3:00

ROLE OF CENTRAL NERVOUS BETA-ADRENOCEPTORS IN THE PREVENTION OF VENTRICULAR FIBRILLATION THROUGH AUGMENTATION OF CARDIAC VAGAL TONE.

Bengt Åblad, Thorvald Bjurö, Jan-Arne Björkman, Therese Edström, Gunnar Olsson. Hässle Cardiovascular Research, Mölndal, Sweden.

Myocardial ischemia, high sympatho-adrenal and low cardiac vagal tone predispose VF development. To study the interrelation of these factors, rabbits (n=12/group) were pretreated for 3 weeks (s.c. osmotic minipump) with 1) metoprolol (plasma level 260±30 nM); 2) atenolol (plasma level 1450±230nM); i.e. beta-blockers with different degrees of CNS penetration; and 3) control vehicle. During chloralose anesthesia (gives high sympathetic and low cardiac vagal tone) the coronary artery to the free left ventricular wall was occluded (area at risk 35% in all groups). Metoprolol and atenolol caused similar reductions of preocclusion heart rate (metoprolol -34±9 bpm, atenolol -39±9 bpm vs control) and of ischemia 5 min after occlusion (ST elevation in metoprolol and atenolol 45% of that in control). Cardiac vagal tone, measured as s.d. of R-R intervals/respiratory cycle was higher ($p<0.05$) in metoprolol (1.8±0.14 ms) than in atenolol (1.3±0.03 ms) or control(1.4±0.07 ms). In additional experiments, the heart rate response to cholinergic blockade by i.v. methscopolamine was higher ($p<0.05$) after metoprolol (+33±6 bpm) than after atenolol (+16±4 bpm). metoprolol levels were similar in plasma and CSF, whereas atenolol in CSF was only 10% of the plasma level. The incidence of postocclusion ventricular fibrillation (VF) was lower ($p<0.05$) in metoprolol (33%) than in atenolol (83%) or control(92%). Thus, peripheral beta$_1$-blockade effects were not directly related to development of VF. Individual preocclusion levels of cardiac vagal tone were inversely correlated to subsequent VF ($p<0.001$).

Conclusion: Pharmacological concentration of beta-blockade in CNS resulted in signs of increased cardiac vagal tone. This effect was important for prevention of VF.

3:15

EFFECT OF THE POTASSIUM CHANNEL ANTAGONIST, GLYBENCLAMIDE, ON SUDDEN DEATH: PROTECTION FROM VENTRICULAR FIBRILLATION

George E. Billman, Christopher E. Avendano, John R. Halliwill, Jefferson M. Burroughs. The Ohio State University, Columbus, Ohio.

Elevations in extracellular potassium levels during myocardial ischemia have been implicated in the development of cardiac conduction disorders and malignant arrhythmias such as ventricular fibrillation (VF). Recent evidence suggests that ischemically induced potassium efflux results from the opening of ATP-dependent potassium channels. If extracellular accumulation contributes to VF, one would predict that drugs that block the ATP-dependent potassium channels should protect against these arrhythmias. To test this hypothesis, VF was induced in 7 mongrel dogs with healed myocardial infarctions by a 2 min. occlusion during exercise. This exercise plus ischemia test consistently induced VF during each control (no treatment) presentation. However, pretreatment with glybenclamide (10 mg/Kg I.V.), a sulfonylurea drug that blocks ATP dependent potassium channels, completely suppressed VF in all seven dogs tested ($P<0.005$ Chi Squared). Glybenclamide (G) pretreatment elicited significant ($P<0.01$ analysis of variance) reductions in LV dP/dt max. (control 5682 ± 574 vs. G 2970 ± 195.9 mm Hg/sec) and mean coronary blood flow (control 59.7 ± 14.9 vs. G 31.3 ± 8.0 ml/min) both at rest and in response to exercise, while heart rate significantly increased at rest (control 116.9 ± 6.0 vs. G 147.0 ± 16.1 beats/min). These data indicate that drugs that block the ATP dependent potassium channels can prevent VF. However, the data further indicate that glybenclamide can adversely affect inotropic state and coronary blood flow, which may limit the usefulness of this drug in patients with compromised cardiac function.

Tuesday, March 5, 1991
2:00PM–3:30PM, Room 205, East Concourse
Hypertrophic Cardiomyopathy I

2:00

LOCALIZATION OF THE GENE FOR FAMILIAL HYPERTROPHIC CARDIOMYOPATHY TO CHROMOSOME 14q1 IN A DIVERSE AMERICAN POPULATION

J. Fielding Hejtmancik, Paul A. Brink, Jeffrey Towbin, Rita Hill, Lucy Brink, Grazyna Z. Czernuszewicz, Terry Tapscott, Anatole Trakhtenbrot, M. Benjamin Perryman, Robert Roberts, Baylor College of Medicine, Houston, Texas, U.S.A.

Familiar hypertrophic cardiomyopathy (FHCM), an inherited primary cardiac abnormality characterized by ventricular hypertrophy, is the leading cause of sudden death in the young. Attempts to isolate the gene responsible for this disorder has been difficult in part due to the varied phenotypic expression of this disease. Recent application of restriction fragment length polymorphism (RFLP) markers has provided provocative results with localization to chromosome 18 (Japan), 16 (Italy), 14 (French/Canadian) and most recently 2 (NIH) suggesting genetic heterogeneity and possible racial influence. Interpretation remains speculative until one or more of these loci is confirmed in unrelated pedigrees by independent investigators. Thus, we studied 9 unrelated families composed of varied ethnic origin across the USA. There were a total of 174 individuals with 58 affected. The diagnosis of HCM was based on the presence of ventricular hypertrophy without obvious cause as detected by echocardiography. DNA, from each individual, was digested with restriction enzymes Taq1 or BamH1 and analyzed by Southern blots followed by hybridization with probes TCRA, MYHβ, D14S25, and D14S26. Multipoint linkage analysis showed a maximum lod score of 5.6 occurring 8 cM from D14S25 between D14S25 and TCRA. This corresponds to an odds ratio of 398,000 to 1. The 95% confidence limits extend from 1 cM beyond D14S25 to 22 cM beyond D14S25 (2 cM from TCRA). While recombinants occurred with each marker in at least one family, there is no statistically significant evidence favoring genetic heterogeneity among the families but it cannot be definitively excluded. Thus, the probability of linkage to 14q1 > 99%. This suggests that the gene causing FHCM in much of the American population is localized within this region. It is known that myosin heavy chain β, a candidate gene for FHCM, is also within the region of chromosome 14q1. In 2 families, obligate recombinants were noted for the MYHβ marker. These are being investigated for linkage to loci on other chromosomes as suggested for FHCM by others.

2:15

MAPPING OF THE CHROMOSOME CONTAINING THE LOCUS FOR HYPERTROPHIC CARDIOMYOPATHY USING POLYMERASE CHAIN REACTION AND RADIATION HYBRIDS

Adolph Mares Jr., J. Fielding Hejtmancik, Susan A. Ledbetter, David H. Ledbetter, M. Benjamin Perryman, Robert Roberts, Baylor College of Medicine, Houston, Texas, U.S.A.

Hypertrophic cardiomyopathy (HCM), a clinically heterogeneous disease, has been mapped to chromosome 14 by others and ourselves. Isolation and sequencing of the responsible gene for HCM will be necessary to perform genetic diagnosis, treatment, and to unravel the molecular basis for this disease. To develop a physical map of chromosome 14 including the HCM locus, we used HHW890, a Chinese hamster ovary cell line containing human chromosomes 5 and 14. Counterselection with sodium chromate against cells containing human chromosome 5 yielded a hybrid containing only human chromosome 14, MHR14. The presence of human chromosome 14 was confirmed by polymerase chain reaction (PCR) amplification of human interspersed repetitive sequences using either Alu or L1Hs primers (IRS-PCR), and by G-banded chromosome analysis. MHR14 cells, lethally irradiated with 6,000 rads to produce fragments of chromosome 14, were fused with hypoxanthine-phosphoribosyl transferase deficient Chinese hamster ovary cells which yielded radiation hybrids after selection in HAT medium. Forty of 51 hybrids tested contained Alu elements, and 12 of these 40 hybrids contained L1Hs elements. Polymerase chain reaction identified three of the 40 hybrids which contained CRi436, a marker near the HCM locus. Thus, radiation hybrids provide chromosome fragments amenable to identification by IRS-PCR. These techniques provide a specific and sensitive means to physically map genes such as HCM on chromosome 14 and, furthermore, are equally applicable to the mapping of diseases throughout the human genome.