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Effects of β-adrenoceptor stimulation in human atrial repolarizing currents

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β-adrenergic stimulation has profound influence in the genesis and maintenance of atrial fibrillation. Surprisingly, effects of β-adrenergic stimulation on major repolarizing currents and action potential characteristics recorded in atrial myocytes obtained from patients in sinus rhythm (SR) and chronic atrial fibrillation (CAF) have not been compared until yet. Therefore, we analyzed the effects produced by isoproterenol (Iso), a β-adrenoceptor agonist, on the transient outward (I_{to}), the ultrarapid (I_{Kur}) and the slow delayed rectifier (I_{Ks}) K^+ currents recorded in human atrial myocytes obtained from SR and CAF patients. Furthermore, we also analyzed the effects on the inward rectifier K^+ (I_{K1}) and the L-type Ca^{2+} (I_{CaL}) currents.

Currents were recorded in enzymatically dissociated myocytes obtained from right (RAA) and left (LAA) atrial appendages from SR and CAF patients using the patch-clamp technique. Action potentials were also recorded in isolated myocytes. Results are the mean±s.e.m. of ≥10 experiments in each group. Statistical analysis was done by Student *t* test or one-way ANOVA followed by Newman Keuls test. To compare concentration-response curves, an F-test was used. A $P<0.05$ was considered significant.

Iso inhibited the I_{to} with a similar potency in LAA and RAA myocytes from SR patients. In CAF myocytes, the Iso-induced I_{to} inhibition was significantly more marked than in SR cells, the IC_{50} being 0.6±0.09 nM and 1.5±0.2 nM in LAA and RAA myocytes, respectively ($P<0.05$). Iso, also inhibited in a concentration-dependent manner the I_{K1}, this effect being more marked in CAF than in SR cells and in LAA than in RAA myocytes ($P<0.05$). However the effects were only apparent at voltages more negative than the K^+ reversal potential, which limits their impact. Importantly, CAF dramatically enhanced β-adrenoceptor-mediated increase of the I_{Ks}, whose density was already markedly increased by CAF. Furthermore, Iso was significantly more potent to increase I_{Ks} in LAA (EC_{50}=0.2±0.01 nM) than in RAA (EC_{50}=0.5±0.004 nM) CAF myocytes ($P<0.05$). Conversely, the I_{Kur} of both SR and CAF myocytes was insensitive to low isoproterenol concentrations ($P>0.05$). Iso-induced increase of I_{CaL} was significantly more marked in CAF (EC_{50}=8.5±1.1 nM) than in SR (EC_{50}=18.3±1.3 nM) cells ($P<0.05$). However, I_{CaL} density was dramatically reduced in CAF compared with SR cells ($P<0.05$). Quantitative PCR (n=5) revealed that CAF up-regulated β1-adrenoceptor expression, preferentially in the left atria while it did not modify the expression of phosphodiesterase 3A and 4D and adenylyl cyclase V and VI.

As a consequence of all these CAF-induced changes, stimulation of β1-adrenoceptors in SR myocytes significantly lengthened the action potential duration (APD) ($P<0.05$). Conversely, in CAF myocytes isoproterenol significantly shortened the APD ($P<0.05$).The present results demonstrate that CAF increases the effects of β1-adrenoceptor stimulation on repolarizing currents by means of a chamber-specific up-regulation of the receptors. This, together with the ion channel derangements produced by CAF, could contribute to the long-term stabilization of the arrhythmia by shortening the AP duration.