diuretic effect. Lowering of salt entry rates into the target cells slows down the replicating rate of the cells and chronically results in a reduction of transport capacity of the given epithelium. Complete blocking of salt entry into the cells seems to entail cell death by apoptosis.

With respect to the human nephron precise data on the distribution of transport proteins along the distal tubules are lacking. It is unknown whether thiazide treatment has a similar effect on human DCT cells as in rat. However, there are a few clinical case reports, demonstrating focal interstitial inflammation, associated with distal tubules, following treatment with a combination of thiazides and potassium-sparing diuretics [12,13]. These were interpreted as immunological events, but according to our experimental findings, a more direct effect of the diuretics might constitute an alternative explanation. The potential risk of severe tubular or tubulointerstitial lesions during therapeutic use of combinations of different classes of diuretics should be considered.

References
Arterial wall remodelling involves thickening of the media, a process sustained by smooth muscle cells (SMCs) that undergo phenotype modulation to an activated state with increased migration and proliferative properties and that synthesize more extracellular matrix [4,5]. Therefore, in addition to the direct effects of mechanical forces on putative mechanoreceptors, other deleterious triggering mechanisms can contribute to vascular wall remodelling that ultimately predisposes to atherosclerosis.

Wall constituents respond to mechanical forces to reach a new steady state, mainly via wall thickening. However, this compensatory event may indeed perpetuate some of the triggering mechanisms that induce stiffening of the artery.

The biochemical nature of the trigger for remodelling

One of the key factors contributing to vessel wall homeostasis is nitric oxide (NO) which is synthesized during the conversion of L-arginine to L-citrulline in a reaction catalysed by an NO synthase enzyme. Endothelial cells express a constitutive form of this enzyme (NOS III) which can be modulated by mechanical forces [6]. NO is an important mediator that controls vascular tone via a cGMP-dependent signalling pathway leading to tyrosine nitration of contractile proteins in SMCs [7–10]. When present at high concentrations, NO can also induce apoptosis via a cGMP-independent pathway [11,12]. Moreover, NO is a scavenger molecule for a superoxide anion with which it reacts to form peroxynitrites (ONOO⁻) another reactive oxygen species with high cytotoxic effects [11,12]. Thus, the NO concentration in tissues results from the balance between synthesis and scavenging rates.

The role of oxidative stress—the equilibrium between NO and reactive oxygen species

Recent results, obtained in our laboratory suggest that an increased oxidative stress may represent a triggering event for vessel wall thickening during hypertension. Indeed, in a rat model of renovascular hypertrophy (two kidney-one clip), an increased net production of superoxide anion has been detected at 2 and 24 weeks after clipping, concomitant with vascular wall thickening [3].

Both during hypertension and atherosclerotic plaque development, the equilibrium between NO and reactive oxygen species seems to be disturbed [12–14]. In both cases an increased scavenging rate by the superoxide anion is observed without changes in NO synthesis rate. Moreover, an increased superoxide anion production has been observed in angiotensin II-induced hypertension via a membrane-bound NADH/NADPH oxidase activity, but not in cathecolamines-induced hypertension [15–17]. Furthermore, the NADH/NADPH oxidase has been shown to regulate the angiotensin II-induced hypertrophy in SMCs [18]. Evidence for the role of the scavenging rate is provided by the observation that in patients with essential hypertension, sodium nitroprusside-dependent vasodilation is increased by the administration of copper-zinc superoxide dismutase [19]. All these observations suggest that the imbalance between NO and reactive oxygen species plays a pivotal role in sustaining elevated blood pressure. On the other hand, cytokine stimulation of cells results in induction of inducible NO synthase (NOS II) expression and increased oxidative stress [20,21]. The consequent increased NO and ONOO⁻ production is responsible for the loss of cellular respiratory capacity by covalently modifying haeme-containing enzymes, and is also responsible of the contractility of arteries [22–24]. These effects are probably partially mediated by the activation of polyADP ribosyl synthase (PARS), an enzyme which induces DNA strand breakage [25,26]. Moreover, NO donor stimulation of different cell types including SMCs, induces apoptosis by a cGMP-independent pathway [10].

Cross-talk between NO and VEGF?

Until now, involvement of an oxidative stress as a triggering event for arterial wall remodelling has not been definitively demonstrated. However, new evidences suggest the existence of a cross-talk between NO and VEGF/VPF (vascular endothelial growth factor/vascular permeabilizing factor). In response to increased oxidative stress, VEGF synthesis is enhanced [27,28]. VEGF was shown to down-regulate NO production in organ culture [29]. In a recent experiment performed in our laboratory, we were able to show that VEGF is expressed in bovine aortic endothelial cells when these are cultured in static condition, and that VEGF is expressed in bovine aortic endothelial cells when these are cultured in static condition, and NOS III expression is down-regulated to undetectable levels. However, when mechanical forces are applied to endothelial cells, in order to expose them to an environment mimicking in vivo flow conditions, VEGF expression is down-regulated, while NOS III is up-regulated [30]. Therefore, it appears that under normal physiological conditions, endothelial cells are exposed to mechanical forces that maintain NO production within normal levels. Dysfunction of the endothelium can alter NO bioavailability via an increased oxidative state and consequently increase VEGF expression resulting in increased vascular permeability. This in turn leads to SMCs exposition to factors that may modulate their phenotype. The cumulative effects of mechanical forces and oxidative stress may also partly up-regulate manganese superoxide dismutase [31–33]. This enzyme plays an important antioxidant role in cells, reducing the level of reactive oxygen species. In essential hypertension, superoxide dismutase in erythrocytes is decreased [34], providing in vivo evidence that this enzyme could be an important element in disrupting the balance between NO and the
Hypothesis concerning the pathogenic sequence

In conclusion, a reduction of NO bioavailability by superoxide anions, combined with a direct negative effect of blood pressure on superoxide dismutase, may contribute to the perpetuation of elevated blood pressure. This may be especially evident in plaque-prone regions where the mean blood flow is near to zero with consequent decreased NO production and increased superoxide anion concentrations. The ensuing endothelial dysfunction associated with increased concentrations of VEGF results in increased vascular permeability that may participate in the induction of vascular wall remodelling and possibly atherosclerosis.

References

mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc Natl Acad Sci USA 1996; 93: 10417–10422


Goodpasture syndrome and end-stage renal failure — to transplant or not to transplant?

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Although an unusual condition, its association with serious morbidity and mortality confers upon this disease an importance greater than its incidence alone would allow. ... While nephrologists will continue to be satisfied by the immunopathogenetic precision of this disease, they remain challenged by the immediacy of diagnosis and the treatment it demands.

Daly et al., 1996 [1]

Introduction

Goodpasture syndrome is the most common manifestation (60%) of human anti-basement membrane diseases, characterized by the presence of autoantibodies that predominantly recognize the non-collagenous (NC1) domain of the alpha 3 chain of basement membrane (type IV) collagen. The clinical manifestation of Goodpasture syndrome is a rapidly progressive glomerulonephritis and pulmonary haemorrhage, but anti-basement membrane disease can also occur as glomerulonephritis without lung involvement (35%), or as isolated pulmonary haemorrhage (<5%). For reasons summarized in the citation above, Goodpasture syndrome, despite its low incidence, has drawn widespread attention over almost 80 years of research history.

Pathogenesis

The cause of the disease is unknown. Smoking, inhalation of gasoline or other hydrocarbon fumes, as well as viral respiratory infections have been implicated to promote the disease by causing injury to the basement membrane where the antigenic epitope resides in the type IV collagen network. It seems possible that increased quantities of the cryptic epitope thus become exposed to the immune system, triggering an autoimmune response. The disease association with HLA DR2 and DR4 haplotypes implies a genetic susceptibility [2]. There is evidence of T-cell involvement in the autoimmune response, as NC1-specific CD4 and CD8 T cells have been isolated from patients in early and late phases of Goodpasture syndrome, respectively [3,4]. The autoantibodies are predominantly of the IgG1 subtype, and in active disease they may represent up to 1% of total serum IgG [5]. Antibody deposition in the basement membrane is often, but not always accompanied by complement, promoting autoimmune inflammatory damage in those regions where alpha 3 (IV) is expressed and accessible. Serum antibody titres correlate with active disease, but not necessarily with the degree of inflammatory tissue damage and impairment of renal function, or the severity of lung hemorrhage.

Course and prognosis

If left untreated, the course of Goodpasture syndrome is usually fatal. Since the 1970s, a combined therapy with plasmapheresis and immunosuppression has led to a much improved survival. The pulmonary complications usually resolve and do not have much impact on long-term pulmonary function [6]. However, the glomerulonephritis results in terminal renal failure in ~70%. The renal outcome can be predicted from the serum creatinine and the fraction of glomeruli with crescents at the time of presentation [1,7,8]. Patients with creatinine values >600 μmol/1 or >50% crescents at renal biopsy can rarely be expected to retain independent renal function. Early diagnosis and immediate institution of therapy are the only way to improve the dismal renal outcome in Goodpasture syndrome.