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Pairing a place with lithium injection produces conditioning of a salivary response

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Experimental rats were given pairings in which placement in a distinctive chamber was followed by an injection of lithium chloride; control rats received unpaired exposures. After two pairings, some of the experimental rats were observed to salivate in the chamber prior to the injection of lithium. The probability of this response increased with further training. No salivary responses were seen in control rats. This pattern of findings indicates that the pairings of a conditioned stimulus, the distinctive chamber, with an unconditioned effect produced by lithium resulted in Pavlovian conditioning of a salivary response. Since lithium was not observed to evoke salivary responding in the absence of conditioning, the conditioned salivary response was probably compensatory to the drug effect.

While conducting conditioning trials in which placement in a distinctive chamber was the conditioned stimulus (CS) and an injection of lithium chloride was the unconditioned stimulus (US), we noticed that some of the rats were salivating profusely soon after being placed in the CS chamber prior to the injection of lithium. This profuse salivary response could be described as frothing at the mouth or drooling; it resulted in wet, matted fur around the mouth and down the front of the body, and trails of saliva on the clear plastic walls of the chamber could be observed where a rat had rubbed its face. Since this behavior was not observed until the fifth conditioning trial and seemed to occur only in those animals given paired exposures to the place and lithium, it seemed likely that the behavior in question was a conditioned salivary response elicited by the place CS. Here we confirm this conjecture.

METHOD

Subjects

The subjects were 26 male Sprague-Dawley rats with a mean body weight of 284 g. They were individually housed in a standard rack of stainless steel cages. Food and water were continually available in the home cages throughout the experiment.

Apparatus

The stimulus chambers were transparent polycarbonate cages (48.3 cm long, 26.7 cm wide, 15.6 cm high) with straight wire lids and were obtained from a commercial supplier. A piece of paper towel was placed on the bottom of each cage on each conditioning day. The cages were placed on several rows of shelves in a separate room near the colony room in which the rats usually lived.

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Procedure

The rats were divided into two groups of 13 each, equated with respect to mean body weight. During each conditioning trial, each rat was carried from its home cage and placed in a CS chamber; 15 min later it was given an intraperitoneal injection. The rats in the experimental group (Group P) received .15 N lithium chloride solution (2 ml per 100 g of body weight), and those in the control group (Group U) were injected with 2 ml of physiological saline. Then the rat was replaced in the stimulus chamber, where it remained for an additional 30 min before it was carried back to its home cage. Approximately 5 h later, the rats in Group U were injected with the same dose of lithium chloride given Group P, and the rats in Group P were injected with 2 ml of saline. Six such trials were each separated by 2-4 days.

During each conditioning trial, every rat was observed on two occasions for signs of salivary responding. One occasion was 15 min after placement in the CS chamber immediately prior to the lithium or saline injection, and the other was just before the rat was returned to the home cage. The experimenter scrutinized the rat, particularly the area around the mouth, and rated the magnitude of the salivary response as *no response*, *small*, or *large*. A rating of *small* was given when wetness of the fur immediately under the mouth was observed; this was usually a small triangle of wet fur pointing down toward the chin. The rating of *large* was assigned when frothing and drooling of saliva could be directly seen or when the extent of wet fur included not only the mouth area but also a considerable area of the fur on the front of the rat's body.

RESULTS AND DISCUSSION

A conditioned response (CR) was defined as a large or small salivary response that occurred in the CS chamber prior to the injection of lithium chloride. Table 1 shows the percentage of rats in Groups P and U that made a CR during the six conditioning trials. As can be seen, the pattern of results exhibits the two characteristics needed to prove that Pavlovian conditioning has occurred. That is, conditioned salivary responding was observed in animals that received forward pairings of the CS chamber and the lithium US (Group P), but not in those (Group U) receiving unpaired exposures. Moreover, in Group P the probability of a CR increased with training. This trend was also evident when only large salivary responses were considered; no large responses were observed during the first

Table 1
Percentage of Rats in Groups P and U that Made a Conditioned Salivary Response During Trials 1–6

	Trial					
	1	2	3	4	5	6
Group P	0	0	31	38	46	69
Group U	0	0	0	0	0	0

three trials, and the percentage of CRs that were rated as large was 20%, 50%, and 67%, respectively, during the remaining three trials. By the statistical criterion of the Fisher exact probability test, the number of rats in Group P that made a small or large CR was significantly different from that in Group U on Trials 3, 4, 5, and 6 ($p < .05, p < .025, p < .01, p < .005$, respectively).

The rats were also observed for salivary responding as they were returned to their home cages. This occurred 30 min after the rats received their injections of lithium chloride or saline in the CS chamber. Table 2 shows the percentage of rats in Group P that made a small or large salivary response after the lithium injection; none of the rats in Group U showed any signs of salivation during the comparable time period. As was the case with salivary responding occurring prior to the lithium injection, the probability of a response increased with training. During Trials 1 and 2, lithium did not evoke noticeable salivation, suggesting that lithium does not directly increase salivation. Indeed, it seems likely that lithium's direct effect in rats is to block salivation, since human patients undergoing lithium therapy report "dry mouth" as a side effect (Gattozzi, 1970). These considerations indicate that the conditioned salivary response observed in Group P was compensatory to the effect produced by the US drug, as is often the case (e.g., Eikelboom & Stewart, 1982; Siegel, 1972, 1976). If so, the salivary responses observed after lithium injections were also conditioned responses.

Table 2
Percentage of Rats in Group P that Showed Signs of Salivation 30 min After Injection of Lithium

Trial					
1	2	3	4	5	6
0	0	23	39	54	46

Pairings of a place or a drug CS with lithium result in the conditioning of other physiological responses beside salivation. Pairings of a drug CS with lithium have been shown to produce conditioning of a thermic response (Taukulis, 1982) and a heart rate response (Wilkin, Cunningham, & Fitzgerald, 1982). Conditioned delay of stomach emptying can be produced by pairing a place CS or a drug CS with lithium (Lett, 1986). It is noteworthy that the conditioned thermic and salivary responses are compensatory to the direct, unconditioned effects of lithium, whereas the conditioned effects on stomach emptying and heart rate mimic lithium's unconditioned effects.

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