Involvement of the adrenergic system on the release of prolactin and lactogenesis at the end of pregnancy in the rat

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ABSTRACT

The part played by the adrenergic system on the release of prolactin and lactogenesis induced by prostaglandin F₂α and the antiprogestosterone RU 486 was studied in pregnant rats. Two doses of prostaglandin F₂α (150 μg) administered at 08.00 and 12.00 h on day 19 of pregnancy induced, at 12.00 h on day 20 (24 h after administration), a significant increase in the serum concentration of prolactin, with a significant decrease in serum progesterone levels. These hormonal changes significantly augmented casein and lactose levels in the mammary gland. Treatment with RU 486 (2 mg/kg) at 08.00 h on day 19 augmented casein and lactose concentrations in the mammary gland at 12.00 h on day 20 without modifying serum concentrations of prolactin and progesterone. The adrenergic antagonists, propranolol (3 mg/kg), metoprolol (10 mg/kg), ICI 118 551 (200 μg/kg), idazoxan (100 μg/kg) and prazosin (10 mg/kg), were administered s.c. at 12.00 and 20.00 h on day 19 and 08.00 h on day 20 of pregnancy to intact rats or to rats previously treated with RU 486 or prostaglandin F₂α. These adrenergic antagonists did not modify serum prolactin or progesterone levels in intact or RU 486-treated rats, but serum prolactin levels in the prostaglandin F₂α-treated group were significantly reduced by treatment with propranolol, metoprolol or prazosin. In addition, propranolol and ICI 118 551 also decreased the casein and lactose concentrations in the mammary glands of RU 486- and prostaglandin F₂α-treated rats, while the other compounds had no effect. We also studied the effect of adrenergic antagonists on the release of prolactin and lactogenesis induced by the physiological decrease in progesterone at the end of pregnancy. On day 21 of pregnancy at 18.00 h, serum progesterone levels in intact rats were lower than 40 nmol/l, while serum prolactin and casein and lactose concentrations in the mammary gland were higher compared with values measured at 12.00 h on day 20. Treatments with propranolol, metoprolol or prazosin administered at 20.00 h on day 20 and 08.00 and 14.00 h on day 21 of pregnancy were capable of significantly reducing serum prolactin concentrations while only propranolol decreased mammary casein and lactose. The effect of propranolol was not mediated through a reduction in serum placental lactogen measured by Nb2 lymphoma cell bioassay.

These results show that the adrenergic system participates, through α₁ and β₁ receptors, in the regulation of prolactin release induced by the decrease in progesterone in pregnant rats. They also show that β₂ adrenergic receptors play a role in the induction of casein and lactose synthesis in the mammary gland. Journal of Endocrinology (1991) 129, 343–350

INTRODUCTION

The spontaneous fall in progesterone at the end of pregnancy in the rat is followed by an increase in prolactin secretion and initiation of lactogenesis at the level of the mammary gland, demonstrated by the appearance of secretion (Deis, 1968) and increases in mammary tissue casein and lactose concentrations (Rosen, Woo & Comstock, 1975; Kuhn, 1977; Nicholas & Hartmann, 1981). Premature induction of the decrease in progesterone by ovariectomy, luteectomy or treatment with prostaglandin F₂α induces increases in prolactin secretion and casein and lactose synthesis after 12 and 24 h respectively (Vermouth & Deis, 1972, 1974; Bussmann & Deis, 1979, 1985; Bussmann, Koninckx & Deis, 1983). Blockade of the mammary progesterone receptors by the antiprogestrone RU 486 induces lactogenesis without an increase in the secretion of prolactin (Deis & Bussmann, 1986; Deis, Carrizo & Jahn, 1989).

It is well known that catecholamines participate in the regulation of prolactin secretion; they can be...
stimulatory or inhibitory according to the drugs and experimental model used (Wilson, 1979). α-Adrenergic systems are generally stimulatory and may be implicated in oestrogen-induced prolactin secretion, whereas the β-adrenergic component seems to be less effective (Lawson & Gala, 1975; Vijayan & McCann, 1978; Weiner & Ganong, 1978; Wilson, 1979). Furthermore, catecholamine metabolism and concentrations vary during pregnancy and the post-partum period (Greengrass & Tonge, 1974a,b; Moltz, Rowland, Steele & Halaris, 1975; Desan, Woodmansee, Ryan et al. 1988), suggesting that they may be implicated in the regulation of hormone secretion during these periods.

The presence of β2-adrenergic receptors in the mammary gland has been demonstrated (Clegg & Mullaney, 1985; Wellner, He, Marmary & Baum, 1988) and, through the stimulation of cyclic AMP synthesis, adrenergic drugs can inhibit fatty acid and lactose production in mammary tissue (Bar, 1973; Loizzi, de Pont & Bonting, 1975; Muñoz, Lavandero, Donoso et al. 1985; Clegg, Mullaney, Robson & Zammit, 1986).

In the present work, different α and β antagonists were used to investigate whether the adrenergic systems are involved in the central mechanism that leads to increased prolactin secretion after the decrease in progesterone, and whether they participate in the induction of lactogenesis at the level of the mammary gland.

MATERIALS AND METHODS

Animals

Virgin female rats, 3–4 months old (200–220 g), bred in our laboratory and originally of the Wistar strain, were used. They were kept in a light (lights on 06.00–20.00 h)- and temperature (22±2°C)-controlled room; rat chow (Nutric, Cordoba, Argentina) and tap water were available ad libitum. Vaginal smears were taken daily and the rats were caged with a fertile male on the night of pro-oestrus. The presence of spermatozoa in vaginal smears was investigated the following morning, and this day was considered to be day 0 of pregnancy. Rats normally deliver on day 22 in our colony.

Experimental procedures

RU 486 (17β-hydroxy-11β-(4-dimethyl-aminophenyl)-17α-propynyl-estra-4,9-dien-3-one; generously provided by Roussel-Uclaf, Romainville, France) was injected s.c. to pregnant rats at a dose of 2 mg/kg in sunflower seed oil (2 g/l) at 08.00 h on day 19 of pregnancy. Prostaglandin F2α (kindly provided by Upjohn Co., Kalamazoo, MI, U.S.A.), was dissolved in saline (1 g/l) and injected i.p. at a dose of 150 μg/rat at 08.00 and 12.00 h on day 19 of pregnancy. Groups of rats treated with RU 486, prostaglandin F2α or vehicles were subjected to one of the following treatments. The β-adrenoceptor antagonist propranolol (generously provided by Gador, Buenos Aires, Argentina) was dissolved in saline (3 g/l) and injected s.c. at a dose of 3 mg/kg. The specific β1-adrenoceptor antagonist metoprolol (generously provided by Astra, Buenos Aires, Argentina) was dissolved in saline (10 g/l) and injected s.c. at a dose of 10 mg/kg. The specific β2-adrenoceptor antagonist ICI 118 551 ((2RS,3RS)-3-isopropylamino-1-((methyl-indan-4-yl)oxy)butan-2-ol, ICI Ltd, Macclesfield, Cheshire, U.K.) was dissolved in saline (0-2 mg/l) and injected s.c. at a dose of 0.2 mg/kg. The specific α2 antagonist idazoxan (Reckitt & Colman, Hull, Humberside, U.K.) was dissolved in saline (0-1 g/l) and injected s.c. at a dose of 0-1 mg/kg. The specific α1 antagonist prazosin (generously provided by Pfizer, Buenos Aires, Argentina) was dissolved in saline (10 g/l) and injected s.c. at a dose of 10 mg/kg. All the above drugs were injected at 12.00 and 20.00 h on day 19 and at 08.00 h on day 20 of pregnancy. All the rats were killed by decapitation at 12.00 h on day 20 of pregnancy. Blood samples were collected and allowed to clot at room temperature (approximately 20°C), and the serum was separated and stored frozen at −30°C for prolactin and progesterone determinations. Both inguinal mammary glands were dissected out and stored frozen at −70°C until processed for determination of casein and lactose.

Other groups of intact pregnant rats were injected with propranolol, metoprolol or prazosin at the doses indicated above at 20.00 h on day 20 of pregnancy and at 08.00 and 14.00 h on day 21. They were decapitated at 18.00 h on day 21 and blood and mammary gland samples were collected for determination of hormones, casein and lactose.

Determination of casein and lactose

Mammary tissue (200 mg) was cut into small pieces and homogenized in 2 ml 50 mmol sodium phosphate buffer/l, 150 mmol NaCl/l. 0-1% (w/v) NaN3, 0-1% (v/v) Triton X-100, (pH 7-6; radioimmunoassay (RIA) buffer) with an Ultra Turrax homogenizer. The homogenate was centrifuged at 600 g for 30 min and the supernatant used for determination of casein and lactose. The RIA procedure for β-casein was that described by Edery, Houdébine, Dijane & Kelly (1984). Casein iodination was performed by the method of Greenwood, Hunter & Glover (1963) using a low concentration of chloramine T (800 pg) and 5 μg β-casein. Incubation was for 5 min at room temperature. The
iodinated hormone was purified on a column of polyacrylamide agarose (ACA 54; IBF LKB, Villeneuve la Garenne, France) (0-9 × 40 cm) and the tubes containing the protein peak were pooled. All dilutions were made with RIA buffer containing 0-1% (w/v) bovine serum albumin. The samples were incubated at room temperature for 24 h with β-casein antiserum obtained from rabbits (purified β-casein and its antisera were generously provided by Dr L.M. Houdébine, Laboratoire de Biologie Cellulaire et Moléculaire, INRA, 78350 Jouy-en-Josas, France). Precipitation of bound protein was performed by centrifugation after incubating the samples with goat anti-rabbit γ-globulin antibody for 1 h and addition of 0-6 ml 12-5% (w/v) polyethylene glycol (M, 3000) to aid precipitation. The accuracy of the assay was assessed by the recovery of known amounts of unlabelled β-casein added to mammary gland homogenates. The average recovery was 95 ± 3-5% (mean ± s.d.). Parallelism in immunoreactivity between endogenous casein and β-casein was tested by serial dilution of mammary gland homogenates. Further details about the validation of the assay are given by Edery et al. (1984).

Lactose concentrations were assessed by the method of Kuhn & Lowenstein (1967). A portion (0-5 ml) of the 600 g supernatant was precipitated with the same volume of ice-cold 10% (v/v) perchloric acid, centrifuged and the clear supernatant brought to pH 7-0 with potassium hydroxide. The potassium perchlorate precipitate was removed by centrifugation. Duplicate aliquots of the supernatants (0-1 ml) were incubated for 90 min at 37°C with 0-25 units β-galactosidase (Sigma grade XII) in 1 ml phosphate buffer (pH 7-2; 0-1 mol/l) and the glucose released was measured by the glucose oxidase method with a commercial glucose kit (Wiener, Buenos Aires, Argentina). Corrections for endogenous glucose were made by incubating the samples without β-galactosidase. Standard curves for lactose and glucose were run with each batch of experimental samples. All drugs, except when mentioned otherwise, were obtained from Sigma Chemical Co., St Louis, MO, U.S.A.

**Progestosterone determination**

Serum progesterone was measured using an RIA developed in our laboratory (Bussmann & Deis, 1979) with an antiserum raised in rabbits against progestosterone-11-bovine serum albumin conjugate. Assay sensitivity was less than 15 nmol/l serum and the inter- and intra-assay coefficients of variation were 9 and 4% respectively.

**Placental lactogen measurement**

Serum placental lactogen titres in sera from control rats and rats treated with propranolol, RU 486 and RU 486 plus propranolol were measured using the Nb2 cell bioassay as described previously (Tanaka, Shiu, Gout et al. 1980), using the NIADDK rat prolactin RP-3 preparation as standard. No attempt was made to neutralize the amount of prolactin present in the samples, since there was less than 10 μg prolactin/l present in rats at 12.00 h on day 20 of pregnancy, whereas measured lactogenic activity was higher than 1000 μg/l, thus making the amount of prolactin negligible with respect to placental lactogen concentrations. Results are expressed in terms of the rat prolactin RP-3 standard preparation.

Statistical analysis was performed using Student's t-test or one- or two-way analysis of variance followed by Duncan’s multiple range test when more than two experimental groups were compared (Snedecor & Cochran, 1967). Differences between means were considered significant at the P < 0-05 level.

**RESULTS**

**Effect of adrenergic antagonists on serum hormones and mammary casein and lactose concentrations in intact rats, and rats treated with RU 486 or prostaglandin F₂α**

Intact or RU 486-treated rats had low serum prolactin levels at 12.00 h on day 20 of pregnancy, and treatment with propranolol, metoprolol, ICI 118 551, idazoxan and prazosin did not modify these values. The drugs also had no effect on serum progesterone concentrations in intact rats (Table 1). In contrast, after administration of prostaglandin F₂α, serum prolactin levels were significantly increased and serum progesterone concentrations significantly decreased compared with values in intact rats. Treatment with prazosin, propranolol and metoprolol significantly reduced the prostaglandin F₂α-induced stimulation of prolactin release, without modifying serum progesterone values, while ICI 118 551 and idazoxan were not effective (Fig. 1).

Casein and lactose contents of mammary glands were low in the vehicle-treated rats at 12.00 h on
TABLE 1. Effect of propranolol, metoprolol, ICI 118 551, idazoxan or prazosin on serum prolactin and progesterone concentrations at 12.00 h on day 20 of pregnancy in vehicle- or RU 486-treated rats. Results are means ± s.e.m. of groups of seven to nine animals.

<table>
<thead>
<tr>
<th></th>
<th>Serum prolactin (μg/l)</th>
<th>Serum progesterone (nmol/l)</th>
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<tr>
<td></td>
<td>Vehicle</td>
<td>RU 486</td>
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<tr>
<td>Saline</td>
<td>6.3 ± 0.6</td>
<td>6.0 ± 0.3</td>
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<tr>
<td>Propranolol</td>
<td>5.3 ± 0.9</td>
<td>8.8 ± 0.7</td>
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<tr>
<td>Metoprolol</td>
<td>10.2 ± 1.5</td>
<td>7.8 ± 0.7</td>
</tr>
<tr>
<td>ICI 118 551</td>
<td>7.4 ± 1.4</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>Prazosin</td>
<td>5.4 ± 1.1</td>
<td>5.8 ± 1.4</td>
</tr>
<tr>
<td>Idazoxan</td>
<td>7.5 ± 1.1</td>
<td>3.8 ± 0.5</td>
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Figure 1. Effect of saline vehicle (V), propranolol (PRP), metoprolol (MET), ICI 118 551 (ICI), prazosin (PRZ) or idazoxan (IDX) on serum concentrations of prolactin (open bars) and progesterone (hatched bars) at 12.00 h on day 20 of pregnancy in rats treated with prostaglandin F2α. Results are means ± s.e.m. of groups of seven or eight animals.

*P < 0.05 compared with the group of rats treated with vehicle and saline, shown in Table 1 (Student's t-test).
†P < 0.05 compared with rats treated with prostaglandin F2α and saline vehicle (analysis of variance followed by Duncan's multiple range test).

In order to discount an inhibitory effect of propranolol on placental lactogen secretion, which could be responsible for the inhibition of casein and lactose synthesis in RU 486-treated rats, we measured the lactogenic activity in the serum of rats treated with RU 486 and/or propranolol, using the Nb2 lymphoma cell bioassay. Since the amount of prolactin (between 3 and 6 μg/l) present in the sera of these rats was negligible in relation to the lactogenic activity, this activity may be ascribed to placental lactogen. There was no significant effect of RU 486, propranolol, or a combination of both, on the lactogenic activity and hence on serum concentration of placental lactogen (controls 1244 ± 343 μg/l (n = 7); RU 486 1755 ± 399 μg/l (n = 7); propranolol 1467 ± 446 μg/l (n = 6); RU 486 + propranolol 1335 ± 394 μg/l (n = 7).

Effect of adrenergic antagonists on serum concentrations of prolactin and progesterone and on mammary casein and lactose concentrations in rats at 18.00 h on day 21 of pregnancy

The above results showed that catecholamines participate in the lactogenic process induced by RU 486 or prostaglandin F2α. Another series of experiments was performed to study whether this result could also be extended to physiological lactogenesis, observed after the normal fall in progesterone that occurs on day 21 of pregnancy.

At 18.00 h on day 21 of pregnancy, serum progesterone levels were significantly lower and serum prolactin levels significantly higher than at 12.00 h on day 20 of gestation (see Tables 1 and 2). Again, as in the previous experiments, propranolol, metoprolol or prazosin administration significantly reduced serum prolactin concentrations in these rats, without modifying serum progesterone (Table 2).

At 18.00 h on day 21 of pregnancy, the mammary gland content of casein and lactose were also significantly increased with respect to day 20 (shown on Fig. 2) and, again, propranolol administration significantly decreased both milk components, while prazosin and

of cyclic AMP accumulation in hypothalamic and preoptic area (POA) slices was found to be modified by changes in circulating ovarian steroids (Etgen & Petitti, 1986). Thus progesterone treatment of ovariecctomized oestrogen-primed rats decreases the capacity of noradrenaline to induce cyclic AMP accumulation in POA slices (Petitti & Etgen, 1989). On the other hand, it seems that prazosin and propranolol have a selective action on POA slices in reducing the ability of noradrenaline to stimulate cyclic AMP (Petitti & Etgen, 1989). According to Wilson (1979) two types of noradrenergic systems seem to be involved in prolactin release, one acting through α-adrenergic receptors and the other through βadrenergic receptors. It has been shown that the response to noradrenaline in POA slices is mediated by interactions with both α and β receptors (Petitti & Etgen, 1989). The augmentation of β receptor stimulation of adenylate cyclase by α sites has also been demonstrated (Pilc & Enna, 1985; Etgen & Petitti, 1987). The present results clearly show the involvement of the adrenergic system in the induction of prolactin secretion in pregnant rats. The β adrenergic receptor blockers, propranolol and metoprolol, were effective in preventing the increase in prolactin secretion that follows the fall in circulating progesterone. A similar effect was obtained by administration of the α1-receptor blocker prazosin, while treatment with idazoxan, an α2-receptor blocker, did not modify prolactin secretion. The effect of prazosin in lowering serum prolactin may indicate α1-adrenergic participation in prolactin release induced by decreased progesterone concentrations. There may also be a

**DISCUSSION**

Ovarian steroid hormones can modulate the synthesis, release and turnover of noradrenaline and its receptors in the central nervous system (Munaro, 1977; Vacas & Cardinali, 1980; Crowley, 1982; Maggi, Zucchi & Perez, 1985). Noradrenergic induction of prolactin in rats at 18.00 h on day 21 of pregnancy. Results are means ± S.E.M. of groups of seven to nine animals

<table>
<thead>
<tr>
<th>Serum prolactin (μg/l)</th>
<th>Serum progesterone (nmol/l)</th>
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<tbody>
<tr>
<td>Saline</td>
<td>66 ± 21†</td>
</tr>
<tr>
<td>Propranolol</td>
<td>12 ± 2*</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>29 ± 9*</td>
</tr>
<tr>
<td>Prazosin</td>
<td>8 ± 2*</td>
</tr>
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<tr>
<th>Mammary gland casein (μg/mg)</th>
<th>Mammary gland lactose (μmol/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>12.41 ± 1.91†</td>
</tr>
<tr>
<td>Propranolol</td>
<td>7.01 ± 1.09*</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>9.43 ± 1.25</td>
</tr>
<tr>
<td>Prazosin</td>
<td>11.03 ± 2.60</td>
</tr>
</tbody>
</table>

*P < 0.05 compared with intact rats (analysis of variance followed by Duncan’s multiple range test). †P < 0.05 compared with the respective values of the control group at 12.00 h on day 20, shown in Table 1 for prolactin and progesterone and Fig. 2 for casein and lactose (Student’s t-test).

**TABLE 2. Effects of saline, propranolol, metoprolol and prazosin treatments on the concentrations of prolactin and progesterone in serum and of casein and lactose in the mammary glands of rats at 18.00 h on day 21 of pregnancy.**

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**FIGURE 2. Effect of saline (C), propranolol (PRP), metoprolol (MET), ICI 118 551 (ICI), prazosin (PRZ) or idazoxan (IDX) on casein (open bars) and lactose (hatched bars) concentrations in the mammary gland tissue of (a) intact rats and (b) rats treated with RU 486 or (c) prostaglandin F2α, measured at 12.00 h on day 20 of pregnancy. Results are means ± S.E.M. of groups of seven or eight animals.**

- *P < 0.05 compared with its respective control in the intact group (Student’s t-test); †P < 0.05 compared with respective saline-injected (C) group (analysis of variance followed by Duncan’s multiple range test).

Metoprolol were not effective (Table 2). These results confirm the adrenergic participation, at central and peripheral (mammary) levels, on the lactogenic process.
β-adrenergic component, and since metoprolol and propranolol were equally active in inhibiting prolactin release and ICI 118 551 had no effect, we may assume that their effect is mediated through β1-adrenergic receptors. Our results confirm and extend the previously demonstrated stimulatory action of noradrenaline on prolactin secretion (Vijayan & McCann, 1978; Weiner & Ganong, 1978; Wilson, 1979).

At the end of pregnancy a series of events takes place in response to the decrease in progesterone, including the release of prolactin which is involved in lactogenesis (Deis, 1968; Vermouth & Deis, 1972, 1974; Bussmann & Deis, 1979) and maternal behaviour (Bridges, 1984). It has been suggested that an increase in noradrenergic activity may occur near term in the hypothalamus of pregnant rats which may be related to the display of maternal behaviour (Ho, Quadagno & Moltz, 1974; Moltz et al. 1975), which correlates well with the participation of the POA on the onset of maternal behaviour described by Numan, Rosenblatt & Komisaruk (1977). It is interesting to correlate these findings with our present results showing the probable involvement of the adrenergic system on the release of prolactin mediated through α1 and β1 receptors. After considering the part played by the hypothalamus-POA in the release of prolactin in different species (Carrer & Taleisnik, 1970; Tindal & Knaaggs, 1972; Weiner, Blake & Sawyer, 1972; Kawakami, Kimura & Konno, 1973; Velasco, Castro-Vazquez & Rothchild, 1974; Malven, 1975), displays of maternal behaviour and the above mentioned participation of α1 and β1 receptors in the accumulation of cyclic AMP in the POA induced by noradrenaline, we suggest that the fall in serum progesterone concentration at the end of pregnancy may activate the hypothalamic noradrenergic system that mediates the release of prolactin and the development of maternal behaviour.

The presence of β2-adrenergic receptors in mammary epithelial cells has been demonstrated (Clegg & Mullaney, 1985; Wellner et al. 1988). These receptors are linked to the adenyl cyclase second messenger pathway (Bar, 1973; Clegg & Mullaney, 1985; Marchetti, Fortier, Poyet et al. 1990; Marchetti & Labrie, 1990). The concentration of these receptors, which are under the control of prolactin and ovarian hormones (Marchetti & Labrie, 1990), increases moderately during pregnancy, decreases around the time of parturition and increases again to maximum levels around the middle of lactation (Marchetti et al. 1990). Increases in intracellular cyclic AMP levels induced by adrenergic agonists in mammary cells or explants have been shown to inhibit lactose production (Loizzi et al. 1975; Muñoz et al. 1985; Clegg et al. 1986). On the other hand, adrenergic agonists increase fatty acid synthesis in the mammary gland in spite of increased cyclic AMP levels (Plucinski & Baldwin, 1982; Clegg et al. 1986; Munday & Williamson, 1987; Clegg & Calvert, 1988). Our results show a β2-adrenergic participation in the induction of lactogenesis at the level of the mammary gland, since propranolol and ICI 118 551, but not metoprolol, were able to inhibit lactose and casein production after the decrease in progesterone induced by treatment with prostaglandin F2α or blockade by RU 486 on day 19 of pregnancy. This is not due to a decrease in prolactin secretion, since ICI 118 551 did not block prolactin release. Moreover, both compounds were equally effective in rats treated with RU 486, in which prolactin release was not stimulated and lactogenesis was induced by the high levels of placental lactogen that replaced prolactin (Bussmann et al. 1983; Deis & Bussmann, 1986; Deis et al. 1989). Moreover, propranolol did not affect placental lactogen production, as measured by the Nb2 lymphoma bioassay.

When the α- and β-adrenergic antagonists were given before the physiological fall in serum progesterone concentrations and subsequent induction of prolactin secretion and lactogenesis on the afternoon of day 21 of pregnancy, similar patterns of inhibition of casein and lactose synthesis and of prolactin release were found as in the previous experiments. This indicates an adrenergic participation in the physiological induction of lactogenesis at the end of pregnancy in rats.

The stimulatory adrenergic action on lactogenesis shown in the present work is probably not mediated by activation of adenyl cyclase, since, as discussed above, an increase in intracellular cyclic AMP has been shown to be inhibitory to the synthesis of milk products. This conclusion may be supported by the fact that, although mammary β-adrenergic receptors are functionally coupled to adenyl cyclase, their activation leads to significant increases in intracellular cyclic AMP in mammary tissue derived from lactating rats only in the presence of phosphodiesterase inhibitors (Clegg & Mullaney, 1985). At present we cannot rule out the fact that the stimulatory adrenergic action on lactogenesis may be indirect, mediated through actions on other tissues, such as the liver.

It is important to mention that catecholamines are released to the circulation following suckling in lactating rats (Clapp, Martinez-Escalera, Morales et al. 1985). These catecholamines induce a short-term inhibition in the response of the mammary gland to oxytocin and milk ejection (Sibaja & Schmidt, 1975; Grosvenor & Mena, 1979; Mena, Pacheco, Aguayo et al. 1979). Our results have shown that the adrenergic system has a role in the release of prolactin and lactogenesis at the end of pregnancy. In lactating animals the released adrenaline, along with prolactin.

also released by suckling, may also stimulate milk production.

To our knowledge, the present work provides the first evidence of the involvement of the adrenergic system in the central and peripheral mechanisms controlling lactogenesis at the end of pregnancy. The effect of catecholamines seems to be stimulatory at the central level, regulating prolactin secretion, as well as at the level of the mammary gland, modulating casein and lactose synthesis.

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