A Possible Mechanism of Leptaden Action by inhibiting Prostaglandin $F_{2\alpha}$ Synthesis

By

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The effect of oral administration of Leptaden on guinea-pig uterine tissue to biosynthesize prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) from endogenous precursors has been investigated in vitro. Animals were divided into a treated and a control group. Animals in the treated group were treated orally with Leptaden starting from day 1 up to day 13 of the estrus cycle. Those in the control group were given only an equal volume of tap water. All the animals were killed on day 14 of the estrus cycle and their uteri collected. Estimations of $PGF_{2\alpha}$ were carried out using a sensitive radio-immunoassay. The concentrations of $PGF_{2\alpha}$ in samples collected from the treated group were significantly lower ($P =<0.02$) than those collected from the control group. This indicates that Leptaden has an inhibitory effect on the ability of the guinea-pig uterine tissue to biosynthesize $PGF_{2\alpha}$.

Introduction

A substantial amount of clinical evidence indicates that Leptaden is a useful drug in gynaecological practice. A few of the indications for its use have been the different types of abortions, uterine hemorrhages, lactational failures and placental retentions (Patel, 1947, 1965; Naik 1957: Mangeshikar, 1957, Achari and Sinha, 1966; Sharma, 1967; Achari 1975). Inspite of its multiple medicinal uses, the pharmacological actions of Leptaden are largely unknown. Recently much evidence has accumulated to suggest that prostaglandin $F_{2\alpha}$ plays an important role in the female reproductive mechanisms (for review see Horton 1972); and it has been suggested that an inhibitor of prostaglandin synthesis might be used to postpone premature labour (Ramwell and Shaw, 1971). In the present investigation, therefore, the effect of Leptaden administration no prostaglandin $F_{2\alpha}$ biosynthesis by the guinea-pig uterus was studied. It is known that the guinea-pig uterus has the ability to biosynthesize prostaglandin $F_{2\alpha}$ (Poyser, 1972; Pugh et. al. 1975).

Material and Methods

Twelve female guinea-pigs of the Duncan Hartely breed and of known fertility were selected for this study. They were housed in two groups of six and maintained under standard conditions of food and hygiene. One group was treated with leptaden while the other group served as control. Treatment was started on day 1 of the estrus cycle and continued up to day 13. Each animal received leptaden at a dose rate of 100 mg/kg. body weight per day, administered in two divided doses via an intragastric rubber catheter (Sharma, 1970). The control group only received an equal volume of tap water. The length of the estrus cycle was determined from the characteristic vaginal opening as well as by examining vaginal smears. Day 1 of the estrus cycle was taken as the day preceding the post-ovulatory influx of leucocytes when cornification of the vagina was at a maximum. All the guinea-pigs were killed on the morning of day 14 of estrus cycle and their uteri collected in 96 percent ethanol. Each uterine sample (comprising both uterine horns) was then homogenized using a mechanical homogenizer, extracted and assayed radioimmunologically for prostaglandin $F_{2\alpha}$ (Sharma, 1972; Sharma et al, 1973).

Results and Discussion

The results are shown in the Table below which indicates that oral administration of leptaden in the guinea-pig has inhibitory effect on the biosynthesis of prostag landin $F_{2\alpha}$ by the uterine tissue of the cycling animal. The amount of prostaglandin. $F_{2\alpha}$ extracted from the uterine tissue of the treated Group was significantly lower than the untreated Group. When the uterine weights of the two groups were compared statistically, significant difference was however not found.

TABLE 1
The effect of leptaden administration on the guinea-pig uterus

Observation	Experimental group		
	(treated)	(untreated)	
Combined weight of the two uterine horns (g.) mean ± SD.	1.23 ± 0.46	1.30 ± 0.48	P>0.05
$PGF_{2\alpha}$ / Content (ng./100mg tissue)	16.85 ± 4.21	38.91 ± 6.57	P<0.02

These results suggest that leptaden causes inhibition of prostaglandin $F_{2\alpha}$ synthesis by the uterine tissue of the guinea-pig without affecting the uterine weight.

Although the role of prostaglandins in all those conditions which benet from leptaden is not yet understood, circumstantial evidence is available to suggest that prostaglandins are involved in at least some of the conditions, High concentrations of PGE_2 and $PGF_{2\alpha}$ have been found in liquor from the sac of the abortus following spontaneous miscarriage of patients between 13 and 23 weeks of gestation but not in liquor samples obtained from patients during therapeutic termination of pregnancy by abdominal hysterotomy (Karim, 1966: Karim and Hillier, 1970). Prostaglandins $F_{2\alpha}$ and E_2 have been discovered in menstrual fluid and human endometrium (Eglinton et al., 1963) and their in vitro synthesis by endometrial currettings has been demonstrated (Van Drop. 1966). Although these observations, are suggestive of their formation in the endometrium during menstruation, the precise role of prostaglandins in the mechanism of menstruation is not yet known. It is also not known whether prostaglandins are involved in certain uterine hemorrhages. unassociated with pregnancy, although leptaden has been successfully used in some of these conditions (Naik, 1957). The role of prostaglandins in lactational failures and placental retentions is also obscure, although leptaden has been successfully used in both of these conditions (Gokhale, 1965; Sharma, 1967). Nevertheless placental retentions are almost invariably associated with some degree of inflamma tion and prostaglandins are known to be involved in various inflammatory processes (Greaves et al., 1971). From the present limited study, although it is tempting to speculate that leptaden is acting by inhibiting prostaglandin biosynthesis, any such conclusion must await further detailed investigations in human beings.

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