Plenary Lecture

Effects of epoetin on vascular biology

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Abstract In addition to promoting erythropoiesis, chronic administration of epoetin frequently increases blood pressure, ameliorates uraemic platelet dysfunction, enhances platelet production and elevates resting and stimulated cytosolic \([\text{Ca}^{2+}]\). In addition, \textit{in vivo} and \textit{in vitro} studies have demonstrated that epoetin may modify production and activity of certain vasoactive factors and may promote vascular cell growth. Many of the latter effects of epoetin appear to be unrelated to the associated erythropoietic action of the hormone and must, therefore, involve other mechanisms. The present article is intended to provide a brief overview of the effects of epoetin on vascular and haemostatic systems.

Key words: epoetin; haemostatis system; hypertension; systemic blood pressure

Introduction

The availability of epoetin has greatly enhanced the management of anaemia of chronic renal failure (CRF) and has substantially improved quality of life in the dialysis population. However, chronic administration of epoetin can lead to an increase in arterial blood pressure in patients and experimental animals with CRF. Recognition of this phenomenon during the clinical trials of epoetin nearly a decade ago has triggered a large series of clinical and laboratory studies to discern the mechanism(s) by which epoetin therapy increases blood pressure. This communication is intended to provide a brief overview of the effects of epoetin on vascular and haemostatic systems.

Effect on arterial blood pressure

After the initiation of maintenance epoetin therapy, blood pressure frequently increases within several weeks to months in CRF patients [1–3] and after \(\sim 1\) week in CRF rats [4]. The increase in arterial blood pressure usually accompanies an increase in haematocrit. This temporal association has led to the common belief that epoetin-induced hypertension is due to the increase in erythrocyte mass and concentration. However, subsequent studies have provided strong evidence against this proposition and have implicated a number of other mechanisms.

Role of haematocrit

It has been thought that correction of anaemia with epoetin therapy enhances vascular resistance and arterial blood pressure in CRF subjects by increasing blood viscosity [5,6], obviating hypoxic vasodilation [7], and enhancing competition for nitric oxide (NO) by haemoglobin [8]. In addition, expansion of blood volume associated with the increased erythrocyte mass potentially could contribute to hypertension in CRF, which is marked by volume and pressure dysregulation. However, in a series of studies in rats with CRF, we showed that epoetin-induced hypertension is clearly unrelated to the increase in haematocrit. To dissect the effect of haematocrit from the effect of epoetin \textit{per se}, we administered epoetin for 6 weeks to CRF animals with adequate iron stores and CRF rats with iron depletion. Blood pressure increased markedly and equally in both groups, despite the fact that anaemia persisted in the iron-depleted group but was corrected in those with adequate iron stores [4]. Moreover, in another group of CRF rats, we successfully corrected the anaemia with multiple small blood transfusions but found no significant increase in arterial blood pressure during the study period. Based on these observations, we concluded that the change in blood pressure was related to repeated administration of epoetin as opposed to the associated increase in haematocrit [4]. These observations are consistent with our earlier study of a group of iron-deficient anaemic CRF patients who, while receiving a constant dosage of epoetin throughout the study period, showed no further increase in blood pressure despite significant increases in haematocrits with iron repletion [9]. It is therefore clear that amelioration of anaemia is not the primary mechanism of epoetin-induced hypertension.

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Role of vasoactive hormones

Catecholamines

Plasma catecholamines are not significantly affected by epoetin therapy [10]. However, epoetin has been reported to enhance the vasopressor response to noradrenaline in vitro and in vivo [11,12]. In contrast, Vaziri et al. found no modification in the vasoconstrictive response to α-1 adrenergic agonist, methoxamine, in tail arterial rings pre-incubated in various epoetin concentrations or rings prepared from epoetin-treated CRF rats [4,13].

Renin–angiotensin system

Chronic administration of epoetin in rats has been shown to increase kidney and aorta expression of renin mRNA and angiotensinogen mRNA [14]. However, epoetin therapy did not significantly change plasma renin or angiotensin [14]. Based on these observations, the authors concluded that epoetin-induced hypertension may be due to enhanced tissue renin–angiotensin activity. In a series of in vivo and in vitro studies, we found no significant modification in pressor response to angiotensin II with chronic or acute epoetin administration [4,13].

Role of endothelin

Data on the effect of epoetin on endothelin production are contradictory. Several studies have shown increased plasma endothelin-1 in patients and animals with chronic epoetin therapy and increased endothelin-1 release by cultured endothelial cells in response to epoetin [15–19]. In contrast, other studies have found no demonstrable increase with epoetin therapy in plasma endothelin-1 concentration in either humans or animals in vivo, or preproendothelin-1 gene expression by endothelial cells in vitro [10,12,20–22].

Role of prostaglandins

Bode-Boger et al. have shown that incubation of isolated rabbit aorta with epoetin at 20–200 IU/ml concentration increases the release of vasoconstrictive prostaglandin F2α and thromboxane B2 and decreases the release of the vasodilatory prostaglandin, prostacyclin, in vitro. They therefore concluded that epoetin may contribute to hypertension by disturbing the balance between vasodilatory and vasoconstrictive prostaglandins [11,17].

Role of vasopressor and atrial natriuretic peptide (ANP)

Based on the available clinical and experimental studies, epoetin therapy does not appear to affect directly the plasma concentration of these hormones [10,20,21]. However, through expansion of blood volume, epoetin may increase ANP release.

Role of 1-arginine–NO system

Given the binding affinity of haemoglobin for NO, it has been speculated that an improvement in haemoglobin concentration with epoetin therapy may decrease the availability of endothelium-derived NO to the underlying vascular smooth muscle cells. The latter is, in turn, thought to reduce NO-mediated vasodilatory tone and increase blood pressure [8]. However, the occurrence of severe hypertension with epoetin therapy despite persistent anaemia in iron-deficient CRF rats, and the lack of hypertension despite correction of anaemia with multiple blood transfusions [4], tend to exclude this possibility. Interestingly, epoetin therapy has been shown to cause NO resistance, as evidenced in epoetin-treated animals by a reduced hypotensive response in vivo and a reduced vasorelaxation response in vitro to the administration of NO-donor, sodium nitroprusside [4]. Recently, del Castillo et al. have demonstrated that the occurrence of hypertension with epoetin therapy in rats is accompanied by an increase in urinary excretion of nitrate and nitrite, suggesting enhanced NO production [23]. The presence of hypertension despite elevated NO production that is reported by these authors is consistent with the NO resistance in epoetin-treated animals reported by Vaziri et al. [4].

Role of altered intracellular cations

Elevation of basal cytosolic [Ca2+] in vascular smooth muscle cells is a common feature of hypertensive disorders. CRF is associated with an elevation of basal [Ca2+], coupled with an attenuation of surge in [Ca2+], following stimulation [4,24]. Epoetin therapy significantly increases both basal and stimulated platelet [Ca2+], in CRF rats and humans [4,24]. In addition, epoetin has been shown to increase [Ca2+], in vascular smooth muscle cells [25]. Since [Ca2+], is the major determinant of vascular tone, the elevation of basal [Ca2+], with epoetin can account for the increased vascular resistance and blood pressure seen in epoetin-treated subjects. In addition, the occurrence of NO resistance with epoetin therapy can be explained by this phenomenon since the vasodilatory action of NO is mediated by a cGMP-induced reduction in [Ca2+]. It therefore follows that an abnormal elevation of basal [Ca2+] can cause resistance to the action of NO.

Role of epoetin as a direct vasopressor

At high concentrations, epoetin has been shown to exert a fast-acting vasopressor action on rat mesenteric and renal resistance vessels, as well as rat caudal artery rings in vitro [13,26]. However, no such effect was found using rings prepared from the rabbit aorta, which is a conduit artery [17]. Although epoetin can cause direct vasoconstriction in muscular arteries in vitro, it has no fast-acting effect on blood pressure in vivo in either rats or humans [13,21]. We have shown...
that the lack of a short-acting pressor effect of epoetin in vivo, despite a demonstrable vasoconstrictive action in vitro, is due to a rapid increase in cGMP production, which offsets the vasoconstrictive action of epoetin [13].

Effect of epoetin on vascular cell growth

Epoetin has been shown to stimulate endothelial cell proliferation and DNA synthesis in vitro. [27]. Likewise, epoetin has been shown to up-regulate the expression of several early-response proto-oncogenes and to increase DNA synthesis in cultured aortic smooth muscle cells [28,29]. If true, epoetin potentially could cause structural modifications that could contribute to sustained hypertension.

Effect of epoetin on the haemostatic system

Epoetin administration has been shown to ameliorate uraemic platelet dysfunction and the associated prolongation of bleeding time. We have shown recently that the observed improvement of platelet function with epoetin therapy is due to correction of the defective Ca$^{2+}$ signalling in the platelets [4]. In addition to improving platelet function, we have found that epoetin increases platelet production [30]. In fact, epoetin recently has been shown to potentiate the growth-promoting action of thrombopoietin on megakaryocytes. In contrast to the platelets which are clearly affected, epoetin therapy does not appear to have a significant effect on various blood coagulation and fibrinolytic factors.

In summary, chronic administration of epoetin can result in an increase in systemic blood pressure in patients and animals with CRF. Although the elevation in blood pressure frequently is accompanied by an increase in haematocrit, the two are not linked causally. Instead, epoetin-induced hypertension is related to increased basal and stimulated [Ca$^{2+}$], which elevates vascular tone and causes NO resistance. In addition, stimulation of the vascular tissue renin-angiotensin system, enhanced endothelium production and the disturbed balance between vasodilatory and vasoconstrictive prostaglandins may contribute to the pathogenesis of epoetin-induced hypertension.

References

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