ACE inhibitors can reverse blood vessel damage

It is beginning to be recognized that the goal of antihypertensive therapy is not merely to reduce blood pressure, but also to prevent – and even reverse – the damage to vessels and to organs associated with hypertension. Only in this way can one break out of the ‘vicious circle’ of hypertension and vascular and organ damage and overcome the widespread morbidity and mortality in hypertension-related heart disease, cerebrovascular accidents and renal failure. At a recent series of workshops, the causes and consequences of end-organ and vessel wall damage, as well as the role of angiotensin I converting enzyme (ACE) inhibitors, such as cilazapril, were discussed.

Hypertension and vessel wall damage

A. Doyle (University of Melbourne) pointed out that hypertension is associated with proliferation and remodelling of the vascular smooth muscle cells. These changes are aggravated by atherosclerosis, leading to clinical consequences dependent on the end-organ affected: coronary atherosclerosis, angina, myocardial infarction and heart failure, renal insufficiency, and cerebrovascular accidents. The precise signal for the vascular changes is not well understood, but physical factors, mainly the increase in blood flow rather than of the pressure per se, seem to play an important role (M. Mulvany, University of Aarhus). Moreover, it is becoming clear that the vascular hypertrophy and tissue damage are related to the induction of a number of growth factors (platelet-derived, epidermal and fibroblast growth factors), proto-oncogenes, and hormones (insulin, glucocorticoids and angiotensin II). Angiotensin II can promote growth in cell cultures by a variety of mechanisms (M. Paul, Institute of High Blood Pressure Research, Heidelberg).

Recent work has focused on the endothelium, which produces several vasoactive substances, in particular endothelium-derived relaxing factor. The inhibitory effects of the endothelium against vasoconstrictor stimuli decrease with age and hypertension (T. Lüscher, University Hospital, Basel).

Although it is relatively easy to determine the extent of vascular damage due to hypertension in experimental animals, this is much more difficult in patients. However, the relationship between blood pressure and arterial diameter or compliance can be used as an index of arterial stiffness and structural changes in humans (A. Simon, Broussais Hospital, Paris). Moreover, W. Birkenhager (Erasmus University, Rotterdam) described several other parameters that can be used in situations such as clinical trials, where the available technological potentials have to be weighed against factors such as convenience, compliance of trial subjects, and cost.

Hypertension and the heart

The changes that hypertension induces in the structure and function of the heart and its associated vasculature are clearly of great clinical significance, but which changes can best be used to predict outcome and to direct therapy? In uncomplicated essential hypertensive patients, left ventricular hypertrophy emerged as a significant risk factor for future morbidity – independent of age, blood pressure or cardiac output (R. Fagard, University of Leuven). Although the left ventricular systolic function may be normal in hypertension, the diastolic function is frequently impaired (J. Rosenthal, University Medical Centre, Ulm). Another major risk factor in hypertension, particularly of the renovascular type, is the slowness of the response of the coronary blood flow to increasing myocardial demand. This ‘inappropriate’ coronary blood flow appears to be related to elevated angiotensin II levels (F. Magrini, University of Milan).

Hypertension and the kidney

Renal disease is both the cause and consequence of hypertension and the total available glomerular filtration area is the prime factor involved in the ‘vicious spiral’ of increasing high blood pressure and diminishing renal function. Therefore, the higher the microalbuminuria, the higher the incidence of hypertension (B. M. Brenner, Harvard Medical School). While no therapy is available for directly increasing the number of glomeruli or the growth of glomerular capillaries, interventions that control systemic and glomerular-capillary hypertension could interrupt this cycle.

Angiotensin and the brain

Although the existence of a renin-angiotensin system has been established in several tissues, an appreciation of its importance, particularly in the brain, is only now emerging. Ligand-binding studies in the rat brain have identified two types of angiotensin receptor (see also Ref. 7): one located in the periventricular areas (AT1 receptor) and the other in midbrain, brain stem and cerebellum (AT2 receptor). The majority of the pharmacological actions of angiotensin in the periphery and, probably, in the brain are mediated by AT1 receptors, while the function of AT2 receptors is not known (T. Unger. University of Heidelberg).

B. Bunnemann (Karolinska Institute) reported that angiotensin fragments are released from nerve endings to activate postsynaptic receptors (‘hard-wired’ transmission), but they may also diffuse to adjacent areas or be released from glial cells to act on other specific receptors (‘volume’ transmission). Among the several central effects of angiotensin II, the increase in sympathetic activity is well recognized (P. R. Saxena, Erasmus University, Rotterdam), but the peptide may also disrupt

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ACE inhibition and vessel and organ damage

Several speakers addressed the question: does treatment with antihypertensive drugs, especially ACE inhibitors, reverse vessel and organ damage in addition to lowering blood pressure? Reviewing the limited data available on this subject, Doyle pointed out that methyldopa and, particularly, ACE inhibitors can generally reverse or prevent the cardiac hypertrophy, vascular proliferation and renal damage associated with experimental and clinical hypertension, but antihypertensive drugs such as hydralazine, prazosin and β-adrenoceptor antagonists usually fail to do so. Simon reported that in hypertensive subjects no active or passive changes in arterial compliance are observed after treatment with ketanserin or urapidil, but the Ca²⁺ channel blockers nitratedipine and nicardipine actively increase compliance as well as large artery diameter. W. H. Van Gilst (University of Groningen) reported that ACE inhibitors increase coronary blood flow in the rat isolated heart; it is, however, unclear whether these effects are due to a decrease in angiotensin II or to an increase in bradykinin concentration in the heart. In humans, although the effects of ACE inhibitors on coronary blood flow per se may not be consistent, these drugs do antagonize exercise-induced coronary vasoconstriction (Magrini).

In patients with renovascular hypertension, particularly those with bilateral stenosis or stenosis of a solitary kidney, the use of ACE inhibitors may be associated with a reversible deterioration of renal function (A. Mimran, Lepeyronie Hospital, Montpellier). However, these drugs cause fewer metabolic side-effects in patients with diabetic nephropathy (M. Beaufils, Tenon Hospital, Paris) and they lower urinary protein leakage by decreasing intra-glomerular pressure, both in diabetic and non-diabetic renal disease (P. E. de Jong, Academic Medical Hospital, Groningen and H. H. Parving, Hvidore Hospital, Klampenborg, Copenhagen).

In the CNS, Williams reported that ACE inhibitors can improve both basal and impaired (e.g. by scopolamine or nucleus basalis lesion) cognitive function in rodents; this improvement seems to be related in part to acetylcholine release in the brain. In humans, the data suggest that centrally acting antihypertensive drugs such as methyldopa are clearly associated with cognitive impairment, whereas β-adrenoceptor antagonists are only weakly implicated and ACE inhibitors are least likely to affect cognitive function (C. J. Bulpitt, Royal Postgraduate Medical School, London).

Preclinical data on the new ACE inhibitor cilazapril, which has a potent antihypertensive effect in both experimental animals and humans, demonstrated that chronic administration to spontaneously hypertensive rats decreases cardiac mass, increases coronary and cerebral vascular reserve, and prevents and reverses media hypertrophy in, for example, the coronary, mesenteric, renal and carotid vascular beds (J-P. Clozel, Hoffmann-La Roche; see Fig. 1). Moreover, in the rat
carotid artery, the drug reduces myointimal proliferation associated with balloon catheterization, suggesting that cilazapril may also prevent re-stenosis in cardiac patients subjected to percutaneous transluminal coronary angioplasty. The results of an ongoing clinical trial with cilazapril (MERCATOR: Multicentre European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Re-stenosis) are awaited.

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Current Awareness

Specificity in the recognition process between charged carbohydrates and proteins

Recent research on glycoconjugates (e.g. glycolipids and glycoproteins) has revealed the important role that carbohydrate moieties may play in specific interactions with proteins. This type of recognition phenomenon triggers various biological processes such as the adhesion of pathogens to cells, regulation of the activity of protease inhibitors, reactions between antigens and antibodies, fertilization, endocytosis and cell differentiation (see also Review article pp. 265-272). In higher organisms, the glycosaminoglycans are part of larger proteoglycan molecules. They are located mainly in extracellular matrices and at cell surfaces, and interact strongly with a broad range of proteins (e.g. growth factors, lipoproteins, complement components, cell-attachment glycoproteins and protease inhibitors). These high molecular mass (50-100 kDa) polyionic polysaccharides are divided into different classes according to their carbohydrate composition (heparin, heparan sulphate, dermatan sulphate, chondroitin sulphate, hyaluronic acid and keratan sulphate). Within each class, further structural diversity can occur through variation of specific carbohydrate residues and by varying the position of N-acetyl and N,O-sulphate groups. The polysaccharide chain of glycosaminoglycans consists of long stretches of structurally well-defined alternating sequences, together with small heterogeneous domains. These domains are most likely to confer functional specificity for protein interactions. For example, in the heparin-antithrombin III interaction, binding of heparin induces a conformational change in antithrombin III, thereby accelerating the inactivation of blood coagulation factor X. Analogues in which only one chiral centre has been inverted (indicated by # in Fig. 1) were found to be inactive (M. Petitou and C. A. A. van Boeckel, unpublished), while the presence of a rigid carbohydrate moiety (i.e. the glucuronic acid unit) may be as important as the presence of the essential charged groups. Furthermore, analogues with extra sulphate groups may become less active (particularly unfavourable for sulphate groups cannot be replaced by phosphate groups). The heuristics described above indicate that for a good interaction with antithrombin III the pentasaccharide region of heparin must adhere to very stringent criteria imposed by the three-dimensional structure of the protein. However, no crystallographic studies have yet been reported from which such specific protein-glycosaminoglycan interactions can be visualized. Indeed, there is a paucity of three-dimensional structural information on carbohydrate-protein interactions in general, and studies to date have the protein (see Fig. 1) become apparent when heparin pentasaccharide analogues were synthesized and tested for inhibition of blood coagulation factor X. The presence and spatial orientation of particular sulphate and carboxylate groups (highlighted in red in Fig. 1) were shown to be essential for biological activity. Moreover, essential sulphate groups cannot be replaced by phosphate groups. Analogs in which only one chiral centre has been inverted (indicated by # in Fig. 1) were found to be inactive (M. Petitou and C. A. A. van Boeckel, unpublished), while the presence of a rigid carbohydrate moiety (i.e. the glucuronic acid unit) may be as important as the presence of the essential charged groups. Furthermore, analogues with extra sulphate groups may become less active (particularly unfavourable for sulphate groups cannot be replaced by phosphate groups). The heuristics described above indicate that for a good interaction with antithrombin III the pentasaccharide region of heparin must adhere to very stringent criteria imposed by the three-dimensional structure of the protein. However, no crystallographic studies have yet been reported from which such specific protein-glycosaminoglycan interactions can be visualized. Indeed, there is a paucity of three-dimensional structural information on carbohydrate-protein interactions in general, and studies to date have