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Papel del endotelio en la progresión de la enfermedad renal y el daño cardiovascular

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Endothelin-1 (ET-1) was discovered by Yanagisawa et al[1] in 1988; it is known as the most potent vasoconstrictor produced by endothelial cells. ET-1 is a 21 aminoacids protein which is formed via post-translationale modification from PrePro-ET-1 and Big-ET-1. Other family members are ET-2 and ET-3 which differ from ET-1 in 2 and 6 aminoacids, respectively. ET signaling is mediated via 3 different receptors: the ETA-, ETB and ETC-receptors. The ETA-receptor mediates mainly the vasoconstrictory effect on vascular smooth muscle cells whereas the ETB-receptor transduces mainly the vasodilatatory effect of ET-1. Meanwhile it is known that ET-1 does not only possess a vasoconstrictory function, but mediates also plenty of other effects on endothelial cells, smooth muscle cells, leucocytes, platelets and macrophages[2]. In several diseases (see tab. 1) a major pathophysiological role of ET-1 is discussed. In particular, a potential role of ET-1 in the pathogenesis of various kidney diseases is postulated. Important data concerning the renal effect of ET-1 have been collected in ET-1 transgenic mice[4] which develop renal cysts as well as glomerular and interstitial fibrosis. A potential role of ET-1 in the pathogenesis of cardiovascular complications in renal failure is discussed as well[5-7]. Increased concentrations of immunoreactive ET-1 are found in several vascular beds, the glomeruli and the tubulointerstitium in experimental renal failure as well as in patients with renal insufficiency. Urinary ET-1 excretion is also increased in renal failure and can be lowered by treatment with a selective ETA-receptor antagonist. In parallel, proteinuria is reduced and creatinin-clearance improved by ETA-receptor blockade. In various experimental models of acute and chronic renal disease structural parameters or renal damage were also reduced after treatment with ETA-receptor blockade and this was independent of blood pressure reduction. In type 1 and 2 diabetic nephropathy ET-1 seems to play a pathophysiologcal role as well since glomerular, tubulointerstitial and vascular alterations can be experimentally prevented by ETA-receptor blockade. Increased formation of ET-1 may also be of importance for physiological aging not only of the kidney, but also of the whole organism[8]. Significantly increased tissue levels of ET-1 are found in aged animals compared to younger ones in different vascular beds, in the glomeruli and in the tubulointerstitium. In addition, there is evidence for a role of ET-1 in the pathophysiology of atherosclerosis[9] and of uremic cardiomyopathy[7]. Clinical studies of Demuth et al.[6] as well as experimental and autoptical studies documented significantly increased ET-1 plasma- and tissue levels in patients with chronic renal failure. Against this background it is of interest that left ventricular hypertrophy, interstitial myocardial fibrosis and cardiac microarteriopathy in experimental renal failure can be prevented by treatment with an ETA-receptor antagonist.

Table I. Diseases with a potential pathophysiological role of ET-1

- Essential hypertension.
- Kidney diseases.
- Ischemic heart disease and congestive heart failure.
- Atherosclerosis and stroke.
- Diabetes mellitus.
- Disease of the lung (pulmonary hypertension and asthma).
- Gastrointestinal diseases (ulcus, M. Crohn, Colitis ulcerosa).

In summary, there is increasing evidence for a pathophysiologic role of ET-1 in various kidney diseases, as well as in aging, in atherosclerosis and in cardiovascular alterations in chronic renal failure. From a therapeutic perspective it is important that in experimental models the majority of alterations associated with these diseases could be experimentally prevented or at least ameliorated by specific ET-1 receptor blockade. Whether this is also true for patients remains to be proven in clinical studies.

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