Abstract: P514

Investigating the mechanistic role of PDE2 in cardiac arrhythmia

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Topic(s):
Basic Science - Cardiac Diseases: Arrhythmias

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S125

Funding Acknowledgements:
This study was supported by the Deutsche Forschungsgemeinschaft (DFG) and Bayer AG

Background: Phosphodiesterase 2 (PDE2), a key regulator of cellular cAMP levels, is upregulated in human as well as in experimental heart failure (HF) models. Moreover, cardiac-specific PDE2 overexpression in transgenic mice mediated a PDE2 cardioprotective effect against ventricular arrhythmia. Nevertheless, the mechanistic role of PDE2 in heart rate regulation and protection against arrhythmia remains to be resolved.

Purpose: To investigate the mechanistic role mediated via PDE2 in cardiac arrhythmia at a cellular level and elucidate underlying signalling mechanisms.

Methods: Left ventricular cardiomyocytes were isolated from PDE2 transgenic mice (PDE2-TG) and wildtype (WT) littermates. Whole-cell as well as perforated-patch were used to assess action potentials, L-type Ca2+ current (ICa,L), late Na+ current (INaL) and cellular arrhythmia by patch-clamp. Ca2+ sparks were assessed by confocal microscopy.

Results: PDE2-TG exhibited similar resting membrane potentials, action potential duration (APD90) and upstroke velocity when compared to WT. Likewise, ICa,L recorded at 0 mV was comparable at baseline. However, the isoprenaline (Iso) (100 nM) induced increase in ICa,L observed in WT was completely abolished in PDE2-TG mice (+6.0±5.8%, n=15, vs. +43.3±9.7%, n=12, p<0.01). Moreover, upon β-adrenoceptor stimulation, the Epac- and CaMKII-dependent increase in INaL integral was blunted in PDE2-TG (+13.5±14.4%, n=17, vs +192.1±16.9%, n=16, p<0.001). On the other hand, the effect of direct Epac activation was similar in both groups. Similarly, Iso-stimulated Epac- and CaMKII-dependent increase in Ca2+ spark frequency was abrogated in PDE2-TG (p<0.01). To evaluate the impact of the aforementioned differences at ion-channel level and Ca2+ handling on arrhythmia susceptibility, isolated cardiomyocytes were subjected to an arrhythmia provocation protocol (4 Hz pacing) using perforated patch. While Iso lead to a significant increase in the total number of delayed after depolarizations and spontaneous action potentials in WT (N=8, n=21-25, p<0.01), this increase in arrhythmic events was blunted in PDE2-TG (N=8, n=22-25, n.s. vs. control, p=0.01 vs. WT-Iso). Furthermore, quantification of early after depolarization events displayed a similar tendency.

Conclusion: Myocardial PDE2 overexpression protects against Iso-induced cardiac arrhythmia at a cellular
level. Abrogated increase in ICa,L, INaL and SR Ca2+ leak upon β-adrenergic stimulation were identified as underlying mechanisms. To this, specific activation of myocardial PDE2 may serve as a potential antiadrenergic cardioprotective strategy in cardiac arrhythmia and HF therapy.