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Dopamine and Epinephrine Infusion Reduce Clearance Rate of Rat Prolactin in the Female Rat (40818)[1]

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Evidence obtained both *in vivo* and *in vitro* strongly implicates dopamine in the inhibitory mechanism controlling prolactin (PRL) secretion (1). In the lactating rat, dopamine appears to inhibit the depletion phase of PRL secretion which occurs within the pituitary during the initial minutes of stimulation, and not the actual release of PRL into the circulation (2). Recently, we observed that the high plasma PRL levels resulting from suckling in the rat fell more slowly after suckling was terminated if dopamine was infused intravenously, starting at the time of pup removal (unpublished data). This observation suggested that dopamine in the systemic circulation either had released PRL from the pituitary into the circulation or had altered the distribution volume and/or the rate of clearance from the circulation of that PRL previously released during suckling. We have investigated the effects of dopamine infusion upon the clearance of PRL in the present paper.

Materials and methods. Adult cycling female rats (230–260 g) of the Holtzman strain were housed in a room maintained at 23–25°C with alternating 14-hr light: 10-hr darkness. Food (Purina Lab Chow) and water were available at all times.

Effect of dopamine (DA) and epinephrine (Epi) upon metabolic clearance rate (MCR) of infused rat PRL. Each rat was anesthetized with urethane (ethyl carbamate) administered ip at a dose of 115–130 mg/100 g BW. A double lumen catheter was placed in the right atrium, and a cannula was placed in the trachea. Groups of 4–6 rats so prepared were placed on their backs on a slide warmer maintained at 32–35°C. Each was attached to an infusion pump (Harvard apparatus model 600-900), and rat PRL (NIAMDD preparations B-1, 7 IU/mg or RP-1, 11 IU/mg) dissolved in 0.9% saline was continuously infused through one lumen of the intraatrial catheter at a dose of 200 ng RP-1 (or an equivalent dose [314 ng] of B-1) each minute. The infusion volume was 2.5 μl/min. After 35 min of infusion, the PRL solution in the syringes and catheters comprising the infusion apparatus was withdrawn, and a solution containing the same concentration of PRL to which various concentrations of either DA or Epi had been added was substituted. This exchange required about 1 min per rat. The PRL-catecholamine mixture then was infused for an additional 20 min. At intervals during the infusion, the infusion pump was stopped for 15 sec. This was to ensure uniform distribution of the infused PRL throughout the circulation of the rat before the withdrawal of each blood sample (0.3–0.35 ml) through the other channel of the double lumen catheter. The blood remaining in the catheter after each blood sample had been taken was flushed back into the rat with 0.35 ml heparinized saline.

In one group of rats, a single iv injection of 1 μg, rather than an infusion of dopamine, was given at the 35th min of infusion of PRL. Control rats were not infused with PRL, but were infused continuously for 30 min with either DA or Epi.

RIA of rat PRL. The plasma was separated from each blood sample and stored at −20°C until assayed for PRL by RIA. The concentration of immunoreactive rat PRL was determined in duplicate 25-μl samples of each PRL solution infused and in duplicate 25 μl plasma samples using the NIAMDD rat PRL RIA system (see (3) for procedures and validation data). All PRL values are expressed as nanogram equivalents of the RP-1 standard.

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Metabolic clearance rate (MCR) of rat PRL. The MCR of immunoreactive rat PRL was calculated as follows (4):

$$\text{MCR (ml/min)} = \frac{\text{Infusion dose (ng/min)}}{\text{Increment in plasma concentration at equilibrium (ng/ml)}} \quad (1)$$

We showed previously (3) that the plasma concentration of immunoreactive rat PRL in the rat reached equilibrium after approximately 20 min of continuous infusion. The plasma PRL concentration used in the computation of MCR for each rat was the average of the three individual values obtained during the equilibrium period minus the PRL concentration in the plasma before the start of PRL infusion.

Results. The intravenous infusion of 200 ng rat PRL/min into cycling female rats under urethane anesthesia resulted in the establishment of an equilibrium PRL concentration of about 150 ng/ml (Table 1). The addition of either 250 or 500 ng DA/min (Fig. 1) or 500 or 1000 ng Epi/min (Fig. 2) resulted in the attainment of a new equilibrium PRL level within 10 min which was approximately threefold greater than existed prior to the onset of catecholamine infusion. Neither the simultaneous infusion of 50 ng DA/min nor a single iv injection of 1 μg DA altered the equilibrium PRL level resulting from the continuous infusion of rat PRL (Table 1). In 11 rats, either DA (250 ng/min) or Epi (1000 ng/min) was infused

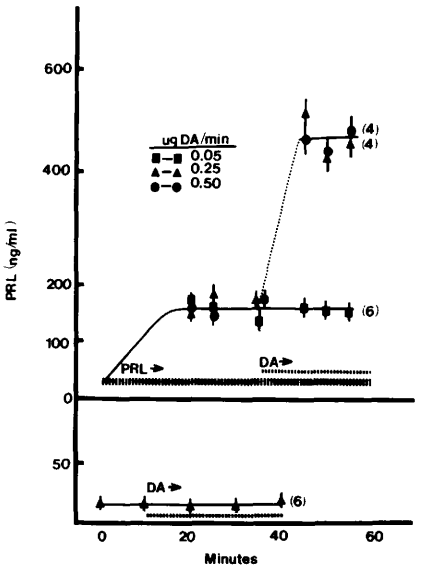

FIG. 1. Effect of iv infusion of dopamine (DA) upon equilibrium plasma prolactin (PRL) levels resulting from iv infusion of 200 ng rat PRL/min (upper graph) and basal PRL levels (lower graph). Values are means ± SEM; numbers in parentheses refer to number of rats.

TABLE I. INFLUENCE OF DOPAMINE AND EPINEPHRINE INFUSION FOR 20 MIN UPON EQUILIBRIUM PLASMA CONCENTRATION AND MCR OF PRL RESULTING FROM CONTINUOUS INFUSION OF RAT PRL (200 ng/min)

Treatment	No. of rats	Before treatment		During treatment	
		Plasma PRL concentration at equilibrium[a] (ng/ml)	MCR (ml/min)	Plasma PRL concentration at equilibrium[a] (ng/ml)	MCR (ml/min)
Dopamine					
1 μg bolus iv	5	140	1.43 ± 0.28	144	1.39 ± 0.06
0.05 μg/min infusion	6	148	1.35 ± 0.30	155	1.29 ± 0.20
0.25 μg/min infusion	4	150	1.34 ± 0.21	458	0.44 ± 0.08*
0.50 μg/min infusion	4	148	1.35 ± 0.26	455	0.44 ± 0.06*
Epinephrine					
0.5 μg/min infusion	4	175	1.14 ± 0.23	541	0.37 ± 0.02*
1.0 μg/min infusion	4	128	1.56 ± 0.32	308	0.65 ± 0.09*

[a] Each value is the average of 3 and has subtracted from it the plasma PRL concentration prior to infusion of PRL.

* Significantly different from MCR before treatment at $P = <0.05$.

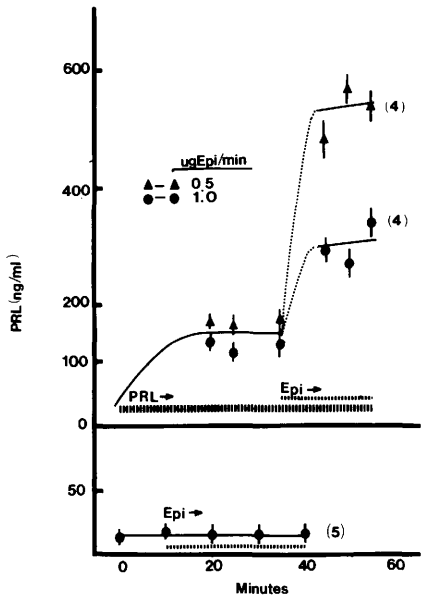

FIG. 2. Effect of iv infusion of epinephrine (Epi) upon equilibrium plasma prolactin (PRL) levels resulting from iv infusion of 200 ng rat PRL/min (upper graph) and upon basal PRL levels (lower graph). Values are means ± SEM; numbers in parentheses refer to number of rats.

intravenously without PRL for 30 min. The low basal PRL levels remained unchanged in each rat tested (Figs. 1, 2), indicating that neither catecholamine stimulated the secretion of PRL from the anterior pituitary.

Calculations of MCR of PRL revealed that infusing either 250 or 500 ng DA/min significantly reduced the MCR from 1.35 to 0.44 ml/min. Infusing 500 ng Epi/min significantly reduced the MCR from 1.14 to 0.37 ml/min, whereas the 1000 ng/min dose significantly reduced the MCR of PRL from 1.56 to 0.65 ml/min (Table 1).

Discussion. The results of the present study reveal that continuous infusion of either DA (250 or 500 ng/min) or Epi (500 or 1000 ng/min) caused a rapid, threefold increase in the steady state circulating PRL level resulting from continuously infusing rat PRL in the urethane anesthetized female rat. Neither the infusion of 50 ng/min nor a single iv injection of 1 μg DA altered the circulating PRL concentration. Concentrations of Epi less than 500 ng/min were not infused. We have shown (5) that the steady state circulation level of PRL resulting from continuous infusion of the hormone is not substantially altered in the rat by urethane anesthesia. This suggests that studies of PRL clearance mechanisms in urethane-anesthetized rats can reflect accurately similar processes occurring in the conscious animal.

The mechanisms responsible for the elevated PRL levels are not completely known at present. Since the normally low basal PRL concentrations were unaffected by infusing either catecholamine, it would appear that the rapid elevations in the equilibrium PRL concentrations were not achieved through a catecholamine-induced release of PRL from the anterior pituitary. The elevated plasma PRL concentrations probably were caused by reductions in the normal rate of degradation and/or excretion of PRL as a consequence of catecholamine-induced reductions in blood flow through the ovary, liver, and kidney, which along with the mammary glands in the lactator are the major clearing organs for PRL in the rat (6–9). The distribution volume of PRL probably also was reduced as a consequence of altered rates of blood flow through various organs. Vasoconstriction occurs within many organs, including the liver and kidney, as a consequence of DA and Epi administration. It is unclear, however, to what extent the vasomotor effects of DA are mediated via adrenergic receptors and to what extent neurogenic mechanisms are implicated (10, 11).

The present results with dopamine should not be interpreted as contradictory to its well-known central inhibitory effects upon PRL secretion (1). However, the reduced capacity of the rat infused with DA to clear PRL from the circulation could cause misinterpretation of the extent of DA-induced reductions in PRL secretion where such secretion had been previously elevated, e.g., by electrolytic lesion of the median eminence (12, 13), implants of anterior pituitary glands under the kidney capsule (14, 15), or by pretreatment with α-methyl-*p*-tyrosine (13). It is likely that a greater reduction in PRL secretion actually occurred in those studies.

Summary. The iv infusion of dopamine (250 or 500 ng/min) or epinephrine (500 or 1000 ng/min) into adult female cycling rats in each instance caused a threefold elevation in the equilibrium concentration of prolactin (PRL) in the plasma resulting from the continuous infusion of 200 ng rat PRL/min. A single iv injection of 1 μg dopamine had no effect upon equilibrium PRL levels. The metabolic clearance rate of PRL was significantly reduced from 1.35 to 0.44 ml/min as a result of infusing either 250 or 500 ng dopamine/min, and from 1.14 to 0.37 and from 1.56 to 0.65 ml/min from infusing 500 and 1000 ng/min, respectively, of epinephrine.

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