ATRIAL NATRIURETIC PEPTIDE STIMULATES THE HYPERPOLARIZATION-ACTIVATED CURRENT, I_F : A POSSIBLE LINK BETWEEN CELL-STRETCH AND ARRHYTHMOGENESIS?

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Atrial natriuretic peptide (ANP), synthesized and stored as a pro-hormone in the atrium[1,2], is released by atrial distension, i.e., stretching of human atrial myocytes (HuAM)[3,4]. The relationship between atrial stretching and arrhythmogenesis is well documented[9,10,11]. Receptors for ANP (ANPR) are present on atrial cardiomyocytes, having an intrinsic guanylyl cyclase (GC) activity. The hyperpolarization-activated current, I_f is an inward Na/K current constitutively expressed in human atrial myocytes where it may modulate the diastolic membrane potential. An increase of I_f current may play a relevant role in triggering human atrial arrhythmias[6,7,8]. The aim of this study was to investigate the effect of ANP on I_f and to evaluate the underlying metabolic pathway. HuAM were isolated from specimens of right atrial appendages, collected during cardiac surgery procedures. All patients were in sinus rhythm and gave their informed consent. HuAM were freshly utilized for patch-clamp recording of I_f in the whole-cell configuration. I_f was recorded in 67 cells (density: 34.1±2.8 pS/pF; midpoint activation voltage, $V_{1/2}$: -90.4±1.3mV). ANPR stimulation was obtained by superfusing the cells with hANP 10 nM. hANP was able to induce a positive shift ($ÄV_{1/2}$) of the I_f activation curve ($ÄV_{1/2}$=16.3±2.2 mV, n=12, p<0.0001 vs control) resulting in an increase of active current at voltage nearby to the physiological diastolic potential. The hANP effect was absent in HuAM preincubated for 30 minutes with the GC inhibitor ODQ (10 ìM) ($ÄV_{1/2}$=3.6±1.8 mV n=12, NS vs control) and in presence of LY83583, another GC inhibitor, ($ÄV_{1/2}$=0.3±2.6 mV n=5, NS vs control). Moreover, the membrane permeable 8Br-cGMP (100 ìM) mimicked the effect of hANP ($ÄV_{1/2}$=13.6±3.1 mV n=8, p<0.03 vs control), even in presence of 100 nM KT5823, a selective inhibitor of Protein Kinase G ($ÄV_{1/2}$=10.8±1.5mV n=9, p<0.0001 vs control), thus suggesting that hANP effect was due to a direct interaction of cGMP on the f-channel. Preincubation with Pertussin Toxin did not alter hANP effect ($ÄV_{1/2}$=11.4±1.6mV n=7, NS vs hANP). Our data demonstrate, for the first time, that ANP is able to modulate I_f by increasing its amplitude at diastolic potentials, likely through a direct modulation of f-channels by cGMP. This effect could have implications in the relationship between stretch and arrhythmogenesis in the human atrium.

References

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