# Prostacyclin ($PGI_2$) inhibits the formation of platelet thrombi in arterioles and venules of the hamster cheek pouch

E.A. Higgs, G.A. Higgs, S. Moncada & J.R. Vane

## *Commentary by*

S. Moncada

This work demonstrated the inhibitory effect of prostacyclin on platelet aggregation *in vitro*, *ex vivo* and *in vivo* for the first time in the same species. The potent effect of prostacyclin as an inhibitor of platelet aggregation had already been shown *in vitro* and *ex vivo* in a number of species including rat, rabbit, sheep, horse and human (Bunting *et al.*, 1976; Moncada *et al.*, 1977; 1978). In each of these prostacyclin was found to be more potent than prostaglandin $E_1$ which had, until then, been the most powerful known inhibitor of platelet aggregation (Kloeze, 1967). What remained to be shown was the inhibitory effect of prostacyclin on thrombus formation in a suitable animal model.

The hamster cheek pouch had been developed some years earlier as a model of thrombus formation (Begent and Born, 1970). Platelet thrombi are induced in venules by iontophoretic application of ADP to the vessel walls (Begent & Born, 1970) and in arterioles by electrical micro-damage to the vessel wall, followed by application of ADP (Westwick, 1977). This model had previously been used to demonstrate the antithrombotic actions of a number of agents including sulphinpyrazone, sodium aspirin, oxprenolol (Lewis & Westwick, 1975) and prostaglandins $E_1$, $E_2$, $D_2$ and $G_2$ (Westwick, 1977). Using this model, we first demonstrated that prostacyclin prevents ADP-induced aggregation of hamster platelets *in vivo* with a similar potency to that observed in platelets from other species. We then showed that hamster aortae produce prostacyclin. To do this we used a technique that we had developed previously in which the supernatant from chopped fresh vascular rings is assayed against standard prostacyclin for its ability to inhibit platelet aggregation (Bunting *et al.*, 1976). Finally, we showed that thrombus formation in arterioles and venules could be inhibited by exogenously applied prostacyclin at concentrations as low as 100 ng/ml and was completely prevented by prostacyclin at 0.5-1.0 µg/ml. The maximum inhibitory effect of prostacyclin infusion occurred after 10 mins and was immediately reversible after low concentrations, whereas a recovery period of up to 30 minutes was observed after the highest concentration. We also showed in this study that treating the hamsters with aspirin prevented the *ex vivo* generation of prostacyclin by the aortae. A similar effect had previously been shown in rabbits after indomethacin treatment (Bunting *et al.*, 1976).

The importance of this paper was that it not only showed clearly the potent anti-thrombotic action of prostacyclin but also that it brought together several concepts and techniques that were later used on their own or in combination to demonstrate many of the characteristics and biological actions of this powerful endogenous anti-aggregatory substance. These data formed the basis for the later development of clinical applications of prostacyclin (see Rubanyi & Vane, 1992).

From the point of pharmacology, this paper also illustrates the way in which *in vitro*, *ex vivo* and *in vivo* results are often required to obtain a clearer idea of the phenomenon which is being investigated.

## References


BEGENT, N.A. & BORN, G.V.R. (1970). Growth rate *in vivo* of platelet thrombi, produced by iontophoresis of ADP, as a function of mean blood flow velocity. *Nature*, **227,** 926-930.

BUNTING, S., GRYGLEWSKI, R., MONCADA, S. & VANE, J.R. (1976). Arterial walls generate from prostaglandin endoperoxides a substance (prostaglandin X) which relaxes strips of mesenteric and coeliac arteries and inhibits platelet aggregation. *Prostaglandins*, **12,** 897-913.

KLOEZE, J. (1967). Influence of prostaglandins on platelet adhesiveness and platelet aggregation. In *Prostaglandins*, **2** vol. Nobel Symposium. ed. Bergstrom, S. & Samuelsson, B. pp. 241-252. Stockholm: Almquist and Wiksell.

MONCADA, S., HIGGS, E.A. & VANE, J.R. (1977). Human arterial and venous tissues generate prostacyclin (prostaglandin X), a potent inhibitor of platelet aggregation. *Lancet*, **i,** 18-20.

MONCADA, S., VANE, J.R. & WHITTLE, B.J.R. (1978). Relative potency of prostacyclin ($PGI_2$), prostaglandin $E_1$ and prostaglandin $D_2$ as inhibitors of platelet aggregation in several species. *J. Physiol.*, **273,** 2-4P.

RUBANYI, G.M. & VANE, J.R. (1992). Prostacyclin: New perspectives for basic research and novel therapeutic indications. Excerpta Medica, Elsevier.

WESTWICK, J. (1977). Modulation of thrombus formation *in vivo* by prostaglandins. *Br. J. Pharmac.*, **61,** 138P-139P.