9:00

831-3 β-Adrenergic Stimulation Induces Cardiocyte Apoptosis Which Is Not Mediated by an Increase in Heart Rate

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Background: Both persistent tachycardia and β-adrenergic stimulation cause progressive heart failure. To explore possible mechanisms, we asked whether either stimulus was associated by apoptotic myocardial cell loss.

Methods: Four groups of rats treated for 24 hrs were compared: Control (C); Isoproterenol (Iso) of either 40 μg/kg/hr or 400 μg/kg/hr via Alzet minipump; mechanical pacing (500 bpm). Following treatment, hearts were formalin fixed, embedded in paraffin and cardiocyte apoptosis (Apo) was evaluated using TUNEL method on 5 μm sections from the mid-ventricle wall.

Results:

	C	Iso 400	Iso 40	Pacing
HR (bpm)	424 ± 16	517 ± 21*	497 ± 8*	509 ± 6*
SBP (mmHg)	85 ± 6	82 ± 2	84 ± 7	97 ± 6
Apo (per area)	0.3 ± 0.3	7.9 ± 2.5*	0.8 ± 0.5	1.7 ± 0.7
Apo (per cells)	0.04 ± 0.04	1.26 ± 0.39*	0.13 ± 0.08	0.23 ± 0.08
Number of rats	5	4	6	5

(Data are mean ± SEM. SBP: systolic blood pressure, per area, per cm^2, per cells, per 10,000 cardiocytes. *$p < 0.05$ vs. C).

HR was increased by Iso 400, Iso 40, and pacing. SBP was similar amongst all four groups. Apo was increased by Iso 400, but not any the other treatments.

Conclusions: Thus, 24 hours of continuous β-adrenergic stimulation induces significant cardiocyte apoptosis and this effect is not mediated solely by an increase in HR.

9:15

831-4 Alterations in Myocardial β-Adrenoceptor Subtypes and Signal Transduction Pathway in Nerve Growth Factor Overexpressing Transgenic Mice

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Background: We have established a transgenic mouse model in which selective overexpression of nerve growth factor (NGF) results in cardioselective sympathetic hyperinnervation and cardiac hypertrophy.

Methods: To determine whether the cardioselective sympathetic hyperinnervation alters the norepinephrine (NE) uptake function and myocardial β-adrenoceptor (βAR)-coupled adenylyl cyclase signal transduction system, we measured cardiac NE uptake site density (fmol/mg) by ^{3}H-nisoxetine binding, total βAR and β_1, β_2 subtype density (fmol/mg) by ^{125}I-iodocyanopindolol radioligand assay, dissociation constant (K_I, nM) of the βAR for isoproterenol, and maximum increase in cyclic AMP (cAMP, pmol/mg/min) produced by isoproterenol in 4 week-old control and transgenic mice.

Results:

	NE-uptake	βAR	β_2	K_I	cAMP
Control	186 ± 55	35 ± 5	12 ± 2	0.17 ± 0.05	4.6 ± 0.8
NGF	1706 ± 221*	55 ± 5*	28 ± 3*	0.39 ± 0.07*	1.6 ± 0.2*

Values are means ± SE. *$p < 0.05$, vs. Control. N = 11.

Conclusion: Cardioselective sympathetic hyperinnervation in the transgenic mouse causes an increase in NE-uptake sites, an increase in β_2AR density, and no change in β_1AR density. The adenylyl cyclase response to isoproterenol, however, is reduced, probably because of the marked uncoupling of βAR to G-protein. The findings show that increased cardiac NE causes βAR subsensitivity without receptor downregulation.

9:30

831-5 Age-dependent Decrease in Human Cardiac β-Adrenergic and Muscarinic Receptor Function: In Vitro and in Vivo Study

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In ageing cardiac β-adrenergic receptor (AR) function declines while little is known on muscarinic M_2-R changes. To study possible mechanisms of β-AR and M_2-R changes with age we assessed a) in vitro in right atria (RA) from 91 patients of different age (5 d–83 yrs) without apparent heart failure β-AR and M_2-R densities. 10 μM GTP, 100 μM isoprenaline (ISO), 10 mM NaF and 10 mM Mn^{++}-activated and carbachol (CAR 10 nM–100 μM)-inhibited adenylyl cyclase (AC) activity and b) in vivo in 6 young (< 30 yrs) and 6 elder (60 yrs) volunteers ISO-infusion (3.5–35 ng/kg/min)-caused increase and pirenzepine (PIR 0.32 and 0.64 μg i.v. bolus)-caused decrease in heart rate (HR).

Results: 1) β-AR: In vitro β-AR density and -subtype distribution did not change while GTP, ISO, NaF and Mn^{++}-activated AC declined with age. In vivo ISO-infusion evoked HR-increases were not different between young and elder volunteers; after pretreatment with atropine, however, ISO-evoked HR-increases were markedly enhanced in young but not in elder volunteers. 2) M_2-R: In vitro M_2-R density was significantly negative correlated with age; concomitantly CAR-evoked AC-inhibition declined with age. In vivo PIR-induced decrease in ISO-evoked HR-increase was significantly reduced in the elderly.

Conclusion: In human RA β-AR and M_2-R function decreases with age. The β-AR decrease is due to a reduced activity of AC-catalytic unit; the M_2-R decrease is due to a reduced R-density. The decrease in M_2-R density is accompanied by a blunted negative chronotropic response to M_2-R stimulation in vivo, while the decrease in β-AR function can be demonstrated in vivo only when the counterregulatory action of parasympathetic activity is removed.

9:45

831-6 Echocardiographic and Histopathological Characterization of Young and Old Transgenic Mice Over-expressing the Human β1-Adrenergic Receptor

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Background: The β1-adrenergic receptor (β1-AR) is central to regulation of myocardial contractility. In the failing heart, the β1-AR is chronically over-stimulated due to high concentrations of norepinephrine. Therefore, we wished to examine the effect of constitutive β1-AR over-expression in myocardial tissues.

Methods: The human β1-AR was overexpressed in transgenic (TG) mice, in a cardiac-specific context, using an α-myosin heavy chain promoter. Receptor expression ranged between 1 and 2.5 pmol/mg membrane protein. Cardiac function (echocardiography) and histopathology (Trichrome and H&E) were examined at 4–5 months (young (yng)), and 8–20 months of age (old).

Results: Old TG mice had significantly greater left ventricular chamber sizes in both systole (LVIDS) and diastole (LVIDD) and a significantly reduced fractional shortening (FS) compared to young and old control and to young TG mice.

	CON-yng	TG-yng	CON-old	TG-old
FS (%)	58 ± 1	59 ± 1	60 ± 2	30 ± 4*
LVIDS (mm)	1.5 ± 0.02	1.3 ± 0.1	1.3 ± 0.03	3.2 ± 0.4*
LVIDD (mm)	3.5 ± 0.03	3.2 ± 0.1	3.4 ± 0.2	4.5 ± 0.3*

(*$p < 0.05$ by ANOVA)

Histopathologically, both young and old TG mice had substantial myocardial remodeling with myocyte hypertrophy and large areas of interstitial replacement fibrosis.

Conclusions: Constitutive cardiac-directed over-expression of the β1-AR in TG mice appears to produce a time-dependent remodeling resulting in ventricular dilatation and eventual cardiac failure. The β1-AR transgenic mouse should be a highly useful model of adrenergically mediated dilated cardiomyopathy.

832 Coronary Blood Flow and Endothelial Dysfunction

Tuesday, March 31, 1998, 8:30 a.m.–10:00 a.m.
Georgia World Congress Center, Room 254W

8:30

832-1 Effect of the Menstrual Cycle on Endothelium-dependent Vasodilation of the Brachial Artery

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Background: Estrogen alone or in concert with progesterone therapy has beneficial effects on endothelium-dependent vasodilation in postmenopausal women and such improvement in endothelial function may explain the reduction in cardiovascular events associated with hormone replacement therapy.