

Aromatase activity in fetal rat gonads

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Introduction

The transformation of androgens into oestrogens occurs by aromatization. It involves loss of the C-19 angular methyl group and aromatization of ring A. It is catalysed by aromatase, a microsomal cytochrome P-450, which executes 3 successive monooxygenations on androstenedione or testosterone resulting in the formation of oestrone or oestradiol (Fishman & Goto, 1981; Fishman & Raju, 1981). The present paper reviews studies on aromatase activity in fetal rat gonads. It was felt that there was need for such a review considering the discrepancy in the results obtained by various laboratories.

Aromatase activity in the ovary

Demonstration of activity

Weniger *et al.* (1984) cultured ovaries from 19- to 20-day-old rat fetuses in Wolff & Haffen's (1952) semi-solid, agar-containing medium in a 5- μ l droplet of a 2 μ M solution of [³H]testosterone in Tyrode's physiological saline. After a 24-h culture time, 100 μ g radioinert oestrone and oestradiol were added as carriers to the medium, as well as tracer amounts of the ³H-labelled compounds to permit correction for analytical losses. Oestrogens were extracted and [³H]oestrone and [³H]oestradiol formed from [³H]testosterone were identified by recrystallization to constant specific activity. Knowing the exact amount of [³H]testosterone used as precursor, its conversion percentage into both oestrone and oestradiol could be calculated.

Oestrone was readily identified and represented 5% of the added precursor. However, oestradiol was not identified with certainty and its synthesis level was calculated to be <0.1% (Weniger *et al.*, 1984).

Two conclusions can be drawn from this experiment. The 19- to 20-day-old fetal rat ovary possesses aromatase activity, and 17 β -hydroxysteroid oxidoreductase favours the formation of oestrone. Studies with fetal rabbit or human ovaries yielded much more oestradiol than oestrone (Milewich *et al.*, 1977; George & Wilson, 1978), perhaps because of a difference in the culture methods used. However, this hypothesis loses strength because chick embryo ovaries cultured under the same conditions as used in the fetal rat ovary produced mainly oestradiol (Weniger *et al.*, 1983). It can be dismissed in view of the results obtained when culturing fetal rat ovaries in Medium 199, in which synthesis was almost exclusively of oestrone (Weniger & Zeis, 1987b). This result was confirmed independently by Picon *et al.* (1985), who found that oestrone production was 12-fold that of oestradiol.

Change in the relative importance of oestrone and oestradiol synthesis was observed with increasing age. In the 14-day-old infantile rat ovary, synthesis of oestradiol supplanted that of

oestrone. It looks as if the weaker oestrogen is produced during fetal life and the stronger oestrogen with approaching puberty.

Action of FSH and cAMP

Although stimulation of aromatase activity by cAMP is certain, the action of FSH is controversial. In none of 3 successive studies could stimulation of aromatase activity by FSH be demonstrated unequivocally (Weniger *et al.*, 1985; Weniger & Zeis, 1987b, 1988b). Nor did George & Ojeda (1987) notice any augmentation of aromatase activity in 19–22-day-old fetal rat ovaries treated with FSH. However, Picon *et al.* (1985) reported doubling of oestrogen synthesis in the 20-day-old fetal rat ovary in the presence of FSH. Likewise, in the 17–18-day-old fetal mouse ovary, Terada *et al.* (1984) detected aromatase activity in the presence of FSH, but not in its absence.

Aromatase activity in the testis

Demonstration of activity

Testes from 18–21-day-old fetal rats were cultured in semi-solid medium in a 10- μ l droplet of a 10 μ M solution of [3 H]testosterone, [3 H]androstenedione or [3 H]dehydroepiandrosterone in physiological saline (Weniger & Zeis, 1987a) or in liquid medium containing 0.15 μ M-[3 H]testosterone (Weniger & Zeis, 1988a). The analytical procedure was the same as indicated above. In contrast with the ovaries, the testes formed mostly oestradiol, but total oestrogen synthesis was \sim 10% that in the ovaries. Significant differences in the efficiency of the various precursors were not noticed. It is remarkable that the testis secretes the stronger oestrogen from fetal stages, whereas the ovary produces the weaker oestrogen during fetal life and turns to significant oestradiol production only in the neonatal period.

Action of FSH and cAMP

Testes were cultured in [3 H]testosterone-containing media to which FSH or cAMP had been added. In the presence of both substances oestradiol synthesis was increased approximately to the same extent, i.e. 3–4-fold (Weniger & Zeis, 1988a, b). This result suggests that the action of FSH is mediated by cAMP.

How can one explain that the testis but not the ovary is sensitive to FSH? It is well known that the presence of appropriate receptors is a prerequisite for hormone action. The fetal rat testis contains FSH receptors from 17 days of gestation (Warren *et al.*, 1984), whereas the fetal ovary lacks such receptors (Smith-White & Ojeda, 1981).

Conclusion

Although aromatase activity is detectable in the fetal rat ovary and testis, it is not known whether the oestrogen produced plays a physiological role during fetal life. Oestrogen is apparently not necessary for normal differentiation of the genital tract in the female, as shown by the castration experiments of Jost (1947). It has been suggested that oestradiol controls testosterone secretion in the immature rat testis (Tsai-Morris *et al.*, 1985; Papadopoulos *et al.*, 1986). Indeed, in the fetal rat, testosterone production is greatly depressed by oestradiol injection (Chouraqui *et al.*, 1979). As regards a possible role for FSH, FSH-containing cells have been revealed by immunocytochemistry in the adenohypophysis of rat fetuses from 19 days of gestation (Tougaard *et al.*, 1977; Watanabe & Daikoku, 1979) and FSH has been detected by radioimmunoassay in the pituitary of male fetuses from 17 days of gestation (Chowdhury & Steinberger, 1976).

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