SCIENTIFIC LETTERS

Decreased adrenomedullin production in the coronary circulation of patients with coronary artery disease

Adrenomedullin is a novel peptide first isolated from human pheochromocytoma¹ and later proved to be secreted from the adrenal medulla, heart, vascular smooth muscle cells, and endothelial cells.² Adrenomedullin has not only vasoactive but also antimitogenic effects on the vascular tissue.³ However, endothelin-1 has been widely known to be a potent atherogenic factor.⁴ We investigated adrenomedullin and endothelin-1 production in the coronary circulation of patients with coronary artery disease.

We studied 18 patients with coronary artery disease (12 men and six women, mean age 61.2 (10.0) years, range 36–83 years) and seven control subjects without coronary artery lesions (six men and one woman, mean age 60.0 (10.5) years, range 46–72 years) who underwent diagnostic coronary angiography. All subjects gave their informed consent to participate in the study. Subjects with heart failure, renal failure, hepatic failure or contraindication for cardiac catheterisation were excluded. Blood samples were drawn from the ascending aorta and coronary sinus via heparin coated catheters. Plasma adrenomedullin and endothelin-1 concentrations were measured by radioimmunoassay as described previously.^{5,6}

In the control subjects, plasma adrenomedullin concentrations in the coronary sinus were significantly higher than those in the aorta (fig 1A), suggesting that adrenomedullin is produced in the coronary circulation. In contrast, in patients with coronary artery disease, adrenomedullin concentrations in the coronary sinus did not differ from those in the aorta. Adrenomedullin concentrations in the coronary sinus, not in the aorta, were significantly higher in the control subjects than in the patients. The difference in adrenomedullin concentrations between the coronary sinus and aorta, which reflects adrenomedullin production in coronary circulation, was significantly lower in the patients (0.7 (0.3) fmol/ml) than in the control subjects (3.2 (0.9) fmol/ml). On the other hand, plasma endothelin-1 concentrations in the aorta and coronary sinus did not differ between patients with coronary artery disease and the control subjects (fig 1B).

Intravenous administration of adrenomedullin elicits a potent and long lasting vasodilating effect in vivo. Adrenomedullin also inhibits proliferation of vascular smooth muscle cells in vitro.³ Kohno and colleagues⁷ found that adrenomedullin inhibits endothelin-1 synthesis in vascular smooth muscle cells. We reported that adrenomedullin stimulates nitric oxide production by vascular smooth muscle cells.⁸ These observations support the premise that adrenomedullin could act as a potent antiatherogenic factor in vivo. Although the precise kinetics of adrenomedullin in the coronary circulation are still unclear, the present study suggests that decreased adrenomedullin production in the coronary circulation may be related to the formation

Figure 1 Plasma adrenomedullin (A) and endothelin-1 (B) concentrations in the aorta and coronary sinus in patients with coronary artery disease (white columns) and control subjects (black columns). Comparisons between the two groups were analysed by unpaired or paired Student's *t* test. Data are mean (SEM). **p* < 0.05; ns, not significant.

and progression of coronary artery lesions in patients with coronary artery disease.

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Commentary

Adrenomedullin is a circulating vasodilator peptide expressed in a number of cell types with several potentially important antiproliferative actions on vascular cells. It inhibits angiotensin II stimulated smooth muscle cell migration, stimulates nitric oxide release from smooth muscle cells, and inhibits endothelin release from endothelial cells. The present report shows that basal production of adrenomedullin in the human coronary circulation is attenuated in subjects with coronary atherosclerosis. This observation could be relevant for extending our understanding of this peptide's regulatory role in the development of coronary artery disease.

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