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Rat Placental Lactogen-I Abolishes Nocturnal Prolactin Surges in the Pregnant Rat

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The twice-daily surges of prolactin (PRL) present during the first half of pregnancy abruptly terminate at midpregnancy concurrent with the appearance of high levels of placental lactogen-I (PL-I) in the blood. This study addressed the role PL-I and other pituitary or placental hormones have in terminating PRL surges in pregnant rats. Implantation of rat PL-I (rPL-I) or ovine PRL into the arcuate-median eminence area of the hypothalamus of day 7 pregnant rats totally eliminated nocturnal PRL surges on days 8 and 9. To assess the specificity of the inhibitory effects of hormones from the PRL-growth hormone (GH) family, rat growth hormone (rGH), human growth hormone (hGH), and rat prolactin-like protein-A (PLP-A) were tested. Only the lactogenic hormone, hGH, had any effect. Since lactogenic hormones may inhibit PRL by stimulation of dopamine synthesis and release into the hypophysial portal blood vessels leading to the anterior pituitary, the effect of these hormones on tyrosine hydroxylase (TH), the rate-limiting enzyme for the synthesis of dopamine activity, was determined. In pregnant rats, both ovine prolactin (oPRL) and hGH significantly increased (64%) TH activity, whereas rPL-I was less effective. In ovariectomized, bromocriptine-treated rats, both rPL-I and oPRL increased TH activity 207 and 151%, respectively. This supports the concept that termination of PRL surges at midpregnancy are owing to secretion of placental lactogens (PLs) from the placenta. However, the mechanism for the inhibition cannot be entirely attributed to an increase in tuberoinfundibular dopaminergic neuronal activity.

Key Words: Prolactin; dopamine; placental lactogen; tyrosine hydroxylase.

Introduction

Pregnancy in the rat is characterized by twice-daily prolactin (PRL) surges until day 10, after which time PRL remains at low levels until just before parturition (Butcher et al., 1972; Smith and Neill, 1976). The luteotropic function of PRL presumably is assumed by placental hormones that are PRL-related, especially placental lactogen-I (PL-I) and PL-II. Several studies report that there is a temporal relationship between the appearance of PL-I and the disappearance of PRL surges (Yogev and Terkel, 1980; Voogt et al., 1982; Tonkowicz and Voogt, 1983). This suggests that PL-I may exert a negative feedback on PRL, which is sustained by the appearance of PL-II on day 11 at the time PL-I secretion ceases. Further support for this concept comes from experiments in which human PL (Voogt, 1980) or secretions of rat choriocarcinoma cells (Rcho), which include PL-I, were shown to inhibit PRL (Arbogast et al., 1992; Tomogane et al., 1992). This cell line has a trophoblast lineage and, in vitro, expresses several members of the placental PRL family, including PL-I, PL-II, PRL-like protein A (PLP-A), and PRL-like protein C (PLP-C) (Faria and Soares, 1991). Expression in vivo has been characterized only in immature rats and is restricted to PL-I (Faria et al., 1990). When Rcho cells were transplanted either under the kidney capsule (Tomogane et al., 1992) or in the lateral ventricle of the brain (Arbogast et al., 1992), the PRL surges of pregnancy were inhibited. However, it is important to recognize that in these experiments, the absence of placental factors other than PL-I was not demonstrated. It is possible that Rcho cells transplanted to the pregnant rat secrete several of the PRL-like proteins.

Secretion of dopamine from the tuberoinfundibular dopamine (TIDA) neurons of the hypothalamus into the hypophysial portal blood acts to inhibit PRL secretion chronically (for review, *see* Ben-Jonathan, 1985). The activity of these dopamine neurons is, in part, regulated by the level of PRL in the circulation, such that hypoprolactinemia decreases and hyperprolactinemia increases neuronal activity (Gudelsky and Porter, 1980; Demarest et al., 1985b; Moore, 1987; Arbogast and Voogt, 1991a). Measurement of the catalytic activity of tyrosine hydroxylase (TH) in the stalk-median eminence (SME), where the TIDA nerve terminals are located, provides a useful index of TIDA neuronal function. TH is the rate-limiting enzyme in the synthesis of dopamine, catalyzing the conversion of tyrosine to L-dihydroxyphenylalanine (DOPA).

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We hypothesize that rat placental lactogen-I (rPL-I) exerts a negative feedback on PRL secretion, and does so by stimulating TIDA neurons. Therefore, the objectives of this study were:

1. To determine the effect of rPL-I, implanted in the region of the TIDA neurons, on the nocturnal PRL surge during pregnancy;
2. To compare the effect of rPL-I on PRL surges to other lactogenic (ovine PRL and human growth hormone [GH]) and nonlactogenic (PLP-A and rat GH) hormones of the PRL/GH family; and
3. To evaluate the role of TIDA neurons in the feedback effects of lactogenic hormones on PRL.

Results

Effect of Lactogenic Hormones on PRL Surges

Total elimination of nocturnal PRL surges occurred following hypothalamic implantation of either recombinant rat PL-I or oPRL (Fig. 1). Both basal and surge levels of PRL on days 8 and 9 were reduced significantly compared to controls. Implantation of the hormone was done on day 7 of pregnancy, and blood sampling was done throughout the nocturnal surge time on days 8 and 9. In almost all rats treated with rPL-I or oPRL, plasma PRL was <4 ng/mL at 0400 h, compared to levels >600 ng/mL in albumin controls. It is possible that the surge occurred at a time later than 0600 h, although this is unlikely since the hormone implant remained continuously present in the brain. To assess the specificity of the inhibitory effect of hormones from the PRL-GH family, several placental and pituitary hormones were used. Trunk blood samples were obtained at 0400 h on day 9, 2 d after hormonal implantation. Both rPL-I and hGH were inhibitory, reducing plasma PRL to 2 ng/mL or less compared to 423 ± 79 ng/mL in albumin-treated controls (Fig. 2). Neither PLP-A nor rat GH had any effect on PRL levels.

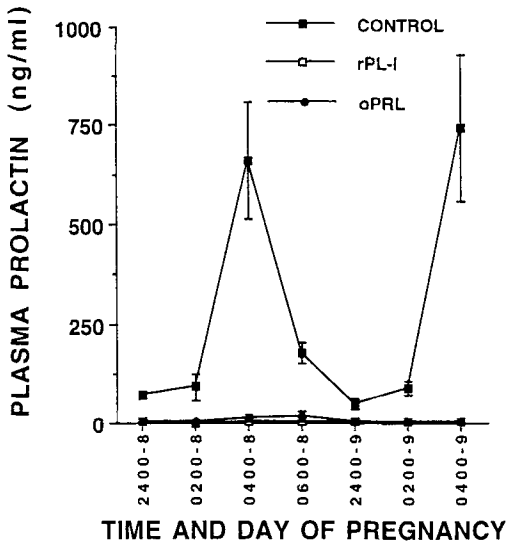

Fig. 1. Effect of rPL-I and oPRL on nocturnal PRL surges. Pregnant rats received hypothalamic implants of albumin (controls), rPL-I, or oPRL on day 7, and blood samples were taken via a carotid cannula on days 8 and 9. At all times, plasma PRL was significantly lower in the two groups receiving hormone implants compared to controls ($p < 0.001$); $n = 6$–8/group.

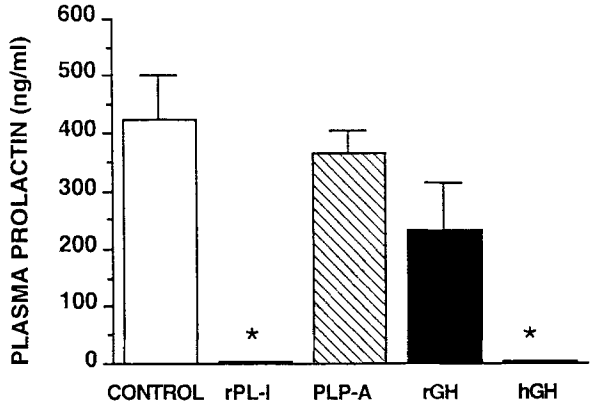

Fig. 2. Effect of rPL-I, PLP-A, rat GH, and hGH, on plasma PRL levels at 0400 h on day 9 of pregnancy. Pregnant rats received hypothalamic implants of hormones on day 7 and were sacrificed at 0400 h on day 9. Only rPL-I and hGH were significantly different from controls, and these two groups were also different from the PLP-A and rGH groups. *$p < 0.01$; $n = 4$–14/group.

Effect of Lactogenic Hormones on TH Activity in Pregnant Rats

To determine what effect pituitary and placental hormones have on TH activity in the TIDA neurons, pregnant rats received hormonal implants in the hypothalamus on day 7 and were decapitated at 0400 h on day 9. This time was chosen because TH activity in TIDA neurons is lower during the nocturnal PRL surge than during the intersurge period (Arbogast and Voogt, 1991b). TH activity, measured as DOPA accumulation, was significantly increased 64% ($p < 0.05$) in both the hGH and oPRL groups, whereas the rPL-I group had an increase of 32% compared to controls, which was not statistically significant (Fig. 3).

Effect of Lactogenic Hormones on TH in Ovariectomized Bromocriptine-Treated Rats

To remove the effect endogenous PRL or ovarian steroids might have on TH activity, rats were ovariectomized and treated with bromocriptine (3 mg/kg) every 12 h for 2 d, with the last injection 2 h before rats were sacrificed. The hypoprolactinemia induced by this treatment has been shown to lower TH activity (Arbogast and Voogt, 1991a). Implantation of rPL-I or oPRL was done when the bromocriptine injections were started. Bromocriptine-ovariectomy treatment resulted in lower TH activity (1.14 ± 0.13 pmol/mg protein/min) in the SME compared to pregnant rats (1.93 ± 0.21 pmol/mg protein/min), seen by comparing albumin-treated controls (Figs. 3 and 4). Both rPL-I and oPRL caused large increases in TH activity (207 and 151%, respectively) in ovariectomized, bromocriptine-treated rats (Fig. 4).

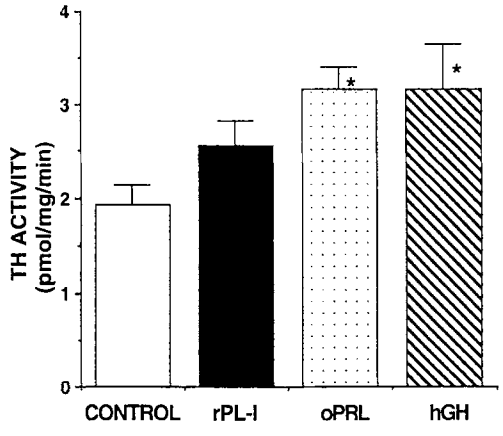

Fig. 3. Effect of rPL-I, oPRL, and hGH on TH activity (pmol/mg protein/min) in the SME of pregnant rats. Rats were sacrificed at 0400 h, 2 d after receiving the hormonal implants. TH activity was significantly higher in the oPRL and hGH groups than in the controls, whereas rPL-I caused no significant change. $*p < 0.05$; $n = 7$–17/group.

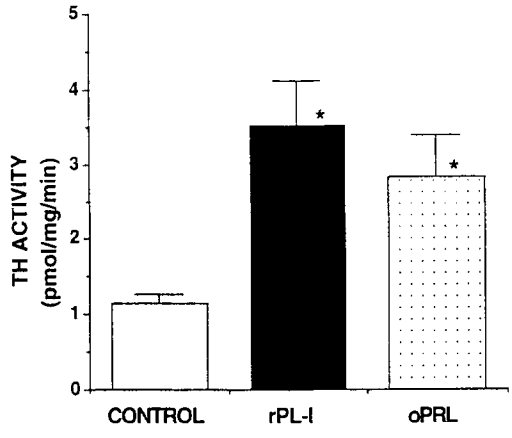

Fig. 4. Effect of hypothalamic implants of rPL-I and oPRL on TH activity in the SME of ovariectomized, bromocriptine-treated rats. Both rPL-I and oPRL caused significant increases in TH activity compared to albumin- implanted controls. $*p < 0.05$; $n =$ 10/group.

Discussion

This study demonstrates for the first time that purified rat PL-I is inhibitory to PRL secretion. When rPL-I was placed in the medial-basal hypothalamus, it reduced basal PRL levels, and completely inhibited the nocturnal PRL surge during pregnancy. Neither PLP-A, a placental protein, nor rGH, a pituitary hormone, had any effect on PRL, whereas both oPRL and hGH were as effective as rPL-I in inhibiting PRL.

A number of studies have shown that there is a positive correlation between the increase in PL-I concentrations in the plasma and the disappearance of the PRL surges at midpregnancy (Yogev and Terkel, 1980; Tonkowicz and Voogt; 1983). Infusion of conditioned medium from incubation of day 11 placentas, which contained PL-I, blocked the nocturnal PRL surge (Voogt and deGreef, 1989). Transplantation of rat Rcho cells, which secrete PL-I, either under the kidney capsule or into the lateral ventricle of the brain caused early termination of the PRL surges (Tomogane et al., 1992; Arbogast et al., 1992). On the other hand, removal of the products of conception prolonged the occurrence of the PRL surges (Voogt, 1980). However, none of these studies were able to attribute the inhibition of PRL solely to the presence of PL-I, since it could not be demonstrated that PL-I was the only parameter that was altered.

Rat placental lactogens are not unique in their ability to inhibit PRL secretion. Numerous studies have shown that PRL is capable of exerting a short-loop feedback on its own secretion (Voogt, 1987; Ben-Jonathan et al., 1989). This is best demonstrated during physiological states in which there is a surge or elevation in PRL. Ovine PRL, either systemically (Selmonoff and Gregerson, 1984) or via the hypothalamus (Voogt and Meites, 1973), inhibited the PRL surge during proestrus or in response to suckling. When oPRL or human PL were implanted into the hypothalamus during pregnancy, the PRL surges were abolished (Voogt, 1980; Vidal et al., 1991). In the present study, rPL-I, oPRL, and hGH all were equally effective in totally inhibiting the nocturnal PRL surge of pregnancy. All of these hormones can bind to PRL receptors on the Nb_2 lymphoma cell and cause these cells to divide (Tanaka et al., 1980). Human GH and rat PRL displaced rPL-I from binding sites in the antimesometrial stroma of pregnant rats, whereas rGH was ineffective (Freemark et al., 1993). Rat PL-I is capable of binding to choroid plexus and hypothalamus of pregnant rats, and unlabeled hGH and rPRL (but not rGH) inhibited this binding (Pihoker et al., 1993). Both oPRL and hGH are lactogenic in the rat, and we have preliminary evidence that rPL-I is able to initiate and maintain lactation in the absence of PRL. Neither PLP-A, which has sequence homology with rat PRL, nor rGH was effective in inhibiting PRL. They also are not capable of binding to PRL receptors (Deb et al., 1993) and, at least in the case of rGH, are not lactogenic. Thus, there exists a strong correlation between the lactogenicity of hormones and their ability to inhibit PRL.

Several studies have shown that a semicircadian rhythm of activity of tuberoinfundibular dopamine neurons exists during the first half of pregnancy, which is out of phase with the PRL surges (DeGreef and Neill, 1979; McKay et al., 1982; Arbogast and Voogt, 1991b). At midpregnancy, this pattern is terminated, coincident with loss of the PRL surges, and is replaced by tonic high levels of dopaminergic neuronal activity and low plasma levels of PRL (McKay et al., 1982; Demarest et al., 1983; Arbogast and Voogt, 1991b). Feedback from the uterine-placental unit contributes to this change at midpregnancy (Demarest et al., 1983, 1985a). In fact, transplantation of Rcho cells to the lateral ventricle increased tuberoinfundibular dopaminergic activity during the time of the PRL surge, which in effect, abolished the semicircadian rhythm of the TIDA neurons (Arbogast et al., 1992). Since PL-I is secreted by Rcho

cells, it may be responsible for or contributes to the elimination of the semicircadian rhythm in TH activity. Based on these findings, one would predict that placement of rPL-I in the area of the cell bodies of the TIDA neurons would result in a large increase in TH activity in the SME. However, the results in Fig. 3 show that TH activity, measured at 0400 h on day 9 of pregnancy, increased only 32%. Implantation of hGH or oPRL was somewhat more effective, resulting in a 64% increase in TH activity. All three hormones profoundly reduced PRL levels. One explanation for the limited effectiveness of the lactogen hormones on TH activity may be the timing of the experiment. Measurements were made on day 9 of pregnancy, a time when endogenous PL-I secretion has already begun, thus partially masking the effect of PL-I implants. However, given the lack of a significant effect of rPL-I on TH activity and the modest stimulatory effect of hGH and oPRL, it is not likely that the major inhibitory action of these lactogenic hormones on the PRL surge is via TIDA neurons. Inhibition of PRL releasing factors or stimulation of another PRL inhibiting factor also might be part of the mechanism whereby lactogenic hormones inhibit PRL secretion.

In ovariectomized, bromocriptine-treated rats, hypothalamic rPL-I and oPRL implants resulted in much larger increases in TH activity in the SME than seen in the pregnant rats. This model was chosen because bromocriptine treatment lowers TH activity by reducing the stimulatory effect of PRL. We previously reported that chronic treatment with bromocriptine reduced TH activity in the SME and TH mRNA signal levels in the arcuate nucleus, and concomitant treatment with oPRL (Arbogast and Voogt, 1991a) or Rcho cells (Arbogast et al., 1992) reversed this effect on TH. Thus, it appears that if TH activity is low owing to the lack of the stimulatory effects of PRL, then lactogenic hormones exert a significant positive effect on TH. However, when plasma PRL levels are normal or elevated, as occurs in pregnancy, the addition of lactogenic hormones is not as effective in stimulating dopamine neurons, which may be in a more active state. Also the presence of ovarian steroids may alter the response of TH to lactogenic hormones (Demarest et al., 1984). Chronically elevated estradiol profoundly reduces TH mRNA signal levels in the arcuate nucleus and modestly reduces TH activity in the SME. Progesterone reverses both of these effects of estradiol (Arbogast and Voogt, 1993). Progesterone is the dominant ovarian steroid in the pregnant rat.

In summary, rat PL-I or other lactogenic hormones, when placed in or near the arcuate nucleus of the hypothalamus, reduces baseline PRL levels to that seen following bromocriptine treatment, and completely abolishes the nocturnal PRL surge of the pregnant rat. This supports the concept that the disappearance of PRL surges at midpregnancy is owing to secretion of PLs from the placenta. An increase in tuberoinfundibular dopaminergic activity may be a partial explanation for the rPL-I-induced decrease in PRL in the pregnant rat, but other factors are likely involved as well.

Materials and Methods

Animals

The protocols for animal use were approved by the Institutional Animal Care and Use Committee at Kansas University Medical Center. All animals were housed in an AALAC accredited facility. Sprague Dawley rats purchased from Sasco Co. (Omaha, NE) were used in this study. They were kept in temperature- and light-controlled rooms in which the lights were on 12 h/d (0600–1800 h). A reversed lighting schedule was used in some studies to allow experiments to be done during the day. Rat chow and water were supplied at all times. On the evening of proestrus, one male was placed into the cage with the female, and the first day sperm was detected in the vaginal lavage was designated as day 0 of pregnancy.

Left intracarotid arterial cannulations were performed under ether anesthesia, and the rats were used during the next 2 d. The carotid artery was exposed, and a polyethylene (PE-50) cannula was inserted 2.5 cm into the artery, secured, and exteriorized through the skin in the back of the neck. The cannula was protected with a flexible steel spring, which was connected to a swivel above the cage. This allowed for withdrawal of blood samples without disturbing the rat. Four blood samples (200–300 μL) were taken each day for 2 d and the volume replaced with heparinized saline.

Implantation of hormones into the arcuate-median eminence area was done at the same time of the arterial cannulation, using a Koph small animal stereotaxic instrument, as described earlier (Clemens and Meites, 1968). Briefly, peptide hormones (25 μg) or albumin were mixed with cold cocoa butter and tamped into a glass tube. The coordinates used were described previously (Vidal et al., 1991). At the end of the experiment, the location of the implant was determined by visual inspection of the ventral surface of the hypothalamus. Only rats in which the tip of the glass tube was in the basal portion of the hypothalamus midway between the rostral and caudal boundaries of the hypothalamus and within 1 mm of the midline were included.

Hormones and Drugs

Highly purified oPRL (oPRL-20), rGH (B-5), and hGH (AFP-9755-A) were obtained from the NIDDK. Recombinant rPL-I was purified from the conditioned medium of Chinese hamster ovary cells transfected with the pMSXND expression vector containing the rPL-I cDNA (Robertson et al., 1994). Recombinant rat PLP-A was purified from conditioned medium of Chinese hamster ovary cells transfected with the pMSXND expression vector containing the PLP-A cDNA (Deb et al., 1993). Purity of both PLP-A and rPL-I was demonstrated using polyacrylamide gel electrophoresis (Deb et al., 1993; Robertson et al., 1994). The same preparation of each of these hormones was used throughout the study. Bromocriptine (3 mg/kg, sc) was dissolved in a 30% ethanol–0.3% tartaric acid solution.

Experimental Design

Pregnant rats received hypothalamic implants of hormones on the morning of day 7 of pregnancy and were sacrificed by rapid decapitation on day 9 at 0400 h. Trunk blood was collected, allowed to clot, and centrifuged to separate cells from serum. Samples were frozen and stored at –20°C until assayed for PRL. Brains were removed and processed for TH activity as described below. In one experiment, rats also received carotid cannulas at the same time hormones were implanted in the hypothalamus. Blood samples were obtained at various times beginning at 2400 h on days 7 and 8. These rats also were sacrificed at 0400 h on day 9, and processed as described above. Rats not used in the pregnancy study were ovariectomized 2 wk prior to receiving hypothalamic implants of hormones. All ovariectomized rats received bromocriptine myselate (3 mg/kg) every 12 h with the last injection 2 h before sacrifice, or 50 h after hormonal implantation. Trunk blood and brains were removed and processed in a manner identical to the pregnant rats.

TH Activity

TH activity was determined in vitro as described previously (Arbogast et al., 1992). Briefly, the dissected portion of the hypothalamus containing the arcuate nucleus and median eminence was preincubated in medium containing 20 μ*M* tyrosine. Following removal of the preincubation medium after 15 min, medium containing 100 μ*M* brocresine (4-bromo-3-hydroxybenzyloxyamine), an aromatic-L-amino acid decarboxylase inhibitor, was added. After 30 min, the stalk-median eminence was dissected from the tissue fragment, homogenized in 0.1*N* perchloric acid, and centrifuged. The pellet was analyzed for protein content by the method of Bradford (1976)

The tissue content of DOPA in the SME was determined by HPLC, as described previously (Arbogast et al., 1992). The amount of DOPA was quantitated with a built-in integrator by comparing the peak area of the unknown with the peak area of a standard.

Hormone Determination

Prolactin levels were determined by RIA using materials supplied by the NIDDK. Rat PRL labeled with ^{125}I was purchased from Dupont (Boston MA). The reference preparation used was NIADDK rat-PRL-RP-1, and the limit of sensitivity of the assay was 50 pg. The intra- and interassay coefficient of variation were 10.7 and 9.1%, respectively.

Statistical Analysis

Results are expressed as the mean ± SEM. Two-way ANOVA for repeated measures was used to compare plasma PRL values between treatment groups across time within one group. One-way ANOVA was used to compare PRL or DOPA accumulation values across groups at one time. Scheffe F-test or Fischer's test was used to make individual comparisons.

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