1039
Neurohormones, Cardiac Function, and Pericardial Delivery

Monday, March 30, 1998, Noon-2:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: Noon-1:00 p.m.

1039-23 Melatonin, a Pineal Hormone With Antioxidant Property, Protects Against Adriamycin Cardiomyopathy in Rats

I. Morishima, Y. Toki, K. Okumura, T. Ito, Internal Medicine II, Nagoya University, Nagoya, Japan

Background: The clinical use of adriamycin (ADR) is limited by its cardiotoxicity in which free radicals and lipid peroxidation may be involved. Melatonin (MEL) has gained increasing interest as a strong antioxidant. Accordingly, the protective effects of MEL against ADR cardiomyopathy was evaluated.

Methods: Male Sprague-Dawley rats were divided into 4 groups as follows: ADR (ADR treated, cumulative dose 15 mg/kg bw, ip, for 2 weeks), MEL (MEL treated, cumulative dose 84 mg/kg bw, ip), MEL + ADR (MEL + ADR treated, and CONT (control). After 3 weeks of post treatment observation, their cardiac performance was assessed, and their hearts were used to study myocardial lipid peroxidation by measuring thiobarbituric acid reactive substance (TBARS) along with ultrastructure as well as parameters shown below.

Results: MEL restored the ADR induced changes in myocardial ultrastructure as well as parameters shown below:

<table>
<thead>
<tr>
<th>CONT</th>
<th>ADR</th>
<th>MEL</th>
<th>MEL + ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb/Bw ratio</td>
<td>2.83 ± 0.06</td>
<td>2.30 ± 0.06</td>
<td>2.91 ± 0.06</td>
</tr>
<tr>
<td>Aspartate (a)</td>
<td>317.1 ± 0.7</td>
<td>317.1 ± 0.7</td>
<td>322.6 ± 0.2</td>
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<tr>
<td>SBP (mmHg)</td>
<td>194.4 ± 1.4</td>
<td>194.4 ± 1.4</td>
<td>189.5 ± 1.4</td>
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<tr>
<td>FS (%)</td>
<td>58.6 ± 1.1</td>
<td>54.0 ± 1.1</td>
<td>53.4 ± 1.1</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TBARS (nmol/h)</td>
<td>54.3 ± 1.1</td>
<td>63.2 ± 2.0</td>
<td>49.2 ± 1.9</td>
</tr>
</tbody>
</table>

Our data mean ± SEM, *p < 0.01. *p < 0.05 vs all other groups. Hb/Bw: Heart weight/body weight. SBP: Systolic blood pressure. FS: Fractional shortening.

Conclusion: MEL may be highly effective in protecting against ADR cardiomyopathy by preventing lipid peroxidation.

1039-24 Tumor Necrosis Factor α Induces Contractile Dysfunction in Conjunction With Nitric Oxide Production in Conscious Dogs

D.R. Murray, B. Chandrasekar, G.L. Freeman, Medicine/Cardiology, The University of Texas Health Science Center, and ALUMWH, San Antonio, TX 78284-7874, USA

Tumor necrosis factor (TNF)-α promotes elaboration of the inducible isozyme of nitric oxide synthase (iNOS); however, the relationship between subsequent NO production and the development of contractile dysfunction in vivo is not known. Accordingly, six chronically instrumented, conscious dogs pretreated by end-systolic elastance, Ees (mm Hg/ml), and plasma nitrate-nitrite levels (NO3−+NO2−, μM) by vanadium reduction. Dogs were killed 24 hours after TNF-α or saline; hearts were frozen and assessed for iNOS protein by western blot (IB), fractional cell shortening (FS) was 7.9 ± 1.4% and intracellular pH (pHi, 7.0 ± 0.2); 10−4 M L-NAME increased FS by 1.4 ± 0.2 (p = 0.02). TNF-α increased FS by 1.8 ± 0.2 (p < 0.05).

Summary: TNF-α administration upregulates functionally active iNOS in the heart, possibly through activation of NF-κB. Increased plasma metabolites of NO strongly correlate with in vivo cardiac depression after TNF-α.

1039-25 Positive Inotropic Effect of Bradykinin: Role of Cardiac Endothelin, Nitric Oxide, Prostaglandins and Endothelin

P. Mohan, D.L. Brutsaert, S.U. Sys, University of Antwerp, Antwerp, Belgium

Background: Bradykinin (Brd) causes endothelin-dependent vascular smooth muscle relaxation and may explain some of the beneficial cardiac effects of angiotensin converting enzyme inhibitor therapy. Brd receptors are also present on cardiomyocytes. However, the inotropic effect of Brd on myocardium, in particular role of endothelin (ET), media tors released by E-Nitro-oxide (NO), prostaglandins (PG) and endothelin, and interaction with concomitant β-adrenergic stimulation have not been investigated.

Methods: We examined myocardial effects of Brd (10−8 M to 10−5 M) in isolated rat papillary muscles (Kroes-Finger 1.25 mM Ca2+, 37°C, enalaprilat, B: 10−6 M, atenolol: 2 × 10−6 M) before (B+ET: n = 7) and after selective damage of ET-1 (ET: n = 7; 1 μM in Tiron-X: 0.5%). To investigate role of NO, PG and endothelin, Brd was added in subgroups of B+ET muscles incubated with L-NAME (10−5 M, n = 8), indomethacin (INDO: 10−6 M, n = 8) or BQ123 (10−6 M, n = 7).

Results: (mean ± SE, % baseline) In +ET, Brd induced an dose-dependent increase in peak active tension (AT: 10−5 M = 93 ± 3%) with no change in time to half relaxation (T1/2: 1.4). This response was blocked by the bradykinin receptor antagonist (HOE 140: 10−7 M, n = 3) and was absent in -ET. The inotropic response to Brd was not inhibited by L-NAME, INDO or BQ123 alone but was inhibited by L-NAME + INDO (Brd: 10−5 M; AT: 1 ± 1.6). iNOS immunoreactivity (3 × 10−7 M) induced increases in AT (14.4 ± 2.0) was abolished by Brd (10−5 M) (0.2 ± 4.2), which was not modified by L-NAME + INDO (O ± 4.3).

Conclusion: Brd induced a cardiac endothelium-dependent positive inotropic myocardial effect with no effect on relaxation, which was mediated by both NO and PG. Brd abolished the effect of concomitant β-adrenergic stimulation, independent of NO and PG.

1039-26 Atrial Natriuretic Peptide Decreases Contractility and Intracellular pH in Adult Ventricular Myocytes

M. Tayma, J. Bartune, B.H. Leder, B. Israel, Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

Atrial natriuretic peptide (ANP)-cGMP signaling modifies cardiac function by natriuresis and vasodilation but inotropic effects are controversial. We studied effects of ANP on cell shortening and intracellular signaling in HEPES-buffered adult ventricular rat myocytes (n = 26) paced at 0.5 Hz. At baseline (B), fractional cell shortening (FS) was 7.0 ± 0.2% and intracellular pH (pHi, SNAP-F-1) was 6.9 ± 0.05. ANP caused a dose-dependent depression of contractility (Fig. 1) associated with intracellular acidification (Fig. 2). In cells loaded with Fluoresc (n = 5), ANP caused no change in systolic Ca++

Summary: ANP directly depresses contractility via intracellular acidification and decreases myofilament Ca++ sensitivity. Similar to negative inotropic action of nitric oxide, this may be related to cGMP-mediated disabling of forward Na++ - H+ exchange.