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Effect of Ergotamine on Milk-Ejection in Lactating Rat.* (22242)

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It has been generally accepted(1-5) that the oxytocic principle from the posterior pituitary gland is the humoral agent responsible for "let-down" of milk from mammary gland. It has further been demonstrated(6) that adrenalin, fright, and other stimuli, interfere with this effect, whereas acetylcholine, when injected, acts similarly to "let-down" hormone(7-8). Evidence is presented in this paper that ergotamine also interferes with normal "let-down" of milk in lactating rats.

Materials and methods. Docile lactating rats, each with its first litter and weighing 230-260 g. were housed in individual cages and given Purina Dog Chow and water *ad libitum*. Seasonal greens were fed twice weekly. Each litter was reduced to 6 young shortly after birth and, whenever possible, these were equally distributed as to sex. Rats with less than 6 young were discarded. Ten control and 10 experimental animals each with litter of 6 were used. Ergotamine tartrate‡ was injected subcutaneously into lactating mothers 3 times a day at 6-hour intervals, from ninth through twelfth days postpartum, at dosage of 3 mg/kg/day. Half of the controls received comparable injections of physiological saline to test whether or not frequency of injection and/or amount of fluid injected would affect the pattern of maternal behavior. The remaining controls were uninjected. One and one-half hours following the second of 3 injections of the day, each litter was weighed, then isolated from the mother for 6 hours during each day of injection period. The young were kept warm to prevent any undesirable effects from exposure. In some preliminary experiments, stomachs of several litters, killed at end of 6-hour isolation period, contained no milk. One and one-half hours after third injection of the day, each litter was again weighed to determine weight loss during the 6-hour interval. The young were then placed back with the mother and allowed to suckle for exactly 20 minutes. Length of time before each mother began nursing was recorded. The litter was then removed and weighed to determine amount of milk obtained during the 20-minute interval. (Table

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TABLE I. Average Quantity of Milk, Expressed as % Body Weight Gain, Secured in 20 Min. by Litters of 10 Control Lactating Rats, and 10 Experimental Animals Injected with Ergotamine from the 9th to 12th Days Postpartum.

Day of lactation	Group	%	S.E.	P
9	Control	5.59	.87	
	Treated	.36	.53	.001
10	Control	4.03	.54	
	Treated	2.22	.84	.1
11	Control	4.18	.69	
	Treated	2.46	.90	.2
12	Control	2.87	.82	
	Treated	2.27	.79	.7
Mean	Control	4.17	.73	
	Treated	1.83	.76	.001

I). All young were killed on twelfth day postpartum immediately after they had suckled. Their stomachs were opened and semisolid curds removed and weighed as a check against amount of milk calculated by weighing litters before and after sucking.

Results. Control offspring lost an average of 2% (±.15%) of their body weight during isolation period of 6 hours on each of days 9 through 12 postpartum, whereas litters of experimental group lost 2.2% (±.14%) during the same period. This difference is significant (P = .02). There is, however, no apparent difference between the 2 groups in the time it takes for mothers to commence nursing after their offspring have been returned to them following the isolation period of 6 hours. All mothers were nursing their young within 5 minutes. The quantity of milk obtained by experimental litters on the first day of treatment was very small in comparison with that obtained by control offspring on the same day. The difference was highly significant (P = .001). This difference progressively diminished, however, following additional treatment on days 10, 11, and 12 as animals became more resistant to the drug. (P = .1, .2, and .7 respectively.) The average amount of milk obtained over the 4-day period of treatment by experimental rats, nevertheless, was significantly less (P = .001) than that obtained by control offspring over the same period.

The combined weights of the semisolid curds, removed from the stomachs of each litter after they had been killed averaged 20% less than values calculated from weighing litters before and after the 20-minute period of nursing (Table II). This indicated that the method used in determining quantity of milk secured by young was accurate.

Discussion. It was expected that young of ergotamine-treated rats would lose a significantly higher percentage of body weight than control animals during the 6-hour isolation period. Offspring of treated rats are significantly lighter in weight at end of period of treatment than are control litters. Being of smaller size, there is a relatively greater surface area for heat loss than in larger control offspring. Greater energy, therefore, is expended by the smaller animal to maintain integrity of its internal environment.

It is well known(9-12) that with interruption of suckling, the mammary gland becomes engorged with milk. It was observed in the present study that when young were isolated from the mother for 6 hours and then replaced, the mother hastily gathered her young for feeding, apparently to relieve the turgidity in her mammary glands.

It was observed that within 20 minutes after being so isolated, young of untreated animals stopped sucking. Offspring of ergotamine-treated rats, however, were still sucking actively at the end of this period and had to be pulled away from nipples. It was apparent that they had not secured all the milk they wanted. The results for untreated litters (Table I), though not obtained under identical conditions, are similar to those obtained by other investigators(13-14).

Our studies(15) have shown that ergotamine does not impair synthesis of milk in mammary gland nor does it affect behavior of

TABLE II. Comparison of Calculated Quantity of Milk Obtained on 12th Day Postpartum and That Obtained from Stomachs of Litters of 10 Control Lactating Rats, and 10 Experimental Animals. Data expressed as % body wt gain.

Group	Calculated	Obtained	% difference
Control	2.87	2.24	21.9
Treated	2.27	1.84	18.9

the mother as evidenced by incidence of sucking during period of treatment.

Ergotamine apparently interferes, in some way which can only be explained theoretically, with release of milk from the gland. It has been demonstrated that definite contractile myoepithelial cells are present in mammary glands of the rat which contract apparently in response to oxytocin released from the posterior pituitary gland by nerve impulses stimulated by nursing(16-18). These cells are abundantly distributed around the alveoli and ducts and are not innervated. They are, furthermore, ideally arranged for squeezing milk out of acini and from small ducts into large ducts.

It is therefore likely that ergotamine may exert its inhibitory influence on milk "let-down" in rat mammary gland by interfering in some way with normal action of oxytocin on myoepithelial cells. In view of our results, further experimentation is planned with hope that the mechanism of ergotamine inhibition of milk "let-down" will be clarified.

Summary. 1. The quantity of milk secured in 20 minutes by litters of ergotamine-treated rats on the first of 4 days treatment was small in comparison to that obtained by control offspring on the same day. The difference was significant. This difference progressively diminished, however, following additional treatment on the following 3 days, as the animals became more resistant to the drug. The average amount of milk obtained by experimental animals over the 4-day period of treatment, nevertheless, was significantly less than that obtained over the same period by control offspring. 2. The possible mechanism by which ergotamine interferes with "let-down" of milk from rat mammary gland is discussed.

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