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Conditioning of Gastric Secretion by Epinephrine in Rats (38445)

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Many Soviet workers have established conditioned responses in animals using varieties of drugs as the unconditioned stimuli (1). Atropine or atropine-like drugs have been used as the unconditioned stimulus to produce paradoxical conditioned response in dogs (2, 3). Increased salivation occurred in these animals, when they were brought to the same environment where they previously received injection of such a drug, although the drug itself inhibited the same function. The object of the present study was to investigate whether epinephrine that also inhibits gastric secretion (4) can be used as an unconditioned stimulus to condition gastric secretion.

Methods. Albino rats of Wistar strain weighing 250–300 g and of either sex were implanted with stainless steel cannula in their stomach according to the method of Pare (5) for repeated collections of gastric secretion over prolonged periods. Experiments were started following a postoperative period of 2 weeks. Further, they were placed in restraining holders daily for several hours, in order to adapt themselves to conditioning experimental situations.

During a daily session lasting for 2 hr, animals were kept inside a sound-proof cabinet fitted with a speaker, for collection of gastric secretion every hour. Experimental sessions were carried out 7 days a week at the same hour of the day. Prior to daily sessions the stomach of each animal was gently lavaged several times with warm saline to remove residual food particles.

The experimental period of 21 days was equally divided into three phases. During the first phase the rats of the drug-conditioned group were used for collection of gastric juice which served as their own control. During the second phase they were injected ip with epinephrine bitartrate (0.2 mg/kg in 0.2 ml saline) after first hour collection concomitant with presentation of a tone (3000 Hz; 60 dB; duration 30 sec). In the third phase the above procedures were repeated, but epinephrine was replaced by same volume of saline. The control rats were subjected to the same conditioning procedures, except that during the second phase epinephrine was substituted by saline.

This investigation involved two experiments. In experiment I the drug-conditioned group consisted of 20 rats for which the data from the first and the third phases served as controls for comparison with those from the second (drug) phase; five rats identically treated through various phases (except for substitution of epinephrine by saline) served as additional controls. Experiment II consisting of six rats each of the drug-conditioned and the control groups was designed more vigorously for further confirmation of the previous data.

The mean and the standard error of the mean for the volumes of gastric secretion for the first and the second hours of daily sessions during different phases of the experiments were calculated. Paired comparison between the corresponding categories of data from drug-conditioned and control rats was done by Student's t test.

Results. Experiment 1. The mean volumes of gastric secretion for the first and the second hours of daily sessions during the three phases of experiment with the drug-conditioned and the control rats from experiment I are presented in Table I. For facilitation of description, data for respective hour during a phase for all rats from either group have been designated as a "category" which is serially numbered in this and the other tables.

In the control group, the category means did not differ from each other except for category number 12 which appeared to be slightly lower. In the drug-conditioned group, there was also no apparent difference between the category means in the first and third phases. During the second

TABLE I. Data from Experiment I. Average Volumes of Gastric Secretion for the First and the Second Hours of Daily Sessions during Three Phases of Experiment in the Control and Drug-conditioned Rats.

	Gastric secretion (ml)			
	Drug-conditioned rats[b,c]		Controls[b,c]	
Phase[a]	1st hour	2nd hour	1st hour	2nd hour
	(1)	(4)	(7)	(10)
I.	1.334 ± 0.062	1.231 ± 0.062	1.466 ± 0.077	1.454 ± 0.087
	(2)	(5)	(8)	(11)
II.	1.777 ± 0.073	0.735 ± 0.049	1.509 ± 0.092	1.495 ± 0.084
	(3)	(6)	(9)	(12)
III.	1.614 ± 0.093	1.501 ± 0.085	1.326 ± 0.097	1.160 ± 0.081

[a] Seven day periods. Rats of the drug-conditioned group were injected between the first and two hours with epinephrine and saline during the Phases II and III, respectively. Saline was given to the control during both the phases.

[b] Mean ± SE of the data for the respective hour from all rats during a phase. Data for the respective hour during a phase for all rats from either group have been designated as a "category" which is serially numbered.

[c] $N = 20$ for the drug-conditioned group and $n = 5$ for the controls. Student's t test showed significant difference between data from the following paired categories: 2 vs 1 or 5 and 5 vs 4, 6 or 11 $P < 0.005$; 4 vs 6 $P < 0.01$.

phase when epinephrine was administered between the hours, a marked decrease was observed in the second hourly means. Moreover, the first hourly mean of this phase (category 2) was significantly higher than that of the first phase (category 1). Although the increase in first hourly secretion of phase II in the drug-conditioned group was much reduced during the third phase, some residual increase still persisted during the first three days of the third phase leading to higher mean values compared to those of phase I. In contrast, in the control group a slight decrease in secretion was observed during the third phase.

Experiment 2. Results of this experiment as shown in Table II are basically similar to those observed in experiment 1. However, increase in the first hourly mean (category 2) of the second phase was more pronounced than that of the previous experiment. A further analysis of the first hourly data during phase II on day-to-day basis (Fig. 1) shows a progressive increase from the second to the fourth day followed by a slight gradual decline, although a significant difference from the control was maintained throughout the phase except the first day. Such increase also persisted over the first and second days of the next phase.

Discussion. Following epinephrine injection there was marked reduction of gastric secretion, but in the first hour during the drug sessions there was paradoxical increase in the daily rate of

TABLE II. Data from Experiment 2. Details same as in Table I.

	Gastric secretion (ml)			
	Drug-conditioned rats[b,c]		Controls[b,c]	
Phase[a]	1st hour	2nd hour	1st hour	2nd hour
	(1)	(4)	(7)	(10)
I.	1.75 ± 0.07	1.63 ± 0.12	1.77 ± 0.07	1.74 ± 0.12
	(2)	(5)	(8)	(11)
II.	3.01 ± 0.28	0.70 ± 0.07	1.51 ± 0.07	1.49 ± 0.09
	(3)	(6)	(9)	(12)
III.	2.00 ± 0.12	1.85 ± 0.1	1.52 ± 0.04	1.58 ± 0.11

[a] Same as in Table I.

[b] Same as in Table I.

[c] $N = 6$ rats in each group. Student's t test showed significance ($P < 0.01$) between the data from the following paired categories: 2 vs 1, 3, 5 or 8; 5 vs 4, 6 or 11; 6 vs 12; 7 vs 9.

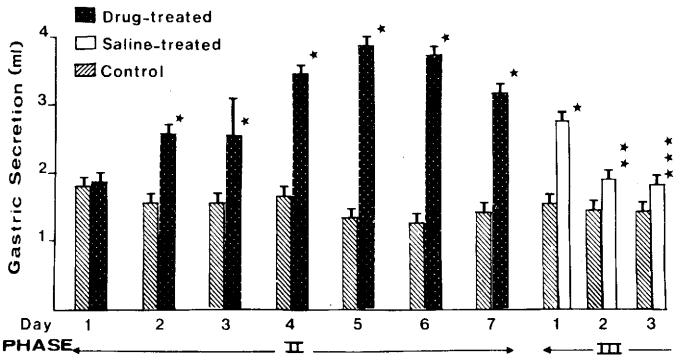

FIG. 1. Daily first hourly gastric secretion of epinephrine-conditioned rats during the Phase II (drug-treated) and the first 3 days of Phase III (saline-treated) of Experiment II compared to that of the corresponding controls. Each group contained six rats. Bars with vertical lines at the top indicate means with SE, and the levels of significance of the difference between the data are given by $*P < 0.001$, $**P < 0.005$ and $***P < 0.01$.

gastric secretion. This observation is similar to increase in salivation induced as conditioned response by atropine and atropine-like drugs (6–8). Increased gastric secretion may be attributed to an adaptive compensatory mechanism in anticipation of its marked inhibition by epinephrine.

It has been reported by Pradhan and Wingate (4) that adrenergic inhibition of gastric secretion is mainly a peripheral β-receptor function. The present study clearly indicates that such an effect of epinephrine can be conditioned by the usual conditioning procedures. In this respect it is difficult to reconcile Astrup's concept (9) that only the centrally mediated effects and not the peripheral effects of a drug are conditionable.

Summary. Conditioning of gastric secretion was studied in rats using epinephrine as unconditioned stimulus. Although epinephrine itself produced a marked inhibition of gastric secretion, a conditioned paradoxical increase was noted during the 1-hr period of observation immediately prior to drug administration. It appears that the initial increase of secretion during the sessions of drug phase occurred as a result of an adaptive compensatory mechanism in anticipation of its marked inhibition.

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