ORAL CONTRIBUTIONS

860 Mechanisms of Heart Failure, Imaging, and Pathophysiology

Tuesday, April 01, 2003, 4:00 p.m.-5:00 p.m.
McCormick Place, Room S105

4:00 p.m.

860-1 The Design, Synthesis and Cardiorenal Actions of a New Chimeric Natriuretic Peptide CD-NP

Ondrej Lisy, John C. Burnett, Jr., Mayo Clinic, Rochester, MN

Background: C-type natriuretic peptide (CNP) is a 22-amino-acid (AA) peptide of endothelial cell origin which is powerful venodilator but lacks renal actions. Dendroaspis natriuretic peptide (DNP) is a recently discovered 38-AA peptide structurally similar to ANP, BNP and CNP with potent natriuretic and vasoactive actions. Data suggest that among natriuretic peptides DNP may be the most resistant to degradation by neutral endopeptidase which may contribute to enhanced biological actions.

Methods: Based upon such potent biological properties of both peptides, we designed, synthesized and assessed the cardiorenal actions of a chimeric peptide CD-NP, which possesses the 22-AA core ring structure of CNP and the 15-AA linear C-terminus of DNP. We assessed the therapeutic potential of parenterally administered CD-NP upon cardiorenal and endocrine function in 6 normal anesthetized dogs. Intravenous CD-NP was infused after baseline measurements at 10, 50 and 100 ng/kg/min. * p<0.05 vs. baseline.

Results: Administration of low, medium and high dose CD-NP decreased MAP (from baseline 137±6 to 134±6 and 128±5 and 118±6* mmHg), RAP (from 1.0±0.3 to 0.5±0.4 and -0.03±0.6* and -0.4±0.6* mmHg) and PCWP (from 6.4±0.4 to 5.2±0.5* and 4.4±0.6* and 3.6±0.5* mmHg). These actions were associated with a decrease in heart rate (from 130±2 to 124±5 and 115±3* and 119±4 bpm). CD-NP increased GFR (from 37±3 to 33±2 and 50±8 and 55±6* ml/min), enhanced natriuresis (UNaV from 48±17 to 123±23 and 326±51* and 462±69* µEq/min) and diuresis (UV from 0.7±0.2 to 1.7±0.3 and 4.0±0.7* and 4.5±0.7* ml/min) and activated cGMP in plasma (from 8.5±1.5 to 13.5±1.8 and 28.1±2.1* and 50.1±2.1* pmol/ml) and urine. All three doses of CD-NP decreased plasma renin activity (from 8.2±1 to 5.9±1* and 3.9±0.7* and 6.3±1.1* ng/ml/hr).

Conclusion: We report the design, synthesis and cardiorenal actions of a new chimeric peptide CD-NP, which activates the cGMP pathway, reduces cardiac filling pressures, augments natriuresis and diuresis and possesses renin-suppressing properties. These findings support a possible therapeutic role for this new designer peptide in the treatment of cardiovascular diseases such as heart failure and hypertension.

4:15 p.m.

860-2 Angiotensin II Type 1 Receptor and Endothelin Type A Receptor Antagonists Prevent Ventricular Fibrosis in the Hypertensive Heart Through Different Mechanisms

Junichi Yoshida, Kazuhiro Yamamoto, Toshiaki Mano, Yasushi Sakata, Nagahiro Nishikawa, Masatsugu Hori, Tohur Masuyama, Osaka University Graduate School of Medicine, Osaka, Japan

Background: LV fibrosis contributes to the development of heart failure. Extracellular matrix (ECM) is regulated by its synthesis and degradation, and the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) mainly determines the degradation. Blockade of renin-angiotensin and endothelin systems prevented the transition to overt heart failure in hypertensive hearts and their beneficial effects were accompanied with inhibition of LV fibrosis. However, mechanisms how the antagonists exert their effects on ECM regulatory system remain unclear.

Methods: Dahl salt-sensitive rats (DSR) fed on 8% NaCl from 7wks were divided into 3 groups: 6 untreated rats, 6 rats treated with subdepressor dose of angiotensin II type 1 receptor antagonist (ARB), candesartan, since 8 wks, and 6 rats treated with subdepressor dose of endothelin type A receptor antagonist (ETB), TA-0201, since 8 wks. Six DSR fed on normal chow served as control.

Result: Data at 19 wks are shown in the table. ARB and ETB similarly inhibited fibrosis. ARB, not ETB, normalized collagen mRNA level. ETB suppressed gene expression of TIMP-2 without affecting that of MMP-2 and increased a ratio of MMP-2 to TIMP-2 mRNA levels. ETB provided greater gelatinolytic activity as assessed with in vitro gelatin zymography than ARB, suggesting augmented collagen degradation in the rats treated with ETB.

Conclusion: ARB and ETB inhibit ventricular fibrosis through different modulation of ECM regulatory system.

	LVEDP (mmHg)	area of fibrosis (%)	collagen-1 mRNA (arbitary units)	MMP-2 mRNA (arbitary units)	TIMP-2 mRNA (arbitary units)	MMP-2/ TIMP2
control	8±1	1.7±0.15	1.0±0.15	1.0±0.11	1.0±0.8	1.0±0.08
untreated	17±1†	6.8±1.2†	3.46±0.42†	2.42±0.35†	2.31±0.06†	1.12±0.11
ARB	6±1‡	2.9±0.2‡	1.03±0.17‡	1.59±0.24‡	2.37±0.55†	0.92±0.19
ETB	7±1‡	2.3±0.3‡	1.78±0.7†‡#	2.54±0.24†#	1.38±0.13‡#	1.86±0.1†‡#

mean±SEM, †p<0.05 vs control, ‡ p<0.05 vs untreated, # p<0.05 vs ARB, LVEDP:LV end diastolic pressure.

4:30 p.m.

860-3 Comparison of Vasodilation by CVT-3146, a Novel $A2_A$ Receptor Agonist, and Adenosine in Different Vascular Beds in Awake Dogs

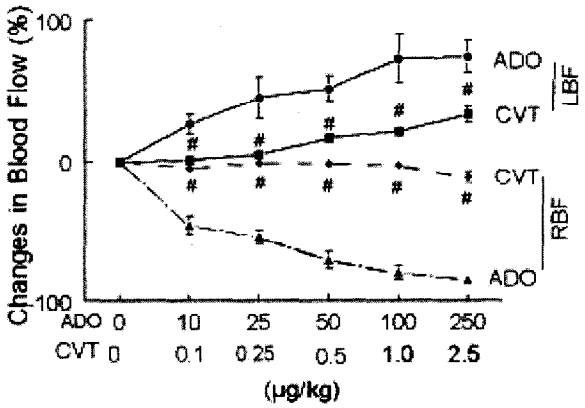
Gong Zhao, Axel Linke, Xiaobin Xu, Manuel Ochoa, Francis Belloni, Luiz Belardinelli, Thoams Hintze, CV Therapeutics, Palo Alto, CA, New York Medical College, Valhalla, NY

Background: We have previously shown in awake dogs that CVT-3146 (CVT) causes a smaller decrease in total peripheral resistance compared to adenosine (ADO), but it causes an equal or greater increase in coronary blood flow than ADO. In this study, we compared vasodilator effects of CVT to those of ADO in different vascular beds in awake dogs.

Methods: Dogs were chronically instrumented for measurements of the blood flow in coronary (CBF), mesenteric (MBF), hindlimb (LBF), and renal (RBF) vascular beds, and hemodynamics.

Results: Bolus injections (iv) of CVT (0.1 to 2.5µg/kg) and ADO (10 to 250µg/kg) caused significant increases in CBF (35±6 to 205±23% and 58±13 to 163±16%) and MBF (18±4 to 88±14% and 36±8 to 84±5%). CVT is a more potent and longer lasting coronary vasodilator compared to ADO (the duration for CBF above 2-fold of the baseline: CVT (2.5µg/kg): 130±19s; ADO (250µg/kg): 16±3s, P<0.05). As shown in the figure (mean±SE, n=6), CVT caused a smaller increase in LBF than ADO. ADO caused a dose-dependent renal vasoconstriction (RBF -46±7 to -85±4%), whereas CVT has no or a little effect on RBF (-5±2 to -11±4%, P<0.05, compared to ADO).

Conclusion: CVT-3146 is a more selective and potent coronary vasodilator than ADO. CVT-3146 has no significant effect on renal blood flow in awake dogs. These features of CVT-3146 make it an ideal candidate for radionuclide myocardial perfusion imaging.



4:45 p.m.

860-4 A New Perspective on the Pharmacological Treatment of Vagal Induced Atrial Fibrillation: Combined Inhibition of Muscarnic Potassium Current and IKr

Bodo Brandts, Marc Van Bracht, Rolf Borchard, Ingo Wickenbrock, Daniel Dirkmann, Magnus Prull, Nadine Bodanowski, Hans-Joachim Trappe, University of Bochum, Herne, Germany

Background: Pharmacological treatment of atrial fibrillation (AF) is limited by induction of malignant ventricular arrhythmias. Developing new drugs one promising strategy is a more specific treatment of the atria. Muscarinic potassium current (IK(ACh)) is predominantly expressed in supraventricular tissue. We studied the profile of representative class III drugs in respect to their effect on IK(ACh).

Methods: In guinea-pig atrial myocytes IK(ACh) was activated by using acetylcholine