Cardiac-Specific Gain-of-Function Mutation in the Natruretic Peptide A Receptor is Associated With Improved Diastolic Function in Presence and Absence of Pressure Overload Hypertrophy

Allison M. Pritchett, Maria L. Valencik, John A. McDonald, Gerald E. Harder, Margaret M. Redfield, Mayo Clinic Foundation, Rochester, MN, Salt Lake City Veterans Administration Medical Center, Salt Lake City, UT

Background: Few therapies are known to enhance diastolic function. Systemic administration of natriuretic peptides (NP) improves diastolic function. However, this may be due to effects on load, rather than a direct myocardial action. We generated mice with a cardiac-specific (α-MHC promoter) gain-of-function mutation (GoF; HCAT/E) in the natriuretic peptide A receptor (NPRA) resulting in myocyte-specific constitutive NPRA activation. We hypothesized that GoF mice would exhibit enhanced diastolic function and develop less diastolic dysfunction with pressure-overload.

Methods: GoF mice (n=12) and their wild type (WT; n=18) littermates underwent abdominal aortic banding to generate pressure-overload hypertension. LV structure and function (echo, catheterization, autopsy) were assessed three weeks after banding. Non-band GoF (n=15) and WT (n=13) groups were controls.

Results: See table (mean ±SD): With aortic banding, both GoF and WT mice developed LV hypertrophy. While load and systolic function were similar between WT and GoF mice without and with banding, the time constant of LV relaxation (Tau) was decreased in GoF mice as compared to WT indicating improved diastolic function.

Conclusion: Chronic cardiac-specific NPRA activation via the GoF mutation enhanced diastolic function in mice and markedly attenuated diastolic dysfunction associated with pressure-overload hypertension. These data suggest that NP improve diastolic function via a direct myocyte effect.

Variable | HCAT/E Control | HCAT/E Banded
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GoF | Titer | P | GoF | Titer | P
LV End-diastolic dimension, mm | 3.5±0.2 | 3.4±0.4 | 0.45 | 3.7±0.3 | 3.5±0.2 | 0.03
Fractional Shortening, % | 96±5 | 34±4 | 0.33 | 33±4 | 34±3 | 0.89
LV Mass, g | 0.90±6 | 0.90±5 | 0.02 | 0.92±0 | 0.11±0 | 0.01 | 0.49
Heart Rate (anesthesia), bpm | 60 | 50 | 0.03 | 50±2s | 39±3s | 0.76
Maximal LV Pressure, mmHg | 45±5 | 39±5 | 0.04 | 40±5 | 39±5 | 0.04 | 0.05
End-diastolic LV Pressure, mmHg | 6±6 | 5±6 | 0.05 | 7±8 | 8±5 | 0.10
Tau, msec | 3±2 | 16±3 | 0.04 | 14±5 | 21±4 | 0.05
Heart weight / Body weight, mg/g | 4.2±0.3 | 4.1±0.3 | 0.36 | 4.5±0.4 | 4.6±0.5 | 0.30

Improved Diastolic Function in Presence and Absence of Pressure Overload Hypertrophy

Chronic A1 and A2b Adenosine Receptor Blockade Improves Diabetes and Attenuates Renal and Cardiac Histopathology in Animals With the Metabolic Syndrome

Steven P. Tofolli, Eman M. Selah, Glenn Smits, Eric Whalley, Barry Ticho, Edwin K. Strohman, University of Pittsburgh School of Medicine, Pittsburgh, PA, Biogen, Inc., Cambridge, MA

Background: In animals and patients with left ventricular dysfunction, short-term A1 adenosine receptor (A1R) blockade causes diuresis/natriuresis without altering potassium excretion and, in contrast to loop diuretics, improves renal function. A2b adenosine receptor (A2bR) antagonist has an anti-diabetic effect. The purpose of the present study was to examine the long-term effects of A1A2bR blockade in an animal system designed to model the complex pathology that characterizes, with increasing frequency, the modern cardiac patient.

Methods: B6Hfr2 mice is a novel, orally active and selective adenosine receptor antagonist which has high affinity for A1R and moderate affinity for A2bR. The ZSF1 rat is a model designed to model the complex pathology that characterizes, with increasing frequency, the modern cardiac patient.

Results In non-failing myocytes Ang II type 1 receptor stimulation significantly activated mainly ERK1/2 and also SAPK/JNK pathways but no JAK2 phosphorilation was detected. In A2bR knockout mice treated with Ang II, most of the A2bR mediated effects were suppressed and ERK1/2 and SAPK/JNK activation was significantly decreased in A2bR knockout mice (p<0.05 vs controls) with unchanged JAK2 phosphorylation. In failing myocytes Ang II mediated ERK1/2 activation was selectively preserved (~8% vs controls).

Conclusion: In failing myocytes Ang II activates different intracellular pathways from normal cells as indicated by the impaired Ang II mediated activation of the growth promoting (ERK1/2) signalling with contemporaneous activation of the proapoptotic (JAK2) pathway.

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Alessandro Catalotti, Hong H. Chen, Guido Boerrigter, Lisa C. Costello-Boerrigter, Toshihiro Tsuruda, Lorenzo S. Malatino, John C. Burnett, Jr., Mayo Clinic and Foundation, Rochester, MN

Background: Congestive heart failure (CHF) is characterized by avid sodium and water retention. While loop diuretics are powerful natriuretic agents, they can reduce glomerular filtration rate (GFR) and activate the renin-angiotensin-aldosterone system (RAAS). Studies have reported that Ang II is a key predictor of mortality in CHF. Therefore, new therapeutic strategies are warranted to both minimize side effects of conventional diuretics and to potentiate their renal actions. Brain natriuretic peptide (BNP) has natriuretic and diuretic properties. The diuretic actions of BNP mainly located in the tubules and are associated with preserved GFR. We characterized the renal actions of BNP alone and in combination with Lasix (L). We hypothesized that BNP in combination with L maintains GFR and suppresses RAAS.

Methods: CHF was induced in two groups of dogs by rapid ventricular pacing (10 days at 240 bpm). At day 11 one group received continuous (30 min) intravenously administered low dose (2 pmol/kg/min) followed by 30 min high dose (10 pmol/kg/min) of BNP. A second group (BNP+L) of dogs received i.v. co-infusion of 150 min of L (1mg/kg) and low high dose of BNP. * indicates p<0.05 vs baseline