Prostaglandins in reproductive physiology*

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Summary

The role of prostaglandins in reproductive physiology is reviewed with particular emphasis on their possible importance in ovulation in humans. A possible interaction between gonadal steroids, biogenic amines and prostaglandins at hypothalamic-pituitary level, in relation to the release of luteinizing hormone releasing factor, and LH, is discussed. Anomalies regarding the role of oestrogens in LH release are noted, and it is suggested that high oestrogen levels may release prostaglandins from the uterus and/or centrally in humans, in connection with the mid-cycle LH surge and ovulation. A hypothetical role for prostaglandins in sexual behaviour and premenstrual changes is discussed.

The hypotheses open up new areas for clinical research to establish the role of prostaglandins in human endocrinology. The need for measurement of prostaglandin metabolites in blood and urine is emphasized.

Introduction

The purpose of this article is to review the role of prostaglandins in reproductive physiology. Established knowledge is outlined briefly and used as a basis for speculative thought on certain aspects. No attempt is made to cover the field in exhaustive detail and pertinent observations may well have been inadvertently overlooked, as the background literature is vast. However, it is hoped that the overall picture given will help to clarify ideas on the subject and lead to further constructive discussion and research.

The role of prostaglandins in fertilization and their effect on the uterus are mentioned briefly. Their effect on the ovary in relation to progesterone synthesis, luteolysis and ovulation are discussed in more detail. Interactions between gonadal steroids, catecholamines and prostaglandins on the hypothalamus are discussed in relation to the release of luteinizing hormone releasing factor (LRF). LRF, a polypeptide, is the hypothalamic hormone that controls the secretion of luteinizing hormone (LH) and of follicle stimulating hormone (FSH) from the pituitary (Schally *et al.*, 1971). It is suggested that prostaglandins may be of importance in human ovulation and spermatogenesis. The hypothetical role of prostaglandins in sexual behaviour and premenstrual psychological changes is discussed.

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Historical outline

In 1930, Kurzrok and Lieb reported that human seminal fluid altered the contractile state of isolated strips of human uterus; the active principle was originally thought to be acetyl choline (Kurzrok and Lieb, 1930; Cockrill, Miller and Kurzrok, 1935). Euler and also Goldblatt described the vaso-depressor and smooth muscle stimulating properties of human semen (Euler, 1934; Goldblatt, 1933). Euler found that the active principle was a lipid soluble fatty acid, and named it prostaglandin (Euler, 1936). Prostaglandin F (PGF) was obtained in pure crystalline form in 1957 (Bergström and Sjövall, 1957), and prostaglandin E (PGE) was isolated in 1960 (Bergström and Sjövall, 1960).

Chemistry

Prostaglandins are carboxylic acids derived from arachidonic or closely related fatty acids. They are 20-carbon-atom molecules containing a cyclopentane ring with two adjacent carbon side chains. Natural prostaglandins are divided into five groups, designated by letters E, F, A, B and C, depending on the arrangement of hydroxyl and/or ketone groups and double bonds on the cyclopentane ring. The principal groups are subdivided according to the number of additional side chain double bonds present, and this is indicated by a numerical suffix; thus, the suffix '2' in prostaglandin E₂ (PGE₂) indicates the presence of two double bonds. The stereochemistry of prostaglandins is understood, and with the F series the term α or β is always added (e.g. PGF_{2 α}) to denote the configuration of the C₉ hydroxyl group (Caton, 1973).

Prostaglandins of the E and F groups are formed from a common intermediate (Samuelsson *et al.*, 1971) and the A and B prostaglandins are derived from the E prostaglandins. Prostaglandins are now known to have a wide distribution in mammalian

tissues and there are many hypotheses about their physiological role (see Horton, 1969; Hinman, 1970).

Prostaglandins and fertilization

Since prostaglandins were first discovered in seminal fluid and were found to influence smooth muscle contractility, it is natural that attention was first directed towards their action on the smooth muscle of the reproductive tract. In 1936, Euler suggested that prostaglandins might be important in ejaculation, but it is still uncertain whether this is so (Horton, 1969). Seminal fluid prostaglandins may facilitate sperm transport within the female reproductive tract by a local effect on uterine muscle (Eliasson, 1959). Prostaglandins can be absorbed from the vagina and enter the circulation in amounts sufficient to alter muscle tone in the uterus and fallopian tube (Horton, 1969).

Prostaglandins and the uterus

PGE₁, PGE₂ and PGF_{2α} cause uterine contraction in man, and the F prostaglandins contribute to uterine contraction at parturition. Intravenous infusions of PGF_{2α} have been used to induce uterine contractions in women at term (Karim *et al.*, 1970) and there is a wide literature on their use in therapeutic termination of early pregnancy. Indeed, consideration of the value of prostaglandins in the contraceptive field has been virtually confined to their role as abortifacients. Prostaglandins are thought to play a part in menstruation (Eglinton *et al.*, 1963).

PGE₂ causes relaxation of the human isolated non-pregnant cervix, whereas PGF_{2α} produces a variable effect (Najak, Hillier and Karim, 1970).

Prostaglandins and the ovary

1. Role in progesterone production.
2. Role in luteolysis.
3. Role in ovulation.

Prostaglandins are involved in LH-induced progesterone synthesis (Kuehl *et al.*, 1970) and have a role in luteolysis (Pharriss and Wyngarden, 1969; Kirton, Pharriss and Forbes, 1970). Recent work in animals suggests that they may be closely linked with ovulation itself (Orczyk and Behrman, 1972; Armstrong and Greenwich, 1972). This may be a local effect on the ovary, but there is some evidence that prostaglandins function as central neurotransmitters (Horton, 1969, 1973) and influence the hypothalamic pituitary axis (Prostaglandins, 1972).

Prostaglandins and progesterone production

Prostaglandins are closely linked with LH-induced progesterone formation in the ovary. Kuehl and his co-workers (1970) have demonstrated a dose-response relationship between prostaglandins and cyclic AMP formation in excised mouse ovaries. A

specific inhibitor of the prostaglandin contractile response, 7-oxa-13 prostynoic acid, blocked not only the effect of PGE₁ and PGE₂, but also that of LH on cyclic AMP and progesterone formation. The inhibition was competitive, and the data were compatible with the concept that activation of a prostaglandin receptor is an essential step in the action of LH to stimulate cyclic AMP formation and steroidogenesis (Kuehl *et al.*, 1970).

Although prostaglandins stimulate progesterone production *in vitro*, they may inhibit progesterone synthesis *in vivo*. This apparent conflict can, according to Caldwell *et al.* (1972), be resolved by the observation that in monkeys, *in vivo*, a low dose of PGF_{2α} stimulates, whereas a high dose inhibits, progesterone synthesis—the inhibition being overcome by HCG. According to Behrman *et al.* (1971), the fall in progesterone synthesis caused by a high dose of PGF_{2α} may be due to loss of stored cholesterol ester, with eventual depletion of free cholesterol available for progesterone synthesis.

Role in luteolysis. Factors determining the life span of the corpus luteum

Initially, a pituitary luteotrophin was considered to be important, but later it was realized that stimuli applied to the uterus caused luteolysis (Hawk, 1968; Anderson, Bland and Melampy, 1969). Bland and Donovan in 1968 established that a local factor involving a uterine horn and the neighbouring ovary was important (Donovan, 1971). Pharriss postulated that the luteolytic factor might be a vasoconstrictor; he subsequently tested prostaglandin F_{2α} and found that it had a luteolytic effect in rats (Pharriss and Wyngarden, 1969).

Pharriss (1970) reviewed evidence suggesting that, in rats, PGF_{2α} enters a common utero ovarian vein, causes venoconstriction of the ovarian vein and reduces ovarian blood flow. This, occurring at a time of peak progesterone production (influenced by PGF_{2α}), may lead to a build-up in intracellular steroid concentration with consequent increase in lysosomal fragility and autolysis of luteal cells (Dingle, Hay and Moor, 1968).

In sheep, the addition of PGF_{2α} to the blood perfusing a transplanted ovary causes a fall in progesterone synthesis to less than 50% of the control level within 1 hr (McCracken, Glew and Scaramuzzi, 1970).

In monkeys, the plasma progesterone concentration falls within 24 hr and menstruation begins within 48 hr of twice daily prostaglandin injections (Kirton *et al.*, 1970). There is some evidence that pharmacological doses of oestrogen are luteolytic in the monkey and that the F prostaglandins are released in response to oestrogen in monkeys and in sheep. Oral diethylstilboestrol 10–25 mg for 1–6 days in the

luteal phase in six monkeys caused a rapid fall in blood progesterone levels and a rapid rise in PGF levels (Caldwell *et al.*, 1972).

In humans, PGF_{2α} given intravenously during the early luteal phase can cause a slight transient fall in peripheral progesterone levels and bleeding from the uterus (Kirton, 1972). However, if prostaglandins are involved in luteolysis in humans, it is unlikely that the uterus is the source of the prostaglandins, since hysterectomy does not prolong the life of the corpus luteum (Beling, Marcus and Markham, 1970). It is possible that in women luteolysis is induced by prostaglandins produced by the ovary under the influence of gonadotrophins, since in monkeys HCG increases the PGF concentration in ovarian vein to a level 5–10 times higher than the plasma level (Caldwell *et al.*, 1972).

Although the vascular hypothesis for prostaglandin-induced luteolysis is attractive, Pharriss (1970) does not regard it as proven. Changes in progesterone secretion do not always parallel changes in ovarian blood flow (McCracken *et al.*, 1970; Caldwell *et al.*, 1972), and prostaglandins may inhibit progesterone synthesis in other ways.

Prostaglandins and ovulation. Interactions at hypothalamic pituitary level

The factors controlling the release of LRF from the hypothalamus and of LH from the pituitary are complex and many facets remain uncertain. The processes are influenced by changes in circulating levels of gonadal steroids, by changes in intracerebral catecholamines, and by prostaglandins and prostaglandin inhibitors.

Central effects of gonadal steroids

Donovan in 1971 discussed the importance of gonadal steroids in determining the reaction of the brain to neural stimuli. From studies of the effect of electrical stimulation of the amygdala and hippocampus on ovulation in the guinea-pig, he postulated that the brain of a guinea-pig is rendered refractory to stimulation by the feedback action of ovarian progesterone. Moreover, he stated that 'whatever the precise trigger for ovulation may be it is certain that the mechanism is cocked by the decline in plasma progesterone that accompanies regression of the corpora lutea'.

In sheep, a rise in oestrogen causes PGF release from the uterus and the PGF causes luteolysis and a fall in progesterone levels (Caldwell *et al.*, 1972). Caldwell suggested that the oestrogen stimulated the release of LRF. Donovan's work raises the possibility that the fall in progesterone levels may have reduced central inhibition of LRF. It is most unlikely that prostaglandins released from the uterus could directly influence central release of LRF in

sheep or other animals, in view of the extremely rapid inactivation of circulating prostaglandins. Evidence that prostaglandins are involved at hypothalamic pituitary level will be discussed later.

Frith and Hooper (1971a) have demonstrated an inverse relationship between enzyme activity in the hypothalamus and LRF release in rabbits. Moreover, the ovulation inhibitors chlormadinone acetate, norethindrone, ethinyl oestradiol and oestrone all increase enzyme activity in the rabbit hypothalamus and so inhibit LRF release (Frith and Hooper, 1971b).

Adrenergic mechanisms in ovulation

Catecholamines have long been thought to have a role in the neural control of pituitary secretion. Studies lending support to this concept were cited by Donoso *et al.* (1967). Adrenergic-blocking drugs delay ovulation in rats, and block ovulation in rabbits. Reserpine, a catecholamine-depleting drug, interrupts the normal oestrus cycle in rats and reduces LH concentration in the hypophysis. Injection of adrenaline or nor-adrenaline into the cerebral ventricles in rabbits produces ovulation and previous treatment with sympatholytic drugs prevents this effect.

Interactions between monoamine neurotransmitters and neuropharmacological agents, in relation to hypothalamic-releasing factors, have been reviewed by Frohman (1972). The phenothiazine, chlorpromazine, blocks the hypothalamic receptor site to nor-adrenaline, dopamine and serotonin (Frohman, 1972). Women treated with relatively high doses of chlorpromazine develop amenorrhoea and galactorrhoea (Deshaies, Richardeau and Dechosal, 1957); doses of 200–500 mg daily decrease FSH secretion (Hauser *et al.*, 1958). Sawyer and associates (1963) believe that one region of the hypothalamus exerts a reciprocal control over ovulation and lactation. Arguing on the basis that FSH-LH and prolactin are reciprocally released, De Wied (1967) postulated that chlorpromazine, by its anti-adrenergic action, blocks hypothalamic structures that normally inhibit the release of prolactin, or stimulate the release of FSH-LH. Recent evidence suggests that prolactin-inhibition is related to dopamine (see Frohman, 1972).

Interrelationships between gonadal steroids and hypothalamic catecholamines

There is a rise in noradrenaline in the anterior hypothalamus and a fall in the concentration of the noradrenaline precursor dopamine in rats 10–20 days after castration (Donoso *et al.*, 1967). These changes correlate well with changes in MAO levels reported by Kobayashi *et al.* in 1964. They observed that the MAO content of the anterior hypothalamus of rats falls initially after castration, but rises above

normal after 30–40 days, returning to control levels after 60 days; there were reciprocal changes in choline acetylase (Kobayashi *et al.*, 1964). Studies of noradrenaline turnover in rat brain following oophorectomy have demonstrated a decreased rate of retention of ^3H -labelled noradrenaline in the absence of any decline in endogenous brain noradrenaline, indicating an increased rate of synthesis as well as release and metabolism of noradrenaline (Anton-Tay and Wurtman, 1968).

Donoso *et al.* (1967) pointed out that the rise in noradrenaline concentration in the rat hypothalamus correlates in time with an increase in gonadotrophin secretion and suggested that noradrenaline may act within the hypothalamus as a neurotransmitter in the mechanisms controlling gonadal function.

Dopamine, rather than a metabolite such as noradrenaline, may be the synaptic transmitter involved in the release of LRF from hypothalamic secretory neurones (McCann, 1970). The effect of dopamine is maximal near the pre-ovulatory surge of LH, and the response is inhibited by the α -blocker phenoxybenzamine (Schneider and McCann, 1970a) and by oestradiol *in vitro* (Schneider and McCann, 1970b) and *in vivo* (McCann, 1970).

In man, L-dopa administration causes a consistent rise in plasma FSH and a more variable rise in plasma LH (Dickey, Marks and Stevens, 1971, quoted by Frohman, 1972).

Effects of prostaglandins on hypothalamus and pituitary

Evidence suggesting that prostaglandins may act as central nervous transmitters has been reviewed (Horton, 1969, 1973). In brief, they have potent central actions, are widely distributed throughout the central nervous system, and are released from the brain and spinal cord on nerve stimulation.

There are two main hypotheses regarding the mode of action of hypothalamic releasing factors. They may modify the permeability of pituitary membranes, causing depolarization and a rise in calcium activity, which activates hormone release, or they may activate cell membrane adenyl cyclase, causing a rise in cyclic AMP and consequent hormone release (McCann, 1970). It is noteworthy that prostaglandin E_2 increases vascular permeability and prostaglandins may regulate the action of many hormones by modifying intracellular cyclic AMP concentrations (Ramwell and Shaw, 1967). There is a possibility that a prostaglandin receptor system may exist in the pituitary, perhaps as part of the cyclic AM mechanism, and that the synthesis and release of trophic hormones by the pituitary in response to releasing factor stimulation is mediated via the prostaglandins (Prostaglandins, 1972). Prostaglandins *in vitro* stimulate release of pituitary GH

(Schofield, 1970), ACTH and TSH (Vale, Rivier and Guillemin, 1971).

Prostaglandins and LH release

In vitro, the prostaglandin antagonist 7-oxa-13 prostynoic acid blocks LRF stimulation of LH secretion (Amoss *et al.*, 1971). PGE_1 increases the pituitary content of cyclic AMP (Zor *et al.*, 1970) and $\text{PGF}_{2\alpha}$ increases the pituitary content of LH (Labhsetwar, 1970). Indomethacin, an inhibitor of prostaglandin synthesis, blocks ovulation *in vivo* in rats (Orczyk and Behrman, 1972; Armstrong and Grinwich, 1972).

Labhsetwar made his important observations during the course of research undertaken to study the effect of $\text{PGF}_{2\alpha}$ on pituitary LH content of pregnant rats, with a view to explaining the luteolytic effect of $\text{PGF}_{2\alpha}$. He noted that the pituitary LH content of rats treated with $\text{PGF}_{2\alpha}$ was more than 200 times greater than that of pregnant controls. From various observations he concluded that $\text{PGF}_{2\alpha}$ increased pituitary LH content by acting centrally, either directly on the pituitary gland or indirectly through the hypothalamus. He found no evidence for a decreased output of LH and suggested that the high LH content resulted from increased synthesis and was perhaps associated with increased secretion. He suggested that the rise in LH was responsible for luteolysis and did not discuss the importance of his observations with regard to ovulation (Labhsetwar, 1970).

Inhibitors of prostaglandin synthesis, aspirin and indomethacin inhibit ovulation *in vivo* in immature rats pre-treated with pregnant mare serum (Orczyk and Behrman, 1972). Both drugs reduced plasma PGF content and indomethacin reduced pituitary and hypothalamic concentrations of PGF. Chronic and acute administration of either indomethacin or aspirin blocked ovulation. Injection of either LH or a mixture of PGE_2 and $\text{PGF}_{2\alpha}$ at the time of the expected ovulatory surge of LH reversed the blockade produced by a single injection of indomethacin given 3 hr earlier, but LH did not reverse the blockade produced when indomethacin was given for 30 hr before the anticipated LH surge. The authors suggested that chronic administration of indomethacin may have prevented maturation of follicles through suppression of FSH and/or LH.

Armstrong and Grinwich (1972) reported similar results in PMS-primed rats, but thought that failure of ovulation was due to an action of indomethacin at ovarian level, rather than to blockade of endogenous LH secretion.

Interaction between prostaglandins and the sympathetic nervous system

Hedqvist (1970) has put forward a strong case for

the hypothesis that endogenous PGE_1 and PGE_2 may play a physiologically significant regulatory role in sympathetically innervated tissues. This homeostatic action of PGE_1 and PGE_2 possibly, but not necessarily, triggered by the mechanical response to nerve stimulation, appears to be exerted by inhibition of the noradrenaline release from the sympathetic neurones, and to some extent by inhibition of the effector response to the noradrenaline released.

Hedqvist (1970) based his hypothesis on observations from his own and other experimental work. PGE_2 at all doses reduced noradrenaline outflow in response to sympathetic nerve stimulation in the isolated perfused cat spleen (Hedqvist, 1970; Blakeley *et al.*, 1968). Phenoxybenzamine abolishes the outflow of endogenous PGE_2 in response to nerve stimulation in dog spleen (Davies, Horton and Withrington, 1967) and causes a huge increase in the output of noradrenaline from cat spleen in response to nerve stimulation (Brown and Gillespie, 1957). Hedqvist suggests that the latter observation may be due to removal of endogenous PGE_2 acting as a feedback inhibitor of noradrenaline release from sympathetic neurones in cat spleen.

Hedqvist (1970) discusses available evidence and concludes that PGE_1 probably does not alter the release of noradrenaline from storage granules, nor inhibit noradrenaline synthesis. It does not depress the outflow of noradrenaline by increasing its enzymatic degradation, or inactivate noradrenaline by facilitating re-uptake and protein binding by sympathetic nerves. A rise in calcium ions reduces PGE inhibition of noradrenaline release on nerve stimulation in cat spleen, which may indicate that PGE_2

interferes with the transmitter release by inhibition of calcium influx induced by depolarization, or by preventing calcium from reaching specific reactive sites in the interior of the neurone (Hedqvist, 1970).

Possible sequence of neuro-hormonal interactions

On the basis of the experimental evidence discussed, it seems reasonable to suggest that the neuro-hormonal interactions within the hypothalamus resulting in ovulation may occur in the sequence indicated in Fig. 1.

Prostaglandin produced within the hypothalamus as a result of adrenergic stimulation may not only act as a feedback inhibitor of noradrenaline release, but also stimulate the release of LRF or enhance its effect. Inhibitors of prostaglandin synthesis may interfere with the release of LRF and/or block the action of LRF on the pituitary, where prostaglandin-induced cyclic AMP formation may be essential for LH synthesis.

The α -blocker phenoxybenzamine blocks the dopamine induced LRF release in rats (Schneider and McCann, 1970a) and also abolishes the outflow of endogenous PGE_2 in response to nerve stimulation in dog spleen (Davies *et al.*, 1967). Thus, phenoxybenzamine blockade of dopamine induced LRF release could be due to α -receptor block, or to prevention of prostaglandin release.

Consideration of events in humans

Caution must be exercised in applying animal results to humans, and differing time relationships between luteolysis and ovulation must be taken into account. In sheep, for example, a rise in oestrogen

FIG. 1. Possible sequence of events leading to ovulation.

and PGF levels, luteolysis, the LH surge and ovulation occur within the space of 48 hr (Caldwell *et al.*, 1972).

The hormone changes in peripheral blood in the normal human menstrual cycle are well known (Fig. 2) (Bonnar, 1973), but events at hypothalamic and pituitary level are poorly understood.

The fall in serum progesterone level following luteolysis may render the brain more susceptible to neural stimuli (Donovan, 1971) and permit sufficient release of FSH and LH to cause follicular ripening. Conversely, serum LH and FSH levels are relatively low in the post-ovulatory phase when progesterone production is maximal. However, there are no dramatic changes in serum progesterone levels to account for the pre-ovulatory LH surge.

Changes in serum oestrogen levels are more difficult to equate with experimental work. What causes the dramatic mid-cycle peak in oestrogen levels? Is it really simply due to an exponential rise in oestrogen production from ripening follicles? It is generally assumed that the oestrogen peak reaches a critical level and triggers off the ovulatory surge of LH and FSH (Bonnar, 1973; Caldwell *et al.*, 1972), yet some evidence suggests that oestrogens inhibit LH release. Oestrogens inhibit dopamine-induced LRF release from rat hypothalamus *in vitro* (Schneider and McCann, 1970b) and *in vivo* (McCann, 1970), and ethinyl oestradiol and oestrone inhibit LRF release in rabbits (Frith and Hooper, 1971b).

Oestrogen suppresses the LH response to exogenous LRF in women with secondary amenorrhoea (Thompson, Arfania and Taymor, 1973). Oestrogen-progesterone contraceptive pills depress both the secretion and mid-cycle peak of pituitary gonadotrophins in women, and in one patient with galactorrhoea there was a rapid return of LH following withdrawal of the oestrogen component (Bonnar, 1973). It is tempting to suggest that both the LH suppression and the stimulation of lactation in this case was due to oestrogenic antagonism of dopamine-induced phenomena, namely dopamine-induced LRF release (Schneider and McCann, 1970b) and prolactin inhibition (see Frohman, 1972).

The differing effects of high and low levels of oestrogen on gonadotrophin release have been explained by a positive and negative feedback hypothesis (see Bogdanove, 1964). Perhaps, when the oestrogen peak reaches a critical level, it triggers off the release of prostaglandins, which stimulate the ovulatory surge of LH and FSH (Fig. 3). Oestrogens release prostaglandins from the uterus of sheep, just before the LH surge (Caldwell *et al.*, 1972). It may be necessary to postulate an oestrogen-induced release of prostaglandins within the hypothalamus, since it is unlikely, but not impossible (see Horton, 1969), that prostaglandins released proximal to the pul-

FIG. 2. Hormone changes in the normal menstrual cycle. (Reprinted from Bonnar, 1973, by courtesy of the author and editors of *Proceedings of the Royal Society of Medicine*.)

monary circulation reach the hypothalamus in a metabolically active form.*

* Addendum. Recent work supports this hypothesis. Carlson and co-workers have shown that Indomethacin, an inhibitor of prostaglandin synthesis, blocks the LH peak produced by oestrogen in anovulatory ewes (Carlson *et al.*, 1974).

FIG. 3. Possible interaction between high oestrogens and prostaglandins at ovulation.

Prostaglandins and ovulation in humans

There is, as yet, no experimental evidence to support the suggestion that prostaglandins are responsible for ovulation in humans. However, some clinical observations would appear to favour this contention. Prostaglandin release within the hypothalamus could perhaps account for the rise in temperature that accompanies ovulation, since the rise in temperature in a fever is thought to be due to synthesis or release of PGE_1 either in the temperature regulating area of the hypothalamus or at a place from which it can reach this area (Vane, 1971; Stitt, 1973). Some women experience headache and nausea at the time of ovulation (Dalton, 1973). These symptoms could be attributable to prostaglandins, since prostaglandin infusions induce headache (Bergström, Carlson and Weeks, 1968) and nausea. It is possible that the phenomenon of 'ovulation bleeding' could be a prostaglandin-induced effect, since in humans $\text{PGF}_{2\alpha}$ given intravenously during the early luteal phase can cause uterine bleeding (Kirtton, 1972).

Changes in serum levels of $\text{PGF}_{2\alpha}$ have not been shown to correlate with the menstrual cycle in female subjects (Wilks, Wentz and Jones, 1973). However, it is known that prostaglandins are rapidly metabolized and inactivated by 15-hydroxy prostaglandin dehydrogenase. They may even be formed and inactivated within the cell, leaving as 15-dehydro metabolites (Ånggård, 1971). Circulating prostaglandins, with the exception of PGA_1 and PGA_2 (McGiff *et al.*, 1969) are inactivated during passage through the pulmonary circulation (Ferreira and Vane, 1967). Granström (1972), studying the met-

abolism of $\text{PGF}_{2\alpha}$ in female subjects, found that only 3% of labelled $\text{PGF}_{2\alpha}$ was detectable in the blood, 1.5 min after intravenous injection. The $\text{PGF}_{2\alpha}$ was converted into the metabolites 9 α ,11 α -dihydroxy-15-ketoprost-5-enoic acid and 9 α ,11 α ,15-trihydroxyprost-5-enoic acid. Essentially, all the radioactivity was excreted in the urine in 5–6 hr. It seems likely that measurement of prostaglandin metabolites in blood or urine will reflect physiological changes in prostaglandin metabolism more accurately than measurement of prostaglandins themselves.

Studies in two pregnant women indicated that the blood level of the prostaglandin metabolite 9 α ,11 α -dihydroxy-15-keto-prost-5-enoic acid is about twenty-five times that of $\text{PGF}_{2\alpha}$ during intravenous infusion of $\text{PGF}_{2\alpha}$ (Green *et al.*, 1972). Hence, measurement of this metabolite in peripheral blood may be suitable for monitoring the endogenous synthesis of $\text{PGF}_{2\alpha}$ in humans in relation to physiological and pathological states. This metabolite can be measured by quantitative gas chromatography mass spectrometry using a deuterium carrier technique; however, the method is at present confined to a few research centres (Green, Granström and Samuelsson, 1972).

It is obviously essential to ascertain whether changes in prostaglandin metabolites correlate with changes in the menstrual cycle of normal women. It would be of particular interest to observe a rise at the time of ovulation, and during the premenstrual phase coinciding with luteolysis. We need to know whether ovulation in normal women or spermatogenesis in normal men, can be suppressed by a prostaglandin antagonist such as indomethacin.

There is a correlation between abnormally low seminal prostaglandins and infertility in normal men (Bygdeman, 1969) and those with oligospermia (Hawkins, 1967). The prostaglandin E and F content of human semen is reduced by therapeutic doses of soluble aspirin, a less potent inhibitor of prostaglandin synthesis than indomethacin (Collier and Flower, 1971).

If prostaglandins are shown to have a crucial part to play in the release of LRF and of LH in humans, it should be possible to find a prostaglandin antagonist that will specifically antagonize this action and act as an effective contraceptive.

Hypothetical role of prostaglandins in sexual behaviour and premenstrual psychological changes

Factors influencing sexual behaviour

Sexual behaviour is influenced by changes in circulating gonadal hormones, and by changes in brain biogenic amines. Androgen probably influences libido in women as well as men (Mills, 1972).

It is recognized that sexual desire in women undergoes cyclical changes. Early work by Benedek and Rubenstein (1939) indicated that oestrogen production was accompanied by active sexual energy and progesterone production correlated with calmness and more passive sexual behaviour. A more recent review indicated that sexual desire was maximal during the oestrogen phase of the menstrual cycle and immediately before the menses when progesterone levels are falling (Hampson and Hampson, 1961, cit. Kane *et al.*, 1967). It would be biologically advantageous in a species that ovulates infrequently to have a positive correlation between ovulation and libido, indeed the reverse would be disastrous for the survival of the species. Since sexual desire correlates with oestrogen production, one might expect a mid-cycle peak in libido, coinciding with the pre-ovulation surge in oestrogen production. Conversely, a reduction in libido has been reported in women on oral contraceptives, in whom the normal cyclical changes in oestrogen production are absent (Kane *et al.*, 1967; Herzberg *et al.*, 1971).

Biogenic amines are important in determining sexual behaviour. In animals, there is an inverse relationship between brain serotonin levels and sexual activity and the effect of low serotonin is reinforced by a concomitant rise in catecholamines. Treatment of rats or rabbits with a serotonin antagonist (*p*-chloro-phenylalanine) and a monoamine oxidase-inhibitor (pargyline) causes compulsive sexual behaviour (see Mills, 1972). Mills draws parallels between these animal experiments and the sexual behaviour of modern man under stress.

It is interesting that McCann, Dhariwal and Porter (1968), discussing the work of Lisk (1965) and Davidson (1966) in rats, conclude that 'the receptors

which react to gonadal steroids and stimulate LH secretion may be the same detectors which evoke mating behaviour following implantation of these steroids into the suprachiasmatic region'. In the preceding discussion, I have suggested that prostaglandins released in the hypothalamus as a response to adrenergic stimuli, or possibly in response to a rise in oestrogen levels, are involved in the release of LH at ovulation (see Fig. 1). Prostaglandins should be considered as possible mediators of human libido and thus it may follow that the peak times of sexual desire may be shown to correlate with peak prostaglandin production.

Premenstrual psychological changes

The premenstrual tension syndrome, so fully described by Rees (1953), consists of nervous tension, irritability, anxiety, depression, bloated feelings of the abdomen, swelling of the fingers and legs, headaches, nausea and vomiting, dizziness and palpitations. Less commonly, there may be hypersomnia, excessive thirst and appetite, increased sexual desire, and in some affected subjects an increased tendency for asthma, migraine, vasomotor rhinitis, urticaria and epilepsy.

The cause of these symptoms is uncertain, but it is thought by some to be due to low progesterone and relatively high oestrogen levels (Morton, 1950). However, Loraine and Bell (1971) found normal patterns of excretion of pregnanediol in patients with premenstrual tension, and concluded that there is no significant abnormality of progesterone secretion in this condition. Many of the symptoms described by Rees could, by extrapolation of animal experiments to humans, be attributed to prostaglandins.

Rees (1953) cites clinical reports mentioning a tendency to water retention during the premenstrual phase, but Russell (1972) demonstrated only minor weight gain premenstrually, with a more significant rise at mid-cycle. Weight gain due to water retention might be related to the vasopressin-releasing action of PGE (Vilhardt and Hedqvist, 1970).

With regard to excessive thirst, it is worth recalling that the centres for thirst and vasopressin release lie in close proximity and respond to the same stimuli (Andersson and McCann).

Prostaglandins given intravenously cause sedation and stupor in the cat and chick (Horton, 1969), thus fatigue and hypersomnia in humans premenstrually may be a prostaglandin effect. Morton, however, attributed the fatigue to hypoglycaemia and noted low plateau-shaped glucose tolerance curves in patients with premenstrual tension (Morton, 1950).

Nakano (1973) quotes evidence that PGE₁ or PGE₂ increase heart rate in human subjects and that this effect can be blocked by propranolol, hence

prostaglandins could perhaps be blamed for palpitations experienced premenstrually.

Rees demonstrated a positive correlation between rating of neurotic constitution (as measured by an estimate of whether the patient was meek, dependent, timorous, anxious, obsessional, hysterical or hypochondriacal) and rating of premenstrual tension. There was a positive correlation between the severity of the neurosis and the intensity of the premenstrual symptoms; premenstrual tension preceded the neurosis in over 90% of cases. Patients with severe premenstrual tension had a significantly higher incidence of moderate and severe degree of maladjustment at school, work or marriage. The condition cannot be dismissed as being neurotic or primarily psychogenic (Rees, 1953).

We need to study prostaglandin metabolism in women with premenstrual tension, and such studies should include measurement of urine prostaglandin metabolites, and an assessment of the effect of prostaglandin antagonists on the condition. An understanding of premenstrual tension may found an understanding of many psychological disorders.

Finally, since seasonal changes in sensitivity to bradykinin have been demonstrated in some animals (Sternieri *et al.*, 1969), there may be a seasonal variation in sensitivity to prostaglandins.

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