EDITORIAL

Basic Res. Cardiol. **76**, 239–249 (1981)

ISSN 0300–8428

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Possible role of prostaglandins in the regulation of coronary blood flow

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(Received January 5, 1981)

Summary

Prostaglandins may represent one group of local chemical factors that control coronary perfusion and adapt it to the metabolic demands of the heart. Present study summarizes the current knowledge in this field with particular reference to prostacyclin (PGI_2). The major biosynthetic pathways and their modification by drugs are briefly outlined. The sources and fates of cardiac prostaglandins are described and possible mechanisms of action discussed in both physiological and pathophysiological (myocardial ischemia) situations. Attention is focussed on the interplay between catecholamines, adenosine and PGI_2. A model is presented, based on the hypothesis that adenosine from myocardial metabolism and PGI_2 from vascular sites are acting in concert to antagonize sympathetic metabolic and vasoconstrictory influences and to maintain an adequate blood supply to the heart.

Key words: heart, myocardial ischemia, prostacyclin (PGI_2), thromboxanes, coronary vessels, cyclic AMP

Introduction

One of the first biological findings that finally resulted in the isolation of prostaglandins was the detection of the blood pressure-lowering activity of some acidic lipids in human seminal fluid by von Euler 1935 (54). However, more than 30 years passed before more systematic investigations on the actions of prostaglandins in the cardiovascular system were begun. This was mainly due to the failure to demonstrate convincing evidence that endogenous prostaglandin-like substances, known at that time, might be significant for the cardiovascular system. The situation has been changed after the detection of new, unstable prostaglandin derivatives, namely thromboxane A_2 and prostacyclin (PGI_2) (31). In addition to their actions on blood platelets, both compounds were found to possess also potent vasoactive properties (35).

In this paper, we will summarize present knowledge suggesting a participation of endogenous, prostaglandin-like substances in regulation

of coronary vascular tone. This discussion will be focussed mainly on PGI_2, because among the prostaglandin family this seems to be the most likely candidate as endogenous vasodilating principle (12, 16, 36, 41, 49).

Prostaglandin-formation and inactivation

The major source of endogenous prostaglandin-formation is arachidonic acid, which is set free from its binding-sites in cell membranes by a variety of mechanical and chemical stimuli that are evoking membrane disturbances. This is antagonized by membrane-stabilizing agents (local anaesthetics) and glucocorticoids. The availability of free precursor fatty acid is the rate-limiting step for prostaglandin-formation. Free arachidonic acid can be metabolized by a variety of enzymes, among them a fatty acid-cyclooxygenase which forms the prostaglandin-endoperoxides PGG_2 and PGH_2 and is inhibited by "aspirin-like" drugs (fig. 1). PGG_2 and PGH_2 are short-living compounds that are rapidly transformed into several final products of the cyclooxygenase pathway. In contrast to the wide distribution of the cyclooxygenases throughout the body, these further transformations of prostaglandin-endoperoxides are highly specific, yielding PGI_2 as a major derivative in vascular tisse (31, 41), and the vasoconstrictory thromboxane A_2, but no PGI_2, as a major product in blood platelets. The prostacyclin-synthetase is mainly located in the endothelial lining of the vessel wall (33). This means that each damage of the endothelium will be followed by a diminished capacity for vascular PGI_2-formation. In addition, several lipid peroxides, present in atherosclerotic plaques, are specific inhibitors of the PGI_2-synthetase (32). Interestingly, the formation of PGI_2, but not of thromboxane A_2, is specifically inhibited by nicotine (55).

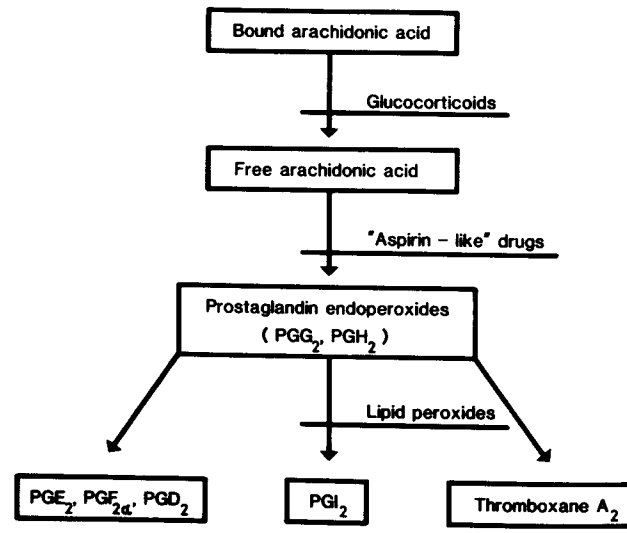

Fig. 1. Prostaglandin- and thromboxane-biosynthesis and inhibition by drugs.

Exogenous PGI_2 undergoes a rapid metabolic conversion *in vivo* (12) and is excreted as inactive product (35). Details of this inactivation are poorly understood at present. PGI_2, in contrast to other prostaglandins, is apparently not inactivated by the lung but might rather be formed by this organ and released into the circulation (19). However, whether this PGI_2 might be considered as a "circulating hormone" (34) or not (9), is still a matter of controversy. In particular, it is not clear whether 6-keto-$PGF_{1\alpha}$, the stable inactivation product of PGI_2 *in vitro,* is also formed in significant amounts in the circulation. Measurements of 6-keto-$PGF_{1\alpha}$ are probably not sufficient to estimate PGI_2 *in vivo* (21), and, according to recent investigations, the plasma level of PGI_2 in man should be below 10 pg/ml (9). However, all of the present studies agree that PGI_2 can be continuously formed in the circulation. Moreover, this vascular PGI_2-formation might be significantly increased by some plasma components or blood platelets (29, 47).

Sources and fate of cardiac PGI_2

PGI_2 within the heart or coronary vessels might derive from extracardiac sources. All vascular tissue studied so far is capable of PGI_2-biosynthesis and therefore can feed the heart with PGI_2 (35).

However, the heart is also able to produce PGI_2 by itself. This has been studied in more detail under better-controlled *in vitro* conditions. The basal release of PGI_2 from isolated perfused hearts seems to be less than 100 pg/ml (47). PGI_2 is the major prostaglandin species, released under both basal conditions as well as following stimulation by arachidonic acid, bradykinin, catecholamines or platelet infusion (9, 47, 49, 57). The most important and presumably only source of cardiac PGI_2-formation is the vascular compartment. This was suggested first by demonstrating a nearly complete conversion of exogenous prostaglandin-endoperoxides into PGI_2 by isolated coronary arteries (13), whereas cardiac microsomes failed to produce significant amounts of PGI_2 (40). Recent studies on isolated cardiac tissue in cell culture have confirmed this idea and have additionally demonstrated that cardiac myocytes are not able to form PGI_2 (2). There is also production of other prostaglandins by the heart, which, however, is low in physiologic situations (10, 49) and probably does not involve thromboxane biosynthesis (36, 49). This does not exclude that under certain pathophysiological conditions (myocardial ischemia, cardiac anaphylaxis) these non-vascular compartments of the heart together with cells of the ciruculating blood (platelets, leukocytes) become involved and produce arachidonic acid-derived vasocactive products, others than PGI_2 which might be responsible for the disturbances of coronary flow in these situations (5, 14, 25, 28). However, these considerations do not touch the basic position of a vasodilating prostaglandin species, i.e. PGI_2, and its availability for cardiac and coronary effector sites. This is also stressed by the low if any inactivation of exogenous PGI_2 during the passage of the coronary vascular bed (49).

Actions of PGI_2 on the heart and coronary vessels

There is a general agreement that the major site of action of PGI_2 in the heart is the coronary vasculature (12, 49, 52). PGI_2 relaxes coronary arteries

in vitro (13) and decreases the coronary vascular resistance *in vivo* (11). The doses, required for a 50 %-decrease in coronary vascular resistance, are in the range of a few nanograms in most of the species studied so far. Neither *in vivo* nor *in vitro* studies have provided convincing evidence that PGI_2 directly alters the myocardial force of contraction. Changes in the heart rate, sometimes observed in anaesthetized animals (11) or in man at higher doses (53), may be reflex in origin and caused by the blood pressure-lowering activity of the compound.

Stimulation of endogenous PGI_2-formation by bradykinin or arachidonic acid is associated with a decrease in coronary vascular tone (49, 52). Catecholamines stimulate PGI_2-release from the heart (57), and this might explain the enhancement of the catecholamine-induced coronary vasoconstriction after administration of indomethacin (43). However, this mechanism has to be established *in vivo*. It is also not clear whether there are direct interactions between adenosine and other coronary vasodilators, such as dipyridamole and PGI_2-release *in vivo* (48, 58).

Inhibition of basal prostaglandin-release from isolated hearts (46) or coronary arteries *in vitro* (24) is followed by an increase in the coronary vascular tone. This increase is parallelled by an inhibition of PGI_2-synthesizing capacity of the coronary vessels (26) indicating that a small, though functionally significant PGI_2-release is involved in maintenance of coronary vascular tone *in vitro*.

Comparable studies *in vivo* gave different results (1, 3, 23, 39). Certainly, it will be difficult to extrapolate one mechanism that might be involved in coronary tone-regulation, from others by measuring only the net-response of coronary flow without determination of quantitative contributions of other factors. Moreover, recent studies indicate that vascular cyclooxygenases in general might be quite resistant to inhibition by "aspirin-like" drugs (8, 51) – a finding with particular significance for selective inhibition of prostaglandin-formation by different tissue cyclooxygenases.

Exogenous PGI_2, administered at concentrations that are found endogenously, produces a dose-dependent coronary vasodilation (49). This indicates the intrinsic ability of PGI_2 to dilate coronary vessels at concentrations that can be formed by the coronary vasculature, and that this effect can be detected after removal of other modifying influences.

The D-, E- and F-type prostaglandins seem to be less important for coronary vasomotor responses (12), although one should keep in mind that some of them, e.g. PGD_2 and $PGF_{2\alpha}$, are quite potent coronary vasoconstrictors in some animal species and perhaps, are more active on a molar basis than it is thromboxane A_2 (47).

Sites and mechanisms of action

Along the coronary vascular tree the vasodilating activity of PGI_2 seems to be restricted to the arterial part. PGI_2 has little effect on coronary veins at concentrations that produce maximum relaxation of large and small coronary arteries, although coronary veins may produce significantly more PGI_2 than the arteries do (Schrör and Matzky, unpublished).

These coronary actions of PGI_2 might either be directly caused by interference with specific receptors, or indirectly mediated by interference with other mediators. The low concentrations of PGI_2, necessary to elicit coronary vasomotor responses as well as the stereoselectivity of this action, strongly suggest the presence of specific receptor sites. However, there is no direct evidence so far for the existence of specific PGI_2-receptors in vascular tissue. Certainly, the lack of specific receptor-blocking agents has considerably contributed to this dilemma. The bulk of indirect evidences today clearly suggests that PGI_2 acts on specific vascular receptors (12, 48, 50).

Alternatively, PGI_2 might interfere with formation or release of other vascular mediators, such as adenosine or catecholamines. As far as catecholamines are concerned, all of the present studies were unable to find significant alterations of nerve-stimulated transmitter release in heart (56) or arterial blood vessels (4) by PGI_2. However, PGI_2 might functionally antagonize any α-adrenoceptor-mediated coronary vasoconstriction by a direct relaxing effect on the vasculature. PGI_2 was found to reduce the adenosine release into the coronary perfusate *in vitro* (48), and the opposite was seen after inhibition of basal PGI_2-formation (43). This was not confirmed by others (58). As far as the biological significance of adenosine-PGI_2-interactions is concerned, it should be kept in mind that, on a molar basis, PGI_2 and other vasodilating prostaglandins are considerably more active than it is exogenous adenosine (44, 48).

PGI_2 and cyclic nucleotides

If PGI_2 relaxes coronary vessels after binding to a specific membrane receptor, a second messenger has to be proposed that transfers the membrane signal to the cellular effectors. PGI_2 might decrease the cAMP level of coronary arteries and hearts *in vitro* (30, 48, 50). This effect is observed at concentrations of PGI_2 lower than those which affect vascular tone (50). Others failed to detect a decrease in cAMP by PGI_2 in coronary vessels but rather observed an increase at concentrations of 10 μM PGI_2 and more (27). Certainly, the experimental design in those *in vitro* studies is quite important and a most careful attention has to be paid to establishing stable baseline conditions as indicated, e.g. by intrinsic active basal tone and time-dependent PGI_2-formation by tissue incubates. Depolarizing agents, such as potassium chloride even at "lower concentrations" of 25–30 mM, will significantly attenuate the vasodilating responses to both PGI_2 (Schrör and Kuhn, unpublished) and adenosine (22), which might be an explanation why working on potassium-contracted vessels requires such high amounts of PGI_2 for construction of dose-response relationships. It seems to be fair to conclude that the final answer to the question of whether the coronary vasodilation by PGI_2 *in vivo* is associated with changes in cyclic nucleotide content is still open. It will be interesting to speculate that the decrease of cAMP-level in coronary vascular tissue and the heart by PGI_2 might antagonize the increase in cAMP by catecholamines, being the subcellular basis for protection of the heart against catecholamine "overdrive"(52).

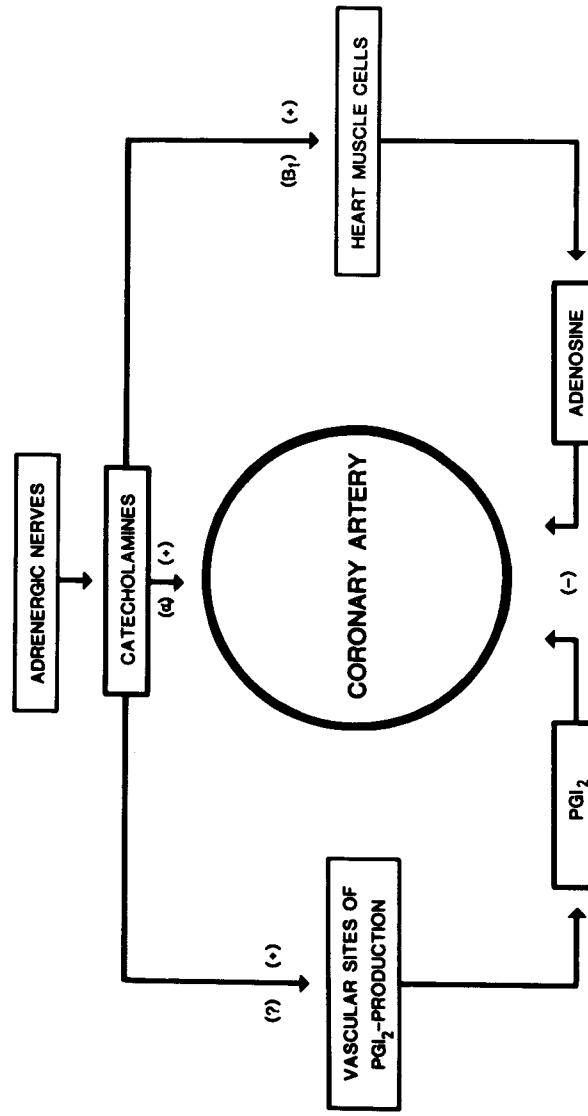

Fig. 2. The possible roles of prostacyclin (PGI_2), adenosine, and catecholamines in regulation of coronary vascular tone.

Functional significance of endogenous PGI_2 for control of coronary vascular tone

After discussion of the arguments, why the coronary vasculature of heart might be exposed to a more or less intensive continuous production of PGI_2, the question of its functional significance, in particular with respect to other mediators, such as catecholamines and adenosine, is still remaining.

A working hypothesis is demonstrated in figure 2. It is assumed that the local control system of coronary vascular tone consists of a myogenic precapillary activity, which is modulated by local positive and negative feed-back mechanisms, forming in concert the background of autoregulation (17).

The degree of myocardial oxygen demand and therefore the blood supply to this organ is decisively influenced by the adrenergic nerve activity (7) and the stimulatory action of the released catecholamines on the myocardial metabolism via β_1-adrenoceptors. On the other hand, catecholamines might directly contract coronary vessels via α-adrenoceptors (15, 43) and stimulate PGI_2-release from vascular sites via other "atypical" adrenoceptors (57). Thus, the generation of vasodilating PGI_2 from the coronary vessels and adenosine from myocardial metabolism will antagonise the catecholamine- and pressure-induced myogenic activity (17) and adapt the coronary perfusion to the oxygen demand of the heart. It is important to remember that adenosine and PGI_2 are derived from different sources and, therefore, might participate in coronary tone regulation for differing degrees, dependent on the actual base-line conditions. Thus, it is difficult to understand the degree of coronary relaxation in non-hypoxic, non-ischemic hearts in terms of the amounts of endogenously produced adenosine (18, 43). Moreover, in comparison to vasodilating prostaglandins, exogenous adenosine is a weak coronary vasodilator (44, 48). Agents like PGI_2, continuously produced by other compartments and controlled by other factors, might act in concert with adenosine to establish a most effective local vascular control and autoregulation. It is interesting to note that methylxanthines, which effectively inhibit the adenosine-induced vasodilation (18), are probably not active against PGI_2 (48), whereas adenosine (20, 45) but not PGI_2 (56) can inhibit nerve-stimulated catecholamine release and actions.

Are prostaglandins essential for coronary autoregulation? Probably, the answer will be "no". It should be realized however, that this has never been sufficiently proved, because elimination of vascular PGI_2-production by drugs is obviously incomplete and, in addition, functionally compensated for by an increase in sensitivity against exogenous PGI_2 (12, 43).

PGI_2 and myocardial ischemia

Myocardial ischemia is associated with considerably increased prostaglandin release (5, 25), and the question arises of whether this only indicates cell damage, associated with enhanced availability of precursor fatty acids, or represents some protective mechanism. Studies with inhibitors of prostaglandin formation gave conflicting results (1, 3, 39). One explanation for this might be an altered composition of the prostaglandin-fraction

and the generation of vasoconstrictor species, such as thromboxane A_2 (14). In addition, PGI_2 formation might be specifically inhibited by lipid peroxides, present in sclerotic altered vessel wall (32). Administration of PGI_2 was found to significantly protect the myocardium during acute ischemia following coronary artery obstruction in animal experiments (37, 38). Thus, myocardial ischemia might be one pathophysiological situation, associated with an increased requirement of PGI_2 to maintain sufficient regional perfusion and cellular integrity.

Zusammenfassung

Prostaglandine können als eine Gruppe chemischer Substanzen angesehen werden, die lokal entstehen und die koronare Perfusion an die Stoffwechselerfordernisse des Herzens anpassen. Vorliegende Arbeit gibt eine Zusammenfassung des heutigen Wissensstandes auf diesem Gebiet unter besonderer Berücksichtigung von Prostacyclin (PGI_2). Neben Biosynthese und Metabolismus sowie ihrer Beeinflussung durch Pharmaka werden kardiale und koronare Wirkungen von PGI_2 beschrieben und mögliche Wirkungsmechanismen der Substanz unter physiologischen und pathophysiologischen (myokardiale Ischämie) Bedingungen diskutiert. Im Mittelpunkt stehen Wechselwirkungen zwischen PGI_2, Adenosin und Katecholaminen und ihre möglichen Konsequenzen für die Regulation des koronaren Tonus. Hierzu wird ein Modell vorgestellt, bei dem die direkt-vasokonstriktorischen und stoffwechselsteigernden Katecholaminwirkungen durch Bildung von PGI_2 im Gefäßbereich und Adenosin im Herzmuskelstoffwechsel funktionell antagonisiert werden.

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