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BASIC MECHANISMS OF PROSTAGLANDIN ACTION ON AUTONOMIC NEUROTRANSMISSION

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INTRODUCTION

More than 40 years ago Euler (1) and Goldblatt (2) independently described the striking pharmacodynamic actions of human seminal plasma and extracts of sheep vesicular gland added to isolated organs or injected into the whole animal. Since the biological effects could not be accounted for by any known naturally occurring compound, the active substance(s) was named prostaglandin (3). Today prostaglandin (PG) is recognized, not as one, but rather a family of fatty acids of almost ubiquitous distribution in the mammalian organism. The principal biosynthetic pathways of the PGs and certain nonprostanoic compounds from their precursor, arachidonic acid, are shown in Figure 1. It should be recalled that PGs are formed from two other precursors as well, the only difference being the number of double bonds in the side chains, as indicated by the subscript numbers of the different PGs.

Although the PG principle has been known for many years, it is only within the last decade that the pharmacology of the PGs has been systematically and extensively investigated. These efforts, greatly aided by the availability of synthetic PGs and potent inhibitors of PG synthesis, have demonstrated that the PGs possess an impressive range of biological activities, which has given rise to many speculations concerning their physiological or pathophysiological significance. Admittedly, the PGs have distinct actions on most mammalian tissues, but few effects seem to be of the same widespread significance as those on autonomic nerves, since the autonomic nervous system is such an essential regulator of the activities of a large number of organs and organ systems.

There is a rapidly growing body of evidence indicating that PGs are released in the vicinity of autonomic neuroeffector junctions, both spontaneously and as a result of physical, chemical, and electrical stimuli; that PGs influence both transmitter release from nerve terminals and the response to the secreted transmitter; and that inhibitors of PG synthesis produce effects opposite to those of the PGs. Taken

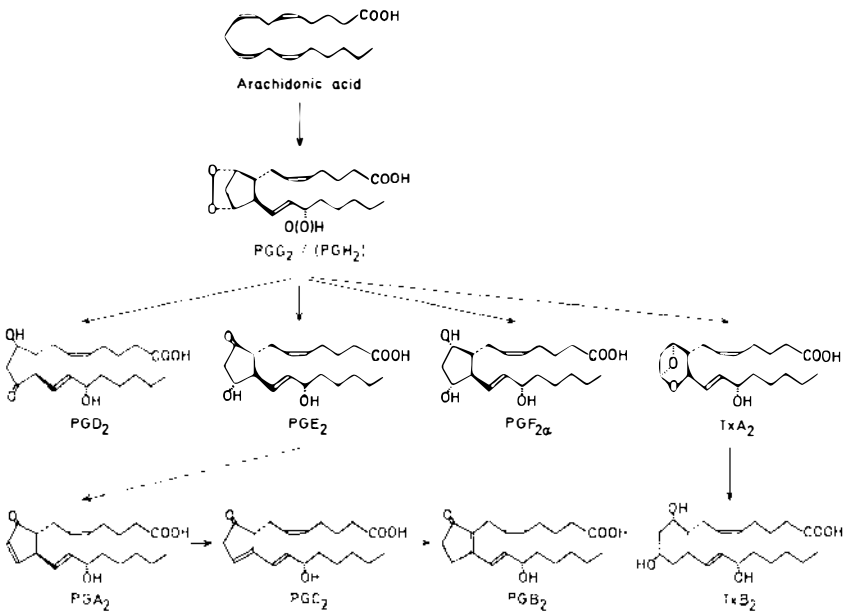

Figure 1 Pathways of biosynthesis of PGs and thromboxanes (Tx) from arachidonic acid.

together, these observations suggest that PGs are important as modulators of the autonomic neuroeffector transmission. In this review special attention is paid to work in which an action on the transmission has been demonstrated directly, rather than implied by the fact that the studied organs or organ systems are autonomically innervated. The presentation focuses on events in the adrenergic neurotransmission, and in particular on the presumed feed-back control mechanism that regulates the release of transmitter in response to forthcoming nerve impulses. Sections on ganglionic and cholinergic transmission are also included, although the available literature on PG actions in these systems is scanty and even controversial. The effects of PGs within the central nervous system are beyond the scope of this presentation.

In order to avoid confusion, contact elements in the neurotransmission are defined. The term *junction* is used when the contacted element is a muscle or a gland cell; *prejunctional* refers to events in the axon terminal membrane or intraaxonally, and *postjunctional* to all events linked to the action of the secreted transmitter on the effector cell membrane. The terms *presynaptic* and *postsynaptic* are used when dealing with ganglionic transmission.

ADRENERGIC NEUROEFFECTOR JUNCTIONS

Action of Prostaglandins of the E Series

Since the discovery of PG in the 1930s much interest has been devoted to its action on the cardiovascular system. Numerous reports have shown that crude PG and

synthetic PGEs, although rather modest in their direct action on the heart, are extremely potent as vasodepressors and also reduce the blood pressure–augmenting effect of norepinephrine (NE). These observations are difficult to evaluate in terms of an action on the adrenergic neurotransmission, since the induced vasodilatation alters the geometry of the vascular wall, and, hence the response to pressor agents.

SPLEEN The first systematic studies were made in 1968 when it was reported that PGE_1 diminished vasoconstrictor responses to nerve stimulation and NE in the feline spleen (without significantly affecting basal perfusion pressure) (4) and that it inhibited the luminal occlusion by nerve stimulation and NE in the rabbit oviduct (5). Although these studies did not permit any conclusion as to a prejunctional inhibitory action on NE release, such an effect was later demonstrated with PGE_1 in the feline spleen (6) and with its congener, PGE_2, in rabbit and human oviduct (7, 8).

In a subsequent study on the feline spleen (9) PGE_2 was shown to inhibit dose dependently and reversibly the release of NE and the splenic contraction response to nerve stimulation. The vascular response was progressively inhibited in the lower dose range, but less so when high doses of PGE_2 were applied. The reason for this escape phenomenon became apparent when nerve stimulation was replaced by intra-arterial injection of NE. NE-induced capsular responses were little affected by PGE_2, while vasoconstrictor responses were inhibited by low PGE_2 doses and markedly enhanced by high doses. It is apparent from these observations that PGE_2 affects adrenergic neurotransmission in the feline spleen in a multifaceted way. It produces prejunctional inhibition of transmitter release and as a consequence also inhibition of the effector response. There are also postjunctional actions which may either further depress or augment the response.

PGE_1 and PGE_2 have little effect on adrenergic neuroeffector transmission in the canine spleen, because reduction in splenic volume (index of capsular contraction) and blood flow induced by nerve stimulation or catecholamines occurred to approximately the same extent before and after administration of PGE, unfortunately given only in one concentration (10). It was also concluded that the PGEs have no effect on induced vasoconstrictor responses. However, the results are difficult to evaluate since the responses were hardly visible even in the control experiments. On the other hand, vascular responses induced by epinephrine in the canine spleen are enhanced after inhibition of local PG synthesis by indomethacin (11). More experiments are needed before the issue can be settled.

HEART The isolated heart of most laboratory animals is relatively insensitive to the direct action of PGs, and chronotropic effects often observed after intravenous administration of PGEs seem to be mediated largely through reflex sympathetic stimulation as a consequence of decreased arterial blood pressure. On the other hand, chronotropic and inotropic responses to sympathetic nerve stimulation in the isolated rabbit heart are dose dependently and reversibly inhibited by PGE_1 and PGE_2 (12, 13). Positive chronotropic responses to transmural stimulation of the rabbit sinoatrial node preparation are also blocked by PGE_2 in low concentrations (14). Because the PGEs inhibit the overflow of NE in the rabbit heart, at least to

the same extent that they depress the effector response to nerve stimulation, and because they have no effect on responses to added NE, the inhibition appears to be solely prejunctional and to consist of reduction of transmitter release from the nerve terminals (12, 13). In agreement with this view is a report that PGE_1 and PGE_2 inhibit the release of NE by nicotine and potassium in the guinea pig heart (15).

VASCULAR BEDS Besides the spleen PGE_1 and PGE_2 have been tested for actions on adrenergic responses in a great number of vascular beds. In most cases the PGEs have proved inhibitory on responses to sympathetic nerve stimulation, while often causing mixed inhibitory and stimulant effect on responses to NE.

Topical application of PGE_1 to mesenteric and cremasteric vessels in the rat results in a reduced responsiveness to NE which persists long after the direct vasodilating effect has vanished (16, 17). While these observations substantiate a postjunctional inhibitory action, PGE_1 has also been reported to potentiate responses to NE in the rabbit aorta and mesenteric artery in vitro (18, 19), as well as vascular responses to NE in canine uterus in situ (20) and in perfused rat kidney (21).

Vasoconstrictor responses to nerve stimulation are inhibited by PGE_1 and/or PGE_2 in feline and canine hindleg (22–26), and in the kidney of the rabbit, dog, and cat (21–29). Because in most of these cases the responses to NE were less depressed, unchanged, or even enhanced, the PGEs seem to act also by inhibiting the release of transmitter from the adrenergic nerve terminals in vascular tissue. Such an effect has been demonstrated directly in the perfused rabbit kidney and ear (30, 31) and in isolated mesenteric arteries from cat and man (32, 33). An inhibitory action on NE release might be present also in canine subcutaneous adipose tissue, although the effect could be demonstrated only after prior α-adrenoceptor blockade (34). Exceptions may be formed by the canine hindpaw and rat kidney, where PGE_1 and/or PGE_2 enhance the vasoconstrictor responses to nerve stimulation (21, 35). However, at least in the latter case a stimulant postjunctional action might have overshadowed a prejunctional effect which is inhibitory. Admittedly, PGE_1 has been reported to increase the NE overflow response to nerve stimulation in the blood-perfused feline spleen (36). However, extremely high doses were used, exceeding those that are inhibitory by approximately 1000 times. Moreover, the effect could be accounted for by inhibition of platelet thrombus formation and hence improved microcirculation and washout of released NE rather than actual enhancement of the NE release mechanism.

There are at least three ways in which PGEs may affect local blood flow and pressure: 1. PGEs cause vasodilatation in most if not all vascular beds. 2. They depress transmitter release from the nerve terminals, and hence the effector response to nerve impulses. Because this effect has been demonstrated in so many vascular tissues (and nonvascular smooth muscle tissues) from different animal species and from man, it can be concluded that this is an essential and widespread action of the PGEs. Admittedly, the PGEs have been postulated to have the opposite action in some vascular beds, notably the canine hindpaw and the rat kidney. However, this assumption was based only on differential effects of the PGEs on responses to nerve

stimulation and NE, and transmitter release, which could have given the proper answer, was not measured. 3. PGEs interact with locally released NE and circulating catecholamines at the level of the effector cell membrane. Both inhibitory effects, probably accentuated by the vasodepressor activity, and stimulant actions have been noted. Although low doses of PGE, which inhibit NE release, often act as postjunctional inhibitors or have no effect at this level, there are several important exceptions to this rule. One can therefore only speculate whether the PGEs, in addition to inhibiting NE release, might serve also another function, that of maintaining the reactivity of the effector cell to catecholamines (37).

MISCELLANEOUS SMOOTH MUSCLE TISSUES It is well established that PGE_1 and PGE_2 inhibit the twitch response to nerve stimulation and enhance that to NE in the guinea pig vas deferens (38–41), and the same pattern appears to hold true also for the guinea pig seminal vesicle (42). While these observations suggest both prejunctional inhibition and postjunctional enhancement, the results are difficult to evaluate in terms of actions on adrenergic transmission, since, at least in the guinea pig vas deferens, the twitch response behaves as if it were of nonadrenergic origin (43, 44). On the other hand, there is no doubt that the vas deferens is supplied with a heavy adrenergic innervation and that the contraction response to prolonged nerve stimulation bears all the characteristics of being adrenergic. Important contributions to the understanding of PG action on adrenergic transmission have also been obtained in studies on the NE release mechanism in this tissue. These aspects are considered in more detail in a following section. At this stage it is appropriate only to summarize that PGE_1 and PGE_2 produce a dose-dependent, inverse frequency–related, and reversible inhibition of NE release induced by nerve stimulation in the guinea pig vas deferens (45–48).

PGE_1 and PGE_2 inhibit the release of NE from the field stimulated rat and rabbit iris (49, 50). The observation that PGE_1 and PGE_2 counteract or even abolish the inhibition of gut motility resulting from stimulation of periarterial sympathetic nerves, without affecting responses to NE, provides indirect evidence that PGEs inhibit NE release also in this tissue. On the other hand, PGEs do not seem to affect contractions of the feline nictitating membrane induced by transmural or postganglionic nerve stimulation (51, 52).

Action of Other Prostaglandins

Relative to the PGEs, less attention has been paid to the capacity of other PGs to influence the adrenergic neuroeffector transmission. A mainly stimulant effect on neurotransmission in vascular tissue seems to occur with PGs of the F series. In the hindlimb of the dog $PGF_{2\alpha}$ causes vasoconstriction, and this effect is abolished after denervation (53). Similarly, $PGF_{2\alpha}$ enhances reflex vasoconstriction, as well as vasoconstriction induced by direct nerve stimulation in the canine hindpaw (52). In the canine gracilis muscle, vascular responses to nerve stimulation are unchanged by $PGF_{2\alpha}$, and those to NE are actually depressed (52). In the canine spleen and tibial artery $PGF_{2\alpha}$ enhances the response to nerve stimulation, without affecting that to NE (52, 54). While these observations provide circumstantial evidence that

$PGF_{2\alpha}$ facilitates the release of NE, a postjunctional stimulant action has also been demonstrated in several tissues. Thus, $PGF_{2\alpha}$ enhances vasoconstrictor responses to NE in the pulmonary lobar artery and vein (55), and to both nerve stimulation and NE in canine hindlimb superficial veins (56), rabbit and rat kidney (21, 57, 58), and in guinea pig vas deferens (P. Hedqvist, unpublished observations).

PGA_1 and PGA_2 inhibit the vasopressor response to nerve stimulation and NE in the canine hindpaw (25, 26). On the other hand, PGA_1 causes a modest enhancement of canine splenic responses to nerve stimulation (54), and in the rabbit kidney PGA_2 increases vascular responses to both nerve stimulation and NE (58). These observations appear unexpected since deficiency of PGA_2 has been assumed to be a significant etiological factor in essential hypertension (59). It should be recalled, however, that PGA_2 might be enzymatically converted to PGC_2 and subsequently to PGB_2. PGB_2 is a potent vasoconstrictor in canine and human superficial and pulmonary vasculature (60–62). This vasoconstriction produced by PGB_2 is blocked by reserpine pretreatment and by decentralization, as shown in the dog. Moreover, in the canine hindpaw it enhances pressor responses to nerve stimulation, but not to NE. At least some of the above-mentioned effects are consistent with a presynaptic or prejunctional stimulant effect on transmitter release.

$PGF_{2\alpha}$, PGA_2, and PGB_2 have been tested for effects
tissues, but in none has a stimulant action been disclosed. In the rabbit heart, $PGF_{2\alpha}$ (in concentrations up to 10^{-6} M) is ineffective in altering the release of NE induced by sympathetic nerve stimulation (12). In both the rabbit kidney and guinea pig vas deferens, $PGF_{2\alpha}$, PGA_2, and PGB_2, in concentrations that enhance the effector response to nerve stimulation, either do not affect NE release or actually decrease it [(57, 58) and unpublished observations]. These observations do not lend any support to a prejunctional stimulant action. Rather they suggest that enhancement of effector responses to adrenergic nerve stimuli by $PGF_{2\alpha}$, PGA_2, or PGB_2 in these and other tissues is mostly, if not wholly, a postjunctional phenomenon.

PGD_2 and the endoperoxides, PGG_2 and PGH_2, are worthy of comment, although so far they have been tested for effects on adrenergic neurotransmission only in the guinea pig vas deferens (57). PGD_2 inhibits the release of NE only in high concentrations, being at least 100 times less active than PGE_2. Moreover, with μg concentrations of this compound, observed effects might be due to the presence of traces of its isomer, PGE_2. Both PGG_2 and PGH_2 inhibit the release of NE induced by nerve stimulation in the guinea pig vas deferens, but they are less than half as potent as PGE_2. One problem when studying the effects of the endoperoxides is that they are nonenzymatically and rapidly ($T_{1/2}$ approximately 5 min in salinic media) degraded mainly into PGE_2. Although attempts were made to minimize this effect by giving the compounds only 30 sec before the stimulation it is conceivable that at least part of the observed effect could be accounted for by newly formed PGE_2.

Mechanism of Prostaglandin-Induced Inhibition of Norepinephrine Release

The demonstration of prejunctional inhibitory action of PGs, in particular the PGEs, in many sympathetically innervated tissues has led to attempts at specifying

the target for this effect. Theoretically, the PGEs might reduce the effective outflow of NE from stimulated tissues by promoting its metabolic degradation or uptake. However, observations that PGEs have no effect on monoamine oxidase and catecholamine-O-methyl transferase activities in guinea pig heart (63), that they cause a parallel reduction in the efflux of total tracer and fluorimetrically determined NE induced by nerve stimulation in feline spleen, preloaded with ^{3}H-(–)-NE (6, 9), and that they have no effect on NE uptake in feline spleen and rabbit heart (9, 13) seem to indicate that altered disposition of NE released from the nerve terminals cannot explain the inhibitory effect of the PGEs. Similarly, there is no independent reason to assume that PGEs interfere with the propagation of impulses in the nerve trunk or with the spread of excitation throughout the terminal arborization, because PGE does not affect the compound action potential in splenic nerves (64), and because it readily inhibits the release of NE evoked by potassium in guinea pig heart and vas deferens (15, 65). Rather, the latter observation implies an action on local electrosecretory coupling. In fact, there is a multitude of evidence that indicates that PGEs inhibit NE release by an action on stimulus secretion coupling, and more specifically on the availability of calcium for the release mechanism.

Release of NE by nerve impulses has an absolute requirement for calcium, and upon arrival of a nerve action potential, depolarization is thought to cause an inward movement of membrane calcium which in turn promotes release of NE into the junctional cleft (66–68). It is therefore of particular interest that calcium interacts with the inhibitory effect of PGEs on release of NE from adrenergic nerves. Thus, increasing the ambient calcium concentration counteracts the inhibitory effect of PGE_2 on NE release by nerve stimulation in feline spleen and guinea pig vas deferens (64, 69). On the other hand, NE release by tyramine, which is a calcium-independent process, is not affected by PGE_2, as shown in feline spleen and guinea pig heart (15, 64). Furthermore, in the guinea pig vas deferens the inhibitory effect of PGE_1 and PGE_2 varies inversely with the environmental calcium concentration (45, 70–72), and kinetic analysis of the effect of PGE_2 on the dependence of the release mechanism on calcium has shown that PGE_2 depresses its apparent V_{max} and enhances its K_m, and progressively more so with falling calcium concentration in the medium (72). The inhibitory effect of PGE_2 on NE release by nerve stimulation in the guinea pig vas deferens and rabbit kidney and heart is diminished by increasing the impulse frequency (30, 45, 48, 73). In fact, shortening the pulse interval is considered to leave more residual calcium at the active releasing sites in the axon (74). Evidently, all these observations suggest that PGEs inhibit NE release by interfering with the availability of calcium for the release mechanism, possibly by closure of the calcium gates in the axonal membrane.

Recently it has been shown that prolongation of the nerve action potential, either by lengthening the applied electric pulse or by administering tetraethylammonium or rubidium (75, 76), significantly diminishes the inhibitory effect of PGE_2 on NE release induced by nerve stimulation in the guinea pig vas deferens (77). This observation seems to further link the inhibitory action of PGEs on NE release to interference with calcium availability, since prolongation of the action potential is thought to allow the calcium gates in the axonal membrane to remain open longer, and as a consequence to allow more calcium to enter the axon (68, 78, 79).

As an alternative it has been suggested that PGEs, by analogy with the fact that they may depolarize smooth muscle and cardiac cells (80–83), might similarly depolarize the nerve terminal membrane, and therefore reduce the amplitude of the action potential on arrival of nerve impulses (81). However, it is not known whether PGEs have such an effect on C-terminal fibers; also, the PGE amounts required to produce even a moderate depolarization of muscle cells are high compared with those that forcibly depress transmitter release. Moreover, the observations that PGE_1 and PGE_2 are equipotent on NE release in the heart (12), but that in reasonable concentrations only PGE_2 depolarizes cardiac cells (83, 84), also suggest that PGEs do not inhibit NE release by depolarizing the nerve terminal membrane.

In summary, the inhibitory effect of PGEs on transmitter release from adrenergic nerves is best explained in terms of a direct action on the availability of calcium for the release process. A closely similar mechanism has been proposed for the feedback control NE release by prejunctional α-adrenoceptors (85).

Prostaglandin Release from Adrenergically Innervated Tissues

It is generally accepted that PGs can be extracted from virtually all mammalian tissues. This does not mean that PGs are stored to any appreciable extent in the tissues, but that there is a continuous, and probably very low, PG synthesis and release that can be markedly enhanced by various maneuvers, e.g. extraction procedures.

Increased release of PGs by nerve stimulation and catecholamines readily occurs in a number of adrenergically innervated tissues, such as canine and feline spleen (86–89), rabbit heart and ear (13, 90), canine and rabbit kidney (91, 92), rat and canine adipose tissue (93, 94), and guinea pig and rat vas deferens (95, 96). In most cases the PG predominantly released is PGE_2 followed by $PGF_{2\alpha}$, except in the case of the guinea pig vas deferens, which appears to produce predominantly PGE_1 and PGE_2 and only traces of $PGF_{2\alpha}$. Even though these results have been obtained in perfused tissues, either isolated or kept in situ, they cannot be regarded as artificial. Thus, while the surgical trauma may certainly cause an increased basal PG release, it cannot explain the increased release induced by nerve stimulation. Hence, these PG output figures are relevant and suggest that nerve impulses cause release of PGs in adrenergically innervated organs even under strict in vivo conditions.

The important information provided by these observations is that significant amounts of a PGE are released when adrenergically innervated organs are stimulated by their nerves and the PGEs are particularly well adapted for inhibition of transmitter release in these tissues. In fact, the amounts of PGEs required to produce such an effect are largely of the same order of magnitude as those that can be released by nerve stimulation. On these grounds it may be justified to postulate that locally formed PGEs are able to restrict the release of NE by a negative feedback loop, and hence to act as significant modulators of adrenergic transmission (97). That $PGF_{2\alpha}$, the second principal PG released from adrenergically innervated tissues, should operate by the same mechanism appears less likely, since the concentrations required to produce inhibition of NE release are high compared with the amounts actually released from stimulated tissues. Even though the presence in

some tissues of a PGE 9-ketoreductase (98) (which transforms PGE to PGF) might change the pattern into preferential release of $PGF_{2\alpha}$, an inhibitory modulating role is still unlikely since the net effect of $PGF_{2\alpha}$ on adrenergic transmission, if anything, is stimulant.

ORIGIN OF RELEASED PROSTAGLANDINS Several studies on spleen and kidney have revealed that α-adrenoceptor blockers abolish the release of PGs and the smooth muscle contraction induced by nerve stimulation or catecholamines (86, 88, 89, 99). These observations indicate that contraction of the effector cell, or structural change of its membrane (100), is an essential trigger mechanism for PG synthesis. The finding that PG release in the rabbit heart induced by infusion of NE is inhibited neither by α-adrenoceptor blockers nor by β-adrenoceptor blockers (101) is certainly at variance with this concept, and is difficult to explain.

The observation that the release of PGs from canine spleen and rabbit heart induced by catecholamines is not greatly impaired by surgical or chemical sympathectomy (89, 101) has been regarded as evidence that the source of PGs released by nerve stimulation is strictly extraneuronal. However, none of the studies seems to provide evidence of a complete destruction of all the nerves. Moreover, it is unlikely that destruction of the nerves would significantly alter the total amount of PG overflowing stimulated tissues, because the nerves make up only a fraction of a percent of the total tissue mass. Therefore, possibly a small but nevertheless important fraction of the PGs overflowing from stimulated tissues is neuronal in origin. In fact, PGs have been demonstrated in several different types of nerve tissue (102). The observation that PG synthesis inhibitors enhance NE release by nerve stimulation in the guinea pig vas deferens even in the absence of visible contraction response also seems to support this view (103). On the other hand, it is not contradicted by the finding that α-adrenoceptor blockers abolish the release of PG, since α-adrenoceptors are both pre- and postjunctionally located (104–106). However, more experiments are needed before this issue can be settled.

The inhibitory effect of α-adrenoceptor blockers on PG release may be interesting also from another point of view. α-Adrenoceptor blockers powerfully enhance the release of NE by nerve stimulation (107), and concomitantly fortify the inhibitory effect of exogenous PGEs (8, 42), as would be expected after removal of a significant PGE-mediated feedback control of NE release. However, part of the enhancing effect of α-adrenoceptor blockers on NE release appears to be due to a PG-independent action on prejunctional α-adrenoceptors (45, 47, 108).

Action of Prostaglandin Synthesis Inhibitors

In the search for physiologically relevant functions of the PGs, the experimenter is greatly aided by the availability of specific PG antagonists or of PG synthesis inhibitors. Of these two approaches only the latter has so far proved to be promising.

The literature concerning drugs that inhibit PG biosynthesis has recently been reviewed (109). Principally, two classes of PG synthesis inhibitors have been used. One includes the aspirin-like drugs (110), which, although of diverse chemical structures, all share the analgesic, antipyretic, and anti-inflammatory actions which

are characteristic of aspirin. The other consists mainly of substrate analogues, of which only one, the acetylenic derivative of arachidonic acid, 5,8,11,14-eicosatetrayonic acid (ETA) (111), has been tested for effects on adrenergic transmission.

In rabbit heart, feline spleen, and guinea pig vas deferens, ETA blocks the release of PGs and simultaneously enhances the release of NE induced by nerve stimulation (112–114). ETA also has been reported to enhance the release of NE induced by field stimulation in the rabbit iris (50).

Similarly, indomethacin and/or meclofenamic acid, members of the aspirin family, have been shown to increase the release of NE induced by nerve stimulation in the rabbit heart (115), guinea pig vas deferens (47, 116), rabbit kidney (30), and mesenteric arteries from cat and man (32, 33), but not in the feline spleen (117, 118).

The effects of PG synthesis inhibitors on effector responses to nerve stimulation have also been studied in most of the above-mentioned tissues, although the results are somewhat less consistent. The vasoconstrictor responses to nerve stimulation in rabbit kidney are either increased or unchanged by indomethacin (21, 30, 99). In the guinea pig vas deferens, only the initial part of the contraction response to nerve stimulation is markedly affected and enhanced, which is exactly opposite to the effects of exogenous PGEs (39, 96).

Contradictory results have been obtained in the rat kidney, where indomethacin has been reported both to enhance (119) and to inhibit (21) the vascular response to nerve stimulation. However, the results are logical in that exogenous PGEs also caused the opposite effects in the two studies, inhibition when indomethacin was the stimulant and enhancement when indomethacin caused inhibition. There are some inconsistencies in the effects of PG synthesis inhibitors also in the feline spleen. Thus, while ETA produces only enhancement of the vascular response to nerve stimulation, indomethacin or meclofenamic acid causes either enhancement (120, 121) or no effect at all (117, 118). The controversial observations with indomethacin in feline spleen and rat kidney are difficult to explain, although differences in strain, experimental procedure, and drug concentration might have contributed to the different results. In particular the use of indomethacin or meclofenamic acid is worth considering in this context, since they cannot be regarded as specific inhibitors of PG synthetase, but may affect other enzyme systems as well, at least in high concentrations (109).

In addition to the above-mentioned in vitro and in situ experiments, there are several in vivo studies pertaining to the action of PG synthesis inhibitors on adrenergic neurotransmission. Thus, indomethacin has been reported to increase urinary excretion of NE in rats, the animals being either cold-stressed or kept at room temperature (122, 123). There is good reason to believe that this hyperexcretion of NE was initially due to increased NE release from the adrenergic nerves. Only after several days did augmented adrenomedullary secretory activity (as reflected by an increase in urinary epinephrine and a fall in NE content of the adrenal medulla) contribute to the hypersecretion of NE.

Recently, an in vivo effect of indomethacin on adrenergic transmission has been more firmly established (124). Thus, oral administration of indomethacin increases NE turnover rate in a number of rat tissues, such as heart, spleen, submandibular

gland, and adipose tissue. Since indomethacin had no effect on monoamine oxidase and catechol-O-methyl transferase activities, or on NE uptake in the different tissues, an action on NE disposition may be excluded. Therefore, the results suggest that indomethacin increased NE turnover, and hence the release of NE per nerve impulse, by blockade of a locally operating feedback inhibition of transmitter release mediated by PGEs. Although forming an important contribution to the concept of PG-mediated control of adrenergic transmission, the results do not exclude the possibility that indomethacin increases also the impulse traffic in the nerves. The significance of such an effect is lessened, however, by the fact that the effect of indomethacin on NE turnover in adipose tissue was low compared with that in heart, spleen, and submandibular gland.

In summary, the bulk of available in vitro and in vivo evidence indicates that inhibitors of PG synthesis increase the release of NE per nerve impulse as a consequence of inhibition of local PGE formation. Admittedly, indomethacin and meclofenamic acid are not exclusive inhibitors of PG synthetase, although the concentrations of these drugs required to inhibit the synthetase are generally much lower than the concentrations that inhibit other enzymes (109). ETA is presumably more specific in its action, but, on the other hand, its metabolic fate is largely unknown (109). However, the finding that members of both classes of PG synthesis inhibitors produce one and the same effect on NE release in several tissues, seems to minimize the possibility that they affect the release of NE by any mechanism other than inhibition of PG synthetase. This view is further supported by observations that PG synthesis inhibitors are unable to enhance NE release when it is sufficiently depressed by administrated PGEs and that the NE release mechanism is hyperreactive to the inhibitory effect of exogeneous PGEs when local PG synthesis is blocked (30, 113, 116). However, conflicting results have been presented and further extensive studies are certainly required before the concept of PG-mediated feedback control can be established as physiologically relevant in adrenergically innervated organs in general, or at least in certain tissues.

GANGLIONIC TRANSMISSION

The information about PG action on ganglionic transmission is sparse and even conflicting. PGE_1 and PGE_2 have been reported to have no effect on postganglionic action potentials elicited by preganglionic stimulation of the feline cervical sympathetic chain (125). On the other hand, the observation that PGE_1 is more prone to inhibit contractile responses to preganglionic than postganglionic nerve stimulation in the guinea pig vas deferens is consistent with PGE_1 interfering with ganglionic transmission (126).

Cardiovascular effects elicited by intracarotid infusion of PGE_1 in intact dogs, or in cross-circulation experiments, are abolished by ganglion blocking drugs (127, 128). At least part of these effects are presumably mediated by the central nervous system, where PGs are capable of either stimulating or inhibiting ganglionic transmission (129–131). Whether or not PGE_1 may have influenced also transmission in peripheral ganglia is not known.

The adrenal medullary cells are homologues to postganglionic nerve cells, and the nerve-effector cell junction may therefore be regarded as a specialized type of ganglionic transmission. It has been shown that PGE_1 and $PGF_{1\alpha}$ do not modify resting outflow or increased secretion of catecholamines induced by acetylcholine, potassium, or splanchnic nerve stimulation in the cat (132). On the other hand, it has been proposed that $PGF_{2\alpha}$ facilitates the adrenal medullary secretion of catecholamines induced by splanchnic nerve stimulation in the dog (52). In this case the venous effluent from the adrenal gland was allowed to perfuse the animal's isolated paw, and variations in perfusion pressure were used as an index of secreted catecholamines. Since $PGF_{2\alpha}$, given in small doses in the left ventricle of the heart, consistently enhanced the vasoconstrictor response to splanchnic nerve stimulation, but not to injected epinephrine, it was concluded that $PGF_{2\alpha}$ actually had facilitated the secretion of catecholamines from the adrenal medulla. Further studies, including direct analysis of catecholamine secretion from the adrenal medulla, are needed to confirm this interesting observation.

CHOLINERGIC NEUROEFFECTOR TRANSMISSION

PGE_1 has been shown to block the negative chronotropic effect of vagal nerve stimulation in the isolated rabbit heart, and in the guinea pig heart in situ (133, 134). In the rabbit study the effect of acetylcholine (ACh) was unaffected by PGE_1, and it was therefore concluded that PGE_1 exerted its effect mainly prejunctionally, that is, on ACh release from the nerve terminals (133). The observation that PGE release from the heart can be induced by vagal nerve stimulation and by ACh (the effect of the latter being blocked by atropine) has subsequently led to the proposal that PGEs might control cholinergic neuroeffector transmission in the heart in a way similar to that proposed for the adrenergic system (13, 135). At least the prejunctional target for such an effect has been questioned, since it has been observed that PGE_1 blocks chronotropic responses to both vagal nerve stimulation and ACh administration in guinea pig atria (136), and that PGE_2 has no effect on negative chronotropic responses (in the presence of propranolol) to electric stimulation of the rabbit sinoatrial node preparation (14). However, the original proposal of a prejunctional action (133) is supported by the recent finding that PGE_1 and PGE_2 inhibit the negative chronotropic responses to vagal nerve stimulation, but not to ACh, in the mouse heart in vivo (137). Further careful characterization of possible prejunctional and postjunctional actions of PGEs in these and other species are needed before this important issue can be settled. In this context it is worth mentioning the inhibitory effect of PGE_1 on gastric secretion induced by vagal nerve stimulation in the rat (138), since besides the heart this appears to be the only case where PGs have been reported to inhibit cholinergic responses. However, the PGs also inhibit the effect of various secretagogues (139), and the effect is presumably postjunctionally located or directly on the secretory cells.

In contrast to the antisecretory property, PGs generally stimulate gastrointestinal smooth muscle, although a few exceptions have been noted (140), and inhibition of

PG synthesis in the intestine is associated with a decrease in muscular tone (141–144). It has been argued that a low continuous PG synthesis may serve the function of maintaining the inherent tone, or that increased PG production might explain the hypermotility that occurs in various pathological conditions in the intestinal tract (141, 142).

Apart from directly affecting gastrointestinal smooth muscle, PGs have also been shown to influence the cholinergic neuroeffector transmission in this region. Thus, PGE_1 and PGE_2 enhance the contraction response to cholinergic nerve stimulation in guinea pig and rabbit ileum (51, 134, 144–146), while the effects on contractions induced by ACh are less clear; both enhanced and unchanged responses have been reported (51, 144). On the other hand, contraction responses to nerve stimulation or administration of angiotensin (a substance which partly acts by releasing ACh) are markedly reduced or almost abolished by indomethacin, and partially or completely restored by subsequent administration of small, subspasmogenic doses of PGE_1 and PGE_2 (134, 144, 147–150). The contraction response to ACh seems to be little affected by indomethacin (144, 151). Taken together, these observations provide evidence that PGEs stimulate cholinergic neuroeffector transmission in the intestinal tract, and imply that part of the stimulant effect is prejunctional on ACh release.

As an alternative to a presumed direct enhancement of ACh release, it has been suggested that PGEs affect ACh secretion indirectly by inhibiting the release of NE from adrenergic nerves (144). The experimental evidence for this assumption is that pretreatment with guanethidine or α-methyl-*p*-tyrosine (in order to block NE release) prevented the inhibitory effect of indomethacin on the muscular responses to cholinergic nerve stimulation. However, experiments in this laboratory (unpublished) have failed to confirm this observation. Indomethacin was found to be as potent in inhibiting the responses to cholinergic nerve stimulation after guanethidine treatment or degeneration of the adrenergic nerves with 6-hydroxydopamine, which implies that the inhibitory effect of indomethacin does not depend on the functional integrity of the adrenergic nerves.

Several attempts have been made to disclose a prejunctional effect of PGEs and indomethacin (or aspirin) by directly measuring the spontaneous and neurogenically induced release of ACh in the guinea pig ileum (51, 134, 136, 143, 149). However, in none of these studies was there any indication that PGE_1 and PGE_2 enhanced and indomethacin (or aspirin) reduced ACh release induced by nerve stimulation. The spontaneous release of ACh was also unchanged in most cases, although it occasionally decreased in the presence of indomethacin (143). Therefore, the observed effects of PGEs and PG synthesis inhibitors on cholinergic neurotransmission in the gut seem to be mostly, if not wholly, a postjunctional phenomenon.

PGE_1, PGE_2, $PGF_{2\alpha}$, and arachidonic acid all enhance contractions induced by cholinergic nerve stimulation and ACh in the sphincter muscle of the iris (152, 153). The effect of arachidonic acid is blocked by PG synthesis inhibitors, which in addition relax the muscle. PG release, both spontaneous and in response to nerve stimulation, has been noted (154). It is conceivable, therefore, that PGs serve the

function of maintaining tone and enhancing motor transmission (presumably postjunctionally) in this muscle. The striking similarities in the actions of PGs and PG synthesis inhibitors in this tissue and the intestinal tract suggests that this might be a principle operating in cholinergically innervated smooth muscle in general.

A mediator role in the cholinergic transmission of salivary glands has been attributed to $PGF_{2\alpha}$ (155–157). This compound, ACh, and stimulation of the corda tympani all induce salivation and increased blood flow in the canine submandibular gland. Tetrodotoxin abolishes the responses to $PGF_{2\alpha}$ and corda tympani stimulation, while those to ACh remain unchanged. Whether or not this means that $PGF_{2\alpha}$ actually facilitates ACh release from the nerve terminals is not clear and can be settled only by direct measurement of ACh release.

CONCLUSION

PGEs are potent inhibitors of neurally induced NE release and effector responses in a great number of tissues. PGEs are also released from adrenergically innervated tissues, and there is considerable in vitro and in vivo evidence that inhibition of local PGE production is associated with increased NE release and effector responses to nerve activity. It is reasonable to assume that NE release from adrenergic terminals is controlled by a local PGE-mediated feedback mechanism, which operates through restriction of availability of calcium for the NE release process, and which seems to be particularly efficient within the "physiological" frequency range of nerve impulses. The fact that even heavy intake of aspirin-like drugs (considered to block almost completely PG synthesis) does not seriously jeopardize the function of adrenergically innervated organs must mean that PGEs are not of vital importance for these organ systems. Rather, the PGEs should be regarded as one of several local inhibitory feed-back control mechanisms that act jointly to regulate adrenergic transmission. PGs other than the PGEs (particularly PGF and PGB) do not appear to take part in this scheme, because their net effect on adrenergic transmission commonly is stimulant, and because they have little or no effect on NE release in concentrations which are of physiological interest. It is conceivable therefore that the spectrum of available PGs influences adrenergic neuroeffector transmission in such a way that, depending on the specialized function of the effector organ and the PG predominantly synthesized (and the level of its synthesis), the overall effect will be either inhibitory or stimulant.

Numerous investigations have dealt with PG action (principally PGE) on cholinergic neuroeffector junctions. On most occasions the effect appears to be stimulant, although vagally induced bradycardia and gastric secretion are inhibited by PGs, and thus seem to form important exceptions. The level of action may be pre- or postjunctional, although most investigations suggest that the latter is principally affected. Release of substantial amounts of PGs occurs from stimulated tissues, and PGs and PG synthesis inhibitors generally produce opposite effects on cholinergic neuroeffector junctions. These observations merit the assumption that this system also is subject to control by locally formed PGs.

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