A nitric oxide-releasing derivative of enalapril, NCX 899, prevents progressive cardiac dysfunction and remodeling in hamsters with heart failure

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4507753
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Year 2004
Title A nitric oxide-releasing derivative of enalapril, NCX 899, prevents progressive cardiac dysfunction and remodeling in hamsters with heart failure
Journal FASEB Journal
Volume 18
Number 1
Pages / **Article-Number** 587-+
Mesh terms Angiotensin-Converting Enzyme Inhibitors, pharmacology, therapeutic use; Animals; Aorta; Cardiomyopathy, Dilated, complications, diagnostic imaging, genetics; Cricetinae; Cytoskeletal Proteins, deficiency, genetics; Disease Models, Animal; Disease Progression; Drug Evaluation, Preclinical; Enalapril, analogs & derivatives, pharmacology, therapeutic use; Endothelium, Vascular, drug effects; Enzyme Inhibitors, pharmacology; Heart Failure, diagnostic imaging, drug therapy, etiology; Hemodynamics, drug effects; Male; Membrane Glycoproteins, deficiency, genetics; Mesocricetus; Myocardial Contraction, drug effects; Nitrates, blood; Nitric Oxide, metabolism; Nitric Oxide Donors, pharmacology, therapeutic use; Nitrites, blood; Oxadiazoles, pharmacology; Quinoxalines, pharmacology; Rabbits; Sarcoglycans; Ultrasonography; Vasoconstriction, drug effects; Ventricular Remodeling, drug effects
Nitric oxide (NO) production is known to be impaired in heart failure. A new compound (NCX 899), a NO-releasing derivative of enalapril was characterized, and its actions were evaluated in Bio 14.6 cardiomyopathic (CM) hamsters with heart failure. The hamsters were randomized to oral treatment for 4 weeks with vehicle (n=11), NCX 899 (NCX, 25 mg/kg, n=10), or enalapril (25 mg/kg, n=10). In the vehicle group, fractional shortening by echocardiography decreased (-23.6+/-2.0%) and LV end-diastolic dimension) increased (+10.9+/-1.0%), whereas fractional shortening increased (+17.5+/-4.4%) in NCX and was unchanged in the enalapril group (both P<0.01 vs. vehicle). End-diastolic dimension decreased only in NCX. LV contractility (LVdP/dt max and Emax) was significantly greater in NCX than in enalapril or vehicle, while relaxation (Tau) was shortened in both NCX and enalapril vs. vehicle. ACE activity was inhibited equally by NCX and enalapril in the CM hamster, and plasma nitrate levels were increased only in NCX (P<0.05 vs. enalapril and vehicle). In aortic strips endothelium-independent relaxation occurred only with NCX. The superior effects of NO-releasing enalapril (NCX) vs. enalapril alone to enhance vascular effects, increase LV contractility and prevent unfavorable remodeling and are consistent with vascular delivery of exogenous NO. NCX 899 may hold promise for the future treatment of heart failure.
Publisher Federation of American Society of Experimental Biology
ISSN/ISBN 0892-6638 ; 1530-6860
URL https://faseb.onlinelibrary.wiley.com/doi/epdf/10.1096/fj.03-0872fje
edoc-URL https://edoc.unibas.ch/71062/
Full Text on edoc No;
Digital Object Identifier DOI 10.1096/fj.03-0872fje
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/14734637

ISI-Number WOS:000188829300006
Document type (ISI) Article