PROSTAGLANDINS[1]

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The comprehensive review of the biology of the prostaglandins by Bergström, Carlson & Weeks (1) covered the literature through 1967. This family of lipid acids has interesting and potent effects in a bewildering variety of often apparently unrelated biological test systems. This versatility, coupled with their availability in research quantities, has caused the world's scientific literature to increase since 1967 at a prodigious rate of over 400 citations annually.[2] To cover this varied literature, a companion review on the biochemical aspects of the prostaglandins appears in *Annual Review of Biochemistry* for 1972 (Hinman 2). Major topics covered there include: extraction, identification, and assay; biosynthesis, metabolism, and excretion; release from organs and tissues (biosynthesis in situ); actions on cellular metabolism and ion transport; relationships to inflammation, antigen/antibody reactions and allergy; and effects of prostaglandins on adenyl cyclase and cyclic AMP-mediated systems. Neither review covers clinical applications, chemical synthesis, or chemical and physical properties. The goal of these reviews is to survey the current research developments in the prostaglandins and to provide a key to the literature since the 1968 review. For further details, there are several specialized reviews covering chemistry (Pike 3), physiological significance (Horton 4), gastrointestinal tract (Bennett & Fleshler 5), eye (Waitzman 6), reproductive physiology and gynecology (Hinman 7, Speroff & Ramwell 8), kidney (Werning & Siegenthaler 9), and clinical applications (Hinman 10).

SMOOTH MUSCLE AND SMOOTH MUSCLE ORGANS

Uterus.—The reaction of the isolated rat uterus can be influenced in many ways. Estrogen pretreatment of ovariectomized rats decreased sensitivity of the rat uterus to PGE_1 and PGF_{2a}, and increased sensitivity to

[1] Prostaglandins are abbreviated as PG followed by an appropriate letter (E, F, A, or B) subscript number (1 or 2) and, in the case of PGF_1 and PGF_2, the subscript α or β. PGE_1 is 9-oxo-11α-15 [S]-dihydroxy-13-*trans*-prostenoic acid. The relationships and names of the various prostaglandins discussed can be deduced from Figure 1.

[2] Prostaglandin bibliography, prepared by J. E. Pike and J. R. Weeks and distributed by The Upjohn Company.

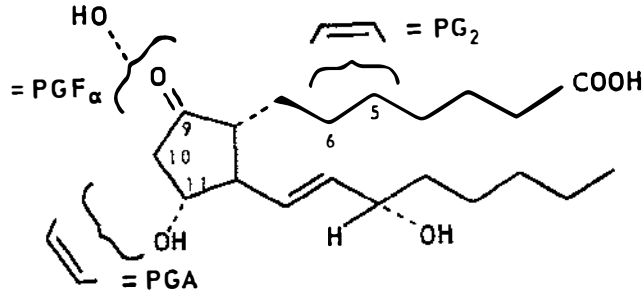

FIG. 1. Prostaglandin E_1 and its relation to other prostaglandins. PG_2s have in addition a 5,6-*trans* double bond; PGFs have an α or β hydroxyl instead of oxo at carbon 9; PGAs are dehydrated analogs of PGEs with a 10, 11 double bond in the ring. Not illustrated are PGBs, isomers of the PGAs with the double bond 8, 12 instead of 10, 11.

oxytocin, but, surprisingly, progesterone pretreatment was without effect (Hawkins et al 11). Eliasson & Brzdekiewicz (12–14) studied a variety of factors contributing to appearance and reversal of tachyphylaxis. Unfortunately, the supporting data for each conclusion consisted only of one kymograph tracing; hence, there was no estimate of the consistency of the responses. Some of their observations, especially on reversal of tachphylaxis by a different prostaglandin or certain other agonists, merit confirmation and further study.

Gastrointestinal.—Since longitudinal strips of gastrointestinal muscle are usually studied, there is the impression that prostaglandins uniformly cause such muscle to contract. On the contrary, in several species, PGE relaxed the circular muscle of the intestine and colon but contracted the longitudinal muscle (15–18). There was reduced propulsive action in the gut (Bennett et al 19). This relaxant action was unaffected by adrenergic blocking agents (15, 16), and so differs from the relaxation of rat duodenum, which is mediated indirectly by catecholamine release (20, 21). $PGF_{2\alpha}$ contracted both circular and longitudinal muscle (Vanasin et al 18). In dogs in vivo PGE_1 infusion reduced gastric antral and intestinal motility, but $PGF_{2\alpha}$ increased intestinal motility (22, 23). PGE_1 relaxed toad intestine by a direct (viz, not adrenergic) mechanism, but, paradoxically, PGE_2 as well as $PGE_{1\alpha}$ caused it to contract (Ng et al 24). Human umbilical and placental blood vessels (Hillier & Karim 25) and the toad intestine are the only tissues yet reported in which the often similar PGE_1 and PGE_2 elicit opposite responses. Muscles with paradoxical responses should be useful to verify hypotheses on the cellular mechanism of action of prostaglandins.

Respiratory tract smooth muscle.—Isolated tracheal or bronchial muscle usually has no inherent tone, so bronchodilator agents are evaluated by their

ability to prevent or reverse contractions induced by some other agent. PGE_1 and PGE_2 were bronchodilators (relaxing agents) in several species, both in vitro (26–28) and in vivo (29–31). Isolated human muscle, however, had inherent tone and, therefore, a relaxing action was elicited directly (26, 32). In asthmatic, but not in normal, humans PGE_1 aerosol inhalation decreased airway resistance (Cuthbert 33). PGF_αs, contrary to earlier reports, are bronchoconstrictors (26, 34–37). Rat trachea may be an exception, in that PGE_1 contracted this muscle (Yoshida & Kawasaki 28).

Miscellaneous.—In lactating rabbits and rats, retrograde intraarterial injections of PGE_1, inactive by themselves, antagonized oxytocin-induced increases in mammary duct pressure (38, 39). PGE_1 inhibited spontaneous activity of isolated rabbit testicular contractions (Hargrove et al 40).

Inhibition, Mediation, and Blockade of Prostaglandin Responses

Prostaglandin actions on most organs or tissue often mimic or modify actions of other naturally occurring mediators. A similar action may be due to release of the natural mediator, action on a common receptor, or other effect on the organ by a mechanism independent of a naturally-occurring mediator. Involvement of known mediators and their receptors may be inferred by use of their pharmacological blocking agents, agents inhibiting their release or causing their depletion. The prostaglandins themselves may serve as physiologic mediators in their own right, either by modulating other mediators or through their own receptors. Compounds that block prostaglandins without affecting similarly-acting agonists can provide more information. Since the liberation of prostaglandins may be "in situ biosynthesis" rather than release from bound stores, inhibitors of biosynthesis show promise of being useful tools somewhat analogous to catecholamine anti-release agents (41–44). Interpretation of many reported synergisms and antagonisms of prostaglandins is complicated by incomplete data and inadequate experimental design. Dose-response data for the prostaglandin alone and in the presence of the inhibiting or synergistic agent, preferably with two submaximal concentrations, are needed. There must also be adequate controls for any independent actions of the other agent.

Interaction with the sympathetic nervous system and its mediators is discussed separately.

Blocking agents.—In line with earlier observations (1), various stimulatory and inhibitory actions of prostaglandins were unaffected by anticholinergic agents (15, 16, 37, 45–51), adrenergic blocking agents (15, 24, 27, 32, 36, 37, 39, 47, 48, 50–52), antihistaminics (15, 50, 51), tetrodotoxin (a paralysant of intrinsic nerves) (47, 48), and morphine (an inhibitor of acetylcholine release in some intestinal muscles) (24, 27). Such negative results imply mediation different from the respective agonists. However, in the colon of human, and the colon and intestine of the guinea pig, prostaglandin-induced contractions were lessened by tetrodotoxin, anticholinergic

and ganglion blocking agents, implying that neural mechanisms accounted for a part of the contractile action (15, 18, 46, 53).

On the isolated dog trachea, PGE_1 inhibited serotonin-induced contractions much more effectively than acetylcholine-induced contractions. Methysergide, in addition to inhibiting serotonin contractions completely, also greatly reduced the ability of PGE_1 to antagonize acetylcholine contractions (Türker & Khairallah 27). Since neither morphine, dihydroergotamine, or propranolol affected PGE_1 inhibition of acetylcholine, the receptor involved in this tissue may be the serotonin "D" receptor.

Prostaglandin antagonists.—Three prostaglandin antagonists have been described. The prostaglandin analog 7-oxa-13-prostynoic acid antagonized the contraction of PGE_1 on isolated intestinal muscle in a dose-related manner (Fried et al 54, 55). It was stated also to inhibit $PGF_{1\alpha}$, but no data were presented. The inhibition was only partially surmountable and the shift in dose-response curves was not parallel. The inhibition was not fully specific, in that the activity of histamine and acetylcholine was also reduced. It may yet be a useful tool, in that it inhibited cyclic AMP formation induced by PGE_1, PGE_2 and LH in isolated mouse ovaries (Kuehl et al 56) and by FSH and ACTH in isolated rat testes and adrenals respectively (Ham et al, cited in 56). Also inhibited was both PGE_1 and TSH stimulation of iodide trapping in isolated bovine thyroid cells (Burke et al 57) and PGE_1 (but not $PGF_{2\alpha}$) and TRF-induced release of TSH in the isolated rat pituitary (Vale et al 58). The use of this compound in systems in which prostaglandins may be released (biosynthesis in situ?) will be complicated by its considerable activity as an inhibitor of prostaglandin biosynthesis (Fried et al 55).

The dibenzoxazepine hydrazide derivative SC-19220 showed a surmountable, dose-related inhibition of PGE_1 and PGE_2 in the guinea pig ileum (Sanner 59, 60). Dose-response curves were consistent with competitive inhibition. At almost complete inhibitory concentrations, SC-19220 had no effect on bradykinin or acetylcholine contractions, but the higher concentrations somewhat reduced serotonin contractions. Histamine contractions also were not inhibited (Ambache et al 61). In other tissues, it inhibited PGE_2 on rat stomach fundus (Posner 62), only partially reduced effect of PGE_2 on the guinea pig detrusor muscle (which responds poorly to PGE_2 itself) (Ambache & Zar 63), but had no effect on PGE_2 inhibition of contractions of the guinea pig vas deferens hypogastric nerve preparation (Ambache & Zar 45). In vivo studies will be complicated by low solubility (on the order of 10 μg/ml).

A high-molecular weight (estimated average mol wt 15,000) polyester of phloretin and phosphoric acid, polyphloretin phosphate, yielded data consistent with its being a competitive antagonist of both PGE_2 and $PGF_{2\alpha}$ on the isolated gerbil (jird) colon (Eakins et al 64, 65). Fractionation indicated its activity associated with the small molecular weight fractions. It had no

effect on angiotensin, bradykinin, or acetylcholine contractions (Eakins 66). The contracting action of $PGF_{2\alpha}$ on isolated human bronchial muscle, but not the relaxing action of PGE_2, was likewise apparently competitively antagonized (Mathé et al 37). In the rabbit eye, the rise in intraocular pressure induced by intracameral injection of either PGE_2 or $PGF_{2\alpha}$ was inhibited by close intra-arterial infusion of polyphloretin phosphate (Beitch & Eakins 67). However, by topical application, the compound blocked the ocular inflammation of topical $PGF_{2\alpha}$, not that of PGE_2 (Bethel & Eakins 68). It inhibited prostaglandins in some, but not all, of a variety of other isolated smooth muscle preparations (Eakins 66). Preliminary experiments have indicated possible inhibition in vivo of prostaglandin action on blood pressure, intestinal motility, and bronchoconstriction (66, 69). Conclusions must be guarded until dose-response data are obtained and there are adequate controls for the actions of polyphloretin phosphate itself.

Morphine, in concentrations as low as 10 ng/ml, can partially inhibit PGE_1 and PGE_2 on isolated guinea pig ileum (60, 70). Prostaglandin contractions in this tissue are mediated both by direct muscle stimulation and release of acetylcholine (Harry 53). Morphine is known to inhibit the release of acetylcholine (see 60 for references).

The Concept of a Prostaglandin Receptor

In view of the differences between prostaglandins and the multiplicity of their actions, it is unlikely that there exists a single prostaglandin receptor. Hypotheses advanced are restricted to certain types of responses. Calcium mobilization or transport in the cell membrane, leading to an increased available intracellular calcium (see review, Hurwitz & Suria 71), has been proposed to explain stimulant actions of prostaglandins (72–74). Greater availability of intracellular calcium, perhaps in the form of a monovalent complex, has been proposed by Eagling et al (75) as an explanation for the potentiating action of subthreshold doses of prostaglandins on other agonists and stimuli (76–81). Conversely, explanations of inhibitory responses have postulated decreased availability of calcium (27, 48, 82, 83).

Smythies (84, 85) has proposed a receptor theory based upon stereochemical relationships between ribonucleic acid and various agonists, including prostaglandins. There is as yet no experimental data either to support or refute his hypothesis. As a pharmacologist, I cannot comprehend "active" and "inactive" prostaglandins without an indication of the biological system involved. Furthermore, he proposes RNA-bound prostaglandins being released upon contact with agonists, when the bulk of evidence favors prostaglandin release as a consequence of phospholipase activation and biosynthesis in situ (see Hinman 2).

The Reproductive System

Prostaglandins and semen.—There appears to be a correlation between male subfertility and seminal PGE content (86, 87). The reasons are not

yet apparent. PGE_1 had no effect on oxidative metabolism of spermatozoa (Eliasson et al 88). Sturde (87) measured only the smooth mucle contracting activity of seminal fluid in atropinized guinea pig ileum, using histamine as a reference standard. Although the activity of the seminal fluid was probably due mostly to prostaglandin, one cannot be certain. His finding that combined treatment of testosterone and chorionic gonadotropin elevated prostaglandin-like activity in the semen deserves further investigation.

Prostaglandins and luteolysis.—Pharriss (89) put forth an hypothesis that $PGF_{2\alpha}$ could be the substance, known to be produced in the uterus, which leads to regression of the corpus luteum when pregnancy has not occurred. Although the general sequence of events in ovarian functions is similar in all mammals, there are species variations in control mechanisms and possibly for physiological roles of $PGF_{2\alpha}$ also. The presentation here will concentrate on observed effects rather than mechanisms of action. It is premature to differentiate between physiological roles and pharmacological drug effects.

A luteolytic effect of $PGF_{2\alpha}$, either inferred by a decrease in blood or ovarian progesterone or by direct observation of the corpora lutea, occurred in rats (90–93), rabbits (91, 94–96), hamsters (97, 98), guinea pigs (99), sheep (100–102), and monkeys (103, 104). Early pregnancy was also terminated in rats (91, 92), rabbits (91), hamsters (97, 98, 105), and monkeys 104). Exogenous progestogen protected pregnant rats and hamsters against $PGF_{2\alpha}$, presumably because it replaced the lost luteal progesterone (91, 97). PGE_2 also has an antifertility effect in rats, but it is not clear whether this effect is secondary to luteolysis (Nutting & Cammarata 106).

Paradoxically, PGE_1, PGE_2, $PGF_{2\alpha}$, and LH all stimulated progesterone synthesis in isolated ovaries and corpora lutea (56, 107–111). This effect may be mediated indirectly by increasing cyclic AMP formation (56, 108).

Mechanism of luteolytic action.—It is not understood how the luteolytic factor of the uterus can affect the ovary by a local mechanism without direct vascular or lymphatic connections (Donovan 112). Pharriss' (89) original hypothesis proposed that the venoconstrictor activity of $PGF_{2\alpha}$ (DuCharme et al 113) restricted venous outflow from the common utero-ovarian vein, resulting in decreased ovarian blood flow and end-product inhibition in the ovary. Indeed, $PGF_{2\alpha}$ decreased ovarian blood flow in rabbits and rats (114, 115) and increased the ratio of the progesterone metabolite 20α-dihydroprogesterone to progesterone in the rat ovary (Pharriss & Wyngarden 93). However, $PGF_{2\alpha}$ caused no apparent damage to the follicles (Labhsetwar 92), which would be inconsistent with a relative ischemia (Blatchley & Donovan 99), and in the transplanted sheep ovary in vivo inhibition of progesterone formation by $PGF_{2\alpha}$ was not necessarily associated with decreased ovarian blood flow (McCracken 101). $PGF_{2\alpha}$ even exerted

a luteolytic effect on an ectopic rabbit corpus luteum transplanted under the kidney capsule (Bullock & Keyes 94).

Since the effect of $PGF_{2\alpha}$ on ovarian progestogens in prolactin-maintained hypophysectomized rats was the same as in pseudopregnant rats (Duncan & Pharriss 116), and since $PGF_{2\alpha}$ did not prevent lactation (Gutknecht et al 91), pituitary involvement in the luteolytic process is not indicated. Still, LH is luteolytic in pseudopregnant rabbits (Gutknecht et al 95), therefore the effect of $PGF_{2\alpha}$ on pituitary LH content in rats was investigated. Labhsetwar (92) found an increase in pituitary LH after $PGF_{2\alpha}$ in pregnant rats, but Pharriss et al (109) saw no effect in ovariectomized rats. Contrary to rabbits, Behrman et al (90) found that LH not only had no luteolytic effect on ovarian progesterone in intact rats, but also partially antagonized $PGF_{2\alpha}$-induced luteolysis. In hypophysectomized rats, both $PGF_{2\alpha}$ and LH increased ovarian progesterone the same as in vitro, suggesting that another pituitary hormone may be involved in the action of LH and $PGF_{2\alpha}$ in rats (Behrman et al 90). In hamsters, combined treatment with prolactin and FSH maintained pregnancy in the presence of luteolytic doses of $PGF_{2\alpha}$ (Johnston & Hunter 98).

Utero-ovarian transfer of prostaglandin.—Another mechanism whereby a humoral substance of uterine origin could affect the ovary locally has recently been described. The ovarian artery follows a tortuous, closely adherent course along the utero-ovarian vein, suggesting a counter-current transfer system (McCracken 101). In sheep, unilateral surgical separation of the ovarian artery led to a persistent corpus luteum (Barrett et al 100), and infusion of labelled $PGF_{2\alpha}$ into the utero-ovarian vein led to radioactivity in ovarian arterial blood thirty times greater than that in systemic arterial blood (McCracken 101). $PGF_{2\alpha}$ has been demonstrated in utero-ovarian blood from estrogen treated guinea pigs (Blatchley et al 117). Distension of the guinea pig uterus in vitro, a maneuver which can cause ipsilateral regression of the corpus luteum in vivo, also causes release of $PGF_{2\alpha}$ (Poyser et al 118).

Abortion and labor induction.—Late in pregnancy, PGE_1, PGE_2, and $PGF_{2\alpha}$ induced abortions and parturition in rats, mice, and monkeys (91, 119, 120). Late pregnancy is maintained by placental rather than luteal progesterone, thus it is possible that uterine stimulation is the primary mechanism. In humans, luteolysis (fall in plasma progesterone) did not seem to be the mechanism for early (about 8 weeks) termination of pregnancy (121, 122), however within the first few weeks it is still possible that luteolysis may account for pregnancy termination (123, 124). The correlation between maternal blood levels of $PGF_{2\alpha}$ and uterine contractions in both humans and sheep implies a physiological role (125, 126) for prostaglandins in labor.

Interaction with the Sympathetic Nervous System

Prostaglandins affect the function of the sympathetic nervous system, both the release of the mediator and the action of the mediator on its effector organ. Generalizations cannot yet be made, since the effects observed may differ quantitatively and qualitatively with the prostaglandin, species, and organ system. An effect on transmitter release may be demonstrated directly by analysis of venous effluent for norepinephrine after nerve stimulation, or inferred indirectly if prostaglandin treatment alters effects of nerve stimulation without affecting exogenously administered norepinephrine. The response of the end-organ to either mediator or nerve stimulation may be complicated by both direct action of the prostaglandin itself (often in the opposite direction) or the still unexplained phenomenon of potentiation of other agonists by subthreshold, often minute, concentrations of prostaglandins (Clegg et al 127). Finally, effects observed may vary with the dose of the prostaglandin and rate of nerve stimulation (45, 128, 129). Unless dose-responses and a range of frequencies in nerve stimulation are included in the experimental design, conclusions may vary among different laboratories.

Prostaglandin (PGE_1 or PGE_2, or both) inhibits the effects of sympathetic nerve stimulation in several systems: the increase in heart rate in the isolated rabbit heart (130, 131), the inotropic actions in isolated guinea pig atria (128), the increase in perfusion pressure and capsule contraction in the isolated cat spleen (129, 132, 133), and contraction of the isolated guinea pig vas deferens (45, 128, 134). Norepinephrine-induced chronotropic and inotropic effects on the rabbit heart and increased perfusion pressure in the cat spleen were only slightly affected by the prostaglandin (130–133). Prostaglandin was a less effective inhibitor of exogenous norepinephrine than of nerve stimulation in isolated guinea pig atria (128), but on the contrary potentiated nerve stimulation of the guinea pig vas deferens (128, 134). These differential effects imply that the prostaglandin inhibits release of norepinephrine at the nerve endings. Norepinephrine output in the venous effluent during nerve stimulation was greatly reduced during perfusion with PGE compared to control periods in both the rabbit heart (130, 131, 135) and cat spleen (132, 133). There was no evidence for an effect of prostaglandin on norepinephrine synthesis (133, 136). PGE_2-inhibition of nerve stimulation in the rabbit heart or cat spleen was not blocked by atropine (137), but there is disagreement as to (action on) the guinea pig vas deferens (45, 134).

Sympathetic nerve stimulation of the rabbit heart and dog spleen induced both norepinephrine release and prostaglandin (primarily PGE_2) release into the venous effluent (135, 138). Since phenoxybenzamine inhibits this prostaglandin release in the dog spleen (Gilmore et al 138), and yet accelerates norepinephrine release in the cat spleen (Hedqvist 139), it is possible that the phenoxybenzamine-induced increase was secondary to re-

moval of a prostaglandin negative feed-back inhibition. Direct evidence for such a negative feed-back system was obtained in the rabbit heart (Samuelsson & Wennmalm 42). An inhibitor of prostaglandin biosynthesis, eicosatetraynoic acid (Ahern & Downing 140), itself without effect on norepinephrine resting release or reuptake, both inhibited prostaglandin release and increased norepinephrine release on sympathetic stimulation. This inhibition of sympathetic nerves occurs at extremely low concentrations, easily within possible physiological ranges. PGE_2 was effective at about 5 pg/ml (sic) on the guinea pig vas deferens (45, 128), 30 ng/ml on the rabbit heart (Hedqvist et al 130) but 30 μg/ml on the cat spleen (Hedqvist 141).

There are some observations inconsistent with the above scheme. Davies & Withrington (142), using a dog spleen in vivo, found that PGE_1 and PGE_2 did not affect responses to nerve stimulation. Blakeley et al (143) added PGE_1 to an isolated, blood-perfused cat spleen preparation to inhibit formation of platelet thrombi. Splenic nerve stimulation in such preparations led to a greater output of norepinephrine than those with PGE_1 in the blood reservoir. Yet, when they tested a cat spleen in situ, a single dose of 70 μg intravenously led to an irregular decrease in norepinephrine output 10 and 20 minutes later. Natural prostaglandins are rapidly metabolized even in isolated organ systems (Piper et al 144) but nevertheless PGE_1 caused prolonged inhibition of platelet aggregation in vivo (Hornstra 145). It is possible that circulating prostaglandins were no longer present in their several-hour long experiments.

A variety of results have been reported for prostaglandin modulation of adrenergic stimulation in the dog hind paw and gracilis muscle. Inhibition or enhancement of a given stimulus or response is best evaluated by showing a horizontal shift in the stimulus (dose)-response curve in the presence of two levels of prostaglandin. The errors of interpretation that may otherwise result have been concisely reviewed by Trendelenburg (146). In most experiments, tissues were perfused with blood from a pump, the pump speed adjusted to provide perfusion pressure about arterial pressure. Prostaglandins were then given at a constant rate, irrespective of the pump speed, so the infused concentrations could vary widely. Kadowitz et al (147) found that PGE_1, infused in average concentrations ranging from about 0.25 to 25 ng/ml (all causing maximal vasodilatation) showed a dose-related inhibition of both nerve stimulation and injected norepinephrine. PGA_1 was similar but weaker. Preliminary reports by Hedwall et al (148–50) confirmed the inhibitory effect of low concentrations of PGE_1 on nerve stimulation, but following a bolus injection of a relatively large dose (2 to 5 μg) both the vasoconstrictor response and amount of epinephrine released were enhanced.

In direct contrast to PGE_1, PGE_{2a} potentiated the response to sympathetic nerve stimulation but not to injected norepinephrine in the perfused dog hind paw and spleen (151, 152). In the dog saphenous vein, PGF_{2a} resembled cocaine in that it potentiated both nerve stimulation and

norepinephrine (153). Either the mechanism here is different or comparisons were made on different portions of a dose-response curve.

In the rat mesocecum preparation, a six-minute intravenous infusion of PGE_1 (but not $PGF_{2\alpha}$) caused a long-lasting (90–120 min) inhibition of the vasoconstriction of topically applied norepinephrine or epinephrine, but not angiotensin (Viguera & Sunahara 154). In contrast, in the saline perfused isolated rat mesenteric arterial bed, PGE_1 alone was without effect (probably no intrinsic tone present), but it potentiated norepinephrine (Tobian & Viets 155).

The effect on adrenal catecholamine release is not clear. PGE_1 had no effect on catecholamine release in cow adrenal slices (Yoshida & Asakawa 156) or by nerve stimulation of isolated, saline perfused cat adrenals (Miele 157), but apparently induced release in vivo in rats (May et al 158) and dogs (Kayaalp & Türker 159, 160).

The Kidney

Renal physiology concerns itself with both excretory and endocrine functions of the kidney. Prostaglandins, primarily PGE_2, are localized mainly in the inner medulla (van Dorp 161) and can be biosynthesized there (162–64). They are readily metabolized by the kidney (Nakano 165), but the enzymes are located in the outer medullary and cortical regions (166, 167). Infused prostaglandins affect excretory functions, but prostaglandins formed within the kidney may well be responsible for some endocrine functions.

Renal release of prostaglandins.—All of the identifications of prostaglandins from venous or lymphatic effluents are provisional, based usually upon solvent extraction and thin-layer chromatography against reference standard prostaglandins, followed by bioassay. When coupled with parallel bioassay on two or more test tissues, identification is almost certain. The superfused blood-bathed organ technique, although limited in specificity and subject to interference by catecholamines and peptides, allows the time-course of release from the kidney to be followed in vivo (McGiff et al 168). PGE-like activity is released from the dog kidney during renal ischemia (168, 169) and during infusion of either norepinephrine or angiotensin into the renal artery (170–72). Intravenous infusion of norepinephrine, but not angiotensin, released a prostaglandin-like material into the renal lymph of cats (Fujimoto & Lockett 173). The diuretic action of norepinephrine may be mediated by renal prostaglandin release (173, 174). When norepinephrine is infused into the renal artery, blood flow decreases and urine formation slows, but there is partial recovery within one to three minutes. This compensatory reaction was correlated with the appearance of prostaglandin E in the renal venous blood (McGiff et al 174). Renal nerve stimulation induced similar initial effects, but there was neither recovery nor prostaglandin release. Prostaglandin concentration in the renal vein blood during re-

lease averaged 0.9 ng/ml, while the threshold arterial concentration needed for vasodilatation and diuresis was only 0.1 ng/ml (172, 175). Infused norepinephrine may first constrict the sensitive cortical vessels, forcing drug into the medullary portion, where prostaglandins are formed, whereas norepinephrine released from renal nerves would be limited primarily to the cortex. Dunham & Zimmerman (170) said that nerve stimulation also released prostaglandin. The kidneys they tested were perfused at a constant rate, which may have disrupted pressure-flow relationships (174).

Renal blood flow and diuresis.—Intravenous or renal arterial infusion of PGE_1, PGE_2, or PGA_1 was associated with an increased renal blood flow, urine volume, and sodium excretion (more in proportion to volume), so that T^cH_2O decreased and C_{H_2O} increased (175-82). In man, PGA_1 increased renal blood flow in doses that did not affect systemic blood pressure (176, 178), implying a selective action. In dogs, the threshold blood concentration for dilatation of the mesenteric vascular bed was about ten times that of the renal bed (McGiff et al 175).

Barger & Herd (183) explain the diuresis following vasodilators as a shift of renal blood flow from the outer medulla to the cortex. PGA_2 was reported to have such an effect (Lee 184), but Friborg & Carrière (185) reported that PGE_1 increased only cortical flow, and the diuresis was due to more blood flowing through outer cortical glomeruli (whose nephrons are short and have limited sodium resorptive capacity).

The mechanism of the diuresis is still in doubt. The renal papillary concentration gradient is lessened (181, 186), implying an inhibited sodium concentrating system. In vitro, prostaglandins did not inhibit glucose oxidation (Kannegiesser & Lee 187). Very high (36 μg/ml) concentrations of several prostaglandins inhibited PAH uptake (188, 189), but more reasonable concentrations had no effect (190, 191). Micropuncture studies in rats showed no effect of PGE_2 on proximal tubular reabsorption (Fülgraff et al 177).

The studies by Werning et al (182) are particularly interesting. They administered 2.5 μg/kg of PGE_1 to anesthetized dogs by a two-minute intravenous infusion. The onset of diuretic and other typical prostaglandin renal effects were delayed for about 30 min. This observation is counter to the general assumption that prostaglandin effects must be transient because of rapid metabolism.

Renin and hypertension.—Edwards et al (192) detected a PGE_2-like material in the renal vein blood of patients with renovascular hypertension. The presence of prostaglandins in the kidney and their release under various circumstances suggests a relationship to renal hypertension. Neither PGE_1, PGE_2, nor PGA_1 affected angiotensin generation by human renin (Sambhi & Wiedeman 193). Lee et al (178) reported that sub-hypotensive infusions of PGA_1 increased plasma renin in 5 of 6 patients, and in dogs Werning et al (182) found a delayed, prolonged (one hour) increase in

plasma renin following a single, short intravenous infusion of PGE_1.

Nekrasova and her colleagues (194–96) have reported extensive studies on the prostaglandin E-like lipid in the kidneys of renal hypertensive rabbits. The change in renal prostaglandin was correlated with blood pressure changes in malignant (one clipped kidney and contralateral nephrectomy) and in mild (one clipped and one intact kidney) hypertension. The overall conclusion was that the onset of hypertension and elevated pressure was associated with low renal prostaglandin. Conversely, after several months of mild hypertension, and after the blood pressure had returned toward normal, the renal prostaglandins were elevated. There seemed to be a trend toward an inverse relationship between renal renin and prostaglandin. Conclusions were the same whether concentration or total content (allowing for hypertrophy or atrophy) were considered. An inverse relationship (high renin, low prostaglandin) was found in 12 of 16 human kidneys removed for treatment of renovascular hypertension (Nekrasova et al 197). There was no correlation between renal prostaglandin and the severity of the disease, however.

Somova (198) found apparently conflicting changes in renal vasodepressor lipids (presumably prostaglandins) in uninephrectomized perinephritic hypertensive rats. In her rats, renal prostaglandins were initially elevated and then fell. However, in contrast to Nekrasova's rabbits, the blood pressure remained elevated, so an inverse correlation between renal prostaglandin and blood pressure still existed. Lee (199, 200) has proposed that a deficiency of renal prostaglandins could contribute to the pathogenesis of hypertension. In support of this concept, Somova & Dochev (201) found that a 30-day treatment of chronic renal hypertensive rats with PGE_1 or PGE_2 (15 and 30 μg/kg intraperitoneally daily respectively) normalized the blood pressure, but the elevated plasma angiotensinase activity was unaffected and there was a sharp, seemingly compensatory rise in both peripheral venous and renal renin. These exciting findings, obviously so important to the understanding and treatment of renal hypertension, must be confirmed and extended.

The medullary interstitial cell lipid droplets may be related to renal prostaglandins (Muehrcke et al 202). Their number can be influenced by the content of dietary polyunsaturated fatty acids (Tobian & Azar 163) and in normal rats their lipid composition differs from plasma and depot fat, being relatively rich in the prostaglandin precursors, arachidonic and dihomo-γ-linolenic acids (Nissen & Bojesen 203).

The Circulatory System

The circulatory effects of the prostaglandins are complicated by differences among the prostaglandins and by species variations. There are specific exceptions, but generally E and A prostaglandins are qualitatively alike, while the F_α prostaglandins often are very different. Unresolved conflicts in the literature may stem from minor differences in experimental technique,

route and manner of injection, etc, which may affect differently the many factors contributing to cardiovascular reactions.

Heart and coronary circulation.—Prostaglandins E and A are powerful, direct-acting, coronary vasodilators in intact dogs (204–209) and isolated hearts (Katori et al 210). PGF_{α} was without effect (205, 207, 208, 210). PGE and PGA_1 have a positive inotropic action (52, 207–9, 211). $PGF_{2\alpha}$ has been reported as either having no inotropic action (207, 208) or a positive but much weaker action than PGE_1 or PGA_1 (211, 212). Intra-coronary arterial infusion of $PGF_{2\alpha}$ at a very high rate was clearly inotropic, but only after a delay of about one minute (Emerson et al 213). In the dog heart-lung preparation, PGE_1 showed typical heart stimulant action (increased force of contraction and cardiac output, a fall in right atrial pressure, and no change in heart rate) (Katori et al 210). $PGF_{1\alpha}$ was qualitatively similar, but much weaker. Doubt is cast on some of these conclusions by Higgins et al (214), who found that PGA_1 had no direct intropic action in conscious dogs when the indirect effects of heart rate, ventricular afterload, and altered sympathetic tone were controlled.

In line with earlier work (see Bergström et al 1), there is still general agreement that prostaglandins E_1, A_1, and $F_{2\alpha}$ in all increase cardiac output (211, 212, 214). There is some controversy, discussed below, concerning the contribution of increased venous return to the cardiac effects of $PGF_{2\alpha}$.

Pulmonary circulation.—Either single injections or infusions of $PGF_{2\alpha}$ caused a striking rise in pulmonary artery pressure (212, 213). Hyman (215), using intact dogs, concluded that there was active constriction of both the pulmonary arteries and veins. PGE_1, in direct contrast, dilated these vessels. Whether pulmonary vasoconstriction is responsible for the paradoxical depressor response to $PGF_{2\alpha}$ in cats and rabbits has not yet been clarified.

Blood distribution.—On peripheral vascular beds, prostaglandins E and A reduced resistance and $F_{2\alpha}$ increased resistance (184, 208, 212, 216–18). A possible selective action of PGE and PGA on the renal vessels was mentioned above. In depressor doses, no selective action was noted for PGA_1 in dogs or man (217, 219). Compensatory vasoconstrictor reactions may have obscured direct actions.

Capacitance vessels and venous return.—DuCharme et al (113) proposed that the pressor action of $PGF_{2\alpha}$ in dogs was a consequence of venoconstriction, increased venous return, and then increased cardiac output. They also noted that the venoconstrictor action of $PGF_{2\alpha}$ in the perfused dog paw was dependent upon and varied with sympathetic nerve activity. Isolated veins and veins perfused in situ contracted, albeit using rather high concentrations, but there was no evidence for dependence upon sympathetic

nervous activity (216, 220). As discussed earlier, Kadowitz et al (152, 153) found that $PGF_{2\alpha}$, in amounts ineffective alone, markedly potentiated constrictor adrenergic venomotor responses. This potentiation may explain the dependence upon sympathetic innervation reported by DuCharme et al.

An effect of $PGF_{2\alpha}$ on the capacitance vessels of the intact paw was also confirmed (216, 221). However, Nakano & Cole (212), using virtually the same technique, could find no evidence of an increased venous return, and they attributed the rise in blood pressure to a combination of increased peripheral resistance and cardiac stimulation. Emerson et al (213) carefully compared PGE_1 and $PGF_{2\alpha}$ for their effects on venous return, giving the prostaglandins by continuous intravenous infusion to avoid transients induced by bolus injections. (DuCharme et al and Nakano & Cole administered the $PGF_{2\alpha}$ by bolus injection.) They noted that $PGF_{2\alpha}$ infusion caused a transient increase in venous return, apparently due to peripheral venoconstriction. However, during the ensuing steady state, the primary action was one of cardiac stimulation and increased peripheral resistance.

PGE_1 uniformly decreased vascular resistance and increased vascular capacity (152, 212, 213, 222).

Thus, the overall cardiovascular action of prostaglandins seems to be the result of many variables. The portal circulation may also be involved, in that both PGE_1 and $PGF_{2\alpha}$, especially when given directly into the portal vein, increased portal vein pressure (Nakano & Cole 212). Indeed, $PGF_{2\alpha}$ was depressor when injected into the portal vein and pulmonary arterial pressure fell. Presumably, liver metabolism prevented general systemic action, and pooling of blood in the portal vein decreased venous return. Consequently cardiac output and blood pressure decreased.

Prostaglandins can also affect cardiovascular function by direct action on the central nervous system and by modifying cardiovascular and pulmonary reflexes (223–226).

Inhibition of Gastric Secretion

Studies by Robert et al have shown that prostaglandins were formed by rat stomach and that PGE_1, E_2, and A_1 (but not $F_{2\alpha}$) inhibited gastric acid secretion in the dog [see Bergström et al (1) for references]. PGE_1 has since been studied extensively in the dog (Nezamis et al 227). PGE_1 inhibited both pepsin and acid secretion induced by histamine, pentagastrin, 2-deoxyglucose, and food. PGE_1, either by parenteral administration or superfusion of the stomach in situ, inhibited both pentagastrin- and histamine-induced gastric acid secretion in the rat (228–33). Intravenous infusion of PGE_1, PGE_2, or PGA_1 in man likewise inhibited basal and stimulated acid secretion, although the PGEs in effective doses caused a variety of side effects (234–37). Oral PGE_1, even in doses causing gastrointestinal side effects, was ineffective (Horton et al 238).

Since gastric acid is a prime factor in upper gastrointestinal ulceration, it is interesting that Robert et al (232, 239) found that PGEs could prevent

experimental gastric and duodenal ulcers in rats.

The mechanism of the antisecretory effect of prostaglandins is not known. Adenyl cyclase is involved in some actions of prostaglandins (review by Hinman 2), but its relation to gastric acid secretion is uncertain (Levine 240). Effects of gastric acid stimulants and PGE_1 on guinea pig adenyl cyclase were not consistent with their effects on gastric secretion (Perrier & Laster 241). A decrease in mucosal blood flow was associated with PGE_1 inhibition of gastric acid formation in the dog (242, 243), but this decreased flow seemed more likely to be the result rather than the cause of the inhibition. A direct action on acid formation in the parietal cell is most likely. Such a mechanism is supported by the effectiveness of prostaglandins against a variety of different stimuli and also that it inhibited acid secretion in isolated bullfrog gastric mucosa (Way & Durbin 244). Whether gastric prostaglandins play a physiological role, perhaps as feedback inhibitors, is conjectural, but it is intriguing that PGE_2 occurs in highest concentration in the mucosal layer of human stomach (Bennett et al 16) and, in dogs, intravenous infusion of the PGE_2 precursor arachidonic acid (but not its saturated analog) inhibited histamine-stimulated acid secretion in the dog (Bieck et al 245). There may also be interrelationships between prostaglandins and other gastrointestinal secretions, in that in the dog PGE_1 inhibited pancreatic bicarbonate secretion but stimulated enzyme output (Rudick et al 246).

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