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Platelet and vascular prostaglandins in uraemia, thrombotic microangiopathy and pre-eclampsia

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The metabolism of arachidonic acid in platelets and vascular cells is often altered in clinical conditions associated with haemorrhagic or thromboembolic complications.

We have focused on the one hand on uraemia as a condition frequently complicated by bleeding episodes and, on the other, on thrombotic microangiopathy (thrombotic thrombocytopenic purpura, t.t.p.; haemolytic–uraemic syndrome, h.u.s.) and pre-eclampsia as conditions characterized by uncontrolled intravascular platelet activation.

The observation that prostaglandin synthesis may be regulated by factors present in normal human plasma (Saeed *et al.* 1977; MacIntyre *et al.* 1978) prompted us to investigate whether such plasmatic control was altered in the clinical situations mentioned.

Venous specimens removed from uraemic patients during the institution of an artero-venous shunt for haemodialysis generated significantly more prostacyclin (prostaglandin I_2, PGI_2) than control vessels (Remuzzi *et al.* 1977). Similar findings were subsequently reported in aortic tissue from nephrectomized rats and in arterial tissue from uraemic patients (Leithner *et al.* 1978). Uraemic plasma showed a greater capacity for stimulating PGI_2 synthesis by vascular rings or endothelial cultured cells (Remuzzi *et al.* 1978; Defreyn *et al.* 1980).

This suggests that altered prostacyclin generation in vessel walls from uraemic patients is mediated by plasma. In contrast, both malondialdehyde (MDA) and thromboxane B_2 generated in response to relatively high concentrations of arachidonic acid or thrombin were significantly lower in platelets from uraemic patients than from controls. Uraemic plasma inhibited MDA generation in normal platelets, and normal plasma partly corrected the defect in uraemic platelets (Remuzzi *et al.* 1980*a*).

This suggests that an imbalance in the plasmatic regulation of prostaglandin metabolism in platelets and vessel wall from uraemic patients may contribute to their tendency to bleed.

Thrombotic microangiopathy is characterized by thrombocytopenia, haemolytic anaemia, neurological abnormalities and/or renal failure. Microthrombi occluding arterioles and capillaries of different organs are found on pathological examination. This reflects the occurrence of widespread intravascular platelet aggregation, a crucial event in the pathogenetic sequence of thrombotic microangiopathy.

In three patients with t.t.p. or h.u.s. that we studied (Remuzzi *et al.* 1978; Donati *et al.* 1980), no prostacyclin activity was released from vascular specimens obtained during the acute phase of the disease, which suggested that prostacyclin might be the physiological inhibitor of platelet aggregation, postulated as defective in a patient with t.t.p. described by Byrnes & Khurana (1977). Plasma taken from all three patients on admission had very low capacity, if any, for stimulating vascular prostacyclin synthesis. Treatment with plasma exchange or infusion led to

a rapid clinical improvement, and each patient's plasma recovered its capacity to stimulate prostacyclin generation. A deficiency of the plasma factor(s) stimulating vascular PGI_2 activity was therefore suggested as having some role in the pathogenetic sequence of thrombotic microangiopathy (Remuzzi *et al.* 1978). This 'missing factor' hypothesis has gained further support from more recent observations that plasma levels of 6-keto-$PGF_{1\alpha}$ (the chemically inactive derivative of PGI_2) were very low or undetectable in patients with t.t.p. or h.u.s. (Hensby *et al.* 1979; Machin *et al.* 1980; Webster *et al.* 1980). In a patient described recently (Remuzzi *et al.* 1980*c*), the deficiency of the plasma factor persisted for at least a year after clinical remission from h.u.s. without recurrence. A similar deficiency was detected in two of this patient's four offspring, who had never suffered from microangiopathic episodes.

This suggests that, at least in some cases of h.u.s. the plasma defect might be genetically determined. Deficient PGI_2-stimulating activity in plasma would not normally result in any clinical sign of disturbed platelet function as long as no aetiological agent such as an endotoxin triggers the pathogenetic sequence of thrombotic microangiopathy (Donati *et al.* 1980).

Preliminary data in two patients studied during the acute phase of h.u.s. indicate that an increased tendency of activated platelets to generate thromboxane A_2 might be an additional factor favouring disseminated intravascular platelet aggregation in this syndrome. Whether plasma modulates the exaggerated metabolism of arachidonic acid in platelets from patients with h.u.s. has not yet been clarified.

Pre-eclampsia is a major cause of morbidity and death for the pregnant woman and her foetus. Signs of consumptive coagulopathy frequently accompany hypertension, oedema and proteinuria, the triad characteristic of this syndrome. Pathological examination may show placental and glomerular vessels occluded by microthrombi, and utero-placental ischaemia appears to play a central role in the pathogenesis.

We have recently reported that PGI_2 production is significantly depressed in umbilical and placental vessels from patients with severe pre-eclampsia in comparison with a normal pregnancy (Remuzzi *et al.* 1980*b*). Reduced PGI_2 production has now been confirmed in umbilical artery (Downing *et al.* 1980), in amniotic fluid (Bodzenta *et al.* 1980) and in plasma (Bussolino *et al.* 1980). Thus maternal hypertension, platelet consumption and reduced placental perfusion could be triggered or maintained by a defect of the mechanism(s) leading in normal pregnancy to increased levels of PGI_2. Indeed, in normal human pregnancy, both foetal and maternal vessels produce larger amounts of PGI_2 than vessels from non-pregnant women (Remuzzi *et al.* 1979; Lewis *et al.* 1980). This implies that an increase in vasodilatory PGI_2 may account for the low peripheral resistance and the high renin activity of normal pregnancy.

This pathogenetic interpretation is reinforced by earlier observations that pregnant rats fed with a vitamin E-deficient fat diet developed eclamptic crises (Stamler 1959). Indeed, vitamin E deficiency has recently been reported to impair PGI_2 production in rats (Okuma *et al.* 1980). Moreover, administration of indomethacin to sheep is followed by a marked increase in the resistance of uterine and placental vascular beds (Rankin *et al.* 1979).

Plasmatic regulation of vascular PGI_2 generation in pregnancy has recently been studied (Remuzzi *et al.* 1981). No significant difference was found between non-pregnant and pregnant women during early pregnancy, but a significant reduction of prostacyclin-stimulating activity was observed in plasma during late normal pregnancy. In patients with severe pre-eclampsia this plasmatic activity was within the range of control non-pregnant women, but significantly higher than comparable women with normal pregnancy.

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These results are surprising and apparently difficult to reconcile with the good correlation between high plasmatic activity and high vascular PGI_2 in uraemic patients and low plasmatic activity and low vascular PGI_2 in patients with thrombotic microangiopathy. Possibly more than one mechanism operates in the control of vascular prostacyclin production in normal pregnancy. Perhaps the striking similarity between the behaviour of 'plasma factor' and the response of blood pressure to angiotensin II in normal and complicated pregnancies (Ferris 1978) offers a key to a better understanding of the role of prostacyclin and its regulation in pregnancy. It seems pertinent to mention here that in women with recurrent spontaneous abortion a plasmatic activity (linked to the IgG fraction) inhibiting the release of PGI_2 from aortic rings has recently been found (Carreras *et al.* 1980).

Conclusions

The nature of the plasma component(s) modulating platelet and vascular prostaglandin synthesis in uraemia, thrombotic microangiopathy and pregnancy is unknown. Whether such factor(s) are identical to the endogenous modulator(s) described in normal plasma has still to be clarified.

A crucial step in this phenomenon might lie in the balance between free radical formation and removal in plasma (for detailed discussion, see Donati *et al.* (1980)). An imbalance in the synthesis of metabolites of endogenous arachidonic acid in some clinical conditions such as those discussed in this paper is not necessarily corrected either by the removal of the products generated in excess (achievable for instance by using aspirin or more selective prostaglandin synthesis inhibitors) or by replacement of the defective compound (for instance by infusion of prostacyclin or one of its stable analogues). Indeed, beneficial effects of intravenous infusion of prostacyclin in t.t.p. or h.u.s. have been reported in some patients (Webster *et al.* 1980) but not in others (Hensby *et al.* 1979; Budd *et al.* 1980). On the other hand, patients with pre-eclampsia reportedly benefit from aspirin treatment at doses presumably inhibiting prostacyclin generation (Crandon & Isherwood 1979).

Thus, although any new therapeutic attempt to improve the natural course of these diseases must be encouraged, it would be premature to draw any pharmacological implications from pathogenetic hypotheses still awaiting full confirmation.

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