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Editorial: The Impact of Calcium Dobesilate* on Vascular Endothelial Dysfunction

Oxidative stress has been a major topic of research in recent years. It plays a key role in ischemia/reperfusion injury, organ transplantation, atherogenesis, and insulin resistance. Impaired glucose metabolism leads to oxidative stress and the glycation of proteins produces free oxygen radicals. The papers presented at this special workshop focus on some recent findings regarding endothelial dysfunction in the early stages of atherosclerosis and diabetic microangiopathy.

A variety of free radical scavengers have been proposed to restore normal endothelial functions. Among the presently available therapeutic agents with antioxidative and vasoprotective properties, calcium dobesilate (CD) has a particularly interesting profile. It has been used with great success for many years in the treatment of diabetic retinopathy, as well as chronic venous insufficiency. As demonstrated by vitreous fluorophotometry and retinal angiography, it significantly reduces microvascular permeability. The endothelial cells play a key role in both macro- and microvascular lesions in diabetic patients. Impaired vasodilatation is directly related to a defect in endothelial nitric oxide production. CD restores normal levels of NO production, promotes blood vessel relaxation, prevents platelet hyperagreggation and leukocyte adhesion and lowers the level of endothelin-1.

These data are summed up in the following five papers which were presented at the 40th World Congress of ICA.

Suschek et al. observed a dose-dependent increase in constitutive nitric oxide synthetase (ecNOS) activity in both aortic and capillary endothelial cells exposed to magnesium dobesilate. It has no effect on the activity of inducible nitric oxide synthetase (iNOS).

Herbuté and her group investigated the role of CD on vascular smooth muscle cells. They observed a concentration-dependent decrease in smooth muscle cell proliferation and concomitant enhancement of NO formation and NO-synthetase activity. CD also induced a dose-dependent protection against LDL oxidation. These findings may be of considerable interest in the prevention of post-angioplasty restenosis and atherosclerosis. Tejerina studied the effects of CD on the arterioles of diabetic rats. She concludes from her studies that CD significantly increases endothelium-dependent relaxation and reinforces the vasodilatation induced by acetylcholine. Losa's study identifies CD as a scavenger for oxygen radicals and inhibitor of lipid membrane peroxidation in both erythrocytes and polymorphonuclear cells. Similar to the antioxidant N-acetylcysteine, CD exerts its effects by increasing the intracellular concentration of reduced glutathione. By reducing lipid peroxidation, CD possibly also prevents apoptosis. The final contribution to this workshop was made by Garay and coworkers. CD was administered orally to diabetic rats.

Enhanced peritoneal extravasation of Evans blue was induced by phenazine methosulfate a oxygen radical generating system. In animals pre-treated with CD there was an 80% reduction of extravasation of the dye. The authors conclude that CD significantly and in a dose-dependent manner antagonises capillary hyperpermeability induced by oxygen radicals.

Considering the importance of these newly accumulated data on CD and the many challenging implications for the treatment of clinical manifestations of endothelial dysfunction, we strongly suggest initiation of further pharmacological studies which should essentially focus on plasma endothelin-1 (ET-1) activity and vascular endothelial growth factor (VEGF). Endothelin is a potent endothelium-derived vasoconstrictor. There exists strong evidence linking this peptide to vascular dysfunction in diabetic microangiopathy. VEGF increases vascular permeability and promotes angiogenesis. VEGF is presently considered to be directly involved in new vessel formation in proliferative diabetic retinopathy.

The precise interactions between ET-1 and VEGF are complex and not yet fully understood. The editors of the International Journal of Angiology look forward to receiving further contributions in this exciting area of contemporary research.

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