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Relaxin suppresses atrial fibrillation (AF) in spontaneously hypertensive (SHR) and aged rats through electrical and extracellular matrix remodeling via Wnt signaling pathways

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Relaxin, a hormone first described in pregnancy, has more recently been shown to have important cardiovascular effects. Relaxin activates a wide range of signaling pathways through its receptors, RXFP1/2 which are expressed in most organs. RXFP1 signaling stimulates cAMP, NO and several growth factors and inhibits angiotensin-II and TGF-β effects. RLX increases systemic arterial compliance and reverses fibrosis in multiple organs. In the RELAX-AHF trials, patients with acute decompensated heart failure (HF) received RLX (i.v. 2-days) resulting in reduced mortality (37%, 6-months-later) compared to standard of care. Our studies showed that RLX suppresses atrial fibrillation in spontaneously hypertensive and in aged rats through a marked increase in conduction velocity (CV). CV elevation was associated with the remodeling of the extracellular matrix (↓fibrosis: ↓collagen I&III, ↓TGFβ-1, ↓SMA-α, ↑MMP-6&9) and of electrical properties (↑Connexin43 (Cx43) phosphorylation, ↑$I_{Na,}$ ↑$Na_v1.5$). Here, we show for the first time a close interplay between RLX and Wnt signaling. Male aged rats (24-months) were treated with RLX (400μg/kd/day, 2-weeks) or a vehicle delivered with implantable mini-pumps. Langendorff hearts were optically mapped, then analyzed by immuno-fluorescence, voltage-clamp and RT-PCR. RLX-treatment increased Wnt1 (80%) and β-catenin (72%) at intercalated disks (ID) and reversed the lateralization of Cx43 (without changing Cx43 levels) increasing and their co-localization with β-catenin at ID. RLX also reduced Wnt3a (83%) and increased Nav1.5 (80%) and INa (46%) ($p<0.02$, $n \geq 4$ hearts/group). These robust genomic effects of RLX may explain its long-lasting protective actions in HF patients who were treated with RLX (iv) for merely 2-days.

Biography

Guy Salama has completed his PhD in Biophysics and Biochemistry and a Post-doctroal fellowship at the University of Pennsylvania. He is a pioneer in the development of optical probes of membrane potential, high spatial and temporal-resolution imaging of electrical activity and Ca2+ transients and the elucidation of arrhyhtmia mechanisms. He has made significant contributions to elucidate the mechanisms underlying sex differences in long QT-related arrhyhtmias and demonstrated the genomic modulation of cardiac ion channels by estrogen. He has published more than 125 papers in top-tiered journals and has served on numerous study sections for the NIH and the AHA.

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