Probing Adrenergic Function of the Failing Hamster Heart: Neuronal Norepinephrine Release, Uptake-1 Pump, and Receptor Mediated Effects

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Introduction: Hereditary forms of heart failure are responsible for approximately 20% of all cardiomyopathies. The cardiomyopathic (CM) Syrian hamster (TO-2 strain) is a useful animal model of human heart failure because a similar genetic defect, lack of δ-sarcoglycan in the cell-cell adhesion protein complex, has been identified in four separate families. In heart failure, autonomic nervous system function is defective as evidenced by decreased β adrenergic receptor number, increased blood catecholamine (norepinephrine, NE) concentrations, decreased cardiac tissue catecholamine content, and decreased responsiveness to adrenergic stimulation. The β adrenergic receptor agonist, L-isoproterenol and the indirect acting sympathomimetic amine, tyramine, are useful chemicals for probing the functionality of different elements of the adrenergic nerve-effector cell unit within the isolated perfused heart, where the potentially confounding influences central nervous system controls and various blood borne molecules are absent. **Hypothesis:** Cardiomyopathic Syrian hamsters with early-stage compensated heart failure will show decreased response to both direct and indirect adrenergic receptor stimulation as compared with age and sex-matched normal, healthy control hamsters due to the dysregulation of their intact autonomic nervous system. **Methods:** Whole hearts harvested from 6-month old control (C, n = 9) and cardiomyopathic (CM, n = 8) male hamsters were placed on a Langendorff apparatus (i.e. coronary perfusion through the aorta, the left ventricle is not dynamically loaded to perform volume-ejection work). Oxygenated (pO_2 = 600+ Torr), buffered (pH = 7.4), balanced electrolyte, Krebs' solution with glucose (5mM) was the coronary perfusate at 37ºC. Cardiac chronotropic and inotropic variables - chronotropic index (heart rate, HR, in beats per minute, bpm) and inotropic index (maximum rate of left ventricular pressure development, $+dP_{LV}/dt_{max}$, in mmHg/sec) - and a coronary vasomotor status variable (coronary vascular resistance, R, in mmHg/mL/min) were used as outcome measures. After 50 minutes equilibration, hearts were exposed to increasing concentrations of isoproterenol (ISO) or tyramine (TYR) to establish dose-response curves. TYR (10^{-5} M) was also administered repeatedly (7X) at 5 minute intervals to test the neuronal NE release tachyphylaxis response in C (n=2) and CM (n = 2) hearts. **Results:** At baseline, C hearts had higher spontaneous HR (304 ± 33) than CM hearts (252 ± 3); C hearts had a higher $+dP_{LV}/dt_{max}$ (2612 ± 234) than did CM hearts (2012 ± 25); coronary flow was higher in C hearts (10.3 mL/min/g) than in CM hearts (6.6 mL/min/g); R was correspondingly lower in C hearts (7.5 ± .6) than in CM hearts (11.3 ± 1.3). Direct β adrenergic receptor stimulation with ISO (~6 $x10^{-7}$ M) increased HR in C hearts to 360, and in CM hearts to 321. ISO increased $+dP_{LV}/dt_{max}$ to 3738 ± 35 in C hearts and to 3543 ±5 6 in CM hearts. ISO surprisingly increased R in C hearts to 9.9±1.4, but predictably decreased R in CM hearts to 9.5±.2. TYR (10^{-5} M) increased HR from 298 ± 23 to 344±11 in C hearts and from 226±9 to 297±13 in CM hearts. TYR produced no decrease in $+dP_{LV}/dt_{max}$ in C hearts and decreased $+dP_{LV}/dt_{max}$ from 1746 by 9% in CM hearts. TYR-released NE produced a substantially greater increase in R in CM (from 14.0 by 74%) than in C hearts (from 7.57 by 45%). No evidence of tachyphylaxis to repeated TYR was observed in C or CM hearts. **Conclusions:** There are decreased β adrenergic receptor mediated responses (i.e., HR, $+dP_{LV}/dt$) to ISO in CM hearts when compared to C hearts. These altered responses may be due to a decrease in the number of β adrenergic receptors or to diminished sensitivity in other components of the receptor-cell response system. Neuronally-released NE produced coronary vasoconstriction in CM but not C hearts; further supporting a loss of functional β receptors on coronary smooth muscle. The lack of tachyphylaxis in C and CM hearts suggests that the TYR-releasable pool of NE is robust or rapidly renewable by either endogenous biosynthesis or NE reuptake via the uptake-1 pump. This observation fails to implicate any substantial defect in the presynaptic neuronal neurotransmitter mechanisms in CM hearts. Taken together, these data are consistent with the proposed hypothesis, yet confirmation of the molecular mechanisms responsible for response differences in CM hearts will be required.