An investigation of the possible effects of prostaglandins E_1, $F_{2\alpha}$ and $F_{2\beta}$ on pregnancy in mice and rabbits

E. W. HORTON and P. B. MARLEY*, *Department of Pharmacology, School of Pharmacy, University of London*

Prostaglandins modify the activity of the female reproductive tract smooth muscle in several species. It has been suggested (see Horton, 1968) that their action on oviduct smooth muscle may influence sperm and/or ovum transport, whereas their action on uterine smooth muscle may be important in parturition. The effects of some of the prostaglandins have therefore been studied on fertility in mice and as oxytocic substances in mice and rabbits near term.

Mice were injected subcutaneously either with saline ($n=59$) or with PGE_1, 1 mg/kg, ($n=44$) on day 1 (day of mating), days 1 and 2, day 3, days 3 and 4, day 4, day 5, or day 9 of pregnancy and were examined on day 19. There was no significant difference between the two treatments on any one day regarding the percentage of mice pregnant, the spacing of the foetuses or the number of foetuses and resorption sites. Thus there is no evidence to suggest that PGE_1 had altered transport rate in the reproductive tract. However, the mean number of foetuses/pregnant mouse in the PGE_1-treated mice was 22% greater than in the saline-treated mice (mean $\pm$S.E. $9{\cdot}76 \pm 0{\cdot}48$, $n=25$, and $8{\cdot}03 \pm 0{\cdot}42$, $n=33$, $P=0{\cdot}01$), suggesting that PGE_1 may have increased fertility.

In order to study the possible oxytocic effects of prostaglandins, mice were injected on day 19 of pregnancy (parturition normally occurs on day 20) and were observed for 2 hr and then intermittently until they delivered. Parturition was considered to have been induced if one foetus was born before 19.00 hr on day 19.

In groups of six to ten mice injected subcutaneously or intravenously with saline, PGE_1, 1 mg/kg, or with oxytocin, 40 u./kg, parturition was induced in more than 50% of the oxytocin-treated mice but in none of the PGE_1-treated or saline-injected mice. All the mice littered by 18.00 hr on day 20.

When PGE_1, 1 mg/kg, was injected intraperitoneally, 38% (5/13, $P<0{\cdot}02$) of the mice delivered on day 19, compared with 3% (1/29) of mice injected intraperitoneally with saline. With doses of PGE_1 of 0·5 and 2·0 mg/kg, none (0/8 and 0/7 respectively) of the mice delivered on day 19. However, with the higher dose the mice were markedly sedated.

Prostaglandins $F_{2\alpha}$, 1 and 0·25 mg/kg, and $F_{2\beta}$, 10 mg/kg, induced parturition in 44% (7/16, $P<0{\cdot}01$), 13% (1/8) and 8% (1/12) of the mice respectively, when injected intraperitoneally.

The mean times ($\pm$S.E.) between the intraperitoneal injection and the birth of the first foetus on day 19 were as follows: oxytocin, $1{\cdot}00 \pm 0{\cdot}28$ hr, PGE_1 $1{\cdot}23 \pm 0{\cdot}45$ hr, $PGF_{2\alpha}$, $0{\cdot}43 \pm 0{\cdot}13$ hr and $PGF_{2\beta}$, 0·22 hr.

The oxytocic activity of prostaglandins E_1 (100–400 μg) and $F_{2\alpha}$ (100–250 μg) given intravenously or intraperitoneally, was tested in rabbits using the method of Berde & Cerletti (1958). Neither significantly altered the time of parturition (eight and three rabbits respectively), compared with five control rabbits which delivered 16 hr or more after the injection, whereas oxytocin (0·4 u./kg intravenously) induced parturition in four out of six rabbits within 20 min.

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Changes in drug sensitivity in hyperthyroidism

P. F. COVILLE* and J. M. TELFORD†, *Department of Pharmacology, School of Pharmacy, College of Technology, Brighton, Sussex*

Some of the clinical effects of hyperthyroidism resemble those of increased sympathetic activity, and there is evidence that in hyperthyroidism the pharmacological effects of catecholamines are potentiated (Harrison, 1964). Coville & Telford (1968) found that treatment of rats or guinea-pigs with thyroxine increases the sensitivity of the isolated heart and uterus not only to catecholamines but also to acetylcholine, histamine, 5-hydroxytryptamine and calcium. In contrast, thyroxine depresses the sensitivity of the isolated aorta and intestine. Thyroid hormones are known to influence calcium metabolism, and these opposing and non-specific changes in sensitivity may be related to opposing influences on availability of Ca^{2+} ions.

Rats or guinea-pigs were pretreated with L-thyroxine sodium (1–5 mg/kg, subcutaneously, daily, 8–15 days). The influence of both raised and lowered calcium concentration in the bathing fluid was then determined on the 50% maximal responses of the isolated uterus and aorta of the rat and the isolated ileum of the guinea-pig to acetylcholine, histamine or 5-hydroxytryptamine. On the uterus, sensitivity to change in calcium concentration was increased by thyroxine administration, whereas on the intestine and aorta it was depressed.

The ability of uteri from hyperthyroid rats to bind Ca^{2+} was measured by a modification of the method of Knifton (1966). Isolated uteri were driven by optimal field stimulation (usually 80 V, pulse width 5 msec, 20 pulses/sec, for 5 sec every min). The Krebs solution was then replaced by a Ca^{2+}-free solution, stimulation continued, and the time taken for tension to decrease to half the original plateau height. It was found that pretreatment with thyroxine increases the rate of loss of tension in both oestrus and dioestrus uteri. This suggests that binding of Ca^{2+} is reduced so that increased availability of free Ca^{2+} in the uterus could explain the increased sensitivity of this tissue to drugs.

Further experiments showed that on the central nervous system, as on cardiac and smooth muscle, thyroxine in similar dosage likewise induces non-specific changes in sensitivity to drugs. Locomotor activity in grouped rats induced by a single dose (0·5 or 1·0 mg/kg, intraperitoneally) of dexamphetamine is approximately doubled, whilst the LD50 of dexamphetamine is reduced 25 times. Spontaneous locomotor activity is not modified by thyroxine alone, but is reduced by thyroidectomy which also affords partial protection against doses of dexamphetamine (50 mg/kg, intraperitoneally) lethal to control rats. In hyperthyroid rats toxicity to caffeine is increased, a dose of 160 mg/kg producing 100% mortality but no deaths in control rats. Hexobarbitone sleeping time in hyperthyroid mice (thyroxine, 20 mg/kg) is increased by up to 300%. Doses of hexobarbitone (50 mg/kg, intraperitoneally) which in control mice produce slight sedation induce narcosis after thyroxine treatment.