Potential Involvement of Novel Scavenger Receptor in Enhanced Cardiac Beta3-Adrenergic Functional Biventricular Autocrine/Paracrine Systems in Left Ventricular Mass Index and the Common,...

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Background: The presence of LVH in hypertensive subjects.

Results: 112-week-old Wistar rats were examined in 4 groups: normal control (n=20), normal rats pre-treated with normal saline, normal rats pre-treated with a blocking antibody to CD36, and normal rats pre-treated with an antibody to SRECII.

Conclusion: The SRECII scavenger receptor mediates at least two OxLDL-induced pro-atherogenic effects: rise in superoxides and induction of smooth muscle cell apoptosis. The involvement of the SRECII scavenger receptor expression in vascular smooth muscle cells and our finding strongly suggests its involvement in atherogenesis.

Left Ventricular Mass Index and the Common, Functional, X-Linked Angiotensin II Type 2 Receptor Gene Polymorphism (1332 G/A) in Patients With Systemic Hypertension

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Background: A common intrinsic polymorphism, (-1332 G/A) of the angiotensin type 2 (AT2) receptor gene, located on the X-chromosome, has been reported to be biologically functional. The aim of this study was to evaluate this polymorphism for an association with left ventricular hypertrophy (LVH).

Methods: LV mass was measured in 197 patients with systemic hypertension and 60 normal volunteers, using a 1.5-Tesla Philips MRI system. Genotyping was performed using a restriction enzyme digestion of an initial 310 bp PCR product that included the AT2(-1332 G/A) locus.

Results: The mean LV mass index for the male patients was 94.3±19.6 g/m² (n=125) and for the female patients was 71.2±12.0 g/m² (n=72). Seventy three (37.1%) of all patients had an elevated LV mass index, defined as the mean LV mass index for normal volunteers plus 2 S.D (males 77.8±9.1 g/m²; n=36; females 61.5±7.5 g/m²; n=30). Comparison of LV mass index, of the A/A genotype (mean LV mass index = 82±24±21.1 g/m²; n=123) against that of the G/G genotype (mean LV mass index = 88±19.0 g/m²; n=89), as a continuous variable was significant by analysis of variance (p<0.044). Chi-square comparison revealed an excess of the G/G genotype among hypertensives (p=0.031), all subjects compared with normal subjects (p=0.023) and when compared with hypertensives without LVH (p=0.058).

Conclusion: We observed an association between the AT2 receptor (-1332 G) allele and the presence of LVH in hypertensive subjects.

Impact of Protein Kinase C-Epsilon on Myocardial Hypertrophy After Chronic Pressure Overload: In Vivo Study in Protein Kinase C-Epsilon Knockout Mice

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Background: Protein kinase C (PKC) is involved in the signal transduction of myocardial hypertrophy. Overexpression and increased activation of PKCs leads to myocardial hypertrophy in mice. However, if PKCε is required for signaling in myocardial hypertrophy, the lack of PKCε is expected to result in either reduced or even no myocardial hypertrophy after chronic pressure overload.

Methods: Hearts of wild type (WT; n=17) and PKCε-KO mice (KO; n=20) were examined by echocardiography before and after 4 weeks after transverse aortic constriction (TAC). Hearts were excised and preserved in N2 or formalin.

Results: 1. In mice there were no differences in left ventricular dimensions, function and structure. 2. 4 weeks after TAC both groups, WT and KO, developed myocardial hypertrophy to the same extent. 3. Left ventricular systolic function was preserved in both groups after pressure overload. 4. Northern blots of typical markers of hypertrophy, i.e. α-MHC, ANP and α-SMA Activation increased comparably in both groups after TAC. 5. Sirius-red staining showed a significant increase of fibrosis in hypertrophied hearts of KO compared with WT.

Conclusions: 1. Until the age of 12 weeks the lack of PKCε does not lead to alterations in myocardial development in mice. 2. PKCε is not essential for the development of cardiac hypertrophy in mice. 3. The lack of PKCε leads to increased myocardial fibrosis after chronic pressure overload. 4. Further investigations have to elucidate the molecular mechanism leading to increased myocardial fibrosis in PKCε-KO after TAC and its functional consequences.

Enhanced Cardiac Beta3-Adrenergic Functional Response in Alcoholics

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Background: Chronic alcohol intake is associated with attenuated cardiac β-adrenergic receptor (AR)-mediated positive inotropic response. Altered cardiac functional βAR expression may contribute to this effect. However, the effect of chronic alcohol on cardiac βAR has not been examined. Moreover, although βAR has been documented in human, rat, and canine myocardium, its existence and functional role in monkey hearts remains undetermined.

Methods. We compared βAR mRNA levels and myocyte contractile and calcium current (ICa,L) responses to βAR agonist, BRL-37344 (BRL, 10^-M), in freshly isolated left ventricular (LV) cardiomyocytes obtained from 8 normal control cynomolgus monkeys and 6 monkeys with self-administered alcohol for 9 months (models 4 and 2 heavy drinkers with mean daily intake of alcohol of 1.9 and 3.4 g/kg, respectively).

Results. Using RT-PCR, βAR mRNA (a single band about 317 bp) was detected in both normal and alcoholic myocytes. Compared with normal myocytes, the signal ratio of βAR mRNA in moderate and heavy drinkers was significantly increased by 72% to 28.8% and 53.2%, respectively. These changes were associated with altered βAR-mediated inotropic actions. Compared with normal myocytes, in alcoholic cardiomyocytes, cell contraction (dL/dt max -32%, 61.3±10.3 vs 89.9±12.2 mm/s) and relaxation (dP/dtmin, -32%, 59.4±14.0 vs 76.2±10.5 mm/s) and calcium current (ICa,L, -22%, 6.4 vs 5.0 pA/PF) were significantly reduced. In addition, superfusion of ISO (10^-M) caused a much less increase in dP/dtmin (52% vs 79%) and dP/dtmax in contrast, in alcoholic cardiomyocytes, BRL produced a much greater decrease in the percent shortening (17.8% vs 6.5%), dP/dtmin (16.4% vs 7.1%), and ICa,L (22.4% vs 21.4%). These responses were prevented by bupranolol or L-748,337 (βAR antagonists).

Conclusion. In monkeys, chronic alcohol intake (moderate and heavy) increases cardiac βAR mRNA expression and enhances cardiac βAR-mediated negative inotropic response.