Age-Dependent Modulation of Vulnerability to Nicotine for Inducible Atrial Fibrillation

Background: Nicotine (N) has been implicated as a potential cause of a broad spectrum of cardiac arrhythmias including atrial fibrillation (AF). The factors responsible for N's variable influence on AF vulnerability remain undefined. We hypothesized that aging is one factor that modulates AF vulnerability to N. METHODS: Twelve male rats (Fisher-344) were grouped into young (23-35 months, N=4) and old (22-24 months, N=6). The isolated hearts were perfused via the aorta and superfused with oxygenated Tyrode's at 37°C. Atrial effective refractory period (ERP), interatrial conduction time (CT) and AF vulnerability tested by burst pacing were determined before and after 10-100 ng/ml N perfusion. The epicardial surface of the atria was optically mapped using CCD camera. RESULTS: At baseline, CT was significantly greater in the old than in the young rats (52±3 vs. 25±5 ms, P<0.05), however, there was no significant difference in the ERP between the two groups (19.2±4 vs. 19.3±7 ms). Burst pacing induced AF in 5 of the 6 old rats, however, no AF could be induced in any of the 6 young rats. N increased interatrial CT and ERP in a concentration-dependent manner that was significantly (P<0.05) higher in the old than in the young rats (90±34 ms vs. 35±5 ms and 24±3 ms vs. 27±3 ms respectively during 60 ng/ml N perfusion). N at 15-30 ng/ml prevented AF induction in the old rats, however atrial tachycardias (AT) could still be induced by N in 6/6 old rats. N at 50 ng/ml and above prevented AF and AT induction in the old rats. In contrast however N at 10-100 ng/ml significantly (P<0.01) increased AF (N=3) and AT (N=3) induction in the young rats. Optical mapping showed the presence of 2-3 independent wave fronts during AF but only one large periodic wave fronts during AT. Old rats had significantly (P<0.05) greater interatrial atrial fibrilios compared to young rats (1.72±0.81 vs. 0.93±0.45). CONCLUSION: The mechanism of N-induced modulation of AF vulnerability is complex with changes in both CT and ERP. In AT, with less than a critical increase in CT, AF is induced in young rats at baseline or excessive increase in CT/ERP (aged atria exposed to N >50 ng/ml) AF/AT cannot be induced.

Human Beta-3-adrenoceptors couple to the KvLQT1/minK Potassium Channels via Protein Kinase A - Protein Kinase C Cross-talk
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Excessive stimulation of adrenergic beta-receptors in heart has been linked to the occurrence of life threatening arrhythmias in conditions like Long QT-Syndrome and ischemic or diabetic cardiomyopathy. In the pathogenesis of arrhythmias one crucial element is the slow component of the delayed rectifier potassium current (IKs), which triggers and performs repolarization of the cardiac action potential. IKs is known to be coupled to the beta-adrenergic system in cardiomyocytes, but the type of beta-adrenergic receptor and the signal transduction cascade, which regulates this current under physiological and pathophysiological conditions, are unknown. We investigated the functional coupling of the beta-adrenergic system to IKs by expressing heterologously its molecular components, the KvLQT1/minK potassium channel together with human beta receptors, in Xenopus Oocytes. Membrane currents were measured with the double electrode voltage-clamp technique. We found that human beta3-adrenoceptors couple functionally to the KvLQT1/minK potassium channel. Moreover we investigated the signal transduction pathway and identified that Gs-proteins, adenylylcyclase and cAMP are being involved. Further downstream in the signal transduction cascade protein kinase A activates protein kinase C via cross-talk and finally protein kinase C phosphorylates the KvLQT1-protein. The latter has been shown in site-directed mutagenesis experiments, where the putative protein kinase C phosphorylation sites have been destroyed in the KvLQT1-protein. The knowledge about the coupling and the signal transduction cascade between adrenergic beta-receptors and the KvLQT1/minK potassium channel reveals new aspects about the genesis and therapy of cardiac arrhythmias.

Atrial Fibrillation: Antiarrhythmic Drugs

Poster Session
1042
Sunday, March 17, 2002, Noon-2:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

Prevention of Atrial Fibrillation Using Antiarrhythmic Drugs Postcardioversion of New Onset Atrial Fibrillation
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The use of antiarrhythmic drugs to prevent recurrence of atrial fibrillation (AF) is often avoided in patients presenting with new onset AF, especially those who spontaneously convert to normal sinus rhythm. It is uncertain whether patients presenting with sustained AF (new onset) requiring DC cardioversion should be manage differently. Methods: Medical chart review identified 150 consecutive patients who presented with new onset AF (sustained AF>48 hours) and underwent DC cardioversion in our center between 1/1997 and 12/2000. Patients with reversible etiologies or previous paroxysmal AF were excluded. Patients were divided into two groups, those placed on class I or II antiarrhythmic drugs post cardioversion (Group I, n=51) and those not placed on any antiarrhythmic drugs (Group II, n=98). Patients were followed up to 66 months. Results: There were no significant differences in gender distribution, mean age, underlying cardiovascular disease, left ventricular function, left atrial diameter and the use of beta-blockers between the two groups. AF recurrence rate was significantly higher in Group II than Group I patients (p<0.05), with only 25% of the Group II patients remaining in sinus rhythm at 1 year. Conclusion: The data suggest, in the absence of a reversible etiology, an antiarrhythmic drug should be initiated for prevention of AF following DC cardioversion in patients presenting with new onset AF.