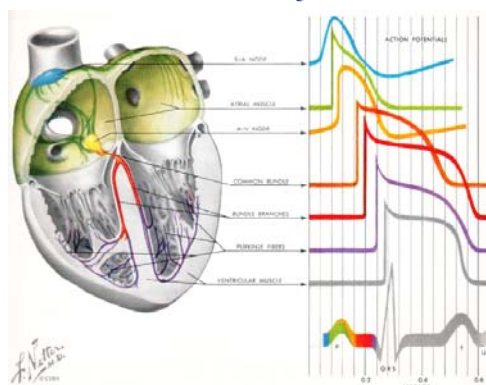


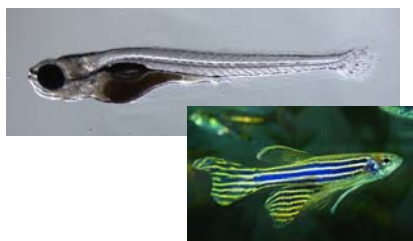
Suppressing cardiac arrhythmia by targeting the voltage-dependent anion channel 2

GUEST LECTURE by



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Auenbruggerplatz 15**

Abstract

Abnormal Ca^{2+} handling in cardiac muscle cells is associated with a wide range of human cardiac diseases, including heart failure and cardiac arrhythmia. Animal models suitable for large-scale screening techniques are potent tools to identify novel Ca^{2+} handling mechanisms associated with these diseases in the search of potential therapeutic targets. Mutant zebrafish *tremblor* embryos, lacking cardiac $\text{Na}^+/\text{Ca}^{2+}$ exchanger activity, manifest only unsynchronized cardiac contractions and can thus serve as a model for aberrant Ca^{2+} homeostasis-induced arrhythmia. We conducted a chemical suppressor screen on *tremblor* and identified a synthetic compound named efsevin based on its potent effect of suppressing cardiac fibrillation and restoring rhythmic contractions in *tremblor* hearts. A biochemical pull-down assay identified a direct interaction between efsevin and the outer mitochondrial membrane voltage-dependent anion channel VDAC2. Knockdown of VDAC2 blocked the suppressive effect of efsevin on fibrillation and overexpression of VDAC2 restored rhythmic cardiac contractions in *tremblor* mutant embryos, indicating that efsevin suppresses cardiac fibrillation by potentiating VDAC2 activity. We further show that in adult murine cardiomyocytes activation of VDAC2 by efsevin restricts spontaneous Ca^{2+} sparks, unitary sarcoplasmic reticulum Ca^{2+} release events, both spatially and temporally and thereby significantly reduces arrhythmogenic Ca^{2+} waves under Ca^{2+} overload conditions. Together these findings suggest a critical role of mitochondria in the control of cardiac rhythmicity and establish VDAC2 as a modulatory protein of cardiac Ca^{2+} handling and a potential therapeutic target for the treatment of arrhythmia.