Arachidonic acid is the parent of all prostaglandins containing two double bonds and is the most abundant fatty acid precursor of prostaglandins in membrane phospholipids. It is released from cell membranes by phospholipases, but not much is known about the activation of these enzymes. However, both chemical and mechanical stimulation can result in the generation of prostaglandins.

For many years it was thought that the only products of arachidonic acid metabolism were the chemically stable prostaglandins such as PGE$_2$ and PGF$_{2\alpha}$. However, in the last 5 or 6 years chemically unstable derivatives of arachidonic acid have been discovered to be of major importance especially in platelets and the vessel wall. In platelets arachidonic acid is mainly converted into thromboxane A$_2$ (TXA$_2$), an unstable vasoconstrictor and platelet-aggregating substance [1], and in the vessel wall to prostacyclin (PGI$_2$), an unstable vasodilator and anti-aggregating compound [2]. Prostacyclin and TXA$_2$ represent therefore, in biological terms, the opposite poles of a homeostatic mechanism for regulation of platelet aggregability in vivo. Manipulation of this control mechanism will affect thrombus and haemostatic plug formation.

The generation of TXA$_2$ in platelets is inhibited by aspirin and other aspirin-like drugs [3] and this explains why, before the discovery of prostacyclin, aspirin was widely promoted as an antithrombotic drug. However, it is now clear that these drugs also inhibit prostacyclin formation in the vessel wall and, therefore, could have a less than beneficial effect.

We have suggested [4] that drugs which selectively inhibit TXA$_2$ formation will have a superior antithrombotic effect to aspirin. Several of these 'thromboxane synthetase' inhibitors have been discovered and some could be ready for testing in humans in the near future.

Prostacyclin inhibits platelet aggregation by stimulating adenylate cyclase, leading to an increase in adenosine 3':5'-cyclic monophosphate (cyclic AMP) levels in the platelets [5, 6]. In both respects, prostacyclin is much more potent than either PGE$_1$ or PGD$_2$ [6]. Prostaglandin endoperoxides and TXA$_2$ reduce a raised cyclic AMP level in platelets [7]. Because of these opposite effects we and others have suggested that a balance between TXA$_2$ and prostacyclin formation regulates platelet cyclic AMP and therefore platelet aggregability in vivo. This proposition has been reinforced by the finding that prostacyclin is a circulating hormone [8, 9]. Unlike other prostaglandins such as PGE$_2$ and PGF$_{2\alpha}$, prostacyclin is not inactivated on passage through the pulmonary circulation [10]. Indeed, the lungs constantly release small amounts of prostacyclin into the circulating blood, perhaps from the huge mass of endothelial cells in the pulmonary vessels [8, 9]. The concentration of prostacyclin is higher in arterial than in venous blood for there is about 50% overall inactivation in one circulation through peripheral tissues [10]. This difference, originally obtained in experimental animals, has now been confirmed in man [11].

We have proposed that prostacyclin protects the vessel wall against deposition of platelet aggregates, so providing at least a partial explanation of the long recognized fact that contact with healthy vascular endothelium is not a stimulus for platelet clumping. Damage to a vessel is followed by platelet adhesion to the affected site. The degree of injury is an important determinant and there is general agreement that, for the development of thrombosis, severe damage or physical detachment of the endothelium must occur. These observations are in accordance with the distribution of prostacyclin synthetase, for it is abundant in the intima.
Indeed, the endothelial cell itself is the most active in generating prostacyclin. There is then a progressive decrease in concentration of the enzyme from the intima to the adventitia [12]. Moreover, the pro-aggregating elements increase from the subendothelium to the adventitia. These trends render the endothelial lining anti-aggregatory and the outer layers of the vessel wall much more thrombogenic.

Prostacyclin inhibits aggregation (platelet–platelet interaction) at much lower concentrations than those needed to inhibit adhesion (platelet–collagen interaction) suggesting that prostacyclin allows platelets to stick to damaged vascular tissue and begin the repair process while at the same time preventing or limiting thrombus formation [13]. Interestingly, in such a situation of close physical proximity, the platelet could contribute endoperoxide intermediates to the vessel wall, thereby increasing prostacyclin generation.

Can disturbances in the \( \text{PGI}_2/\text{TXA}_2 \) balance be linked to any diseases? There are certainly some strong indications that they can. Lipid peroxides are potent inhibitors of prostacyclin synthetase [14] and selective inhibition of prostacyclin formation by these substances could lead to increased platelet aggregation, which in turn could play a role in the development of atherosclerosis. Indeed, lipid peroxidation takes place in plasma as a non-enzymic reaction and atherosclerotic plaques contain lipid peroxides [15, 16]. Hence, lipid peroxides could be shifting the balance of the system in favour of \( \text{TXA}_2 \) and may predispose to thrombus formation. In this context it is interesting that there is a strong reduction in prostacyclin formation by the heart or vessel walls of rabbits made atherosclerotic [17]. Similarly, human atherosclerotic tissue does not produce prostacyclin, whereas tissue obtained from a nearby normal vessel does [18].

There are also now reports that low-density lipoprotein (LDL) inhibits prostacyclin production, an effect neutralized by high-density lipoprotein [19]. One of these (Gryglewski and colleagues, unpublished work) identifies LDL as a lipid peroxide carrier. Increased production of \( \text{TXA}_2 \) \text{in vivo} by platelets has been found in patients with arterial thrombosis or recurrent venous thrombosis [20], conditions associated with a shortened platelet survival time. In addition, increased sensitivity to aggregating agents and increased release of \( \text{TXA}_2 \)-like activity has been described in rabbits made atherosclerotic by diet [21] and in patients who have survived myocardial infarction [22]. Increased levels of \( \text{TXB}_2 \) (a stable end-product of \( \text{TXA}_2 \)) have also been observed in patients during attacks of angina [23]. Moreover, platelets from rats made diabetic release more \( \text{TXA}_2 \) and their vessel walls produce less prostacyclin [24, 25], and there are reports of similar results in man [26, 27]. Other diseases associated with changes in prostacyclin production include uraemia, where the associated haemostatic defect has been attributed to increased prostacyclin production [28]. Conversely, a lack of prostacyclin production has been suggested in patients with thrombotic thrombocytopaenic purpura [29]. Both diseases are linked by the accumulation during uraemia or the lack of production during thrombotic thrombocytopaenic purpura of a 'plasma factor' which stimulates prostacyclin synthesis [30]. Finally, increased prostacyclin production has been described in blood vessels of the spontaneously hypertensive rat [31]. Thus, it seems that diseases which favour the development of thrombosis are associated with an increase in \( \text{TXA}_2 \) and a decrease in prostacyclin formation, whereas an increased prostacyclin formation plus decreased \( \text{TXA}_2 \) is present in some conditions associated with an increased bleeding tendency.

Prostacyclin or chemical analogues will find a use in extracorporeal circulation systems [32] such as cardiopulmonary bypass and renal dialysis. In these systems the main problems are platelet loss with the formation of micro-aggregates which, when returning to the patient, are responsible for the cerebral and renal impairment sometimes observed after bypass [33]. In addition, there are side-effects associated with the chronic use of heparin, especially the development of osteoporosis [34].

Several anti-platelet drugs have been tested in these two situations and some have been used with moderate success. \( \text{PGE}_1 \) has been reported to be beneficial during cardiopulmonary bypass [35]. However, prostaglandins of the E-type induce diarrhoea, an effect not shared by prostacyclin [36, 37]. Therefore prostacyclin is not only more potent but more specific in achieving platelet protection. Prostacyclin was originally used in several systems of extracorporeal circulation in experimental animals, including renal dialysis [38], cardiopulmonary bypass [39] and charcoal haemoperfusion [40]. In these experiments it proved to be active in protecting against platelet loss and formation of micro-aggregates. More recently, clinical trials have been conducted during cardiopulmonary bypass operations [41] and charcoal haemoperfusion [42]. In these trials platelet protection, decreased formation of micro-aggregates and an improved
haemostatic function after the procedure has been demonstrated.

After reports that PGE\(_1\) has been used successfully in the treatment of peripheral vascular disease [43] prostacyclin has been shown to have a similar effect, producing a long lasting increase in muscle blood flow, disappearance of ischaemic pain and healing of trophic ulcers after an intra-arterial infusion to the affected limb for 3 days [44, 45].

Current use of antithrombotic drugs which act on platelets has been largely based on their ability to inhibit platelet cyclo-oxygenase, the foremost example being aspirin. A newer approach is represented by the thromboxane synthetase inhibitors, which might have a superior antithrombotic effect as discussed above. However, the arachidonic acid pathway of platelet aggregation is only one of at least three possible types of aggregation, the other two being the thrombin and the adenosine diphosphate (ADP) pathways. The direct effects of these two substances are not affected by aspirin-like drugs. All three pathways, however, are inhibited by substances which increase cyclic AMP in the platelets either by stimulating the enzyme (adenylate cyclase) which induces this increase, as do PGE\(_1\), PGD\(_2\) and prostacyclin, or by inhibiting the phosphodiesterase enzyme which degrades it, as does dipyridamole.

So far, prostacyclin is the most potent and comprehensive inhibitor of all forms of aggregation. This fact, together with the endogenous nature of prostacyclin, clearly suggests that the future of antithrombotic therapy for cardiovascular disease, including myocardial infarction, deep vein thrombosis, etc., lies in the development of compounds with a 'prostacyclin'-type of action which are long-acting, orally active and probably free from the cardiovascular effects of prostacyclin.

References


