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MEETING ABSTRACT Open Access

TRPC3 overexpression promotes angiotensin II-induced cardiac dysfunction

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Background

TRPC3 was recently demonstrated as a player in pathogenesis of cardiac hypertrophy, while the potential pro-arrhythmogenic role of TRPC3 is incompletely understood. Using a TRPC3 transgenic overexpression mouse model, we examined the involvement of TRPC3 in cardiac actions of angiotensin II (AngII).

Methods

AngII effects on cardiac functions were characterized in Langendorff perfused hearts. Single ventricular myocytes were isolated and field-stimulated to measure effects on sarcomere shortening and Ca^{2+} transients. Furthermore, L-type Ca^{2+} channel current, action potentials and non-selective ion currents were analyzed electrophysiologically.

Results

AngII (100 nM) reduced left ventricular pressure (LVP) within 2 min to 64%, +dP/dt to 50% and −dP/dt to 55% of control in TRPC3(+/−) hearts, while even producing a positive inotropic effect in wild-type (WT) hearts. Simultaneously, ECG recordings demonstrated AngII-induced episodes of acute arrhythmogenicity in all TRPC3(+/−) hearts (n = 6), whereas rhythm of WT hearts (n = 6) remained unaffected. The AngII-induced impairment of cardiac functions in TRPC3(+/−) hearts was partially reversed by Pyr3 (30 μM). The amplitude of Ca^{2+} transient was significantly higher ($p < 0.05$; n = 60) in myocytes from TRPC3(+/−) mice ($[Ca^{2+}]$ F/F_0 0.354 ± 0.024) as compared to WT ($[Ca^{2+}]$ F/F_0 0.262 ± 0.021). Also, the time constant (τ) of Ca^{2+} decline was different between WT (0.196 ± 0.009 ms; n = 61) and TRPC3(+/−) (0.170 ± 0.008; n = 67; $p < 0.05$). Sarcomere shortening showed no significant difference between the two groups (3.80 ± 0.69% vs. 3.52 ± 0.65%; n = 10) whereas the SR-loading estimated from rapid application of caffeine (20 mM) revealed an increased SR loading of up to 40% in TRPC3 (+/−) myocytes as compared to WT ($p < 0.05$; n = 43). The time constant of Ca^{2+} decline during caffeine challenge was also significantly changed ($p < 0.05$) in TRPC3 (+/−) myocytes (3.04 ± 0.44 ms; n = 11) as compared to WT cells (1.65 ± 0.158 ms; n = 16). Importantly, AngII (100 nM) induced a rise in diastolic Ca^{2+} levels, which was accompanied by irregular contractions in TRPC3(+/−) but not in WT myocytes. The rise in the diastolic Ca^{2+} levels was significantly suppressed by Pyr3 (10 μM; n = 16), SEA 0400 (1 μM; n = 14) and KN-93 (1 μM; n = 12). Electrophysiological characterization of L-type voltage-gated Ca^{2+} currents and action potentials revealed that baseline electrophysiological parameters were not affected by TRPC3 overexpression, while AngII induced a transient prolongation of action potential duration only in TRPC3(+/−) myocytes. This TRPC3-dependent response was associated with a higher incidence of delayed afterdepolarizations.

Conclusions

Our results demonstrate that AngII modulation of cardiac functions is strictly dependent on TRPC3 expression and suggest a key role of TRPC channels in AngII-mediated arrhythmogenicity.

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