Oxytocin Release by Infused Prostaglandin

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Summary

Plasma oxytocin levels were measured serially in 22 women receiving prostaglandin E_2 or $F_{2\alpha}$ intravenously for the induction of labour. Oxytocin was detected in the plasma of 19 of the 22 women; positive levels were found in 60 (43%) of 139 plasma samples, an incidence similar to that in the late first stage of spontaneous labour. Oxytocin was found in the maternal plasma even when the fetus was dead, and in the plasma of two men receiving prostaglandin infusions. This indicates that prostaglandins stimulate the pituitary directly and suggests that this mechanism may play a part in the oxytocic action of infused prostaglandins.

Introduction

The prostaglandins produce many diverse actions indirectly by stimulating the hormone system specific to the organ concerned (Flack *et al.*, 1969; Kaneko *et al.*, 1969; Aldridge *et al.*, 1970; Kuehl *et al.*, 1970; Speroff and Ramwell, 1970; Marsh, 1971). We have investigated the possibility that the prostaglandins produce their effect on the uterus by releasing oxytocin from the maternal pituitary.

Patients and Methods

The investigation was carried out on 22 women admitted for induction of labour. The procedure was explained to each patient and her consent obtained. Two male volunteers also received prostaglandin infusions for four hours. The prostaglandin was infused into a large, superficial arm vein at the rates shown in the Table. The duration of infusion varied and

Rate and Duration of Infusion of the Prostaglandin

Duration	PGE_2 ($\mu\text{g}/\text{min}$)	$PGF_{2\alpha}$ ($\mu\text{g}/\text{min}$)
First half hour	0.3	2.5
Second half hour	0.6	5.0
Second hour	1.2	10.0
Third to sixth hours	2.4	20.0
Seventh and eighth hours*	4.8	40.0

*Infusion was usually continued past this time but further oxytocin assays were not carried out.

depended principally on the time taken for labour to become established.

A polyethylene cannula (Bardic A-catheter) was introduced into a vein on the contralateral arm and strapped in position. Serial blood samples, of 10-ml volume, were drawn into sterile 20-ml plastic syringes containing 200 IU of heparin. The blood

was rapidly transferred to a disposable 15-ml plastic centrifuge tube standing in ice. Plasma and cells were separated by centrifugation for 15 minutes at 4°C and a 5-ml aliquot of plasma was taken and acidified with 1 ml of N hydrochloric acid. The samples were stored at -15°C . Subsequently the oxytocin was extracted and measured by radioimmunoassay (Chard *et al.*, 1970).

Urine was collected over an eight-hour period, or until

Plasma and urinary oxytocin levels during prostaglandin infusion. Each section represents one patient. A, seven patients in group A. B, 15 patients in group B. C, two adult male volunteers. Areas below 2 pg/ml (limit of sensitivity) indicate blood sample taken but oxytocin not detected.

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delivery occurred or the infusion was stopped. The total urinary volume was measured, 5-ml aliquots were taken and acidified with 1 ml of N HCl, and the sample was stored at -15°C . Oxytocin was assayed as described by Boyd and Chard (1971).

In an initial study carried out on seven women (group A) blood samples were taken immediately before the prostaglandin infusion, half to one hour later, then at four and eight hours after beginning the infusion. A further 15 women had blood samples taken immediately before infusion of the prostaglandin and hourly for eight hours (group B).

Results

The plasma and urinary oxytocin levels found during the infusion of prostaglandins E_1 or $\text{F}_{2\alpha}$ to the two groups of women and the two men are shown in the Chart. The findings may be summarized as follows: (1) oxytocin was detected in the plasma of 19 of the 22 women receiving a prostaglandin infusion and in 11 of the 16 urine samples tested; of the 139 plasma samples collected 60 (43%) showed positive results; (2) oxytocin release into plasma was intermittent; (3) oxytocin was present in the plasma of two of the three women with intrauterine death of the fetus; (4) oxytocin was not detected in the plasma or urine of one woman in whom the prostaglandin infusion failed to promote uterine contractions; and (5) oxytocin was not detected in the plasma of the men before the prostaglandin infusion, but during the infusion both men showed plasma oxytocin levels similar to those found in women in labour.

Discussion

Prostaglandins of the E and F groups can stimulate the human pregnant myometrium in vitro (Bygdeman, 1964; Brummer, 1971), and in vivo. These materials have now been extensively used in the induction of labour (Karim *et al.*, 1969, 1970; Beazley *et al.*, 1970) and abortion (Embrey, 1970; Karim and Filshie, 1970a, 1970b). Although the action in vitro is probably direct, there is no certainty that this is the case in vivo. Other factors might be involved, including alterations in steroid synthesis within the fetoplacental unit, the release of oxytocic factors, including oxytocin itself, by the mother, or an enhancement of the response of the myometrium to oxytocic factors. Such enhancement has been shown both in vivo (Gillespie, 1972) and in vitro (Clegg *et al.*, 1966; Brummer, 1971) and seems to be specific to the ketonic E prostaglandins.

Of the 139 plasma samples collected during prostaglandin infusion 60 (43%) contained detectable oxytocin. The intermittent nature of oxytocin release has been well documented (Knaggs, 1963). The frequency of release found in the present series corresponds closely to that found in spontaneous late first-stage labour (Gibbens *et al.*, 1972). The finding of circulating oxytocin in cases where the fetus was dead excludes the fetal pituitary as the source of the hormone under these circumstances. Furthermore, the rise in circulating oxytocin during prostaglandin infusion in normal men suggests that the stimulus is directed at the pituitary itself, and not mediated indirectly through spinal reflexes arising from distension of the cervix (Ferguson's (1941) reflex).

The results indicate that prostaglandin infusion can directly stimulate oxytocin release from the maternal posterior pituitary

gland, the intermittent nature of this release being very similar to that found in late spontaneous labour. The question of whether or not a fluctuating level of oxytocin can provide a significant drive to the uterus is unanswered, and has been discussed in detail elsewhere (Chard, 1972). Nevertheless, it may be hypothesized that a release of prostaglandin from the decidua, heralding the onset of labour, causes a release of oxytocin from the maternal pituitary, the effect of which is then "enhanced" in the myometrium by the local action of the decidual prostaglandin. A similar mechanism might also act via the pituitary of the fetus, in which there are consistent and relatively high plasma levels of oxytocin during labour, reaching their maximum during the second stage of labour (Chard *et al.*, 1971). The involvement of the posterior pituitary in the action of prostaglandins could explain the inhibiting effect of alcohol on both spontaneous (Fuchs *et al.*, 1968) and prostaglandin-induced uterine contractions (Karim and Sharma, 1971), but not on those induced by exogenous oxytocin. Alcohol is known to inhibit the release of posterior pituitary hormones (Fuchs, 1971) but is not directly inhibitory to myometrial activity (Wilson *et al.*, 1969).

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