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Prostacyclin and Vascular Disease

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Prostacyclin and vascular disease

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We hypothesize that prostacyclin (PGI_2) is an anti-atherosclerotic hormone and that atherosclerosis develops when endothelial PGI_2 synthetase is inhibited by lipid peroxides. Serum lipid peroxides occur in low-density lipoproteins (LDL). LDL lipid peroxides are elevated in common types of hyperlipoproteinaemias, PGI_2 generation is impaired in atherosclerosis, and infusion of synthetic PGI_2 into patients alleviates symptoms resulting from arteriosclerosis obliterans, central retinal vein occlusion or spontaneous angina.

Introduction

Prostacyclin (PGI_2) is a potent stimulator of platelet adenylate cyclase (Gorman *et al.* 1977; Tateson *et al.* 1977). Therefore, it inhibits platelet aggregation (Gryglewski *et al.* 1976, Moncada *et al.* 1976*a*) and disaggregates platelet clumps (Gryglewski *et al.* 1978*a*). PGI_2 is also a vasodilator, especially in the pulmonary circulation (Kadowitz *et al.* 1980) and stimulates the release of a plasminogen activator from the lungs (Hechtman *et al.* 1980). PGI_2 is generated by arterial walls (Bunting *et al.* 1976; Gryglewski *et al.* 1976; Moncada *et al.* 1976*a*, *b*), lungs (Gryglewski 1978*b*, *c*, 1979*a*, *b*; Moncada *et al.* 1978), kidneys (Whorton *et al.* 1977; Remuzzi *et al.* 1978; Silberbauer *et al.* 1979), uterus (Vesin *et al.* 1979; Williams *et al.* 1978) and the other organs (Pace-Asciak & Rangaraj 1977). The lungs continuously secrete PGI_2 into arterial circulation (Gryglewski *et al.* 1978*b*, *c*; Moncada *et al.* 1978) and this secretion is stimulated by hyperventilation (Gryglewski *et al.* 1978*b*) or activation of chemoreceptors (Gryglewski *et al.* 1978*b*), or activation of chemoreceptors (Gryglewski *et al.* 1980*a*) as well as by angiotensin II (Gryglewski 1979*a*; Gryglewski *et al.* 1979, 1980*b*), bradykinin (Mullane & Moncada 1980) and acetylcholine (Gryglewski *et al.* 1980*a*).

Lipid peroxides, including 15-hydroperoxyeicosatetraenoic acid (15-HPETE, 15-HPAA), inhibit PGI_2 synthetase in porcine aortic microsomes (Gryglewski *et al.* 1976; Moncada *et al.* 1976*b*; Salmon *et al.* 1978). 15-HPETE inactivates the enzyme also in rabbit arterial slices (Bunting *et al.* 1976) and in cultured human endothelial cells (Marcus *et al.* 1978), possibly as the result of peroxidative reduction of lipid hydroperoxides and the release of $[O_x]$ (Kuehl *et al.* 1980). We believe that PGI_2 is a natural anti-atherosclerotic hormone (Gryglewski 1979*a*), and its removal from the body may initiate atherosclerotic process (Gryglewski 1980).

Indeed, the generation of PGI_2 by aorta, mesenteric arteries, heart (Dembińska-Kieć *et al.* 1977; Gryglewski *et al.* 1978*d*), lungs and kidneys (Dembińska-Kieć *et al.* 1979) in experimental atherosclerosis in rabbits, and this can be detected within a week of feeding the rabbits an atherogenic diet (Masotti *et al.* 1979). In atherosclerosis, arachidonic acid metabolism may be diverted from PGI_2 to other prostaglandins (Dembińska-Kieć *et al.* 1979) or to thromboxane A_2 (Szczeklik & Gryglewski 1978; Szczeklik *et al.* 1978*a*; Żmuda *et al.* 1977).

Although there exists no direct evidence that human atherosclerosis is causally associated

with an increased lipid peroxidation, lipid peroxides have been found in human atherosclerotic arteries (Glavind *et al.* 1952; Hartroft & Prta 1965). Human atheromatic plaques generate very little PGI_2 (Angelo *et al.* 1978). Atherogenic low-density lipoproteins (LDL) were reported to inhibit the generation of an anti-aggregatory principle by cultured human endothelial cells (Nordøy *et al.* 1978) and to damage them (Henriksen *et al.* 1979), while anti-atherogenic high-density lipoproteins (HDL) prevented the deleterious action of LDL (Henriksen *et al.* 1979; Nordøy *et al.* 1978). We have recently found (Szczeklik & Gryglewski 1980) that lipid peroxides occur mainly in LDL while HDL are free from them.

The above indirect evidence for involvement of lipid peroxidation and PGI_2 deficiency in pathogenesis of atherosclerosis stimulated clinical trials with PGI_2 in arteriosclerosis obliterans. In 1978 we infused PGI_2 into healthy volunteers (Gryglewski *et al.* 1978*e*, Szczeklik *et al.* 1978*b*) and found that pharmacologically active doses of PGI_2 are within the range 1–20 ng kg^{-1} min^{-1}, intravenously. Moderate lowering of diastolic blood pressure, prolongation of bleeding time, reddening of the face and palms as well as inhibition of platelet aggregation and dissipation of circulating platelet aggregates were the most prominent pharmacological actions of PGI_2. A year later PGI_2 was administered to the first five patients suffering from arteriosclerosis obliterans (Szczeklik *et al.* 1979), and the number of the treated patients has now considerably increased (Szczeklik *et al.* 1980*a*). Patients with central retinal vein occlusion were also treated with PGI_2 (Żygulska-Mach *et al.* 1981).

Patients and methods

Fifty patients (44 men and 6 women) were treated with PGI_2. Arteriosclerosis obliterans was diagnosed in 36 patients (46–76 years old) and thrombangiitis obliterans in 12 (33–44 years old). Two women (24 and 26 years old) suffered from Takayasu disease of the lower extremities. In all but 3 patients the diagnosis was confirmed by angiographic examination.

Ischaemia at rest was recorded in 44 patients as evidenced by rest pain, ischaemic ulceration or necrosis. Only in 6 patients was physical exercise (walking) necessary to induce pain. Of the 50 patients, 7 had undergone vascular reconstructive surgery, 8 perivascular sympathectomy, 5 amputation of toe or foot and 5 amputation of leg beneath knee. In the past, therapy with vasodilators (Complamin, Tolazoline, Bamethan) was tried without success.

Sodium salt of PGI_2 (Upjohn Co., Kalamazoo, U.S.A. and Wellcome Research Laboratories, Beckenham, U.K.) was dissolved in 0.1 M glycine buffer at pH 10·5 and infused into the femoral artery (33 patients) or subclavian vein (17 patients) at a dose of 2–10 ng kg^{-1} min^{-1} for 72 h. The infusion rates of PGI_2 were maintained at as high a level as the patients could tolerate. In 20 patients the PGI_2 therapy was repeated 2–4 times every 1–20 weeks. The total observation period for 50 patients studied was 3–17 months. No pharmacological treatment other than PGI_2 was prescribed.

Three patients (1 man and 2 women, 63–72 years old) with a sudden unilateral loss of vision resulting from the occlusion of the central retinal vein were infused with PGI_2 into a subclavian vein, at the doses indicated above. PGI_2 was administered 24 h, 48 h or 7 days after the first symptom of the disease had been reported by the patient.

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Results

Infusions of PGI_2 made the affected leg become dry and hot. Erythema usually appeared. Platelet aggregability was suppressed for up to 3 h after the termination of the infusion of PGI_2. Side effects of the PGI_2 therapy were, in diminishing order of frequency: pain in the infused leg, headache, jaw articular pain, nausea, lowering of diastolic arterial pressure, cardiac ventricular arrhythmias. Moderate hyperglycemia was recorded in several patients, especially in those with otherwise balanced diabetes. Because of rest pain, 23 patients had to rely on narcotic or non-narcotic pain-killers administered several times daily. In 15 of those 23 patients, the pain was abolished for a period of 4 weeks to 16 months, the day after termination of the infusion of PGI_2. In half of the 32 patients with ischaemic ulcers, partial or complete healing was observed, while in 7 patients with deep penetrating necrosis, no improvement occurred. In 5 out of 6 patients with intermittent claudication, PGI_2 caused a sustained increase in walking distance (4 km/h) by at least 50 %.

Patients with central retinal vein occlusion suffered from generalized atherosclerosis or hypertension. Their visual acuity in the affected eye was 1/50–2/50, while ophthalmoscopic examination revealed venous dilation and tortuosity, oedema of various regions of the retina, and punctate and small round haemorrhages scattered in the fundus. A dramatic improvement was observed in two patients to whom PGI_2 had been administered 24 and 48 h after the sudden diminution of vision.

Two months later their visual acuity was 0.2 and 0.5 and the regression of retinal oedema, haemorrhages and other lesions was nearly complete.

No improvement was observed in the patient who had received the treatment on the seventh day of the disease. Five months later his visual acuity was still 1/50, with oedema of the optic disc and retina, and haemorrhages and dilatation of the retinal vein.

Discussion

The effectiveness of the PGI_2 therapy in arteriosclerosis obliterans seemed to depend on the localization of the obliterating lesions in arteries, the existence of collateral circulation and the advancement of the disease (Szczeklik *et al.* 1980*a*). Our group of patients was not homogeneous; nevertheless, 88 % of them suffered from the symptoms of ischaemia at rest, including focal necrosis, ischaemic ulcers and pain. In those patients, anticoagulant or vasodilator drugs are of little value (Coffman 1979), as we have confirmed in our patients. In 40 % of this group of patients, single or repeated courses of the PGI_2 therapy resulted in a long-term clinical improvement. We therefore assume, from the benefit derived, that in those patients PGI_2 substituted the lacking anti-atherosclerotic endogenous hormone. The results of our clinical trials fully support the initiation of controlled clinical studies on the effectiveness of PGI_2 in arteriosclerosis obliterans.

A therapeutic improvement was achieved in two patients that had been treated with PGI_2 24 and 48 h after a sudden occlusion of central retinal vein but not in the patient that received the treatment on the seventh day of the disease. In 28 patients to whom PGI_2 (5–10 ng kg^{-1} min^{-1}, intravenously) was administered because of arteriosclerosis obliterans of the lower extremities, we did not observe any vasodilatation of retinal blood vessels (our unpublished data). Therefore, it might be that a disaggregatory action of PGI_2 was responsible for the

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reopening of retinal blood vessels that were occluded with fresh platelet clumps. It is tempting to speculate that the PGI_2-induced release of a plasminogen activator from lungs may also contribute to the effectiveness of PGI_2 in occlusive vascular disease (Hechtman *et al.* 1980).

Central retinal vein occlusion is usually treated with heparin, streptokinase, urokinase, steroidal and non-steroidal anti-inflammatory drugs, dextran, vasodilators, vitamin C or P (Anon 1979; Coscas & Dhermy 1978). According to Rubinstein & Jones (1976) of 143 patients treated pharmacologically, the regression of retinal lesions was complete only in 11. In our ophthalmological clinic, 48 patients with acute occlusion of central retinal vein were treated with heparin, vitamin C and nicotinic acid derivatives. In 32 patients visual acuity showed no change.

Patients with occlusion of the central retinal vein suffer from late complications of the disease such as secondary glaucoma, maculopathy and proliferation of new vessels. These are usually treated with xenon-arc or laser photocoagulation (May *et al.* 1979). The above complications have not so far developed in the patients treated with PGI_2. A rapid improvement and lack of late complications in two patients treated with PGI_2 at the early stage of the disease encourages further studies on the therapeutic use of PGI_2 in acute occlusion of the central retinal vein and, possibly, of other cerebral blood vessels.

PGI_2 has also been successfully used in the treatment of spontaneous angina (Szczeklik *et al.* 1980*b*). There exists an experimental basis for clinical trials with PGI_2 in preventing of rejection of renal transplants (Leithner *et al.* 1980), in treatment of pulmonary embolism (Utsunomiya *et al.* 1980) and in supplementation of heparin during haemodialysis and haemoperfusion (Bunting *et al.* 1979; Weston *et al.* 1979). The effectiveness of PGI_2 in vascular occlusive disease seems to be associated with its anti-aggregatory, disaggregatory and anti-releasing actions on blood platelets. The prevention of activation of the coagulation system derives from the effects of PGI_2 on platelets. The activation of fibrinolytic systems by PGI_2 in the lungs constitutes a new concept of its action (Hechtman *et al.* 1980).

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