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Pharmacological interactions between angiotensin-converting enzyme (ACE) inhibitors, bradykinin and nitric oxide

Karin Persson

Division of Pharmacology
Department of Medicine and Care
Faculty of Health Sciences
Linköpings universitet, SE-581 85 Linköping, Sweden

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ABSTRACT

Cardiovascular diseases are a major cause of death in Western countries. Angiotensin-converting enyzme (ACE) is as a key enzyme in the renin-angiotensin system involved in the regulation of blood pressure, and water and electrolyte balance in the body. ACE not only increases the conversion of angiotensin I to the active angiotensin II, but also degrades bradykinin. ACE inhibitors, like captopril, are today first-line treatment in hypertension and heart failure.

We have shown that two structurally different ACE inhibitors, captopril and fosinopril, exhibit anti-atherosclerotic effects in hypercholesterolemic mini pigs. Captopril, but not fosinopril, improved endothelial function in the iliac arteries from the mini pigs.

Bradykinin-induced relaxation of porcine iliac arteries is mediated by bradykinin B_2 receptors and the subsequent release of nitric oxide (NO). ACE inhibitors did not affect the bradykinin-induced relaxation, implying that other enzymes than ACE (e. g. carboxypeptidase M; CPM) are involved in bradykinin degradation in these vessels. Bradykinin B_1 and B_2 receptors on the vascular media elicited a contraction mediated by cyclooxygenase metabolite(s). Treatment with captopril potentiated bradykinin B_1 receptor-mediated contraction, due to CPM becoming responsible for bradykinin degradation.

Captopril potentiated bradykinin- and inhibited angiotensin I-induced contractions only in arteries with intact NO synthesis. This implied that NO synthesis is necessary for an effective ACE inhibition. ACE activity analyses did reveal that both exogenous and endogenous NO are able to inhibit porcine and human ACE activity. It was also shown that this inhibition is additative with captopril and enalaprilat. This additative effect of NO and ACE inhibitors on ACE activity affected not only angiotensin I- and bradykinin-mediated contractions of porcine iliac arteries, but also reduced human platelet aggregation.

In summary, ACE inhibitors show anti-atherosclerotic properties in hypercholesterolemic mini pigs. ACE inhibitor treatment of porcine iliac arteries did not affect bradykinin-induced relaxation, but instead shunted over bradykinin to other enzymes generating the bradykinin B_1 receptor agonist desArg^9-bradykinin. NO was found to be an endogenous inhibitor of ACE, acting in concert with therapeutically used ACE inhibitors to decrease vascular tone and human platelet aggregation.

Keywords: angiotensin-converting enzyme, angiotensin-converting enzyme inhibitors, atherosclerosis, bradykinin, endothelium, *in vitro*, nitric oxide.

Division of Pharmacology, Department of Medicine and Care, Faculty of Health Sciences, Linköpings Universitet, SE-581 85 Linköping, Sweden.

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