedure. One reason for using the suppression-of-consumption test was that it matches the UR; if the suppressed consumption produced directly by an injection of LiCl indicates a state of nausea, it seems reasonable to assume that suppression in the presence of conditioned contextual cues reflects conditioned nausea. Parker (2003) has argued, however, that an injection of LiCl not only induces nausea, it also produces a novel change in physiological state that signals danger to the rat. Both these effects might support conditioning. A taste associated with LiCl does indeed appear to acquire nausea-inducing properties. These can be made evident by the *taste reactivity* test in which a small amount of the conditioned substance is introduced into the rat's oral cavity by way of a cannula. The rat will show a characteristic open-mouthed gaping response (the sort of response that precedes vomiting in species capable of antiperistalsis). But this conditioned aversion need not be responsible for the suppression of intake seen in a standard consumption test for flavor aversion. The taste avoidance shown on such a test, Parker suggests, is supported by an association (akin to fear conditioning) between the taste and the dangerous change of physiological state. A possible implication of this analysis is that the learning produced by context conditioning procedures might be based on this second form of learning—that the context comes to signal potential danger, but does not actually evoke a state of conditioned nausea. A rat might be expected to be reluctant to consume an otherwise palatable substance when it is presented in a fear-evoking context (thus generating the suppression seen in the consumption test).

To investigate this possibility, Limebeer, Hall, and Parker (2006) conducted a study of context conditioning that made use of the taste reactivity test. One group of rats (the paired group) received exposure to a distinctive context while suffering the effects of an injection of LiCl; control subjects (unpaired) experienced the context and the injection on separate occasions. The context was a box specially adapted for recording the rat's orofacial reactions. After conditioning, the rats were put back in the box and a saccharin solution was infused through an intraoral cannula. Subjects in the unpaired group accepted this readily, but, as Figure 4.5 shows, those in the paired group showed the gaping response, taken to be characteristic of nausea. Although their frequency is low, gaping responses do sometimes occur even in the absence of an infusion, and, as Figure 4.5 also shows, they did so more often in the paired than in the unpaired group. Parker's (2003) avoidance learning mechanism may well contribute to the suppression of consumption seen in the presence of conditioned contextual cues, but these new results indicate that conditioned nausea is at work too.

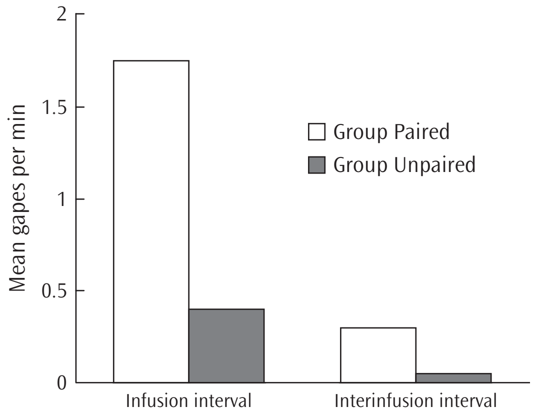

Figure 4.5. Design and test results of an experiment by Limebeer et al. (2006, Experiment 1). The paired group had received pairings of a distinctive context and injections of LiCl; the unpaired group had experienced context and injections on separate occasions. The results show the number of gaping responses made by each group in the context, both during intraoral infusions of saccharin and in the interval between infusions.

Potentiation Reconsidered

Finally, in this section of the chapter, we need to reconsider the notion of potentiation. We have established that context aversion conditioning can be demonstrated when the subjects do not eat or drink during the conditioning phase. Where does this leave the many demonstrations of potentiation? One possibility is that the effect is not all or none—that context conditioning can be obtained when ingestion is not permitted but is enhanced when it is. A second, more intriguing, is that the potentiation effect, at least with regard to context conditioning, is artifactual. The most substantial body of evidence for the effect comes from experiments that make use of a consumption test, and it is most reliably obtained when solutions with a distinctive novel flavor are used both in conditioning and on test (most commonly saccharin or sucrose has been used in training, and saline as the test flavor; see Symonds & Hall, 1999, for a review). This immediately suggests the possibility that the effect is a consequence, not of potentiation of learning about the context but of the direct generalization to the test flavor of an aversion established to the flavor present during conditioning.

This problem can be overcome by using the blocking test rather than the consumption test. Figure 4.6 shows the design of an experiment (Symonds & Hall, 1999, Experiment 2) that does this. Two groups of thirsty rats received conditioning trials in which two distinctive context were associated with injections of LiCl. In one of these contexts (A) the rats were allowed to drink water flavored with the distinctive sour taste of an acid (H: HCl). They then received a compound trial in which consumption of sucrose in the home cage was followed by exposure to one of the contexts (A for the experimental group, B for the control group) and then by an injection of LiCl. When tested with sucrose in the home cage both groups showed an aversion to sucrose that extinguished over successive test trials, but the aversion was more profound in the experimental group. We may deduce, therefore, that the context was *less* effective at blocking conditioning to sucrose in this group—that the context had gained less strength in this group than in the control group. Far from potentiating conditioning to the context, the presence of a novel flavor during the first phase of training detracted from it. From one point of view, this result should not be surprising—*overshadowing* (the attenuation of conditioning to a target cue by the concurrent presence of another competing cue) is routinely found in standard conditioning preparations and is predicted by standard theories of conditioning (e.g., Pearce & Hall, 1980; Rescorla & Wagner, 1972). Symonds and Hall (1999) concluded that the potentiation effect in context aversion conditioning is likely to be an artifact of the use of the consumption test and that context aversions seem to be acquired in the same way and according to the same rules as other CS–US associations.

Group	Pre	Cond	Test
Experimental	A(H) → Li and B(W) → Li	Suc → A → Li	Suc
Control	A(H) → Li and B(W) → Li	Suc → B → Li	Suc

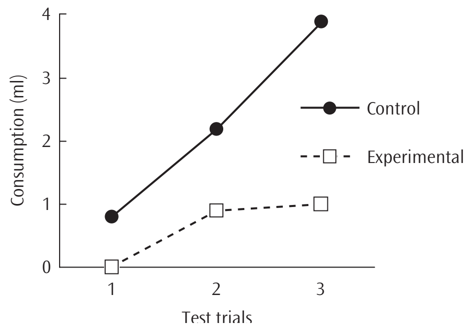

Figure 4.6. Design and results of an experiment by Symonds and Hall (1999, Experiment 2). During preexposure (Pre), all subjects experienced both context A and context B along with an injection of lithium chloride (Li). The sour taste of acid (H) was available in context A, plain water (W) in context B. In the conditioning (Cond) phase, consumption of a sucrose (Suc) was followed by exposure to context A (the experimental group) or to context B (the control group) and an injection of Li. Consumption of sucrose in the home cage was measured in the test phase.

BLOCKING BY CONTEXT

The Role of Cage Cues

What we have now established, after a good deal of effort, is that the procedure of giving a series of injections of LiCl in order to produce a US-preexposure effect is likely to result in establishing the context as a CS for nausea. The way seems clear, therefore, for an explanation of the effect in terms of blocking by context. Indeed, one of the procedures already discussed can be seen as supplying evidence that directly supports the explanation. In the study presented in Figure 4.4, preexposure to injections of LiCl resulted in retarded acquisition of an aversion to sucrose, but only when the context used for preexposure was present on the conditioning trials.

In the absence of a control condition that was given no preexposure to LiCl, this experiment does not include a demonstration of the basic US-preexposure effect itself, but other experiments have addressed this issue fully. The critical prediction of the context-blocking account is that the US-preexposure effect should be found only when conditioning is given in the presence of the contextual cues that were present during US preexposure. A change in context between preexposure and conditioning should abolish or (allowing for the possibility of generalization between contexts) attenuate the effect. This prediction has gained ample support from studies by Willner (1978), Batson and Best (1979), Domjan and Best (1980), and Dacanay and Riley (1982). All these experiments included a condition in which the initial exposure to LiCl was given in a novel context. Some rats then received flavor aversion conditioning in this same context prior to a test given in the home cage; for other subjects, both conditioning and the test occurred in the home cage. Both groups showed some retardation of conditioning (with respect to control subjects given no preexposure to the US), but the effect was less profound in those that experienced the change of context prior to conditioning.

A further prediction of the context-blocking account is that manipulations that limit or reduce the strength of the context–US association should attenuate the US-preexposure effect. Evidence is available on three such manipulations: overshadowing, extinction, and latent inhibition. The first of these has already been discussed. The results presented in Figure 4.6 can be taken as showing that the US-preexposure effect was less profound (i.e., the aversion to sucrose was stronger) in the experimental group than in the control group. The experimental group received its preexposure to the US after consuming a salient flavor, an arrangement that might be expected to overshadow acquisition by the context and thus limit the ability of the context to block in the next stage of the experiment.

The effect of extinction has been investigated by Batson and Best (1979, Experiment 4). They obtained a strong US-preexposure effect when preexposure and conditioning trials occurred in a distinctive black box, but the effect was attenuated when eight trials of exposure to the box were interpolated between the two stages. Batson and Best suggested that these trials allowed extinction of the association between the context and nausea and thus reduced the ability of the context to block subsequent acquisition. Further results consistent with this interpretation come from experiments investigating the effects of inserting a delay (a retention interval) between the phase of exposure to the US and the conditioning and test phases. This procedure has been found to reduce the size of the US-preexposure effect (Aguado et al., 1997; Cannon, Berman, Baker, & Atkinson, 1975). Since, in these experiments, all the procedures were carried out in the rats' home cages, this means that the rats spent the retention interval in the place in which preexposure to the US was given. As Aguado et al. pointed out, this would give ample opportunity for extinction of the context–US association, with the result that blocking by context, and hence the US-preexposure effect, would be less likely to occur (but see Miller, Jagielo, & Spear, 1993, for an alternative analysis).

Evidence on latent inhibition comes from a study by Cole, VanTilburg, Burch-Vernon, and Riccio (1996). They simply compared a condition in which all phases of the procedure (preexposure, conditioning, and the test) were given in the home cage, with a condition in which the procedures occurred in a novel context, different from the home cage. The US-preexposure effect was significantly weaker in the latter case. This outcome, Cole et al. suggested, was a consequence of the fact that the home cage, being very familiar, would have suffered extensive latent inhibition. Context conditioning during the US-preexposure phase would therefore be retarded, and the possibility of context blocking would be reduced. In fact, comparison with a non-preexposed control yielded no indication of any US-preexposure effect in animals trained in the home-cage condition.

Qualifications

This last observation may look like strong evidence in favor of the possibility that context blocking is the entire explanation of the US-preexposure effect, but in fact, closer examination reveals the need to refine this notion. Although Cole et al. (1996) found no US-preexposure effect in rats trained and tested in the home cage, many others have done so (the results presented in Figure 4.1 are just one example). This is not, in itself, evidence against the adequacy of the context-blocking explanation—it is quite likely that, in some circumstances, the latent inhibition suffered by the home cage would not be complete and would not be enough to totally preclude context conditioning and thus context blocking. There are, however, two arguments, one based on empirical evidence and one theoretical, that give grounds for doubting that context blocking, as we have understood it so far, is responsible for the effect in this case.

The empirical evidence comes from the experiment by De Brugada, González, and Cándido (2003b) depicted in Figure 4.7. The two bars on the left of the figure show the US-preexposure effect (a lesser aversion in the preexposed group than in the control group) for rats that remained in the home cage throughout all phases of the experiment. The two bars on the right are the results for rats given similar treatment except that they were switched to a novel context for conditioning and testing. For these subjects, the role of context blocking should be attenuated or even abolished. But although the aversion was somewhat stronger for these subjects, this was true for both the preexposed and the control groups and there was no statistically reliable evidence for any diminution in the size of the US-preexposure effect. De Brugada et al. concluded that contextual cues may play an important role in the US-preexposure effect when these cues are novel during preexposure, but that they have a negligible role when the context is familiar (i.e., when the cues have undergone latent inhibition). In these circumstances some other factors must be responsible for the effect.

The second argument arises from the fact that when the entire experimental procedure is carried out with the rats in the home cage, the magnitude of the CR is necessarily tested in the same context as that used for preexposure, and thus in the presence of the putative blocking cues. In the standard blocking procedure (e.g., Kamin, 1969) the failure of the blocked cue to control a strong CR is evident only when that cue is tested on its own—the compound of blocked and blocking cue evokes a strong CR. It is not easy then for the

Group	Pre	Cond	Test
Pre	3 Li	Sac → Li	Sac
Control	3 Sal	Sac → Li	Sac

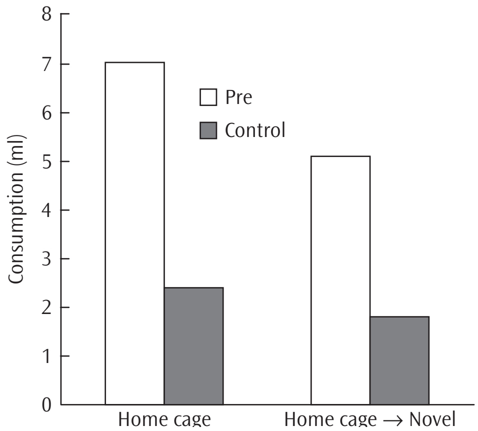

Figure 4.7. Design and results of the experiment by De Brugada et al. (2003b, Experiment 1). The Pre (preexposed) groups received three intraperitoneal injections of lithium chloride (Li); the control groups (Cont) received saline injections. Conditioning (Cond) consisted of consumption of saccharin (Sac) followed by an injection of LiCl (Li). Saccharin consumption was measured on the test. For one pair of groups all these procedures occurred in the home cage. For a second pair (Home cage → Novel), Pre occurred in the home cage, Cond and Test in a novel context.

context-blocking account to predict a weak CR to the flavor CS when the test is given in the presence of the pretrained contextual cues. To maintain this explanation it is necessary to assume that the associative strength gained by contextual cues is capable of restricting the acquisition of strength by the flavor CS during the conditioning phase of the procedure, but not of summating with such strength as the CS may have acquired when it comes to the test. There is reason to doubt the general validity of this assumption—that conditioned taste aversions tend to be stronger when tested in the training context rather than in some other context may be determined by several factors (see, e.g., Boakes et al., 1997), but in at least some cases, the effect seems to depend on a summation of the Pavlovian properties of the context and the substance being ingested (Loy, Alvarez, Rey, & Lopez, 1993).

Injection-Related Cues

These observations lead to the following conclusions. First that the acquisition of strength by distinctive contextual cues (such as those supplied by a novel cage) will allow them to block conditioning to a flavor CS and that the effects of this blocking (a weak CR) will be evident when the flavor is presented in a different context (e.g., back in the home cage). Second that this analysis cannot apply to the US-preexposure effect as it is shown by rats trained and tested in the home cage, at least, if by context we mean just the set of environmental cues that define a particular place. But, as was noted some time ago (e.g., Rudy, Iwens, & Best, 1977), administration of an intraperitoneal injection involves a range of handling and other cues that might well be regarded as constituting a part of the context in which the effects of the injection are experienced.

However we categorize them, such cues are prime candidates when it comes to blocking of flavor aversion learning. Although the environmental context of a US-preexposure experiment may have suffered latent inhibition, the injection-related cues will be novel and will be perfectly correlated with the occurrence of nausea. They can thus be expected to acquire associative strength readily during US preexposure. Because they are present on the conditioning trials they will be able to block acquisition by the flavor CS, and because they are absent on the test trial the full effect of the blocking should be evident.

Empirical support for this interpretation of the US-preexposure effect comes from studies in which the associative strength of the injection-related cues has been manipulated. Willner (1978) included a condition in which saline injections were intermixed with LiCl injections during preexposure, a procedure that reduces the reliability of the injection as a signal for nausea, and might thus be expected to limit the acquisition of associative strength by injection-related cues. The magnitude of the US-preexposure effect was reduced in this condition. Similarly, De Brugada and Aguado (2000; see also De Brugada et al., 2003b) demonstrated an attenuation of the effect in rats given a series of saline injections between the US-preexposure phase and the conditioning phase. Such injections can be expected to bring about extinction of the association between injection-related cues and the US, and thus reduce the ability of these cues to produce blocking. But perhaps the most striking evidence on the role of injection-related cues comes from a series of studies by De Brugada, Hall, and Symonds (2004) in which use was made of a technique that allows LiCl-based conditioning to occur, but does not involve an intraperitoneal injection (or indeed, any handling of the rats at all).

Thirsty rats will readily drink a solution of LiCl—at least, once. Thereafter they will refuse it (and other salty solutions such as NaCl). Loy and Hall (2002) investigated this effect, and demonstrated it to be a consequence of associative learning in which the salty taste of LiCl becomes associated with the nausea induced by its consumption. (The size of the aversion produced in this way proved to be exactly comparable to that produced by intraperitonal injection of the same quantity of LiCl.) Orally consumed LiCl is evidently an effective reinforcer; Loy and Hall went on to show that drinking LiCl can establish an aversion to another taste (such as sucrose) that was consumed at the same time. This phenomenon makes it possible to investigate the effects of preexposure to injections on LiCl on the ability of orally consumed LiCl to support flavor aversion learning and thus to investigate the US-preexposure effect in circumstances in which blocking by injection-related cues cannot play a part.

The design of such an experiment (De Brugada et al., 2004, Experiment 1b) is shown at the top of Figure 4.8. The group labeled LI-LO (LI: lithium by injection; LO: oral consumption of lithium) received US preexposure consisting of three injections of LiCl prior to a conditioning trial on which they drank flavor A followed immediately by oral consumption of a solution of LiCL. The control group SI-LO (SI: saline by injection; LO: oral consumption of lithium) experienced the same conditioning procedure but received saline injections in the preexposure phase. Three injections of LiCl will produce a robust US-preexposure effect when orthodox conditioning procedures are used; the question of interest was whether the effect would be obtained when no injection-related cues were present in the conditioning phase. A further control group SI-SO (SI: saline injections in preexposure; SO: oral consumption of saline on the conditioning trial) that drank a saline solution

Group	Pre	Cond 1	Test 1	Cond 2	Test 2
LI-LO	3 Li inj	Drink A-drink Li	A	B-Li inj	B
SI-LO	3 Sal inj	Drink A-drink Li	A	B-Li inj	B
SI-SO	3 Sal inj	Drink A-drink Sal	A	B-Li inj	B

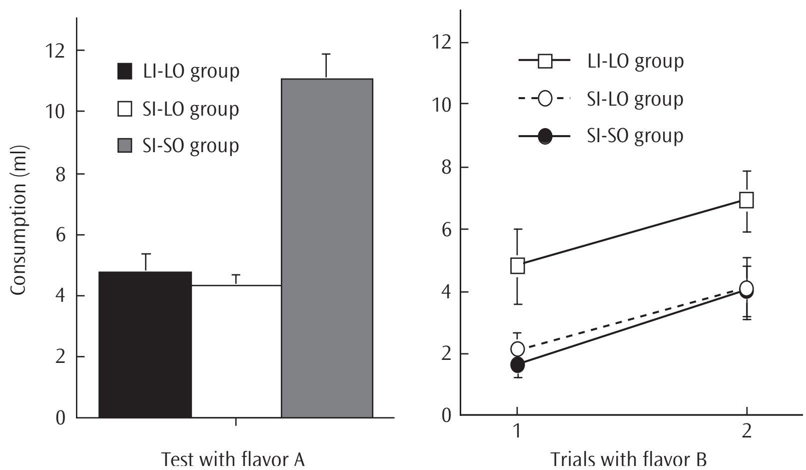

Figure 4.8. Design and test results of the experiment by De Brugada et al. (2004, Experiment 1b). Test 1, with flavor A, was given after rats in the LI-LO and SI-LO groups had experienced A prior to drinking LiCl (Li) (Cond 1). Test 2, with flavor B, was given after all rats had experienced B followed by an injection of LiCl (Cond 2). A and B were solutions of saccharin and vinegar, counterbalanced. Rats in the LI-LO group had received three LiCl injections (inj) during preexposure (Pre). Abbreviations in group labels: L = lithium; S = saline; I = injected; O = oral administration.

rather than LiCl after drinking flavor A in conditioning was included to confirm that oral consumption of lithium could indeed serve as an effective US in this procedure.

The results of a test trial with flavor A are presented in the lower left panel of Figure 4.8. The control group that did not experience lithium on the conditioning trial (group SI-SO) drank A readily, whereas the SI-LO control group showed a marked aversion, thus demonstrating the effectiveness of this conditioning procedure. The important result, however, is that for the LI-LO group. These subjects showed no less of an aversion than group SI-LO; that is, prior experience of injections of LiCl produced no US-preexposure effect when the US during conditioning was administered orally rather than by injection. The critical role of injection-related cues was confirmed by a further test. After the subjects had received the test with flavor A they all (see Figure 4.8) experienced a standard flavor aversion conditioning trial in which consumption of a new flavor (B) was followed by an injection of LiCl. The results of the subsequent tests of consumption of B are shown in the lower right panel of Figure 4.8. On these tests, both control groups showed a strong aversion, whereas that shown by the LI-LO group was markedly less. In this case, then, the US-preexposure effect was obtained. The conclusion prompted by this pattern of results seems clear—prior exposure to (injections of) LiCl retards subsequent flavor aversion learning only when the US is delivered by injection; the US-preexposure effect seen in this situation is entirely a consequence of blocking by injection-related cues.

Conclusions

The general conclusions justified by the results discussed so far can be stated briefly. First, the effects produced by administration of LiCl to the rat will support conditioning not just to flavors, but to a range of exteroceptive cues. These include the physical context (the cage) in which the effects are experienced and also the cues that arise from the procedure of giving an intraperitoneal injection. The associative strength acquired by these cue will block subsequent flavor aversion conditioning resulting in the US-preexposure effect. When the physical context is novel during preexposure (and the test for aversion learning is given elsewhere) contextual (cage) cues contribute to the blocking effect. When the context is familiar, injection-related cues appear to have the dominant role. In no case does habituation (or the development of tolerance) appear to be involved—injections of LiCl that produce the US-preexposure effect do not result in a reduced UR (Figure 4.2) and do not produce any US-preexposure effect when conditioning is achieved by oral administration of LiCl (Figure 4.8).

HABITUATION RECONSIDERED

In spite of what has just been said, there are features of the results discussed in the previous section that might make us want to think again about the role of habituation. Specifically, the fact that contextual (including injection-related) cues can come to function as CSs for nausea complicates interpretation of the habituation test of De Brugada et al. (2003a), presented in Figure 4.2. This study used postinjection suppression of consumption as its measure, and it demonstrated that the size of this response was not influenced by experience of prior injections of LiCl. The conclusion that no habituation had occurred rests, however, on the assumption that this response is a simple UR, something that we now have reason to doubt. Since contextual cues can acquire associative strength, preexposure trials are conditioning trials, and the response shown on the test trial will be combination of the UR evoked by the injection on that trial and the CR elicited by contextual cues.

Symonds and Hall (2002) have investigated this matter directly. They demonstrated that the immediate effects of an injection of LiCl were enhanced when these were experienced in a context that had previously been paired with nausea. They concluded that the suppression of consumption seen in these circumstances reflected a summation of the UR with the CR to the context. What follows is that the development a CR over a series on injections might act to obscure any loss of the UR produced by habituation—that the performance of the Pre group in the experiment by De Brugada et al. (2003a) might indicate not the absence of habituation, but the development of a CR that compensates for the habituation effect. (Indeed, it is quite possible that in some circumstances the development of the CR may more than just compensate, and the summation of CR and UR will make the net effect of a later injection more powerful than that of an earlier one. Symonds and Hall, 2002, offered this as an explanation for the increase in the severity of posttreatment nausea reported by some chemotherapy patients; see also Stockhorst et al., 1998.)

In order to assess the role of habituation it is necessary to have a test procedure that avoids these complications—a test that reflects just the UR and is not contaminated by the CR. The lithium-drinking procedure of De Brugada et al. (2004) can provide what is needed. Here, since the preexposure procedure is carried out in the home cage, the only contextual cues that are of importance are the injection-related cues. These will acquire strength, but this will not be relevant if the LiCl on test is administered orally. The response evoked by such a dose of LiCl may be taken, therefore, to be a pure UR. How is it influenced, if at all, by prior experience of LiCl?

This issue has been addressed in an experiment by De Brugada, González, Gil, and Hall (2005). The critical features of their experimental design are shown in Figure 4.9. In this study the experimental group (the E group in the table) received six injections of LiCl in the preexposure phase (earlier work, see De Brugada et al., 2004, having indicated that habituation effects might be difficult to obtain with fewer preexposure trials). Control subjects were injected with saline during this phase. On the UR test the E group and one of the control groups (C-1) drank a LiCl solution and then were given immediate access to a novel flavor (A). The other control group (C-2) was given A after drinking saline. It was expected that suppression of consumption of A would be seen in rats that had just drunk LiCl; the question of interest was whether the degree of suppression would be influenced by preexposure to LiCl. The results, amounts of flavor A consumed by the three groups, are displayed on the left of the lower left panel of Figure 4.9. They

Group	Preexposure	UR Test	Test Sal	Cond	CR Test
E	6 Li inj	Drink Li -- A	Sal	B-Li inj	B
C-1	6 Sal inj	Drink Li -- A	Sal	B-Li inj	B
C-2	6 Sal inj	Drink Sal -- A	Sal	B-Li inj	B

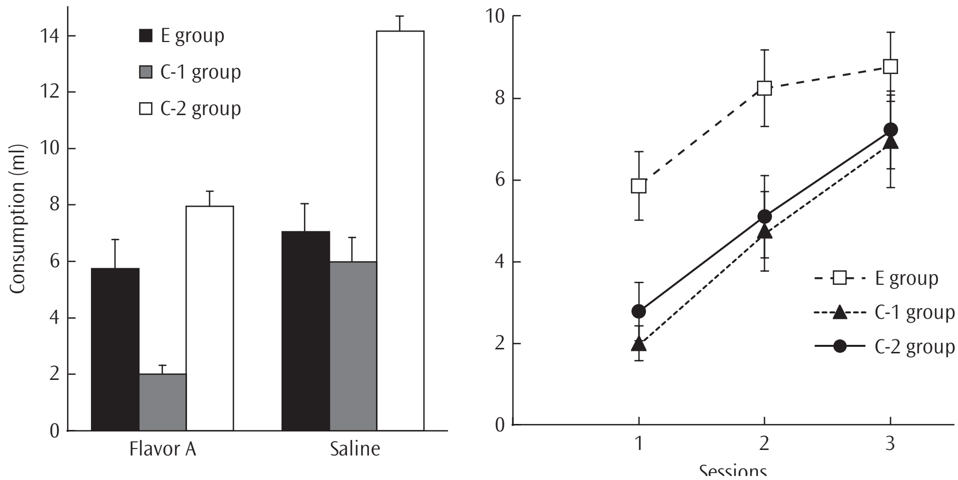

Figure 4.9. Design and test results of the experiment by De Brugada et al. (2005, Experiment 2). The lower left panel shows scores for the UR test (consumption of flavor A) given after consumption of LiCl (Li) in groups E and C-1, and for a test with saline (Sal) given 1 day later. Subjects in group C-2 drank saline rather than LiCl on the UR test. Rats in group E had received preexposure consisting of six injections (inj) of LiCl. The lower right panel shows consumption of flavor B (the CR test) given after conditioning (Cond) in which, for all subjects, drinking B was followed by an injection of LiCl.

show that prior consumption of LiCl resulted in a suppression of consumption of A; the C-1 group drank much less of A than did the C-2 group. But this effect was much attenuated in rats given preexposure to LiCl—the E group drank more than the C-1 group—in other words, habituation was obtained.

The results of the first phase of this experiment establish, for the first time, that habituation to LiCl can occur. It remains to determine what role such habituation might play in the US-preexposure effect. This was the purpose of the subsequent stages of the experiment. The first of these consisted of a test in which the rats were given access to a saline solution. It may be recalled that Loy and Hall (2002) have shown that drinking LiCl establishes a conditioned aversion to salty tastes. This means that the trial labeled UR Test in the table, not only served to test the UR to flavor A but also constituted a conditioning trial for the groups that drank LiCl (groups E and C-1). And indeed, these groups showed an aversion to saline in the subsequent test (see lower left panel of the figure), whereas the C-2 group drank it readily. But the result of central interest for our present concern is that there was no difference between the E group and the C-1 group in the degree of aversion they showed. The preexposure given to the E group appears to produce habituation to the effects of LiCl (the UR test), but it does not result in retarded conditioning (i.e., does not produce a US-preexposure effect).

The final phase of the experiment confirmed that a US-preexposure effect can be obtained in this training preparation, provided the blocking mechanism is permitted to operate. As Figure 4.9 shows, all the rats were given standard flavor aversion conditioning in which consumption of a new flavor (B) was followed by an injection of LiCl. The results of three test trials with B are shown in the lower right panel of the figure. Now the two control groups both show strong aversions, whereas that shown by the E group was much less. This outcome confirms the earlier finding of De Brugada et al. (2004)—preexposure to injections of LiCl will produce the US-preexposure effect, but only when injection-related cues are present in the conditioning phase.

Previous studies (such as those by De Brugada et al., 2003a, 2004) have shown that the US-preexposure effect can be obtained in the absence of any sign of habituation. The experiment just described allows us to take the argument a step further. Clearly, when habituation does not occur it cannot be responsible for the US-preexposure effect. In this experiment, however, we have been successful in obtaining evidence of habituation, allowing us to ask whether habituation contributes to the US-preexposure effect in this case. And the answer appears to be no—when blocking by contextual (injection-related) cues is eliminated, the aversion acquired by preexposed subjects is as great as that shown by controls.

SUMMARY AND CONCLUSIONS

I began this chapter by noting that the UR of nausea appears not to habituate, but that preexposure to a nausea-inducing treatment (a series of injections of LiCl for the rats), nonetheless, reliably reduces the effectiveness of nausea to serve as a US in flavor aversion conditioning. An explanation for both these facts can be provided by the application of standard principles of associative learning. Preexposure to LiCl injections is itself a conditioning procedure that allows contextual cues (those that characterize the place in which the injection is given plus those associated with the injection procedure itself) to become established as CSs for nausea. This has two relevant consequences.

First, it means that our standard tests for habituation, which assess the UR evoked by an injection of LiCl, will be "contaminated" by the fact that the injection procedure will also evoke a CR that can summate with the UR. When this effect is controlled for, a habituation effect (albeit not very powerful, and requiring extensive preexposure) can be obtained. Second, it provides, in itself, an explanation for the US-preexposure effect—the associative strength acquired by contextual cues will be able to block acquisition during flavor conditioning and thus retard the acquisition of an aversion.

What follows is that both of the possibilities mentioned earlier as explanations for the US-preexposure effect (i.e., habituation of the reinforcing power of the US and blocking by context) remain viable. The experimental evidence that has been discussed has amply confirmed the reality of the blocking-by-context effect. The role of habituation, however, is less secure. Not only do we obtain the US-preexposure effect when there is no sign of habituation but also as the last experiment discussed has shown, the effect can fail to occur even in the presence of habituation. This last effect is particularly intriguing theoretically and demands further study. At the very least, it requires us to acknowledge that the event described simply as "the US" in these experiments is rather more complex than this label implies. Standard associative theory (e.g., Wagner, 1981) has assumed that the application of a US activates a single representational node, and that the level of activity in this node determines both the magnitude of the UR and the reinforcing power of the US. The present results may indicate the need to distinguish two nodes, one susceptible to habituation by repeated US presentation and responsible for the UR, and one responsible for conditioned suppression of consumption and susceptible to associative modulation (and thus blocking effects).

It remains to be seen whether these conclusions, derived as they are from a single specific instance of the US-preexposure effect, will have general applicability. A clear and reliable effect has been repeatedly demonstrated with electric shock as the US for rats trained in the conditioned suppression (conditioned emotional response) paradigm. Blocking by context (i.e., by cage cues—there is no equivalent of injection-related cues when the US is a shock) may well play a role here, but the evidence is far from compelling. And the observation that the perceived intensity of a shock (and the UR it evokes) declines substantially and rapidly with repeated applications increases the plausibility of an explanation in terms of habituation. It will be an irony if the US-preexposure effect observed in this procedure (much used in the development of modern associative theory) turns out to be nonassociative in nature, whereas that obtained in nausea-based learning (said by some to be a unique form) turns out to be explicable in terms of standard associative principles.

Note

1. We will examine the validity of this assumption later in the chapter.

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