Metyrapone inhibits prostaglandin synthesis and release from the pregnant rat uterus *in vitro*

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Metyrapone, an inhibitor of corticosteroid biosynthesis (Chart & Sheppard, 1959), causes foetal adrenal hypertrophy (Dupouy, 1972) and prolongs pregnancy in the rat (Parvez, Parvez & Roffi, 1972). As the foetuses exert some form of control over prostaglandin (PG) release from the pregnant rat uterus *in vitro* (Parnham, Sneddon & Williams, 1975), the effect of metyrapone on this uterine PG release has been investigated.

Two experimental approaches were used. First, pregnant rats received daily injections of either metyrapone (150 mg kg^{-1}, s.c. or i.p.) or vehicle (0.33 M (+) tartaric acid, 0.75 ml kg^{-1}, s.c. or i.p.) on days 20 and 21 of pregnancy. The animals were then killed on day 22 and the PG release from single uterine horns determined by the method of Vane & Williams (1973). Secondly, PG synthetase activity in day 22 pregnant uterine homogenates was determined by incubation for 10 min with ^{14}C-arachidonic acid and measuring its conversion to PGE_2 and $PGF_{2\alpha}$ which were separated on silicic acid mini-columns. Incubations were carried out in the presence of metyrapone (0.005-0.05 mM) against boiled blanks and buffer controls.

Metyrapone significantly reduced uterine PG release *in vitro* from 253 ± 35.5 (s.e. mean) ng g^{-1} h^{-1} in control uteri to 174 ± 21.2 ng g^{-1} h^{-1} in metyrapone-treated uteri ($P < 0.05$). The results of Parvez *et al.* (1972) showing prolongation of pregnancy by metyrapone (150 ng kg^{-1}) were also confirmed in a group of 13 rats. Metyrapone showed a dose-dependent inhibition of PGE_2 synthesis *in vitro* as determined by the conversion of ^{14}C-arachidonic acid to PGs. $PGF_{2\alpha}$ synthesis showed an apparent stimulation with metyrapone, probably due to redirection of synthesis from PGE_2. Preliminary experiments with indomethacin have confirmed that this inhibitor blocks the synthesis of both PGE_2 and $PGF_{2\alpha}$.

These results suggest that metyrapone is a selective inhibitor of uterine PGE_2 synthesis and this may account for the prolongation of pregnancy by metyrapone in the rat.

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Action of spasmogenic substances on Ca^{2+} movements of rat uterine smooth muscle

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These experiments were performed on uteri obtained from virgin Wistar rats of 180-200 g weight, pretreated the day before the experiment with 0.5 mg/kg of diethylstilboestrol diproprionate. Myometrium strips were prepared by excising the mucous and submucous layers.

The role of extracellular Ca^{2+} in myometrial contractility was examined on strips mounted isotonically. In at least five experiments angiotensin II (At II) 2.5×10^{-6} M, serotonin (5-HT) 2.5×10^{-5} M and carbachol (CCh) 2.5×10^{-5} M, produce a maximum contraction in a normal Ringer solution. In each experiment the contraction produced was less than 10% of the control as soon as 3 min after exposure of the strips to a solution without Ca^{2+}. The contractile response was restored to control levels less than 3 min after readmitting Ca^{2+} 1.5 mM to the bath. These results suggest that: (1) activation of contraction is due to an increase in membrane