The Lactogenic Action of Human Chorionic Gonadotrophin in the Rat

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The onset of lactation in the parturient rat is triggered by the fall in concentration of plasma progesterone that precedes it (Kuhn, 1969*a,b*, 1971). This fall results from a decreased secretion of luteal progesterone, which is mirrored by an increased secretion of 20α -hydroxypregn-4-en-3-one (Fajer & Barraclough, 1967; Hashimoto *et al.*, 1968). The changed pattern of Δ^4 -steroid secretion is in turn apparently explained by the simultaneous appearance of the luteal enzyme 20α -hydroxy steroid dehydrogenase, which reduces progesterone or pregnenolone (3β -hydroxypregn-5-en-20-one) at the 20-oxo position (Wiest *et al.*, 1968; Kuhn & Briley, 1970).

The opportunity has arisen to test this implied role of luteal 20α -hydroxy steroid dehydrogenase in the onset of lactation, since Wiest *et al.* (1968) have shown that the enzyme may be experimentally

induced with luteinizing hormone or human chorionic gonadotrophin. It is here shown that human chorionic gonadotrophin may be used to induce premature lactogenesis in the late-pregnant rat. Lactose and casein were used as specific markers of milk solids.

Intact or unilaterally ovariectomized primiparous pregnant rats of a Wistar-derived strain were each given subcutaneous injections of human chorionic gonadotrophin (250 units) in saline (0.9% NaCl) or of saline alone at 12h intervals starting 6 days before parturition. 20α -Hydroxy steroid dehydrogenase activity was assayed as described by Kuhn & Briley (1970). Mammary glands were extracted (Kuhn & Lowenstein, 1967) and assayed for lactose (Reithel, 1963). Casein was assayed as protein P (Kuhn, 1972).

Fig. 1 shows the increase of luteal 20α -hydroxy steroid dehydrogenase activity, which approached a

Fig. 1. Effects of human chorionic gonadotrophin on luteal 20α -hydroxy steroid dehydrogenase and mammary-gland lactose

Luteal 20α -hydroxy steroid dehydrogenase activity in intact (●) and unilaterally ovariectomized (○) pregnant rats and the mammary-gland lactose concentration in the same intact (▲) and unilaterally ovariectomized (Δ) animals were measured at the times indicated after the administration of human chorionic gonadotrophin (HCG). Experimental details are given in the text. Each point is a mean value of results for four to six rats, with S.E.M. values shown as vertical bars.

maximum 2 days after the start of treatment with gonadotrophin. This activity was about half that normally reached 1–2 days after parturition. The mammary-gland lactose of intact animals first appeared after a lag of nearly 2 days, and reached a mean concentration of $6.6 \mu\text{mol/g}$ at 3 days. This compares with a normal value of $12\text{--}13 \mu\text{mol/g}$ at parturition (Kuhn & Lowenstein, 1967; N. J. Kuhn, unpublished work). Because 20α -hydroxy steroid dehydrogenase activity normally appears later in pregnancy, at a time when the Δ^4 -steroid secretion has partly declined from the high rate that occurs 6 days before parturition, the natural situation was mimicked by administering human chorionic gonadotrophin to unilaterally ovariectomized rats. Fig. 1 shows that mammary-gland lactose now appeared after a lag of only 1 day, its concentration rising by 3 days to $12.6 \mu\text{mol/g}$. In both intact and unilaterally ovariectomized rats the injection of saline in place of gonadotrophin caused no significant increase of either 20α -hydroxy steroid dehydrogenase activity or of lactose (results not given in detail).

An unexpected finding of secondary interest was the sharp fall in the mammary-gland lactose concentration of intact gonadotrophin-treated rats after 3 days. Thus by 4 days there was a mean concentration of only $0.22 \mu\text{mol/g}$. The fall was not significantly prevented by discontinuing the treatment with gonadotrophin at 3 days. However, bilateral ovariectomy at 3 days resulted in a mean lactose concentration of $2.4 \mu\text{mol/g}$ at 4 days. Thus a contributory factor to the loss of mammary-gland lactose may be an inhibition deriving from the ovary, being possibly a re-surge of progesterone from corpora lutea newly formed as a result of the ovulatory action of gonadotrophin.

In an experiment on a separate group of rats the administration of human chorionic gonadotrophin for 3 days also raised the mean mammary-gland casein concentration to $7.5 \pm 3.1 \mu\text{mol}$ of protein P/g compared with $1.5 \pm 0.7 \mu\text{mol}$ of protein P/g in saline-injected controls. The simultaneous injection of progesterone (7 mg/day subcutaneously) lowered the mean casein concentration to $2.2 \pm 0.6 \mu\text{mol}$ of protein P/g and lowered the mean lactose concentration from 8.8 ± 2.5 to $0.3 \pm 0.2 \mu\text{mol/g}$ (each value a mean of results for four rats).

The lactogenic effect of human chorionic gonadotrophin, and its inhibition by progesterone, therefore supports the proposed role of luteal 20α -hydroxy steroid dehydrogenase in the chain of events that causes lactogenesis in the rat.

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