The importance of the stomach for conditioned place preference produced by drinking sucrose in rats

CECILE ARNOULD

Université de Tours, Tours, France

and

ANDERS ÅGMO

University of Tromsø, Tromsø, Norway

Sucrose produces conditioned place preference when the sweetener is delivered immediately before confinement in the place preference box. To evaluate the role of the oral and gastric effects of sucrose, rats were allowed to drink sucrose or were given sucrose or water intragastrically by gavage. The rats developed a preference in all cases in which the reinforcing event was delivered 3 min 30 sec before confinement, but not when an interval of 15 min was used. Contiguity between reinforcing event and conditioning is of importance. In an additional experiment, we tried to replicate the effect obtained with plain water and evaluated the role of cholecystokinin (CCK) receptors. Before water administration, the rats were subcutaneously injected with saline, devazepide (0.01 mg/kg), or L-365,260 (0.01 mg/kg). Only the group treated with devazepide showed significant place preference. CCK_A receptor blockade seems to enhance the reward value of gastric distension, and distension alone appears to be an unreliable reinforcing event.

Ingestive behaviors are associated with a multitude of physiological reactions. The sight and smell of food activate digestive processes that anticipate the arrival of food in the gut (Brand, Cagan, & Naim, 1982). These responses are further reinforced by taste stimuli and by the activation of mechanoreceptors in the esophagus and, eventually, in the stomach (Fantino, 1984). Food is then digested and absorbed, producing several modifications in the composition of blood. One of these changes is an increase in the concentration of cholecystokinin (CCK; (Lindén & Södersten, 1990; Lindén, Uvnäs-Moberg, Forsberg, Bednar, & Södersten, 1989). This substance may be involved in mechanisms of satiety, since CCK injection reduces food intake (Baile, MacLaughlin, & Della-Fera, 1986; Crawley & Corwin, 1994). It seems that a peripheral action is essential, because intact vagus nerves are required for this effect (Garlicki, Konturek, Majka, Kwiecien, & Konturek, 1990; Smith, Jerome, Cushin, Eterno, & Simasky, 1981).

Ingestive behavior itself or some of its physiological consequences are able to activate a positive affective state. The existence of such a state has been demon-

strated in rats with the conditioned place preference procedure, a procedure originally developed for the study of the affective consequences of drugs (Schechter & Calcagnetti, 1993). At least two different procedures of place preference conditioning have been employed in studies of ingestive reward. In one procedure, the rat is allowed to consume food or to drink a sweet solution within the reinforced compartment, whereas the nonreinforced compartment either is void of programmed reinforcement or only has plain water available instead of sweet (Bechara & van der Kooy, 1992; Nader & van der Kooy, 1994; Spyraiki, Fibiger, & Phillips, 1982; Stefáruk & van der Kooy, 1992, 1994; White & Carr, 1985). In the other procedure, the rewarding event is made available immediately before the animal is exposed to a particular environment at reinforced sessions, whereas no such event is presented at nonreinforced sessions (Ågmo, Fiederman, Navarro, Padua, & Velázquez, 1993; Ågmo, Galván, & Talamantes, 1995). In the first procedure, consummatory behaviors as well as the rewarding consequences of ingestion may become associated with the environment, whereas only the latter may participate in place preference in the second one. Taste alone appears to be sufficient to induce place preference when the reinforcer is consumed within the place preference environment, because saccharin, a sweet nonnutritive substance, is effective (Stefáruk & van der Kooy, 1992, 1994; but see, also, White & Carr, 1985, for a negative finding). In the second version of the procedure, sweet taste, provided by saccharin, is ineffective (Ågmo &

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Arnould, 1995; Ågmo & Marroquín, 1997). However, when saccharin drinking is combined with a subcutaneous glucose injection, a place preference is obtained (Ågmo & Arnould, 1995; Ågmo & Marroquín, 1997).

The purpose of the present experiments was twofold. First, we assessed the importance of contiguity between the taste experience and exposure to the environment for place preference conditioning. In our previous studies (Ågmo & Arnould, 1995; Ågmo et al., 1995), the rats had access to the sweet solution immediately before place conditioning. In the present experiments, an interval between exposure to the tastant and conditioning was imposed. Second, the role of gastric stimulation was evaluated. In the earlier studies, the postabsorptive actions of sucrose were simulated by an injection of glucose. However, it is possible that other events associated with food ingestion are equally important. For example, gastric distension may be involved in the development of preference. Therefore, we tested rats that were gastrically intubated with sucrose, ensuring gastric stimulation and postabsorptive effects. Other groups were intubated with plain water. This would produce gastric distension similar to that produced by an equal volume of sucrose but would not have any appreciable postabsorptive effect in the nondeprived animals that were used. Because water administered intragastrically was, in fact, able to produce place preference, an additional experiment was performed. First, we wanted to replicate this rather surprising observation. Second, we combined intragastric water with an injection of CCK antagonists. Stimulation of gastric stretch receptors produces local CCK release (Davison & Clarke, 1988; Schwartz & Moran, 1994), and such release potentiates the gastric vagal response to distension (Schwartz, McHugh, & Moran, 1991). Moreover, gastric loads enhance CCK-induced inhibition of food intake (Schwartz, Netterville, McHugh, & Moran, 1991). These effects of CCK are mediated by the CCK_A receptor, because the CCK_A antagonist devazepide blocks the vagal response to CCK, whereas the CCK_B antagonist L-365,260 is ineffective (Schwartz, McHugh, & Moran, 1994). Peripheral CCK produces place (Swerdlow, van der Kooy, Koob, & Wenger, 1983) and taste (Deutsch & Hardy, 1977; Ervin, Mosher, Birkemo, & Johnson, 1995) aversion, and release of CCK could activate an aversive state that reduces the reward value of food, thereby promoting the termination of food intake. Thus, we predicted that blockade of CCK_A receptors would enhance the reward value of gastric distension. Groups of rats were treated with devazepide or L-365,260 before being intubated with plain water. If CCK-potentiated vagal responses indeed have aversive consequences, devazepide should enhance place preference, whereas L-365,260 should be ineffective.

It has been shown that the brain structures and neurotransmitters involved in reward are different in sated and

in deprived animals (Bechara & van der Kooy, 1992; Harrington & van der Kooy, 1992). Because we have been interested in the reward value of sweet taste and not in that of need reduction, we have systematically used sated animals in previous studies (Ågmo & Arnould, 1995; Ågmo et al., 1995; Ågmo & Marroquín, 1997). To make this study comparable with the previous ones, sated animals were used here also. That means that the preexperimental gastric distension may vary between individuals (this point will be discussed later).

METHOD

Subjects

Male Wistar rats weighing 410–670 g were used. They were housed individually in 40 × 26 × 15 cm (l × w × h) cages under a reversed light:dark cycle (lights on, 2000–0800). Commercial rat food and water were available ad lib; the animals were not deprived before the experiments. The experiments reported herein were carried out from 1000 to 1300.

Drugs

Devazepide (L-364,718) and L-365,260 (both from Merck, West Point, PA) were suspended in saline, together with a drop of Tween 80 (Sigma, St. Louis). The suspensions were sonicated for 30 min and were freshly prepared on the treatment day. The drugs were administered subcutaneously in a volume of 1 ml/kg of body weight.

Apparatus

When the rats were allowed to drink sucrose solution, a 10-ml graduated pipette was fixed to the front of their home cages, and food and water were removed. The place-conditioning box measured 102 × 34 × 27 cm (l × w × h) and was made of plywood. It consisted of two distinct compartments (38 × 34 cm) separated by a central area that was painted gray. The lateral walls of the central area were of fine wire mesh. One lateral compartment was painted white, and sawdust was put on its floor before each experimental session. The other lateral compartment was black, and its walls were moistened with a few drops of acetic acid (2%) before each rat was tested. The two lateral compartments were very different, to ensure that rats could easily differentiate them (Schechter & Calcagnetti, 1993). The rat's position was observed through the central area's wire-mesh wall. The access to this area could be closed with doors, making it possible to confine the rat in a lateral compartment.

The stomach tube used for the rats' intubation was a curved stainless steel needle (length, 50 mm; diameter, 1 mm).

Design and Procedure

Experiment 1. Four putatively reinforcing events were administered to different groups of animals: (1) The rats were intubated, but no liquid was administered, and immediately thereafter, they were allowed to drink 3 ml of an 18% (w/v) sucrose solution (the ST+SU group; *n* = 11); (2) 3 ml of this solution were administered intragastrically by gavage (the SUST group; *n* = 6); (3) 3 ml of water were administered in the same way (the WAST group; *n* = 5); and (4) to test the possible aversive effect of intubation, rats were intubated in the same way as for the other groups, but no fluid was administered (the ST group; *n* = 9). The stomach tube used for intubation was thoroughly cleaned (inside and outside) between each rat. Before being inserted into the esophagus, the outside was cleaned with a moistened towel and then dried, to avoid oral contact with sucrose or water.

All the rats were familiarized to the stomach tube by introducing it in their esophagus for a few seconds, once a day, for 6 days before the beginning of place preference conditioning. The rats that were allowed to drink sucrose had access to the solution in a pipette mounted on their home cages, as was described above, during two sessions of 1 h each. Next, these rats were familiarized to drinking 3 ml of sucrose in less than 10 min. A maximum of 3 days was required to obtain this performance. Training to drink sucrose was performed just after habituation to the stomach tube (intubation without administration of fluid). In all cases, habituation sessions were performed once a day.

Twenty-four hours after the end of habituation, a pretest was performed in the place preference apparatus. The rats were placed in the middle compartment and were allowed to move freely for 10 min. One day later, conditioning began. The rats received three reinforced sessions and three nonreinforced sessions on alternate days. Sessions were separated by 1 or 3 days. Half of the rats from each group began conditioning with a reinforced session, and half with a nonreinforced one. Reinforcement was always associated with the nonpreferred compartment, as determined at the pretest. The rats were placed in the appropriate compartment for 30 min, 15 min after the end of the administration of sucrose (SUST group) or water (WAST group) or after the stomach tube was removed from the rats' mouths (ST group). In the ST+SU group, placement in the compartment occurred 15 min after the pipette containing sucrose was fixed to the home cage. The pipette was removed when 3 ml of the solution had been drunk. Fluids administered intragastrically were heated to about 35°C. The rats were tested for their preference 2 days after the last conditioning session. Test was performed in the same way as that for the pretest. At the end of each test, the floor of the apparatus was cleaned with water and dried with a clean paper towel, and feces and micturitions were removed from the sawdust. At pretest and test, the time spent in each compartment was recorded. Preference score [(time in the reinforced compartment / (time in the reinforced compartment + time in the nonreinforced compartment))] was used as a measure of conditioned place preference.

Experiment 2. Forty-six rats were assigned to four treatment groups similar to those of Experiment 1 (ST+SU, $n = 14$; SUST, $n = 9$; WAST, $n = 13$; ST, $n = 10$). The procedure was the same as that in Experiment 1, except for the delay between reinforcement and confinement to the reinforced compartment. The rats were placed in this compartment immediately after they finished drinking 3 ml of sucrose for the sucrose drinking group (ST+SU) or 3 min 30 sec after the stomach tube was removed from their mouths for the other groups (SUST, WAST, ST).

Experiment 3. Thirty-six rats were randomly assigned to three treatment groups. In these three groups, 3 ml of water was administered intragastrically with a stomach tube 3 min 30 sec before conditioning. Thirty minutes before, they had received an injection of devazepide (0.01 mg/kg; $n = 11$), L-365,260 (0.01 mg/kg; $n = 12$), or saline ($n = 13$). The procedure used was otherwise the same as that in the preceding experiments. A dose of 0.01 mg/kg of both

antagonists was used, since this dose had been reported to lack intrinsic effects on place preference, while blocking the effects of other rewards (Higgins, Nguyen, & Sellers, 1992).

Statistical Analysis

Preference scores at pretest and test were compared with a Wilcoxon matched-pairs signed-ranks test. A nonparametric test was used, since group variances were not homogeneous. In all cases, the p value for statistical reliability was .05. The purpose of the study was to determine whether a particular reinforcing event indeed produced place preference, but not to compare the intensities of preferences. Therefore, no between-group comparisons were made.

In the Results section, when a treatment induces a place preference, it means that the preference score increased between pretest and test.

RESULTS

Experiment 1

None of the reinforcing events delivered 15 min before confinement to the reinforced compartment produced a significant place preference (Table 1). In fact, preference scores remained remarkably stable between pretest and test. All the rats that drank sucrose (ST+SU group) consumed 3 ml of the solution within a short time (mean, 3 min 32 sec; range, 1 min 25 sec to 7 min 30 sec), making the mean interval between the end of consumption and the beginning of conditioning to be 11 min 28 sec.

Since sucrose drinking did not produce place preference in this situation, in contrast with an earlier study, in which it was consumed immediately before conditioning (Ågmo et al., 1995; Ågmo & Marroquín, 1997), there was not much reason to believe that the other treatments would be effective. In the following experiment, *all* the putative reinforcers were administered 3 min 30 sec before confinement to the nonpreferred compartment of the place preference box. As has been mentioned above, this was the mean time required for consuming 3 ml of sucrose.

Experiment 2

The rats drinking sucrose and the rats that received sucrose intragastrically increased significantly their preference scores between pretest and test ($p = .048$ and $.008$, respectively; Figure 1). Similar results were obtained with the rats receiving water intragastrically ($p = .003$). The rats that were intubated but that did not re-

Table 1
Preference Scores Obtained at Pretest and Test in Rats Drinking Sucrose (ST+SU, $n = 11$), Receiving Sucrose (SUST, $n = 6$), or Water (WAST, $n = 5$) Intragastrically, or Intubated Without Fluid Administration (ST, $n = 9$) 15 Min Before Confinement in the Conditioned Compartment

Group	Pretest		Test		P^*
	Median	Semi-Interquartile	Median	Semi-Interquartile	
ST+SU	0.35	0.02	0.32	0.07	0.66
SUST	0.45	0.05	0.48	0.05	0.75
WAST	0.44	0.03	0.40	0.01	0.89
ST	0.38	0.18	0.43	0.12	0.77

*Wilcoxon matched-pairs signed-ranks test, pretest versus test.

Figure 1. Preference score (median + semi-interquartile range) measured during pretest and test in rats drinking sucrose (ST+SU, $n = 14$), receiving sucrose (SUST, $n = 9$) intragastrically, receiving water (WAST, $n = 13$) intragastrically, or intubated without fluid administration (ST, $n = 10$) just before confinement in the conditioned compartment. * $p < .05$. ** $p < .01$ (pretest vs. test).

ceive fluid developed neither preference nor aversion (pretest vs. test, $p = .28$). The rats that drank sucrose (ST+SU group) consumed the 3 ml within a short time (mean, 4 min 3 sec; range, 1 min 35 sec to 7 min 50 sec).

These results show that a nonnutritive fluid administered intragastrically induced place preference. The effect of CCK receptor blockade on acquisition of this preference was assessed in Experiment 3. Since gastric distension may activate CCK release and ensuing stimulation of CCK_A receptors, and since stimulation of these receptors has aversive consequences (Moshier, Birkemo, Johnson, & Ervin, 1998; Moshier, Johnson, Birkemo, & Ervin, 1996), we hypothesized that a CCK_A antagonist would enhance place preference.

Experiment 3

When the rats were injected with saline 30 min before receiving water intragastrically, preference scores at test were not statistically different from those observed at pretest ($p = .15$; Figure 2). Similar results were obtained

Figure 2. The effects of saline ($n = 13$), devazepide ($n = 11$), or L-365,260 ($n = 12$) injections (0.01 mg/kg), 30 min prior to intragastric administration of water (reinforcing event) during conditioning sessions, on preference scores (median + semi-interquartile range). * $p < .01$ (pretest vs. test).

when L-265,360 was administered ($p = .07$). On the other hand, when devazepide was injected before the intragastric administration of water, preference scores increased significantly between pretest and test ($p = .003$).

DISCUSSION

Our results underline the importance of contiguity between exposure to a reinforcer and exposure to distinctive environmental cues for the establishment of place preference. Furthermore, the present data show that gastric stimulation produced by a nonnutritive fluid (water) alone may be a reinforcing event when administered immediately before conditioning. Blockade of CCK_A receptors appears to enhance the reward value of gastric stimulation.

Experiment 1 showed that none of the putatively reinforcing events were effective when an interval of about 15 min was interposed between exposure to the event and preference conditioning. The volume of sucrose consumed in the drinking group, 3 ml, had previously been found to produce place preference when consumed over about 3 min immediately before conditioning (Ågmo et al., 1995). It seems, therefore, that the lack of an effect is due to the interval between consumption and conditioning, and not to insufficient consumption. Several explanations may be proposed.

One possibility would be that blood glucose levels were too low at the end of the 10-min interval, since a sweet taste without enhanced blood glucose does not produce place preference in the procedure employed here (Ågmo & Arnould, 1995; Ågmo & Marroquín, 1997). However, this possibility seems unlikely. Sucrose is rapidly digested into glucose and fructose, both of which are readily absorbed by the gastrointestinal tract. Blood glucose concentrations peak about 20 min after the beginning of a meal, and they remain elevated for more than 1 h, even when small amounts of food are eaten (Strubbe & Steffens, 1977). These data show that blood glucose attains peak levels during exposure to the place environment, even when the 10-min interval between drinking and conditioning is interposed.

Another possibility is that the establishment of associations between affective state and environmental cues becomes difficult when an interval between reinforcer and exposure to the place environment is interposed. The fact that the same volume of sucrose that was consumed in Experiment 1 was effective when drunk immediately before conditioning, in Experiment 2 and in our previous study (Ågmo et al., 1995), supports this explanation. Place preference is thought to be a kind of classical conditioning in which the reinforcing event is the unconditioned stimulus and the affective state is the unconditioned response (Ågmo et al., 1995; Calcagnetti & Schechter, 1993). The conditioned stimulus is the place environment. In the present procedure (Experiment 1), part of the unconditioned stimulus, a compound of taste and the postabsorptive effects of sucrose, precedes the

conditioned stimulus by several minutes. On the other hand, in Experiment 2 and in the previous study (Ågmo et al., 1995), in which sucrose drinking immediately preceded exposure to the conditioned stimulus, postabsorptive effects were only beginning to appear when conditioning was initiated, which is a more convenient situation for learning (Dickinson, 1981).

In Experiment 2, not only sucrose drinking, but also gavage with sucrose or plain water was effective. These data suggest that neither taste nor a postabsorptive effect of a nutrient is necessary for the establishment of place preference. It rather seems that gastric stimulation alone can induce reinforcement. This stimulation needs to be rather intense, because free drinking of water or of a saccharin solution are inefficient in nondeprived rats (Ågmo & Arnould, 1995; Ågmo & Marroquín, 1997). In these cases, consumption rates are below 0.5 ml/min, and that should produce far less gastric distension than that produced by 3 ml infused over a few seconds.

Gavage with water after saline injection was ineffective in Experiment 3, whereas it had a robust effect in Experiment 2 (without injection). Interestingly, saline injection has been reported to enhance CCK immunoreactivity in the periaqueductal gray region, whereas handling without injection does not have this effect (Rosén, Brodin, Eneroth, & Brodin, 1992). The only procedural difference between Experiments 2 and 3 was that animals in the former experiment were not given any injection, whereas those in the latter were. It could be argued, then, that the lack of effect of water in Experiment 3 was due to enhanced CCK activity in the brain in response to the injection. If this has aversive consequences, the rewarding effects of gastric distension may be reduced or eliminated. This proposal is speculative until the hedonic effects of intracerebral CCK have been analyzed.

It must be noted that fluids administered intragastrically were heated to about 35°C. Barone, Zarco de Coronado, and Wayner (1995) have demonstrated that most of the hypothalamic neurons modulated by gastric distension displayed larger response to cool water than to water at body temperature (37°C). Place preference observed in our experiments could, perhaps, have been enhanced by the use of fluids at room temperature.

No water or food restriction was applied before tests. Deprivation would have confounded any results, since it is generally accepted that water itself is an efficient reward in deprived rats. The role of gastric stimulation in the absence of other effects could, therefore, not have been evaluated if deprived rats had been used. On the contrary, water has no apparent rewarding capacity in nondeprived animals (Ågmo et al., 1995; Ågmo & Marroquín, 1997). This makes it possible to determine the role of mechanical gastric events. However, since the rats were not deprived, it is possible that water or food consumption immediately before the experiments could have distended their stomach to some extent. That might have reduced the possibility of obtaining clear preferences after treatment. Since sated rats were used in our experiments, the preexperimental gastric distension may vary

between individuals. However, since food was not available during the experimental sessions, there should not be any systematic difference between groups. Thus, the use of sated animals may somewhat augment interindividual variation but cannot account for group differences.

The dose of devazepide employed in this study has been found to be ineffective when administered alone, but it reliably inhibits place preference produced by morphine (Higgins, Nguyen, & Sellers, 1991, 1992). These latter observations make it possible to suggest that the effects of gastric distension are not mediated by the activation of central opioid systems, because devazepide enhanced conditioned preference in our experiment. Opioid systems have been shown to be important for the affective reactions produced by several natural rewards, such as copulation, drinking water, and sweet solutions (Ågmo & Berenfeld, 1990; Ågmo et al., 1993; Ågmo et al., 1995). It appears that gastric distension, in the absence of other sensory experiences of food consumption, functions in a way different from that of a natural eating experience. The importance of this observation needs to be determined in future studies.

To summarize, the present data show that exposure to sucrose needs to immediately precede preference conditioning, if a preference is to be obtained. Intra gastric administration of plain water may also produce place preference, although this effect seems to be unreliable or sensitive to details of experimental procedure. When CCK_A receptors are blocked, however, intragastric water seems to be an efficient reinforcer. This observation suggests that gastric distension activates two opposing processes—one that is reward promoting, and another that is aversive. Little is known about the mechanisms responsible for gastric distension-induced reward, but indirect evidence from our results suggests that opioid systems do not participate. The aversive consequences seem to depend on peripheral CCK release and may be associated with activity in the vagus nerve. Interestingly, a rather intense gastric stimulation is necessary in order to activate vagal afferents, since infusion speeds below 2 ml/10 sec are insufficient to activate the vagus (Schwartz, McHugh, & Moran, 1993). It is, therefore, rather unlikely that normal drinking produces a distension sufficiently large to activate the gastric branch of the vagus nerve. However, consumption of foodstuffs with slow gastric emptying might be efficient. It could be speculated that the rewarding consequences of gastric distension are dominant at the beginning of a meal, facilitating food intake, whereas the aversive processes, activated by intense gastric distension, participate in meal termination. These hypotheses need to be confirmed in future studies.

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