Growth Hormone–Releasing Peptide Can Suppress Testosterone Inhibits the Both Beta-Blockers and Amiodarone Increase Speed of

suggest this vasodilatation is due to a calcium antagonistic action upon voltage-gated (Cav1.2), or the action is still to be established. Since both substances were shown to modulate QT/RR areas including those of no clear indication for ICD. However, the mode of synergistic acts as an inhibitor of both human L-type and T-type Ca2+ channels, the major voltage-gated calcium channels expressed in vascular smooth muscle. Inhibition of L-type Ca2+ channel currents (using 20mM Ba2+ as the charge carrier) in HEK 293 cells stably patch clamp methodology to study the effect of testosterone (1nM-1M) upon whole-cell Ca2+ channel currents (using 20mM Ba2+ as the charge carrier) in HEK 293 cells stably expressing either the main pore-forming µ1C Subunit of L-Type Ca2+ Channels (Ca,1,2) and ß1H-Type Ca2+ Channels (Ca,3,2) StablyExpressed in Human Embryonic Kidney 293 Cells

Background: Testosterone therapy reduces myocardial ischaemia in men with coronary artery disease (CAD) [1] and improves symptom scores and exercise capacity in men with congestive heart failure (CHF) [2]. These effects may be attributed to a direct vasodilatory efficacy in the coronary [3] and peripheral [4] vasculature. In vitro studies suggest this vasodilatation is due to a calcium antagonistic action upon voltage-gated Ca2+ channels [5], but this has yet to be investigated directly. Methods: We employed patch clamp methodology to study the effect of testosterone (1nM-1µM) upon whole-cell Ca2+ channel currents, using 20mM Ba2+ as the charge carrier. In HEK 293 cells stably expressing either the main pore-forming µ1C Subunit of a human L-Type Ca2+ channel (Ca,1,2), or the ß1H-Type Ca2+ channel (Ca,3,2) [6]. Results: Testosterone (1nM-1µM) caused a rapid, reversible concentration-dependent inhibition of L-Type Ca2+ currents, with an IC50 value of 61.0±6.6nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ currents, but this effect was partially reversible with a lower IC50 value of 231.9±34.4nM (n = 4-9 cells at each concentration tested). Current-voltage relationships indicated that testosterone caused a similar inhibition at all activating potentials, suggesting that the inhibition was voltage-independent. Testosterone (1nM-1µM) also inhibited currents mediated via T-type Ca2+ channels, the major voltage-gated calcium channels expressed in vascular smooth muscle. Inhibition of L-Type Ca2+ channels occurred at physiological concentrations. This calcium antagonistic action may serve as a novel mechanism for explaining the clinical benefits associated with testosterone therapy in men with CAD and CHF.

Ghrelin, the endogenous ligand of growth hormone secretagogue receptor (GHS-R), acts on the pituitary and the hypothalamus to stimulate the release of growth hormone (GH) and promote appetite and adiposity. It has also been reported to increase myocardial contractility, induce vasodilation, and protect against myocardial-ischemia–induced heart failure. Though principally gastric in origin, it is also produced by other tissues. This work investigated whether cardiomyocytes synthesize and secrete ghrelin, and how its production in these cells responds to stress and exogenous apoptotic agents. Methods and Results: RT-PCR showed that cells of the adult mouse cardiomyocyte line HL-1 expressed mRNA for both ghrelin (GHS-R) and GHS-R, and competitive binding of [125I]-labelled ghrelin showed efficient constitutive expression of GHS-R at the surface of HL-1 cells. Immunohistochemistry confirmed the presence of ghrelin in the cytoplasm of HL-1 cells and of isolated human cardiomyocytes in primary culture. Radiommunossay showed that ghrelin was secreted by HL-1 cardiomyocytes into the culture medium. Ghrelin did not modify the viability of HL-1 cells subjected to 12h starvation, but did protect against the apoptosis induced cytotoxic anabionide (AraC). Finally, production of ghrelin mRNA in HL-1 cardiomyocytes was reduced by AraC but increased if exposure to AraC was preceded by GH treatment. Conclusions: We demonstrate for the first time that ghrelin is synthesized and secreted by isolated murine and human cardiomyocytes, probably with paracrine/autocrine effects protecting these cells from apoptosis. This new axis may play a beneficial role in myocardial dysfunction and heart failure.

ORAL CONTRIBUTIONS

Clinical Trials: Cardiovascular Outcomes

Monday, March 08, 2004, 4:00 p.m.-5:30 p.m. Morial Convention Center, Room 265

4:00 p.m.

Efficacy and Safety of Ximelagatran Compared With Well-Controlled Warfarin in Elderly Patients With Nonvalvular Atrial Fibrillation: Observations From the SPORTIF Trials

B. Bertil Olsson
for the Executive Steering Committee on Behalf of the SPORTIF Investigators, University Hospital, Lund, Sweden, Mount Sinai Medical Center, New York, NY.

Background: Nonvalvular atrial fibrillation (AF) affects 5-10% of people over 75 years of age, in whom the risk of thromboembolism is higher than in younger individuals. Although adjusted-dose warfarin protects against ischemic stroke, many patients cannot sustain treatment because of bleeding, drug interactions, and coagulation monitoring. The oral direct thrombin inhibitor, ximelagatran (ExantaTM, AstraZeneca), is a potential alternative anticoagulant. Both treatments were compared in patients of at least 75 years.

Methods: The SPORTIF III (open-label, n = 3410) and V (double-blind, n = 3922) trials included 2804 patients at least 75 years of age with AF and at least 1 stroke risk factor randomized to adjusted-dose warfarin (target INR 2.0-3.0) or fixed-dose ximelagatran (36 mg twice daily). The primary endpoint was stroke (ischemic or hemorrhagic) and sys-