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Effect of Prostaglandins E_1 and $F_{2\alpha}$ on Milk Yield in Lactating Rats (38236)

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Prostaglandins have been reported to reduce the intramammary pressure of oxytocin-treated rabbits and rats (1, 2). Moreover, McNeilly and Fox (3) have shown that PGE_1, PGE_2, $PGF_{1\alpha}$ and $PGF_{2\alpha}$ exert milk ejecting activities *in vivo* in lactating guinea pigs. Similarly, Batta, Gagliano and Martini (4) have demonstrated that PGE_1 and $PGF_{2\alpha}$ are able to facilitate milk ejection from isolated mammary gland fragments collected from lactating rats. Batta *et al.* (4) have shown, in addition, that pretreatment with oxytocin enhances the sensitivity of the mammary gland fragments to the action of PGs. On the contrary, pretreatment with either PGE_1 or $PGF_{2\alpha}$ reduces the responsiveness of the mammary gland to a subsequent exposure to oxytocin.

The following experiments were carried out in order to study the effects of PGs on lactation in the rat. To this purpose oxytocin, PGE_1 and $PGF_{2\alpha}$ were given either alone or in different combinations and in different time sequences to nursing rats. The effects of the various treatments were quantitated by measuring the weight increase of the pups immediately after nursing.

Materials and Methods. Lactating rats of the Sprague–Dawley strain were used. Arrival in our laboratory was between day 14 and 17 of pregnancy. Animals were maintained in a light- and temperature-controlled room (14 hr light, 10 hr darkness, 25°) and housed in individual cages. The day following parturition was designated as day 1 (D 1). For all experiments, rats were used on day D 7–9, and the size of the litters was kept at 8 pups per rat. The litters were isolated from their mothers around 9:00 AM, returned 6 hr later (around 3:00 PM) and allowed to suckle for 2 hr (2-hr suckling regime). The pups in each cage were weighed before being put with the mothers. After a 2-hr suckling regime, the pups were weighed again. The milk yield in the Tables has been expressed in terms of gain of weight of each individual pup.

In the experiment summarized in Table I, nursing rats have been treated either with oxytocin (12.5, 25, 50 or 200 mU), or with PGE_1 (100, 200 or 600 μg) or with $PGF_{2\alpha}$ (100 or 200 μg) immediately prior to suckling. All treatments were performed intraperitoneally (ip). Animals were weighed at the end of the 2-hr suckling period. This experiment was aimed at evaluating the direct effect of each type of treatment on the milk yield.

The experiments summarized in Table II have been designed to study the effects of PGE_1 and of oxytocin given in different sequence and at different intervals. The pups included in group B were allowed to suckle for a period of 15 min. The mother was then injected ip with PGE_1 (200 μg) and returned to the litters for suckling for another 1 hr and 45 min. This experiment was intended to investigate the effects of PGE_1 on oxytocin endogenously released under the influence of suckling (5). The possible effects of PGE_1 on exogenous oxytocin have been evaluated in groups C and D. In this experiment the mother was injected ip

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TABLE I. Effect of Various Concentrations of Oxytocin, PGE_1 and $PGF_{2\alpha}$ on the Milk Yield of Nursing Rats.

Groups[a]				Weight gain (g/pup)
A	Control		(7)	+0.453 ± 0.157[b]
B	Oxytocin	12.5 IU	(6)	+0.860 ± 0.176
C		25.0 IU	(7)	+0.547 ± 0.105
D		50.0 IU	(7)	+0.255 ± 0.086
E		200.0 IU	(7)	+0.211 ± 0.039
F	PGE_1	100 μg	(8)	+0.025 ± 0.057[c]
G		200 μg	(6)	+0.030 ± 0.030[c]
H		600 μg	(6)	−0.008 ± 0.037
I	$PGF_{2\alpha}$	100 μg	(8)	−0.183 ± 0.241
J		200 μg	(6)	−0.048 ± 0.334

[a] Number of animals in parentheses.
[b] Values are means ± S.E.
[c] F, G vs A: $P \leqslant 0.0125$.

TABLE II. Effect of Oxytocin and PGE_1 and Their Combinations on Milk Yield of Nursing Rats.

Groups[a]			Weight gain (g/pup)
A	Control	(6)	+0.453 ± 0.157[b]
B	15′ suckling + PGE_1 200 μg	(4)	+0.515 ± 0.199
C	Oxytocin 12.5 mU	(6)	+0.860 ± 0.176
D	Oxytocin 12.5 mU + PGE_1 200 μg	(4)	+0.492 ± 0.174[c]
E	PGE_1 200 μg	(6)	+0.030 ± 0.030
F	PGE_1 200 μg + oxytocin 12.5 mU	(4)	+0.342 ± 0.108[d]

[a] Number of animals in parentheses.
[b] Values are means ± S.E.
[c] D vs C: $P \geqslant 0.05$.
[d] F vs E: $P \leqslant 0.0125$.

with oxytocin (12.5 mU) immediately before the onset of suckling. The pups were allowed to suckle for 15 min. At this time PGE_1 (200 μg) was injected ip, and the mother returned to the litters for suckling for another 1 hr and 45 min. In a final experiment (groups E and F) the mothers were injected ip with PGE_1 (200 μg) immediately before being put with the litters. The pups were allowed to suckle for 15 min. After this suckling period oxytocin (12.5 mU) was injected ip and the suckling continued for 1 hr and 45 min. The purpose of this experiment was that of investigating whether the efficiency of exogenous oxytocin might be modified by prior treatment with PGE_1.

Oxytocin was diluted in De Jalon's solution. PGE_1 was prepared by diluting a known amount in a drop of 95% ethanol; this solution was subsequently made up to a concentration of 100 μg/ml with normal saline. The tubes were sealed under nitrogen and frozen until used. $PGF_{2\alpha}$ was dissolved and diluted in normal saline to a concentration of 100 μg/ml, sealed under nitrogen and stored frozen until used. The data were analyzed statistically using the Student's *t* test.

Results. As shown in Table I, oxytocin proved able to significantly increase the output of milk if given in limited amounts immediately prior to suckling. The milk yield dropped when higher doses of oxytocin were administered. Both PGE_1 and $PGF_{2\alpha}$ decreased the milk output when given immediately prior to suckling.

Table II shows that PGE_1, when given 15 min after suckling, does not reduce significantly the milk yield of the treated animals evaluated at the end of the 2-hr suckling period. PGE_1 seems to reduce the milk yield of animals pretreated with oxytocin (group D vs group C). However, the decrease induced by PGE_1 is not significant at the statistical analysis. Oxytocin administered 15 min after PGE_1 proves able to antagonize almost completely the inhibiting effect observed when PGE_1 is given alone. The yield of milk obtained in group F is significantly higher than that obtained in group E.

Discussion. In the investigation carried out, it has been demonstrated that PGE_1 and $PGF_{2\alpha}$ reduce the milk yield in lactating rats, and that the inhibition of milk secretion brought about by PGs may be antagonized by exogenous oxytocin given at a proper time. On the other hand, PGE_1 does not seem able to significantly affect either the effects of exogenous or of endogenous oxytocin.

At a first glance, the results here obtained with the administration of PGE_1 or $PGF_{2\alpha}$ do not seem in agreement with those of Deis (6) and of Smith, Shearman and Korda

(7). Deis (6) has demonstrated that four large doses of $PGF_{2\alpha}$ (0.3 mg every 4 hr) are able to induce lactogenesis in pregnant rats, while Smith *et al.* (7) have observed that lactation will appear in women treated with this prostaglandin for the induction of abortion. It must be pointed out that these authors studied a parameter (induction of lactogenesis) which, in many respects, is different from the one which represents the basis of the present report (effect on milk secretion). Moreover, both Deis (6) and Smith and coworkers (7) have administered PGs during pregnancy rather than during lactation. The response of the mammary gland may obviously be completely different in the 2 conditions.

The question may be asked whether the inhibitory effect PGE_1 and $PGF_{2\alpha}$ exert on the milk yield of lactating rats is due to a central or to a peripheral effect of the two compounds. The data presently available do not permit to choose between these 2 possibilities, which moreover are not mutually exclusive. A peripheral mode of action might find support in recent *in vitro* observations by Batta and co-workers (4). They have reported that, under certain experimental conditions, pretreatment with PGs reduces the sensitivity of the myoepithelium of the mammary gland to the effect of oxytocin. However, the same authors (4) have also found that both PGE_1 and $PGF_{2\alpha}$, when given without oxytocin *in vitro*, are able to mimic peripherally the milk ejecting activity of oxytocin. Consequently, if this direct activity of the 2 PGs on the myoepithelium remains also under *in vivo* circumstances, one would expect an increase rather than a decrease of the milk yields, in case PGE_1 and $PGF_{2\alpha}$ operate only peripherally. On the contrary, the experiments here reported have shown that both PGE_1 and $PGF_{2\alpha}$ reduce milk yields. It is consequently possible that PGs *in vivo* operate mainly through a central effect. The suggestion may be put forward that PGs reduce milk output via a stimulation of the central mechanisms which control oxytocin secretion (5). The hypothesis finds support in the observation that PGE_1 and $PGF_{2\alpha}$ stimulate oxytocin release (8). It is known that high levels of circulating oxytocin inhibit rather than stimulate the output of milk (9), a result which has also been confirmed in the present series of experiments.

Summary. PGE_1 and $PGF_{2\alpha}$ reduce milk yields in lactating rats if given intraperitoneally immediately prior to suckling. The inhibition of milk secretion brought about by PGs may be antagonized by exogenous oxytocin given at a proper time.

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1. Turker, R. K., and Kiran, B. K., Eur. J. Pharmacol. **8**, 377 (1969).

2. Haldar, J., Maiweg, H., and Grosvenor, C. E., *in* "Program of the 52nd Meeting of the Endocrine Society," p. 130 (1970).

3. McNeilly, A. S., and Fox, C. A., J. Endocrinol. **51**, 603 (1971).

4. Batta, S. K., Gagliano, P. G., and Martini, L., Proc. Soc. Exp. Biol. Med. **146**, 912 (1974).

5. Cross, B. A., *in* "Neuroendocrinology" (L. Martini and W. F. Ganong, eds.), Vol. 1, p. 217. Academic Press, New York (1966).

6. Deis, R. P., Nature (London) **229**, 568 (1971).

7. Smith, I. D., Shearman, R. P., and Korda, A. R., Nature (London) **240**, 411 (1972).

8. Gillespie, A., *in* "Advances in the Biosciences; International Congress on Prostaglandins" (S. Bergström, ed.), p. 761. Pergamon Press, Vieweg (1972).

9. Kuhn, E. R., Krulich, L., and McCann, S. M., Neuroendocrinology **11**, 11 (1973).

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