AZT3146, a Novel A2A Receptor Agonist, Selectively Dilates the Coronary Circulation in Conscious Dogs

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Background: Adenosine (ADO) has been used as a coronary dilator for cardiac imaging. However, the ultra-short duration of the coronary vasodilation, and side effects of ADO make it a less ideal agent for the pharmacological test. AZT3146 is a novel, short-acting A2A agonist. The study was to determine the effect of adenosine and AZT3146 on the coronary circulation and peripheral resistance in conscious dogs.

Methods: Dogs were chronically instrumented for measurements of cardiac output (CO), coronary blood flow (CBF), and arterial blood pressure. Late diastolic coronary resistance (LSCR) and total peripheral resistance (TPR) were calculated.

Results: Bolus injections of AZT3146 ranging from 0.1 to 2.5 µg/kg caused dose-dependent increases in CBF (27±8 to 195±18% from 48±9 ml/min) and decreases in LSCR (25±4 to 73±12% from 1.2±0.2 mmHg/ml/min). Adenosine ranging from 10 to 250 µg/kg caused similar increases in CBF (40±10 to 194±23%) and decreases in LSCR (29±3 to 72±2%). Hence, AZT3146 is 100-fold more potent vasodilator than adenosine.

Conclusions: AZT3146 is more potent coronary than peripheral vasodilator, and it is a potent coronary vasodilator with fewer systemic side effects than adenosine.

1082-74 Antioxidant N-Acetylcysteine Inhibits Vasoactive Agents Potentiated Mitogenic Effect of Mildly Oxidized Low-Density Lipoprotein on Vascular Smooth Muscle Cells

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Background: Mildly oxidized low-density lipoprotein (mox-LDL) has been shown to induce monocyte-endothelial interactions and vascular smooth muscle cell proliferation, key events in the formation of the atherosclerotic lesion. Growth factors and vasoactive peptides are also thought to play a major role in atherogenesis. We examined the interaction between ox-LDL and well-known vasoactive agents such as serotonin (5-HT), angiotensin II (AII), endothelin-1 (ET-1), and uric acid (UA) in inducing DNA synthesis in vascular smooth muscle cells (VSMCs).

Methods: Growth-arrested VSMCs were incubated with different concentrations of native LDL (100 µg/mL) and ox-LDL (100 µg/mL) stimulated DNA synthesis in a dose-dependent manner. The increase in 3H-thymidine incorporation into cellular DNA was examined by 3H-thymidine incorporation into cellular DNA.

Results: ox-LDL and ox-LDL stimulated DNA synthesis in a dose-dependent manner with a maximal effect at 5 mg/mL (211%, 154%), which are significantly greater than that of native LDL (125%). 5-HT, AII, ET-1, or UA also stimulated 3H-thymidine incorporation in a dose-dependent manner. 5-HT had a maximal stimulatory effect at a concentration of 50 µM (270%), AII at 17.5 µM (205%), ET-1 at 0.1 µM (205%), and UA at 0.65 µM (161%). When added together, non-mitogenic concentration of ox-LDL (100 ng/mL)-induced 3H-thymidine incorporation was potentiated by low concentrations of 5-HT (1 µM), AII (0.5 µM), ET-1 (1 nM), or UA (10 nM) (114% to 330%, 325%, and 345%, respectively). Synergistic interactions of ox-LDL with 5-HT, AII, ET-1, or UA were significantly inhibited by N-acetylcysteine (400 µM), an intracellular free radical scavenger.

Conclusions: Our results suggest that mild oxidation of LDL may enhance its atherogenic potential and exert a synergistic interaction with vasoactive agents in inducing DNA synthesis via the generation of reactive oxygen species in VSMCs.

1082-75 Azimilide Inhibits Outward Potassium Currents in Human Atrial Myocytes

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Background: Studies in animal cell preparations suggest that azimilide may produce a more desirable dose-dependent profile of Class III action as a result of tonic inhibition of both the slowly(A) and rapidly(B) activating components of IC. However, relatively little is known about the effects of azimilide on K+ currents in human atrial cells. The purpose of the present study is to study the effect of the novel antifibrillatory azimilide, azimilide, on cardiac delayed rectifier potassium current (IKur) and transient outward potassium current (Ito) in human atrial myocytes.

Methods: The right atrial, whole-cell voltage clamp technique was used to investigate the acute effects of azimilide on outward K+ currents in single human atrial myocytes. The cells were isolated enzymatically from atrial tissue, obtained from patients undergoing coronary bypass surgery, with institutional Review Board approval.

Results: The average cell capacitance of the human atrial myocytes was 67±5 pF (mean±SEM, n=11). perfusion with -10 µM azimilide for 8 min inhibited IKur by 38% (from 1.1±0.8 to 0.5±0.5 pA/pF, p<0.01) at the clamping membrane potential of -40 mV. perfusion with the specific K+ blocker, E-4031 (10 µM and 20 µM), did not significantly alter the current amplitude, suggesting that IKur is the dominant component of IK in this preparation. Ct (10 µM) was inhibited with azimilide (10 µM) by 33% (from 3.6±0.5 to 2.4±0.3 pA/pF, p<0.05). We also found that the average peak current amplitude of Ito in these cells was significantly inhibited with 10 µM azimilide by 55% (from 7.6±3.0 to 4.9±0.6 pA/pF, n=5, p<0.01).

Conclusions: The present study provides direct evidence that azimilide inhibits cellular outward potassium currents, IKur and Ito. Inhibition of these outward K+ currents by azimilide, especially of IKur and Ito, may have important clinical implications for its antiarrhythmic profile.

1082-76 Divergent Effects of Short- and Long-Term Exposure to Aspirin on Basal and Beta-Adrenoceptor Stimulated Nitric Oxide Synthesis Activity in Platelets

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Background: Important aspects of human platelet function depend on the activity of both nitric oxide synthase (NOS) and cyclooxygenase (COX). We examined the effects of acute and chronic aspirin on platelet function and COX activity.

Methods: Platelet NO activity was measured from the conversion of L-[3H]-arginine to L-[3H]-citrulline, in platelets from healthy subjects before and after stimulation with β2-AR agonists. Platelet L-[3H]-citrulline increased significantly above basal following in vitro treatment with aspirin 0.4mmol/L, or 4mmol/L (0.39 ± 0.10 to 0.61 ± 0.14 and 0.32 ± 0.05 to 0.53 ± 0.06 mmol/100 platelets respectively, P<0.01) but not in the presence of aspirin 40μmol/L. Albuterol-induced vasodilation in the forearm, as measured by venous occlusion plethysmography, was not affected by administration of 800mg aspirin intravenously (n=8). By contrast, chronic low-dose aspirin therapy (75mg daily for 14 days, n=9) did not affect basal platelet NO activity, but abolished β2-AR-mediated NO activation: the increase in L-[3H]-citrulline to isoproterenol lumol/L was 44 ± 20.3% before and 12.7 ± 2.7% after aspirin and that to albuterol 1mmol/L was 48.1 ± 6.9% before and 3.9 ± 11.7% after aspirin (P<0.05 for each).

Conclusions: Aspirin activates platelet NOS acutely in vitro through a mechanism probably independent of COX inhibition. At high concentration, aspirin can also inhibit platelet NO synthase activity. Long-term, low-dose aspirin therapy abolishes β2-AR mediated NO activity by a mechanism probably independent of COX inhibition. These findings suggest that aspirin has divergent effects on platelet functions including baseline NO activity and β2-AR-mediated NO activation.

POSTER SESSION

1083 Lipoprotein Metabolism and Oxidation

Monday, March 18, 2002, 9:00 a.m.-11:00 a.m.

Georgia World Congress Center, Hall G

Presentation Hour: 9:00 a.m.-10:00 a.m.

1083-76 Variants of the Lipoprotein Lipase Gene Associate With Altered Lipid/Lipoprotein Profiles in the Caerphilly Heart Disease Study

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Background: Epidemiological studies demonstrate a strong link between dyslipidemias and coronary heart disease (CHD). High-density lipoprotein cholesterol (HDL-C) levels have a potent inverse relationship with CHD and elevations of triglycerides and total cholesterol (TC) confer direct risk. Lipoprotein lipase (LPL) is a rate-limiting enzyme in the clearance of triglyceride rich lipoproteins and is important in the activation of HDL particles for reverse cholesterol transport. Recent data implicated two LPL gene mutations.