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Resveratrol reduces myofibroblast arrhythmogenicity

Christian Rosker*, Nicolò Salvarani, Stephan Rohr

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Background

Among grape skin polyphenols, *trans*-resveratrol (RES) has been reported to slow the development of cardiac fibrosis and to affect myofibroblast (MFB) differentiation. Because MFBs induce slow conduction and ectopic activity following heterocellular gap junctional coupling to cardiomyocytes, we investigated whether RES and its main metabolites affect arrhythmogenic cardiomyocyte-MFB interactions.

Methods

Experiments were performed with patterned growth strands of neonatal rat ventricular cardiomyocytes coated with cardiac MFBs. Impulse propagation characteristics were measured optically using voltage-sensitive dyes. Long-term video recordings served to characterize drug-related effects on ectopic activity. Data are given as means ± S.D. (n = 4–20).

Results

Exposure of pure cardiomyocyte strands to RES at concentrations up to 10 μmol/L had no significant effects on impulse conduction velocity (θ) and maximal action potential upstroke velocities (dV/dt_{max}). By contrast, in MFB-coated strands exhibiting slow conduction, RES enhanced θ with an EC_{50} of ~10 nmol/L from 226 ± 38 to 344 ± 24 mm/s and dV/dt_{max} from 48 ± 7 to 69 ± 2%APA/ms, i.e., to values of pure cardiomyocyte strands (347 ± 33 mm/s; 75 ± 4%APA/ms). Moreover, RES led to a reduction of ectopic activity over the course of several hours in heterocellular preparations. RES is metabolized quickly in the body; therefore, we tested the main known metabolites for functional effects and found them similarly effective in normalizing conduction with EC_{50}s of ~10 nmol/L (3-OH-RES), ~20 nmol/L (RES-3-O-β-glucuronide) and ~10 nmol/L (RES-sulfate), respectively. At these concentrations, neither RES nor its metabolites had any effects on MFB morphology and α-smooth muscle actin expression. This suggests that the antiarrhythmic effects observed were based on mechanisms different from a change in MFB phenotype.

Conclusions

The results demonstrate that RES counteracts MFB-dependent arrhythmogenic slow conduction and ectopic activity at physiologically relevant concentrations. Because RES is rapidly metabolized following intestinal absorption, the finding of equal antiarrhythmic effectiveness of the main RES metabolites warrants their inclusion in future studies of potentially beneficial effects of these substances on the heart.

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* Correspondence: rosker@pyl.unibe.ch
Department of Physiology, University of Bern, 3012 Bern, Switzerland