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Drugs Influencing the Vascular Production of Prostacyclin

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Aspirin

Aspirin has the capacity to block completely the release of prostacyclin (PGI_2) from vascular cells: this fact has been demonstrated in vitro for endothelial cells cultured from the human umbilical vein (1, 2) and rat aortic smooth muscle cells (3), as well as for the rabbit aorta, intact or deendothelialized (4), and pieces of human aorta or saphenous vein (5), following in vivo administration of the drug. For example, shortly after the intake of 600 mg aspirin, the increase of plasma prostaglandin 6-keto-$F_{1\alpha}$ (6-K-$PGF_{1\alpha}$) induced by the infusion of bradykinin to human volunteers, was inhibited by 90% (6). Theoretically, this inhibition of PGI_2 might decrease or even neutralize the benefit resulting from the inhibition of platelet endoperoxide and thromboxane (Tx) synthesis. Indeed, at least two studies have shown that high doses of aspirin increase the size of experimental thrombi in rabbits (7, 8). However the study of a patient with congenital deficiency in both vascular and platelet cyclooxygenase (9) suggests that the simultaneous inhibition of TxA_2 and PGI_2 formation would merely result in a mild impairment of haemostasis. A large number of studies have led to the conclusion that the inhibitory effects of aspirin on platelet TxA_2 and vascular PGI_2 are characterized by distinct kinetics and dose-inhibition curves.

A single low dose of aspirin (40 mg) has little effect on the ex vivo production of PGI_2 by human aortic buttons or saphenous vein strips obtained at surgery (5). Multiple low doses of aspirin (0.45 mg/kg per day) produce a complete inhibition of TxB_2 generation by platelets but have no effect on the urinary excretion of 6-K-$PGF_{1\alpha}$ (10). Doses of aspirin below 160 mg per day do not decrease significantly the urinary excretion of 2,3 dinor-6-K-$PGF_{1\alpha}$, an index of PGI_2 biosynthesis (11). This apparent selectivity is not due to a higher sensitivity of platelet cyclooxygenase to inhibition by aspirin, but to the reduced systemic bioavailability of aspirin, resulting from its deacetylation in liver, whereas irreversible acetylation of platelet cyclooxygenase can occur in the presystemic (portal) circulation (12). Indeed, in rats receiving a low oral dose of aspirin, the generation of portal vein PGI_2 was inhibited to almost the same extent as platelet TxA_2, while inferior vena cava PGI_2 formation was spared: this selectivity is not apparent after intravenous injection (13).

Besides differential bioavailability, another difference between platelet and vascular cyclooxygenases lies in the kinetics of recovery from inhibition by aspirin. Since platelets lack the

capacity to synthesize proteins, the recovery of TxA_2 production requires renewal of the platelet population and will be complete only 8 days after aspirin discontinuation (10). In contrast, the turnover rate of PGH synthase in vascular cells is in the order of a few hours. Human umbilical veins preexposed to aspirin fully recovered their capacity to synthesize PGI_2 in 36 hours (1, 2). As expected, recovery was prevented by the protein synthesis inhibitor cycloheximide. In humans, the release of PGI_2 in response to bradykinin infusion, returned to its control value 6 hours after aspirin intake (6). Following a 1g dose of aspirin, the urinary excretion of 2,3-dinor-6-K-$PGF_{1\alpha}$ was markedly decreased, but only for 3 hours (14). Therefore, it is likely that the inhibition by aspirin was underestimated when longer urine collections were performed (11). The rate of recovery was lower in smooth muscle cells than in endothelial cells (4, 15): this difference is likely to be related to the finding that the level of cyclooxygenase in the aortic endothelium is 20 times that of underlying smooth muscle (16). In addition, rat aortic smooth muscle cells recovered their release of PGI_2 in response to thrombin only after cell division (3). This differential recovery of PGI_2 production by distinct vascular cells might explain discrepancies in the literature concerning the time course of 2, 3 dinor-6-K-$PGF_{1\alpha}$ urinary excretion after aspirin discontinuation. After a single 1g dose of aspirin, recovery was complete within 3 hours (14), whereas it was still partial 3 days after the daily intake of aspirin, for weeks at doses up to 650 mg, 4 times a day, was stopped (11).

Steroids

Hydrocortisone and dexamethasone have been shown to inhibit the release of PGI_2 induced by histamine and bradykinin in endothelial cells from human umbilical vein (17) and bovine pulmonary artery (18) and by epinephrine in rat aortic explants (19). The inhibition was optimal after an 18–24 hours delay, but even then remained partial (± 60%). It was correlated with the presence of glucocorticoid receptors in endothelial cells; the inhibition was blocked by the glucocorticoid antagonist RU486 and was not reproduced by either progesterone, testosterone or aldosterone. Blocking of protein synthesis abolished the inhibitory effect of glucocorticoids in endothelial cells (17, 18), but not in the aortic explants (19). The conversion of exogenous arachidonic acid into PGI_2 was maintained in the presence of glucocorticoids, suggesting that their action might involve, like elsewhere, the induction of phospholipase A2 inhibitory proteins of the lipocortin family. In rabbits, the administration of dexamethasone did not decrease the urinary excretion of the major metabolites of PGE_2 and $PGF_{2\alpha}$ (20). The urinary excretion of 2, 3-dinor-6-K-$PGF_{1\alpha}$ by human volunteers was not inhibited by prednisone (60mg/day for 6 days) (Fitzgerald G. A., personal communication). It seems thus that glucocorticoids though active in vitro, do not decrease the basal rate of total body prostanoid, especially PGI_2, production: however they might decrease the elevated production associated with some disease states.

Although estrogen receptors are present in endothelial cells (21), neither 17-β-estradiol nor its analog ethinyl estradiol modified the production of PGI_2 by human umbilical vein endothelial cells (22). On the contrary, estradiol was reported to increase the level of PGH synthase and PGI_2 synthase in rat aortic smooth muscle cells (23), an action which might possibly contribute to the low incidence of atherosclerosis in premenopausal women.

Miscellanea

Tranylcypromine was the first drug reported to inhibit PGI_2 synthase (24). The antihypertensive and hair growth-promoting agent minoxidil (10–100 μM) produced a selective inhibition of PGI_2 synthesis in aortic endothelial and smooth muscle cells, which resulted in a compensatory increase of PGE_2 and $PGF_{2\alpha}$ production (25). In bovine aortic endothelial cells, vitamin K (1–100 μM) decreased the release of free arachidonic acid and the formation of both PGI_2 and PGE_2 (26). The administration of cyclosporin A to rabbits decreased the capacity of their plasma to stimulate the release of PGI_2 from aortic rings, by inhibiting the synthesis or secretion of a poorly-characterized stimulating factor (27, 28).

List of drugs which have been reported to increase vascular prostacyclin

Calcium antagonists

Escoubet et al. (29) have shown that bepridil, diltiazem and verapamil, in the 10^{-9} – 10^{-7}M range, increase the release of PGI_2 from cultured rat cardiac myocytes, but are without effect on fibroblasts; the release of PGI_2 was decreased at higher concentrations of these

drugs. A stimulatory effect of diltiazem (10^{-7} – 10^{-5}M) and nifedipine (10^{-9} – 10^{-7}M) was also observed in rat aortic smooth muscle cells (30), whereas an inhibitory effect of dihydropyridines was observed in rat aortic rings (31). In another study, diltiazem was reported to slightly potentiate the conversion of arachidonic acid into PGI_2 by the human umbilical vein (32). Stimulation of PGI_2 production is unlikely to result from Ca^{++} blockade, since in most cells, an increase of cytoplasmic Ca^{++} enhances prostaglandin synthesis: in particular, it is believed that Ca^{++} elevation is the major stimulus for the production of PGI_2 by endothelial cells (33). It might be related to other actions of these drugs: in particular, nifedipine (34), and also PGI_2 (35), activate the hydrolysis of cholesteryl esters and the efflux of cholesterol, in aortic smooth muscle cells.

Captopril

The effect of captopril on the production of PGI_2 is the subject of numerous and conflicting reports. Increased levels of 6-K-$PGF_{1\alpha}$ in response to captopril were found in: the rat aorta (36), isolated rat glomeruli (37), cultured renomedullary interstitial cells (38), the venous effluent from perfused hog kidneys (39), dog (40) and human (41) urine. Other authors failed to detect a stimulatory effect of captopril on the release of PGI_2 from the rat aorta (37), human umbilical vein endothelial cells (42) and endothelial cells of rabbit preglomerular microvessels (43). In vivo, captopril might raise the vascular production of PGI_2, by preventing the breakdown of bradykinin, a known stimulator of PGI_2 release (6).

Dazoxiben

The urinary excretion of 2, 3-dinor-6-K-$PGF_{1\alpha}$ by human volunteers is increased after a high dose (200 mg) of the thromboxane synthase inhibitor dazoxiben (44). This increase might result from the endothelial steal of platelet endoperoxides, a phenomenon which has been demonstrated in vitro (45, 46). Alternatively, the rediversion from TxA_2 to PGI_2 might occur in an organ which synthesizes both eicosanoids.

Dipyridamole

Several authors reported that dipyridamole enhances the formation of PGI_2 in various experimental models : microsomes of pig aorta (47), rings of rat (48) and rabbit (49, 50) aorta and perfused heart (47). In another study, dipyridamole (1 — 100 μM) did not induce a significant increase of PGI_2 release in any of the following experimental models : rings of rabbit aorta, cultured endothelial cells from bovine aorta or human umbilical vein, cultured explants of bovine aortic smooth muscle (51). In agreement with these negative findings, the oral administration of dipyridamole to healthy volunteers did not alter the urinary excretion of 2, 3-dinor-6-K-$PGF_{1\alpha}$ (52). However, dipyridamole (10–100 μM) prolonged the release of PGI_2 from the deendothelialized rabbit aorta (51) and delayed the exhaustion of rat aortic rings, during repetitive incubations in buffer (53). Like nafazatrom, dipyridamole is a reducing substrate for the peroxidase component of PGH synthase and can thus protect it against oxidative inactivation (54). The relevance of this in vitro effect to the clinical efficacy of the drug is questionable, since it is obtained in the 10–100 μM range, whereas therapeutic concentrations range from 2 to 6 μM, and most of the drug is bound to plasma proteins. The antiplatelet action of dipyridamole is better explained by the decreased uptake into erythrocytes and endothelial cells of adenosine, an inhibitor of platelet activation, than by an hypothetical enhancement of vascular PGI_2 production (52, 55).

Diuretics

It is well-known that furosemide-induced renin release is associated with an increased formation of PGI_2 in the kidney and urinary excretion of 6-K-$PGF_{1\alpha}$ (10, 56). It has been reported that furosemide and bumetanide enhance the transformation of exogenous arachidonic acid into PGI_2 by rat aortic smooth muscle cells (57). Treatment of mildly hypertensive patients with bendroflumethiazide was reported to increase their plasma level of 6-K-$PGF_{1\alpha}$ from ± 80 pg/ml to ± 200 pg/ml (58): the meaning of this observation is questionable, since it was later shown that the true plasma concentration of 6-K-$PGF_{1\alpha}$ is < 3 pg/ml (59).

Interferon

Interferon, now used for the treatment of several neoplasic diseases, enhances the production of PGI_2 by cultured vascular endothelial cells (60). Its action does not involve the release of free arachidonic acid, but rather the induction of

PGH synthase : indeed, interferon had no effect on the basal synthesis of PGI_2 and increased the conversion of exogenous arachidonic acid, but not of PGH_2, into PGI_2 (60).

Magnesium sulfate ($MgSO_4$)

Several studies have suggested that a deficiency in PGI_2 might play a role in the pathogenesis of preeclampsia. A traditional therapy of preeclampsia involves the intravenous infusion of MgSO4. It was recently shown that the release of PGI_2 from human umbilical vein endothelial cells, either under basal conditions or in the presence of exogenous arachidonate, is increased when the extracellular concentration of Mg^{++} is raised, within the 1.5 to 3.0 mM range (61).

Nafazatrom

Nafazatrom has a marked antithrombotic effect on experimentally-induced thrombosis in arteries and veins of various animals (62). No effect on coagulation, fibrinolysis or platelet aggregation could be detected in vitro or ex vivo (62). Vermylen et al (63) made the initial observation that plasma drawn from volunteers after the ingestion of single doses of nafazatrom increased the release of PGI_2 (measured in a platelet aggregation bioassay) from exhausted rat aortic strips (that is strips which have been washed repeatedly until they stop releasing an antiaggregating activity). Similar observations were made with normal and diabetic rabbits (64) and it was later shown that nafazatrom, like dipyridamole, prolongs the release of PGI_2 from the rat aorta (53). Nafazatrom enhanced the conversion of arachidonic acid into PGI_2 and other PGs in kidney cortex microsomes and the production of TxB_2 by platelets having a high level of 12-hydroperoxy-eicosatetraenoic acid (HPETE), which was reduced under the influence of nafazatrom (65). Nafazatrom is an extremely reactive scavenger of free radicals (66) and constitutes a potent reducing substrate for the peroxidase component of PGH synthase (54). It will therefore protect PGH and PGI_2 synthase, against oxidative irreversible inactivation, due to the substrate itself (PGG_2) or to hydroperoxy fatty acids (like 15-HPETE). Other nitrogen heterocycles, like BW-755C at low concentrations (67), or dipyridamole (51, 53), will act in the same way. Nafazatrom also inhibits the C_5-lipoxygenase of neutrophils, but not the C_{12}-lipoxygenase of platelets (62); its capacity to inhibit 15-hydroxyprostaglandin dehydrogenase is unlikely to contribute significantly to an increase of vascular PGI_2 (68). In conclusion, it seems that the effects of nafazatrom on vascular PGI_2 production will be small under normal conditions : however, in particular circumstances, the drug might protect the capacity of vascular cells against "exhaustion" which involves the oxidative irreversible inactivation of PGH_2 (or PGI_2) synthase.

Nitrates

Levin et al (64) made the initial report that nitroglycerin, at therapeutic concentrations (0.1–10 ng/ml), enhanced the release of PGI_2 from human umbilical vein endothelial cells; however, the magnitude of this effect was small (± 60% above the control value). A similar stimulatory effect of nitroglycerin was reported in bovine coronary arteries (70) and in human saphenous vein (71). Further studies by De Caterina et al (72) failed to detect a significant stimulatory effect of nitroglycerin and isosorbide mononitrate or dinitrate on the release of PGI_2 from human umbilical vein endothelial cells and from fragments of human saphenous vein and mesenteric artery. In agreement with these negative results, the infusion of nitroglycerin at a rate inducing a significant hypotension, or the oral administration of isosorbide dinitrate to human volunteers, did not modify their urinary excretion of 2, 3-dinor-6-K-$PGF_{1\alpha}$ (73). Furthermore, indomethacin does not inhibit the haemodynamic effects of nitrates in dogs (74) and man (75). The current consensus is thus that nitrates do not modify significantly the vascular production of PGI_2. Recent data indicate that endothelial cells release an endogenous nitrate, probably NO, which is responsible for endothelium-dependent relaxation and synergizes with PGI_2 to inhibit platelet activation (76). The focus has thus been shifted from nitrates acting on endothelial cells to endogenous nitrates produced by endothelial cells and acting on neighbouring smooth muscle cells and platelets.

Pentoxifylline

Pentoxifylline, an agent known to decrease blood viscosity, has been reported to stimulate the release of PGI_2 from the rat aorta and kidney cortex (77–80). However, these effects had a small magnitude and could not be reproduced in other studies (Boeynaems, J. M., unpublished data).

Streptokinase

The urinary excretion of 2, 3-dinor-6-K-$PGF_{1\alpha}$ was markedly increased after intravenous streptokinase in patients with acute myocardial infarction (81). This increase of PGI_2 biosynthesis is likely to result from platelet activation by streptokinase, which is presumably mediated by plasmin. The vascular production of PGI_2 is indeed increased in a variety of disease states characterized by the intravascular activation of platelets, as for instance unstable angina, during the pain episodes (82). In vitro, several platelet secretory products stimulate the release of PGI_2 from vascular endothelial and smooth muscle cells : ATP and ADP (83, 84), serotonin (85, 86), platelet-derived growth factor (85) and thromboxane A2 (87).

Suloctidil and SKF 525-A

These drugs induced a large and sustained release of PGI_2 from cultured aortic endothelial cells and from aortic fragments, resulting from an increased mobilization of free arachidonic acid (88–90, 76). It is however unlikely that this effect of suloctidil plays a major role in its antithrombotic action, since it was only obtained at high concentrations (89). A preliminary study of structure-activity relationship among various analogs of SKF 525-A, a well-known inhibitor of cytochrome P-450 and drug metabolism, might constitute a starting point for the design of more potent drugs (90). SKF 525-A also induces the release of endothelium-derived relaxing factor (76).

Vitamin C

Vitamin C moderately increased the release of PGI_2 from rat and rabbit aortic rings and completely neutralized the inhibitory effect of 15-HPETE (91). Feeding a cholesterol-rich diet to rabbits results in intimal thickening, lipid infiltration and decreased PGI_2 production in the aorta ; addition of vitamin C (500 mg/day) to the diet kept the intimal release of PGI_2 at normal levels (92). Like in the cases of dipyridamole and nafazatrom, the action of vitamin C is not due to an increased mobilization of free arachidonic acid, but probably to the protection of PGH and PGI_2 synthases against oxidative inactivation

Prostacyclin-stimulating drugs : mechanisms, evaluation and significance

A drug can stimulate the vascular production of PGI_2 by a direct action on vascular cells, or indirectly. Dazoxiben and streptokinase represent two drugs whose mechanism of action is indirect. Streptokinase activates platelets and induces their secretion of factors which can stimulate directly the release of PGI_2 from endothelial and smooth muscle cells. By blocking TxA_2 synthase in platelets and other cells, dazoxiben provokes an accumulation of prostaglandin endoperoxides which can be utilized as substrate by the PGI_2 synthase of vascular cells. Some drugs, like suloctidil and SKF 525-A, have a direct effect on endothelial cells; they stimulate PGI_2 synthesis by increasing the availability of free arachidonic acid. Interferon enhances the endothelial production of PGI_2 in response to agonists which mobilize free arachidonate, via the induction of PGH synthase. Several drugs have been claimed to increase vascular PGI_2, but many of these reports are not convincing. In the case of nitrates, the initial data simply could not be reproduced later. In many studies, the magnitude of the stimulatory effects was so low that their significance is questionable. In some studies, the methodology for the assay of PGI_2 or 6-K-$PGF_{1\alpha}$ was inadequate : reports in which the plasma level of these compounds is 0.1 ng/ml or more (for instance, 49, 57) are clearly inaccurate since the true plasma concentration of 6-K-$PGF_{1\alpha}$ is < 3 pg/ml (59).

Various experimental models have been used to test the action of drugs on vascular PGI_2: microsomes, cultured endothelial and smooth muscle cells, vascular strips. Results obtained in one or the other of these in vitro systems are not necessarily predictive of the in vivo situation. It could therefore be considered that the ultimate criterion would be provided by the measurement of the urinary excretion of 2, 3-dinor-6-K-$PGF_{1\alpha}$, an index of PGI_2 total body production (93). However, this measurement does not distinguish between vascular and extravascular sources of PGI_2. Furthermore, the action of a drug potentiating the synthesis of PGI_2, stimulated for instance by platelet factors, rather than inducing it per se, might not be apparent in healthy volunteers, but only in patients with intravascular platelet activation.

The usefulness of a drug which would induce the release of PGI_2 from blood vessels, more or less everywhere in the body, seems to be questionable. Such a drug would mimic an infusion of exogenous PGI_2 and might induce troublesome haemodynamic effects besides the beneficial

antiplatelet actions. PGI_2 appears now as a local and intermittent mediator of platelet-vessel wall interaction, whose release from vessels following lesions or in response to platelet factors, constitutes a compensatory mechanism, intended to limit platelet aggregation. A drug which could amplify this protective mechanism might be useful : it would act locally without producing systemic side-effects. If PGI_2 release from endothelial cells is controlled exclusively by the cytoplasmic level of free Ca^{++} (33), it would be difficult to potentiate or prolong the rise of this level and hence of PGI_2 synthesis without altering other functions of the endothelium. However, recent studies suggest that, at least in some cell types, the synthesis of prostaglandins is selectively controlled by the coupling of membrane receptors to phospholipase A_2, via stimulatory or inhibitory GTP-binding proteins (94, 95). Cholera and pertussis toxins, which catalyze the ADP-ribosylation of these G proteins and often block their function, amplify the release of PGI_2 from aortic endothelial cells stimulated by ATP (96). These data suggest the existence of an inhibitory mechanism of control, which might become the target of pharmacological agents.

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