Prostacyclin (PGI_2) inhibits the formation of platelet thrombi induced by adenosine diphosphate (ADP) *in vivo*

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An enzyme located in vascular endothelium converts prostaglandin endoperoxides into an unstable substance (prostacyclin; PGI_2) which inhibits ADP-induced platelet aggregation *in vitro* (Moncada, Gryglewski, Bunting & Vane, 1976). It has been suggested that PGI_2 plays an important role in protecting blood vessel walls from platelet deposition.

The formation of intravascular platelet thrombi in the micro-circulation of the hamster cheek pouch was studied using the method of Begent & Born (1970). The everted cheek pouch was superfused at 5 ml/min with a modified Krebs bicarbonate solution at 36°C and micropipettes (tip diameter = 2.5–5.0 μm), containing ADP (10^{-2} M) were placed with micro-manipulators so that their tips were close to the walls of small blood vessels. ADP was applied to the vessel wall iontophoretically with a current between the micropipette and a reference electrode immersed in the superfusing solution.

Currents of up to 500 nA applied to pipettes filled with 0.9% (w/v) saline did not cause formation of thrombi. With ADP-filled pipettes, in the absence of current, platelet thrombi did not appear in the blood vessels. When a current of 200–300 nA was applied, thrombi appeared on the vessel wall close to the tip and at sites downstream from the tip. During continuous application of ADP, thrombi adhered to the vessel walls for up to 3 min before they embolized and were swept away in the blood stream. The embolization of platelet thrombi was filmed at 24 frames/s and a measure of mean blood flow was obtained by analyzing the film (Begent & Born, 1970).

The mean time of ADP application required to induce the formation and embolization of platelet thrombi in venules (30–40 μm in diameter) in which the mean blood flow was 1.0–1.5 mm/s was 20.8 s (±3.2 s.e. mean; range, 4.6–34.1; 8 experiments). Prostacyclin or its stable metabolite, 6-keto $PGF_{1\alpha}$ (Johnson *et al.*, 1976) were dissolved in 50 nM Tris buffer (pH 7.6) and infused at 0.05 ml/min into the inlet of the superfusing stream (5 ml/min). PGI_2 (1, 10 or 100 ng/ml) caused concentration-dependent increases in the time of ADP application required to induce thrombi formation; with 100 ng/ml, the mean time was 110 ± 24.3 s (6 experiments). 6-Keto $PGF_{1\alpha}$ had no effect at concentrations up to 10 μg/ml. In four experiments when the concentration of PGI_2 in the superfusing fluid was 1 μg/ml, repeated application of ADP for periods of 5 min failed to induce thrombi formation. In these experiments the response to ADP returned to normal 30 min after the infusion of PGI_2 had stopped. Concentrations of PGI_2 (up to 1 μg/ml) or 6-keto $PGF_{1\alpha}$ (10 μg/ml) did not cause a change in the mean diameter of the venules. The highest concentration of PGI_2 at which embolization of thrombi could still be used as a measure of blood flow was 100 ng/ml. At this concentration there were no significant changes in mean blood flow.

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