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Regulation of T-type Calcium Channels in Pulmonary Hypertension and Ventricular Remodeling

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Low voltage activated T-type Ca^{2+} channels have long been known to exist in the cardiovascular system; however, their functions have remained elusive. Throughout the years, T-type currents have been observed in various vascular smooth muscle preparations, in the developing heart, and in the mature heart they are primarily limited to pacemaker tissue and the diseased myocardium. While highly specific T-type channel blockers remain undeveloped, the molecular cloning of three T-type Ca^{2+} channel genes, $Ca_v3.1$, $Ca_v3.2$ and $Ca_v3.3$, has helped to advance our knowledge about their functional roles in diverse tissues. Pulmonary artery hypertension (PH) provides a context for the study of multiple aspects of cardiovascular T-type channel function, including (1) a role in pulmonary artery smooth muscle cell proliferation and remodeling; (2) regulation by hypoxia, (3) contribution to pathological vasoconstrictor responses, and (4) a role in pressure overload-induced myocardial remodeling. Recently, experimental data from our laboratory and others have converged to suggest that the $Ca_v3.1$ and $Ca_v3.2$ T-type Ca^{2+} channels carry out separate functions in the cardiovascular system, including providing a compartmentalized pool of calcium targeted to disease-related cellular signaling. Furthermore, their regulatory mechanisms appear to be cell and stimulus specific. Future studies should be targeted to defining cell signaling mechanisms that involve T-type Ca^{2+} channels and the functional contributions of each of the T-type channels as they are re-expressed in pathological conditions.