EFFECT OF L-DOPA ON MILK EJECTION AND PROLACTIN RELEASE IN LACTATING RATS

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SUMMARY

The effect of L-DOPA on milk ejection and on prolactin release during 30 min of suckling was studied in lactating rats. Various doses of L-DOPA (1.25, 2.5, 5 and 10 mg/100 g body wt) were injected i.p. 30 min before the suckling period. Control rats were injected with 0.9% NaCl solution only. An inhibition of milk ejection proportional to the dose of drug administered was obtained. The dose of 10 mg completely blocked milk ejection but 1.25 mg had no effect. A normal milk-ejection response was obtained with a small dose of oxytocin injected immediately before nursing into mothers treated with 10 mg L-DOPA, indicating that the blocking effect was not due to a lack of mammary gland response. In control mothers, serum prolactin levels increased from 67.2 ± 25.9 (S.E.M.) to 950.3 ± 118.7 ng/ml after a 30 min suckling period. L-DOPA (5 and 10 mg) prevented the release of prolactin induced by suckling, but 1.25 and 2.5 mg L-DOPA had no effect. The results indicate that oxytocin and prolactin release induced by suckling in lactating rats is inhibited by an increase of catecholamines at the hypothalamic-hypophysial axis.

INTRODUCTION

It is now accepted that the hypothalamic catecholamines which are present at high concentrations (Vogt, 1954) have an important role in regulating the secretion of anterior pituitary hormones. Drugs which inhibit the synthesis of brain catecholamines or decrease the hypothalamic catecholamine concentration (van der Gugten, Verhofstad, Sala & Kwa, 1970; Lu, Amenomori, Chen & Meites, 1970; Donoso, Bishop, Fawcett, Krulich & McCann, 1971) induce an increase in the synthesis and release of prolactin. On the other hand, the administration of monoamine oxidase inhibitors or L-DOPA, reduces serum prolactin concentration (Donoso et al. 1971; Chen, Mueller & Meites, 1974).

The following experiments were undertaken to study the effect of L,3,4-dihydroxyphenylalanine (L-DOPA) on milk ejection and prolactin release in lactating rats. Previous results have already been reported (Deis & Prilusky, 1973).

MATERIALS AND METHODS

Primiparous white rats weighing 250–280 g were used. Four days after delivery six offspring were left with each mother in single plastic cages with a wire mesh cover. The experiments were started on the 10th day of lactation. The litter was separated from the mother in the early morning for 9 h. Before being returned to the mother, the young were weighed to the nearest 0.1 g. Then they were allowed to suckle for a period of 30 min. They were then reweighed and the gain in weight of the young during the time of suckling was taken as an
index of the amount of milk ejected by the mother and also as indirect evidence of oxytocin secretion. The procedure was repeated on 2 consecutive days and the results obtained on the second day were taken as a control. On the third day measurements were taken after applying the experimental conditions. In this way each lactating rat served as its own control. This method was used to avoid stress which can interfere with prolactin and oxytocin release on the first occasion a mother is separated from the litter (Taleisnik & Deis, 1964).

Various doses of L-DOPA (1·25, 2·5, 5·0 and 10 mg/100 g body wt) suspended in 0·9 % NaCl solution were injected i.p. 30 min before the suckling period. Control rats were injected with saline only. In control rats and mothers treated with L-DOPA, blood samples were obtained by heart puncture without anaesthesia immediately after the suckling period. This simple method takes only a few seconds without disturbing the animal (Vermouth & Deis, 1974). Serum prolactin was measured by radioimmunoassay at two dose levels (Niswender, Chen, Midgley, Meites & Ellis, 1969) using reagents supplied by the NIAMDD; the results are expressed in terms of the NIAMDD-Rat Prolactin RP-1 standard. All serum samples were assayed in a single radioimmunoassay to eliminate variation between assays. Student’s t-test was used to assess the level of significance.

RESULTS

Effect of L-DOPA on milk ejection

No difference was observed between the various control groups, therefore all results for control rats have been pooled (Fig. 1). Doses of 2·5, 5·0 and 10 mg L-DOPA/100 g body wt caused a significant inhibition of milk ejection (Fig. 1) this inhibition being proportional to the dose of drug administered. The dose of 1·25 mg L-DOPA did not affect milk ejection. In order to establish whether the L-DOPA administered could modify the response of the mammary gland to the oxytocin released by suckling instead of blocking its secretion, a small dose of oxytocin (20 mu./100 g body wt) was given just before the start of the suckling period to mothers pretreated with 10 mg L-DOPA. With this treatment the young obtained an amount of milk (5·90 ± 0·47 (s.e.m.) g) which was not significantly different from that obtained by the control group (5·35 ± 0·37 g).

Effect of L-DOPA administration on prolactin release

In control rats after 30 min of suckling, serum prolactin increased from 67·2 ± 25·9 ng/ml (pre-suckling value) to 950·3 ± 118·7 ng/ml. The administration of L-DOPA (10 mg) produced a complete inhibition of prolactin release (18·2 ± 5·3 ng/ml). The dose of 5·0 mg induced a partial but significant inhibition (386·4 ± 102·0 ng/ml) but doses of 2·5 and 1·25 mg did not significantly affect the release of prolactin (see Fig. 2).

DISCUSSION

The present findings show clearly that L-DOPA affected oxytocin and prolactin release in lactating rats. The effect on milk ejection seems to be due to a block of oxytocin release and not to a peripheral effect on the mammary gland since the administration of a small dose of oxytocin to the mothers, immediately before the suckling period, induced a normal ejection of milk. This would indicate that L-DOPA acts at the level of the central nervous system, on the paraventricular and supraoptic nuclei, or may have a direct effect on the neurohypophysis.

It has been shown that adrenaline affects milk release and inhibits oxytocin secretion (Pickford, 1960). Recently, iontophoretic experiments on neurosecretory cells of the paraventricular nucleus identified by antidromic stimulation have demonstrated a preponderant
Fig. 1. Effect of L-DOPA on the amount of milk obtained from lactating rats during 30 min of suckling. Each bar represents the mean gain in weight of the litters and the vertical lines ± s.e.m. Figures in parentheses show the number of rats tested. ***P < 0.001: compared with the control group.

Fig. 2. Serum prolactin concentration (ng/ml) in lactating rats after a suckling period of 30 min in control rats and after L-DOPA treatment. The vertical lines represent ± s.e.m. Number of rats in parentheses. **P < 0.005; ***P < 0.001: compared with the control group.

inhibition of cell activity by noradrenaline, while dopamine and serotonin had variable effects (Moss, Urban & Cross, 1972; Cross, 1973).

Our results which show an inhibition of oxytocin release by L-DOPA, the existence of adrenergic receptors in the paraventricular nucleus (Fuxe & Hökfelt, 1967), and the fact that stimulation of the afferent pathway of the milk-ejection reflex in the rabbit will not induce activation of the paraventricular cells if the brain monoamines are not previously depleted (Novin & Durham, 1973) may indicate the existence of a central monoaminergic system which regulates the secretion of oxytocin. The central inhibition of oxytocin release in lactating rats evoked by stressful stimuli which activate the cerebral cortex (Taleisnik & Deis, 1964) may be induced by an activation of the postulated central monoaminergic system. We have recently observed (R. P. Deis & J. Prilusky, unpublished results) that electrical stimulation of the cerebral cortex inhibits oxytocin release and that this inhibition is suppressed by the administration of reserpine.
As with milk ejection, so prolactin release, induced by suckling, was also prevented by L-DOPA treatment. The inhibitory effect of catecholamines on prolactin release has been demonstrated by experiments in vivo and in vitro (MacLeod, 1969; Birge, Jacobs, Hammer & Daughaday, 1970; Donoso et al. 1971; Chen et al. 1974). The effect of L-DOPA on milk ejection and on prolactin release is probably mediated through dopamine. In our experiment considering the 30 min delay between L-DOPA administration and the suckling period and according to the observations made by Glowinski (1970) and Everett & Borcherding (1970) on L-DOPA metabolism, the decrease of serum prolactin and milk ejection takes place at a time when only the levels of dopamine in the brain are increased.

We have no evidence which indicates whether the drug acts at hypothalamic or hypophysial levels. Several authors have described an effect of dopamine on prolactin release by a direct effect on the pituitary cells (MacLeod, 1969; Birge et al. 1970; Donoso & Bishop, 1971; Takahara, Arimura & Schally, 1974) but there is also evidence indicating an inhibitory effect of catecholamines at the hypothalamic level (Lu et al. 1970; Donoso et al. 1971). Recently Ojeda, Harms & McCann (1974) postulated a dual effect of dopamine, at the hypothalamic level and preventing prolactin release by pituitary cells. These findings support the concept that the monoaminergic tubero-infundibular neural system could be responsible for the direct control of prolactin secretion as proposed by van Maanen & Smelik (1968).

We can conclude that oxytocin and prolactin release induced by suckling in lactating rats can be inhibited by increasing the catecholamines influencing the hypothalamic-hypophysial system, and this may indicate indirectly that suckling facilitates oxytocin and prolactin release by a rapid depletion or inhibition of the synthesis of catecholamines in the brain. The importance of this mechanism deserves additional studies to determine whether it plays a role in the maintenance of lactation.

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REFERENCES


L-DOPA on lactation


