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PROSTAGLANDIN–PROPERTIES, ACTIONS AND SIGNIFICANCE

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Abstract—Prostaglandin is the name given to the lipid-soluble smooth muscle stimulating and blood pressure lowering factor with acidic properties in seminal fluid and in extracts of some accessory genital glands of man and sheep. A number of crystalline active compounds have recently been isolated from total prostaglandin extracts. The biological activity of the most potent of these is weight for weight of the same order as that of acetylcholine and oxytocin. The normal response of the isolated non-pregnant human myometrium to prostaglandin is relaxation, and the sensitivity is highest at the time of ovulation. It is propounded that prostaglandin is of importance for human fertility.

THE pharmacodynamic properties of seminal fluid from man and sheep were independently described by Kurzrok and co-workers,[1, 2] by Goldblatt,[3] and by Euler[4, 5] in the early 1930's. The distribution, biological actions, and chemical nature of the active factor were further studied by Euler.[6, 7] The chemical and biological properties of the active principle differentiated it from all other known autopharmacological substances and it was named prostaglandin (PG). Euler defined prostaglandin as "the acid, lipid-soluble, smooth muscle stimulating and blood pressure lowering principle present in seminal fluid and extracts from some of the accessory genital glands of man and sheep."

The activity of PG-preparations may be determined by bio-assay on the isolated rabbit jejunum against a standard preparation and expressed in units. According to Euler's definition one unit corresponds to the activity of 0·1 mg of a special barium salt preparation of PG. Intravenous injection of one unit in the rabbit, pretreated with atropin, usually causes a fall in the blood pressure of about 30 per cent.

From the vesicular glands of sheep Bergström and co-workers[8] have recently isolated a number of active compounds, one of which is called prostaglandin E (PGE). The activity of 10 μg of this compound on the isolated rabbit jejunum is approximately equivalent to one prostaglandin unit.[9]

The amount of prostaglandin that can be extracted with acidified organic solvents from the accessory genital glands of sheep does not exceed 2·5 units per g. On the other hand, sheep seminal fluid contains from 30 to 50 units per ml. The yield from some of the organs can, however, be increased several times by incubating the minced glands in a suitable buffer before extraction of PG.[10] In Fig. 1 the increase in activity after 5 min incubation of the minced vesicular glands is illustrated. Fig. 2 shows that the yield increases with time in such a way that an enzymatic process can be suspected. The results from a number of other experiments further support the hypothesis

that prostaglandin is present in the tissue in a bound inactive state and liberated by an enzymatic process. Incubation of the various accessory genital glands from sheep and subsequent extraction of PG shows (Table 1) that only the vesicular glands and the ampullae ductus deferens are capable of producing prostaglandin.[10]

In man it became necessary to investigate the origin of prostaglandin by an indirect method. It is known that during ejaculation the three main glandular systems contributing to the ejaculate discharge successively. The first portion of the ejaculate comes

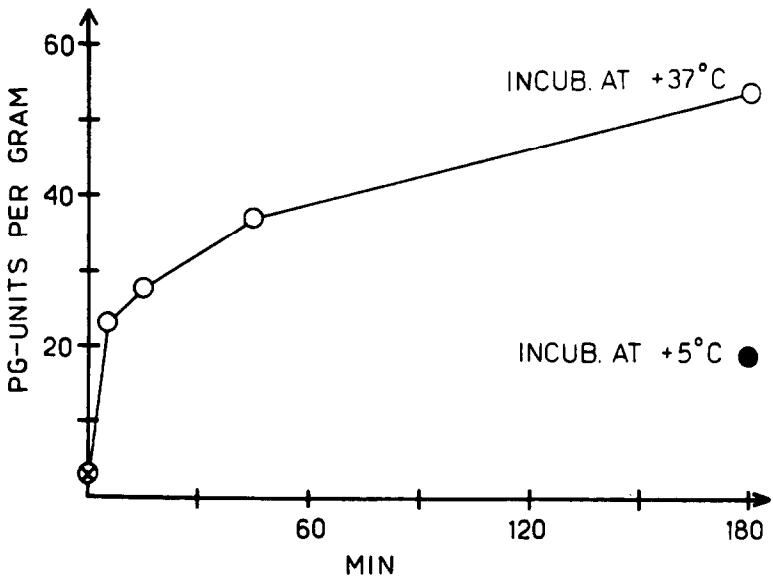

FIG. 2. Increase in yield of prostaglandin (PG) from sheep's ground vesicular glands incubated in 2 vol. of 0·15 M phosphate buffer at pH 7·5. Temperature 37°C. ⊗ = non-incubated control; ● = incubated at 5°C.

TABLE 1. YIELD OF PROSTAGLANDIN (PG) FROM RAM'S ACCESSORY GENITAL GLANDS INCUBATED IN 5 VOLS. OF PHOSPHATE BUFFER AT PH 7·5. TEMPERATURE 37° C

Organ	Incubation (min)	PG-units per g	Organ	Incubation (min)	PG-units per g
Amp. ductus def.	<1	10	Prostate glands	<1	1·5
	15	20–30		20	1·5
	60	30–40	Cowper's glands	<1	0·5
Vesicular glands	<1	10–15		60	0·5–1·0
	15	20–40			
	60	40–80			

from the prostate gland and contains the main bulk of the acid phosphatases, which are secreted solely from this organ. The second portion contains the secretion from the testis, the epididymis and vas deferens and therefore contains the highest concentration of spermatozoa. The third portion contains the highest concentration of fructose, a substance specific for the seminal vesicles.

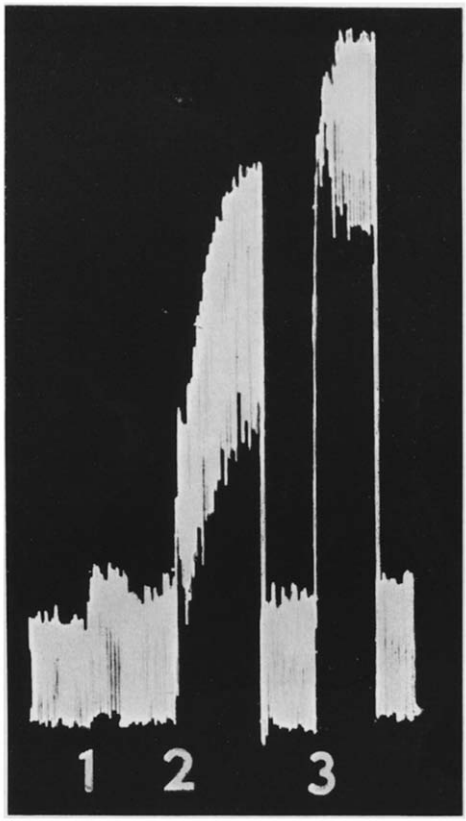

FIG. 1. Effect on the isolated rabbit jejunum of prostaglandin extracted from non-incubated and incubated ground vesicular glands of sheep. Bath volume 15 ml.
Extract from non-incubated organ: 1 = 20 mg tissue, 2 = 100 mg tissue.
Extract from organ incubated for 5 min in 5 vol. of buffer: 3 = 20 mg tissue.

facing page 406

The secretions from these three systems become more or less mixed during the ejaculation. Collection of the ejaculate in four to six separate fractions and subsequent estimation of the concentration of acid phosphatase, spermatozoa and fructose in each fraction makes it possible to calculate the amounts of secretion from each of these glandular systems.

In Fig. 3 the results from such an analysed ejaculate is shown. In addition the amount of prostaglandin in each fraction has been determined and the close correlation between prostaglandin and fructose concentration is obvious.

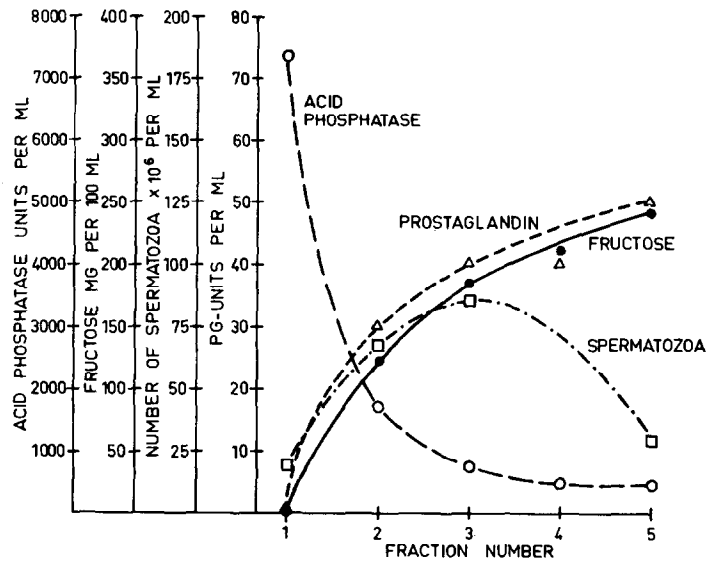

FIG. 3. Concentration of various constituents in different portions of human seminal fluid collected with the split-ejaculation method.

The correlation between prostaglandin and fructose in split-ejaculates from six different subjects is presented in Fig. 4. The conclusion from these experiments is that in man prostaglandin is liberated from the same organ as fructose, i.e. from the seminal vesicles.

The amount of PG in semen from young fertile men usually corresponds to 20–60 units per ml. The mean activity in samples from infertile men is lower, about 10 units per ml. If this difference has any clinical significance is under investigation.

Prostaglandin is the only smooth muscle stimulating factor of any importance in the human seminal fluid. The occurrence of about 2 μg histamine per ml has, however, been advocated by Vandelli.[11] More recently Katsch[12] has stated that human semen contains large amounts of 5-hydroxytryptamine, but this could not be confirmed (Mann *et al.*,[13] Eliasson[14]).

The biological actions of PG can with some generalization be listed as:

(1) Decrease of blood pressure.

(2) Stimulation of most smooth muscle organs like intestine and uterus *in vitro* and *in vivo*.

(3) Inhibition of the motility of the non-pregnant human myometrium.

Both Goldblatt and Euler recognized the prolonged lowering of the blood pressure that follows intravenous injection of prostaglandin containing extracts. Euler[6, 7] could further demonstrate that the fall in blood pressure most likely was due to constriction of the blood vessels in the liver and lungs. Prostaglandin did not affect the heart rate *in vivo* or in heart–lung preparations, nor did it affect the blood vessels in the hind limb of the cat.

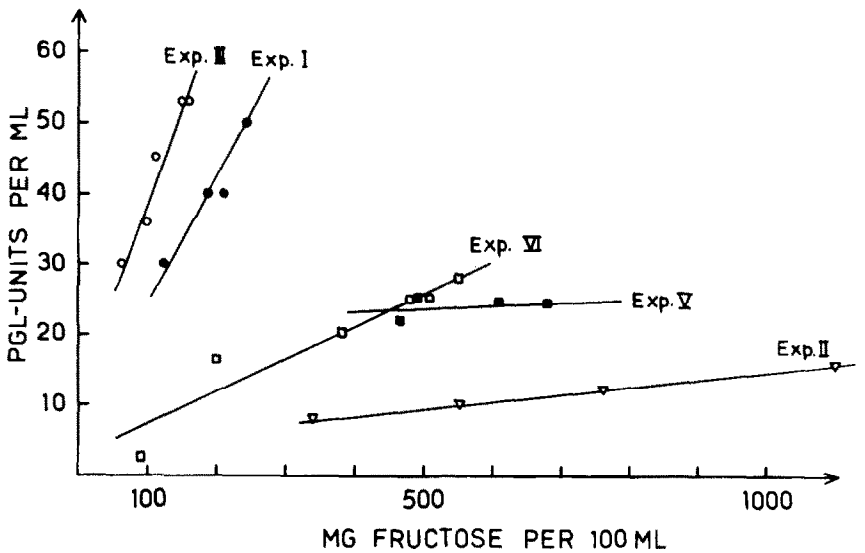

FIG. 4. Correlation between prostaglandin (PG) and fructose in various fractions of human seminal fluid. The close correlation indicates that these substances are secreted from the same organ, i.e. the seminal vesicles.

Bergström, Dunér, Pernow and Euler[15] found that intravenous infusion of the pure compound PGE at a rate of about 0·2 to 0·7 μg/kg per min in man caused an increase in the pulse rate, vasodilatation in the skin and a fall in the systemic arterial blood pressure. There was no marked change of the pressure in the right ventricle, although there was a tendency to a rise in the pulmonary arterial pressure during the infusion. The cardiac output decreased about 20 per cent. The subjective symptoms were quite marked with headache, feeling of constriction in the pharynx and pressure in thorax as most disturbing sensations.

The intestines and uterus of most laboratory animals are stimulated by prostaglandin both *in vivo* and *in vitro*. There are some exceptions. The rat uterus *in situ* is for example highly insensitive to PG and injection of 5 units intramuscularly does not change the motility. The same dose causes, on the other hand, a marked and prolonged decrease in the blood pressure.[10]

Kurzrok and his co-workers[1, 2] observed that the addition of semen to isolated pieces of human non-pregnant myometrium usually caused a marked decrease in tonus and motility of the uterus. Some of the uterine strips did, moreover, respond with increased activity to some specimens of semen but with inhibition to others.

Finally there was a small group of uteri that was stimulated by all semen samples tested. The authors also reported that those uteri that regularly were stimulated by semen had been taken from patients with long-standing infertility, indicating a correlation between reactivity pattern of the uterus and fertility.

The effect of prostaglandin on the motility and reactivity pattern of the human myometrium has been further studied in our laboratory. It has been shown that there is no qualitative or quantitative difference between the effects of semen and/or equivalent amount of purified prostaglandin.

The usual response of the myometrium to prostaglandin is inhibition (Fig. 5). Under some clinical and experimental conditions, however, prostaglandin causes

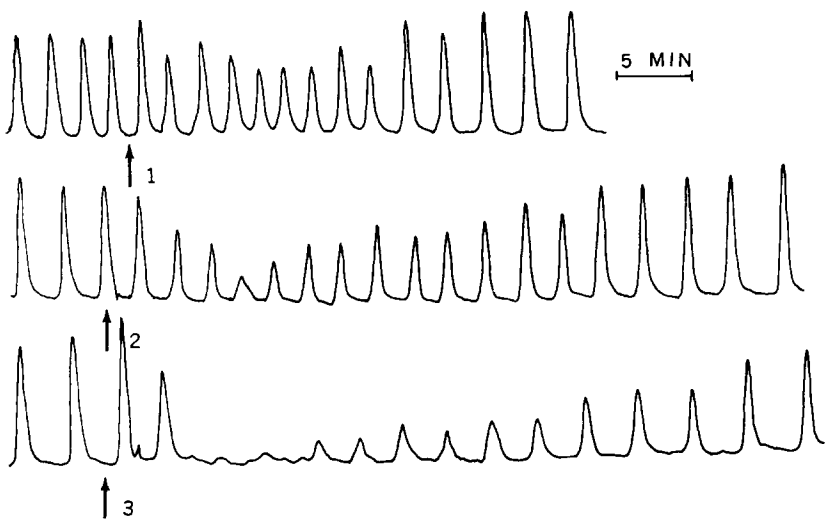

FIG. 5. The dose response of the isolated human myometrium to prostaglandin. The myometrium is in late proliferative phase. (1) = 0·003 U/ml. (2) = 0·01 U/ml. (3) = 0·03 U/ml.

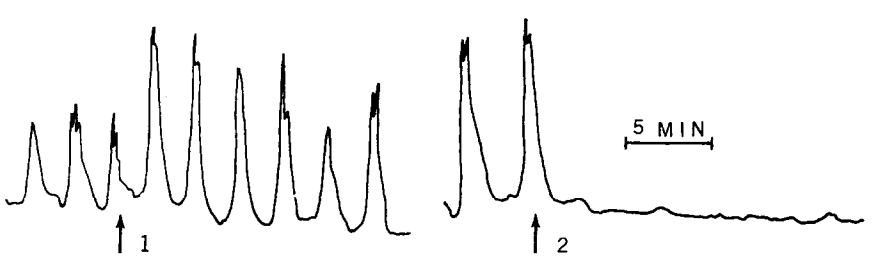

FIG. 6. The effect of prostaglandin on the motility of the isolated human myometrium in late proliferative phase. (1) = 0·0007 U/ml. (2) = 0·003 U/ml. Note the change from stimulation to inhibition.

increased motility and tonus. From our present knowledge it appears that the reactivity pattern of the myometrium to prostaglandin is dependent both on the sensitivity of the uterus and on the amount of prostaglandin. This will be illustrated by two different kinds of experiments. In Fig. 6 is shown that a small dose of prostaglandin increases the motility while a slightly larger dose evokes the usual inhibition in the

same preparation. In Fig. 7 is shown how the reactivity pattern changes when the external potassium concentration is varied in such a way that the sensitivity of the myometrium is decreased. The change in sensitivity was in this case controlled by test doses of acetylcholine. When the potassium concentration is kept low prostaglandin

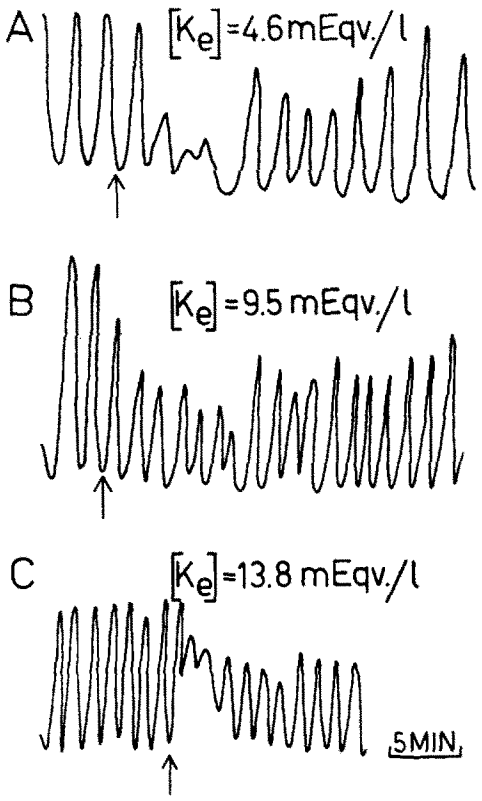

FIG. 7. The effect of extracellular potassium concentration, $[K_e]$, on the response of the isolated human myometrium to prostaglandin. At arrows: 0·01 unit prostaglandin per ml.

causes inhibition while acetylcholine (not shown in the picture) stimulates the myometrium. With high external concentration of potassium the myometrium is insensitive to acetylcholine but is now stimulated by prostaglandin.[16] This reactivity pattern is also of interest with regard to the mode of action of prostaglandin and from our results it is apparent that the mode of action of prostaglandin on the human myometrium is different from that of for example acetylcholine and oxytocin.

The sensitivity of the myometrium to prostaglandin changes during the menstrual cycle and it is most sensitive during the mid-cycle as is illustrated in Table 2. The addition of 0·005 units prostaglandin per ml (equivalent to 0·05 μg PGE/ml) bath fluid is usually sufficient to produce a definite effect at the time of ovulation, but larger doses are necessary early or late in the period. The difference in sensitivity between strips from mid-cycle and those from the early and late phases of the menstrual cycle is statistically highly significant.[17]

The effect of prostaglandin on the non-pregnant human uterus *in vivo* is, of course, of particular interest. In the experiments that have been performed by Karlson[18] and

by Eliasson and Posse[19] the uterine motility has been registered with Karlson's method.[20] Three separate pressure transducers are introduced into the uterine cavity and the pressure changes in the corpus, isthmus and cervix simultaneously recorded.

Prostaglandin or seminal fluid introduced into the vagina exerts an effect on the uterine motility at the time of ovulation but usually not at other times in the period. The usual response is that of stimulation, in some cases followed 20–25 min later by a marked decrease in motility, as illustrated in Fig. 8. As a possible explanation to this

TABLE 2. VARIATION IN SENSITIVITY OF THE NON-PREGNANT HUMAN MYOMETRIUM *in vitro* TO PROSTAGLANDIN IN RELATION TO THE MENSTRUAL CYCLE

Group	Number of uteri	Phase in menstrual cycle	Prostagl. ID_{50} Units/ml Med. val.	Range
1	17	Early–middle proliferatory	0·015	0·0025–0·05
2	14	Late proliferatory	0·0045	0·001 –0·01
3	12	Early secretory	0·007	0·0025–0·03
4	8	Middle–late secretory	0·022	0·01 –0·15

ID_{50} = the lowest dose tested that gave 50 per cent decrease or more of the amplitude of the contractions during 10 min.

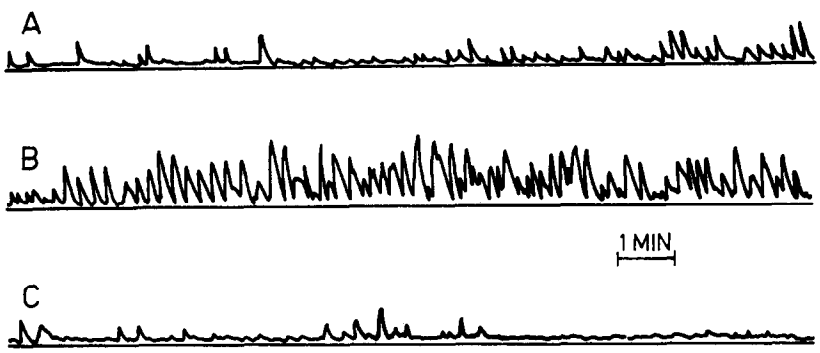

FIG. 8. Effect of prostaglandin on the motility of the human uterus *in vivo*. Registration from corpus at the time of ovulation.

A. Control period.
B. From 5 to 20 min after intravaginal application of 150 units prostaglandin.
C. From 25 to 40 min after the application of prostaglandin.

reactivity pattern it was supposed that prostaglandin was continuously absorbed from the vagina thereby increasing the blood concentration. The reactivity pattern would then be comparable with that observed *in vitro*, i.e. a small dose of prostaglandin causes stimulation and a slightly larger dose inhibition of the motility of the same preparation. On this basis it was assumed that if the sensitivity of the myometrium could be increased then intravaginal application of the same amount of prostaglandin might evoke the inhibitory response more rapidly. At the estimated time of ovulation in a subsequent period the same woman was subjected to a similar experiment but at this time an intravenous infusion of an oxytocic preparation was started some 10 min before prostaglandin was introduced into the vagina. At this occasion the response to prostaglandin was a marked decrease in motility as is illustrated in Fig. 9.

It is likely that during coitus and especially in connexion with orgasm the uterine motility and sensitivity is increased. If then prostaglandin some minutes after the ejaculation causes a marked decrease in the tonus of the uterus this might facilitate the migration of the spermatozoa from the seminal pool around the portio into the uterine cavity.[10]

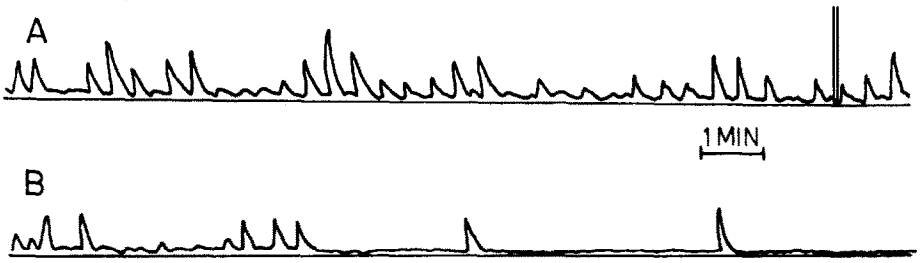

FIG. 9. Effect of prostaglandin on the motility of the human uterus *in vivo*. Registration from the corpus at the time of ovulation. During the experiment an i.v. infusion of 0·1 I.U. oxytocin + 0·1 I.U. vasopressin per min is given.
A. Control period. At signal intravaginal application of 150 units prostaglandin.
B. Records from 6 to 21 min after the application of prostaglandin.

The following experimental data seem to be of importance for the possible physiological function of prostaglandin.

(1) Crystalline prostaglandin exerts a biological activity which is of the same order weight for weight as that of acetylcholine, histamine and oxytocin.
(2) Prostaglandin is present in the ejaculate in amounts corresponding to 1–2 mg of the crystalline compound PGE which are large enough to cause a biological action in the recipient.
(3) The human myometrium is highly sensitive to prostaglandin at the time of ovulation (inhibition), less so at other periods of the menstrual cycle.
(4) Prostaglandin inhibits the motility of the non-pregnant human uterus while the effect of oxytocin, acetylcholine and histamine is one of stimulation.

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