The regulation of intracellular Ca$^{2+}$ is essential for cardiomyocyte function, and alterations in proteins that regulate Ca$^{2+}$ influx have dire consequences in the diseased heart. Low voltage activated, T-type Ca$^{2+}$ channels are one pathway of Ca$^{2+}$ entry that is regulated according to developmental stage and in pathological conditions in the adult heart. Cardiac T-type channels consist of two main types, CaV3.1 (α1G) and CaV3.2 (α1H), and both can be induced in the myocardium in disease and injury but still, relatively little is known about mechanisms for their regulation and their respective functions. This article integrates previous data establishing regulation of T-type Ca$^{2+}$ channels in animal models of cardiac disease, with recent data that begin to address the functional consequences of cardiac CaV3.1 and CaV3.2 Ca$^{2+}$ channel expression in the pathological setting. The putative association of T-type Ca$^{2+}$ channels with Ca$^{2+}$ dependent signaling pathways in the context of cardiac hypertrophy is also discussed.

Introduction

Proper Ca$^{2+}$ homeostasis is of paramount importance for normal physiological function of the cardiovascular system, and it is clear that when the balance of intracellular Ca$^{2+}$ is upset, pathological and in some cases life-threatening conditions arise. Simply stated, Ca$^{2+}$ homeostasis is achieved by the concerted actions of numerous cellular proteins that sense intracellular Ca$^{2+}$ levels, control the movement of Ca$^{2+}$ across the plasma membrane, and orchestrate the distribution of Ca$^{2+}$ amongst the intracellular compartments. In the cardiovascular system, intracellular Ca$^{2+}$ can be sequestered by organelles such as the sarcoplasmic reticulum (SR), mitochondria and the nucleus. Voltage gated Ca$^{2+}$ channels are a primary pathway of Ca$^{2+}$ influx that are regulated both by physical and biochemical interactions with other components of the Ca$^{2+}$ homeostasis apparatus. For many years, research has sought to understand the structure and function of voltage gated Ca$^{2+}$ channels with the ultimate goal of uncovering their relevance in pathophysiological states. In the cardiovascular system, two main types of voltage-gated Ca$^{2+}$ channels are present: (1) the well-characterized, high voltage activated (HVA) L-type Ca$^{2+}$ channels and (2) the functionally distinct and less prevalent class of low voltage activated (LVA) T-type Ca$^{2+}$ channels. Previous reviews have summarized in more detail the expression profile, biophysical and pharmacological properties of T-type Ca$^{2+}$ channels in the heart. This article focuses on consolidating current knowledge regarding the re-expression of T-type Ca$^{2+}$ channels in the diseased heart, and their consequences for remodeling of ventricular structure and function. The relative contributions of the CaV3.1 and CaV3.2 T-type channel isotypes are also discussed.

Low Voltage-activated Ca$^{2+}$ Channels in the Diseased Heart

The most prevalent Ca$^{2+}$ channels in the adult mammalian heart are the high voltage activated (HVA) L-type channels, referred to as Ca$\alpha_{1.2}$ (α1C), which provide the primary signal Ca$^{2+}$ for cardiac contractility via excitation-contraction (E-C) coupling. In addition to L-type channels, two main low voltage-activated (LVA) T-type Ca$^{2+}$ channels are found in the heart, known as Ca$\alpha_{3.1}$ (α1G) and Ca$\alpha_{3.2}$ (α1H). T-type Ca$^{2+}$ channels are more prevalent in the developing heart, they disappear in the myocardium shortly after birth and are localized to the pacemaker tissue in adult hearts where they have an established role in pacemaker function. Although T-type Ca$^{2+}$ channels do not contribute significantly to normal adult cardiac contractile function, accumulating evidence supports significant roles for the T-type Ca$^{2+}$ channels as they are re-expressed in cardiovascular disease and injury.

Prior to the cloning and identification of the Ca$\alpha_{3}$ family of T-type Ca$^{2+}$ channels, LVA T-type Ca$^{2+}$ currents were observed in ventricular myocytes isolated from a feline model of pressure overload-induced cardiac hypertrophy and from cardiomyopathic hamster, where it was suggested that they contribute to Ca$^{2+}$ overload and lead to antiarrhythmic behavior. Both T-type currents and Ca$\alpha_{3.1}$ mRNA were induced in post-myocardial infarction (MI) rat ventricle. In multiple studies using infarct models, it appeared that inhibition of the re-expressed T-type Ca$^{2+}$ channels had a beneficial effect of limiting infarct size and ventricular remodeling. Otherwise, it was established that T-type Ca$^{2+}$ channels are re-expressed in cardiac dysfunction.
hypertrophy and following infarct injury and their functional relevance remains an important area of investigation.

**Regulation of T-type Ca\(^{2+}\) Channels by Hormonal Stimuli**

While the precise stimuli for cardiac T-type Ca\(^{2+}\) channel re-expression in adverse conditions are likely to be complex earlier studies showing that T-type channels can be regulated by various environmental stressors could provide valuable insight into mechanisms for their re-expression. Cardiac stress, hypertrophy and failure are associated with the induction of multiple neurohumoral stimuli, and lines of experimental evidence have shown that such stimuli act in part by regulating the expression of cardiac T-type Ca\(^{2+}\) channels.

Growth hormone secreting tumors caused a significant increase in T-type Ca\(^{2+}\) current density in rat atrial myocytes.\(^{30}\) IGF-1 (Insulin-like Growth Factor-1) is normally associated with growth and proliferation signaling cascades via binding to its plasma membrane receptor (IGF-1R), and cardiomycocyte IGF-1 signaling represents an early cellular response mechanism in myocardial hypertrophy and injury.\(^{31,32}\) In a study of rat atrial tissue, LVA Ca\(^{2+}\) currents, Ca\(^{3+}\).1 and Ca\(^{3+}\).2 mRNAs were all regulated in parallel with IGF-1 and IGF-1R mRNA levels, leading the authors to suggest that IGF-1 may be associated with the T-type Ca\(^{2+}\) channel increases observed during pressure overload or following myocardial infarction.\(^{33}\) In the same study, cultured rat atrial myocytes showed selective induction of T-type, but not L-type Ca\(^{2+}\) currents in an IGF-1 dependent manner.

Angiotensin II (Ang II) is a major signaling effector of cardiac hypertrophy via its binding to the G-protein-coupled Ang II Type I (AT\(_{1}\)) receptors. Early studies in frog atrial myocytes demonstrated enhanced T-type Ca\(^{2+}\) currents following Ang II stimulation,\(^{34}\) and a G-protein mediated mechanism has been suggested, but remains controversial.\(^{3}\) Angiotensin II has also been shown to stimulate gene expression and LVA Ca\(^{2+}\) currents in isolated cardiomycocytes. Ferron et al. used a rat model of abdominal aortic stenosis to induce LV hypertrophy, and showed the Ang II-dependent induction of T-type Ca\(^{2+}\) currents and Ca\(^{3+}\).1 mRNA in isolated, hypertrophied cardiomycocytes.\(^{35}\) T-type currents were also increased by Ang II in isolated ventricular myocytes from chick embryos and human fetuses.\(^{36}\) Notably, when cardiac hypertrophy was stimulated in vivo by treatment of transgenic Ca\(^{3+}\).2\(^{-}\)/- knockout mice with Ang II, the hypertrophic response was suppressed, implicating Ca\(^{3+}\).2 \(\alpha\) Ca\(^{2+}\) channels as an integral component of Ang II hypertrophic signaling.\(^{37}\) Consistent with this notion, treatment of neonatal rat ventricular myocytes with an AT\(_{1}\) receptor antagonist resulted in decreased levels of both Ca\(^{3+}\).1 and Ca\(^{3+}\).2 mRNAs, as well as decreased T-type Ca\(^{2+}\) current density. Furthermore, p38 mitogen-activated protein kinase (MAPK) activation was associated with the same Ang II signaling pathway that involves T-type Ca\(^{2+}\) channels. T-type channels have now been implicated in a number of signal transduction pathways in cardiac myocytes (see below), for which the mechanisms remain largely undefined.

**Regulation of T-type Ca\(^{2+}\) Channels by Hypoxia**

In many cases, T-type Ca\(^{2+}\) channel expression is regulated with little or no effect on L-type channels in the same tissues, emphasizing the idea that T-type channels and by inference, their functions, are an integral part of the response to injury. One study explored the regulation of voltage gated Ca\(^{2+}\) channels by chronic hypoxia in rat PC12 cells, where the Ca\(^{3+}\).2 (\(\alpha\)1H) T-type Ca\(^{2+}\) channel was exclusively upregulated in a hypoxia inducible factor (HIF-1\(\alpha\)) dependent manner with no effects on HVA channel expression.\(^{47}\) Similar results were obtained in rat adrenal chromaffin cells.
where the newly expressed T-type channels serve a function in low voltage stimulated vesicle secretion. In neonatal rat chromaffin cells, T-type Ca2+ channels were suggested to act as an in vivo O2 sensor, which controls vesicle release of catecholamines and excitability in hypoxic environments.49,50 These studies raise the question as to whether or not an analogous O2 sensing mechanism might be active in the ventricular myocardium in ischemia/reperfusion injury. When cultured neonatal rat cardiomyocytes were subjected to hypoxia/reoxygenation injury conditions to model the oxidative stress condition that is particularly relevant in the post-ischemic myocardium, CaV3.1 and CaV3.2 mRNA expression and LVA, T-type currents were regulated.51 Chronic hypoxia resulted in decreased levels of the CaV3.1 mRNA and T-type current density in neonatal rat cardiomyocytes. The downregulation of CaV3.1 channels was HIF-1α dependent and upon reoxygenation, CaV3.1 mRNA levels and LVA Ca2+ currents were restored. Whether or not adult cardiomyocytes respond in a similar fashion to hypoxic conditions is not known; however when expressed, T-type channels could conceivably result in a sustained increase in Ca2+ influx at less depolarized voltages through the window current, which would be relevant for Ca2+ overload and pathogenesis.

Recently, Pastukh et al. reported that prolonged maintenance of neonatal rat ventricular myocytes in elevated Na+ (hypernatremia) resulted in downregulation of the CaV3.1 T-type Ca2+ channel, associated with a concomitant reduction of intracellular Ca2+ when the myocytes were exposed to energy-deficient conditions.52 In this context, CaV3.1 channel downregulation could be interpreted as a protective mechanism to counteract damages due to Ca2+ overload that would tend to occur in conditions of stress (e.g., as in hypoxia). In the same cell cultures, the cytoprotective phosphatidylinositol 3-kinase (PI3-K)/Akt signal transduction pathway was also stimulated by hypernatremia, and it is interesting to speculate on how these interactions might coordinate the cardiomyocyte’s responses to environmental stress.

Transcriptional Regulation of T-type Ca2+ Channels

An increasing number of stimuli have been indentified that regulate T-type Ca2+ channel mRNA expression in the heart, and several transcriptional mechanisms have now been proposed. Neuron-restrictive silencer factor (NRSF) is a developmental gene transcription regulator that also regulates the CaV3.2 mRNA, presumably via regulatory elements found within the first intron.46,47 Thus, NRSF has been proposed as a transcriptional regulator of the cardiac CaV3.2 gene in conditions of hypertrophy and MI.2,53 Csx/Nkx2.5 is a cardiac homeobox transcription factor that stimulates expression of the fetal gene program and also regulates the expression of CaV3.2 T-type channels in neonatal cardiomyocytes48 and notably, its downregulation is also correlated with the downregulation of CaV3.2 mRNA and currents in cardiomyocytes by 17ß-estradiol.

Expression of T-type Ca2+ Channels in Right-Sided Heart Failure

The aforementioned studies demonstrating the re-expression of T-type Ca2+ channels in the failing heart were carried out in the more conventional setting of LV pressure overload, LV hypertrophy and animal models of LV injury/MI. Another clinically significant and distinct form of heart failure accompanies diseases of pulmonary insufficiency that lead to pressure overload of the right ventricle (RV), RV hypertrophy and cardiac dysfunction. Right sided heart failure is a dire complication of pulmonary arterial hypertension, RV function is a strong predictor of mortality,55,56 and the fact that therapeutic strategies to treat LV failure are less effective for RV failure indicates that unique mechanisms are in play.57 In a rat model of pulmonary hypertension that leads to selective RV hypertrophy, Takebayashi et al. first demonstrated that both CaV3.1 and CaV3.2 mRNAs were significantly induced in the RV myocytes, whereas HVA channel mRNAs remained unchanged.58 In the same pulmonary hypertension model, T-type Ca2+ channels were re-expressed in cardiomyocytes isolated from the right atrium even though CaV3.3 mRNA levels were not affected, suggesting additional, post-translational modulatory mechanisms that may be chamber specific.59 In addition to increased wall stress due to pulmonary hypertension, right atrial oxidative stress and increased oxidant production were suggested to contribute to alterations in gene expression and ion channel modulation. These results demonstrate distinct regulation of T-type Ca2+ channels in RV pressure overload, suggesting that further elucidating the role of T-type Ca2+ channels in the unique pathogenesis of right-sided heart failure could provide useful insights into alternative therapies to treat this disease.

Functions of Re-Expressed T-type Ca2+ Channels in Heart Failure

Until recently, there was little direct evidence to support the notion that T-type Ca2+ channel re-expression plays a distinct role in the pathogenesis of the diseased heart. As previously mentioned, studies using animal LV infarct models in the presence of mibefradil suggested that interfering with T-type Ca2+ channel activity would be cardioprotective with the presumption that T-type channels were the primary target of mibefradil’s action. Experiments with the pulmonary hypertension model of RV failure also showed that, in conjunction with LVA T-type Ca2+ current increases, twitch tension of RV muscle isolated from rats with pulmonary hypertension was selectively reduced with mibefradil at a concentration selective for T- over L-type channels, suggesting that in addition to preserving myocardial structure as in the LV infarct models, T-type Ca2+ channel inhibition could restore RV contractile function.58 Furthermore, by using either mibefradil or the more selective T-type channel blocker R(-) efonidipine in a mouse model of dilated cardiomyopathy and arrhythmia, Kinoshita, et al. demonstrated a reduction in the occurrence of arrhythmias and an increase in survival of the animal model that was not accomplished with the L-type Ca2+ channel blocker nifedipine.60 In the same report, both mibefradil and R(-) efonidipine were also protective against sudden death (presumably via preventing T-type channel-induced arrhythmias) in normal mice subjected to experimental MI. The transgenic mouse model of arrhythmia used in these studies
had been shown previously to overexpress the CaV3.2 T-type channel, but since neither mibefradil nor efonidipine distinguish between T-type channel isotypes, the relative contributions of the CaV3.1 vs. CaV3.2 channels to arrhythmogenesis were not addressed.

Transgenic mouse knockout models have shed additional light on the respective roles of T-type Ca2+ channels in the pathogenesis of LV cardiomyopathy. T-type channels are prevalent in early development, where mRNA studies showed a switch from early expression of CaV3.2 channels to predominantly CaV3.1 channels, the significance of which is unknown. However, knockout of one or the other of the two cardiac T-type channels results in viable animals, suggesting if LVA Ca2+ channels play vital roles in cardiogenesis, their actions may be compensatory. In keeping with previous experiments implicating T-type channels in cardiac pacemaker function, the CaV3.1-/- knockout mice displayed a depression in heart rate and pacemaker activity was slowed in isolated atrial pacemaker myocytes. The complete lack of LVA currents in the atria of these mice indicated that (at least in mice) the CaV3.1 channels are the primary LVA pacemaker channels.

Separate studies have used CaV3.1 transgenic mouse models to further address the putative role of CaV3.1 T-type Ca2+ channels in the development of cardiac hypertrophy. In transgenic mice that inducibly express CaV3.1 channels in the heart, enhanced T-type currents resulted in significantly increased Ca2+ transients and sarcoplasmic reticulum (SR) Ca2+ load, and enhanced contractile function, yet CaV3.1 T-type channel overexpression clearly did not induce cardiac hypertrophy. When the role of these channels was further investigated in an experimental model of LV hypertrophy, transgenic overexpression of CaV3.1 channels was instead cardioprotective, and their absence in CaV3.1-/- knockout mice increased susceptibility to the hypertrophic response. Additional experiments provided compelling evidence that CaV3.1 channels may be associated in macromolecular signaling complexes localized to membrane microdomains in cardiac myocytes, which might enable localized Ca2+ influx to influence hypertrophic signaling pathways. In the case of the CaV3.1 channel, anti-hypertrophic signaling may be mediated by the Ca2+ dependent action of NOS-3 on cGMP-dependent protein kinase type 1 (PKG-1), which is a negative mediator of calcineurin/NFAT signaling (Nuclear Factor of Activated T-cells). According to this scenario, the re-expression of CaV3.1 T-type channels in the diseased heart would be identified as a key regulator of anti-hypertrophic signaling. Further investigation is needed to determine exactly how the CaV3.1 channel interacts with PKG-1-mediated, and possibly other Ca2+ dependent signaling mechanisms in the heart.

In some cases functional overlap of the CaV3.1 and CaV3.2 channels is suggested, and in other cases it is clear that the two T-type channel isotypes respond differently in pathological settings. Whereas cardiac development and function did not appear to be significantly altered in CaV3.2-/- knockout mice, CaV3.2 loss of function had consequences for the hypertrophy response in these animals. In contrast to the CaV3.1-/- mice, when subjected to an aortic constriction model of LV hypertrophy, the absence of CaV3.2 channels suppressed (rather than enhanced) the hypertrophy response in CaV3.2-/- mice. Further experiments suggested that pathological re-expression of CaV3.2 channels exerts a pro-hypertrophic response through an interaction with the well-known Ca2+ dependent calcineurin/NFAT signaling pathway. An interaction of T-type Ca2+ channels and NFAT hypertrophic signaling was previously implicated in neonatal rat cardiomyocytes.

The contribution of CaV3.2 T-type Ca2+ channels to contractile and pacemaker function remains unclear. The CaV3.2 channels appeared to be absent in CaV3.1-/- mouse pacemakers, and were only mildly upregulated in CaV3.1-/- mice subjected to the hypertrophy. Nevertheless, the induction of CaV3.2 channels in adrenal chromaffin cells and in cultured neonatal cardiomyocytes led to increased cell excitability and in myocytes treated with corticosteroids, accelerated spontaneous contractile activity. The cardiac transcription factor Csx/Nkx2.5 mediates the upregulation of CaV3.2 channels in rat neonatal cardiomyocytes which results in significantly increased spontaneous beating rate. Negative regulation of CaV3.2 mRNA and currents by 17β-estradiol in rats was also associated with decreased heart rate, which was reversed by ovariectomy. Thus, multiple lines of evidence suggest an important role of the CaV3.2 T-type channel in pacemaker function, and it would be interesting to address whether similar effects on in vivo pacemaker activity would result from the overexpression of CaV3.2 channels in the hearts of transgenic mice.

The analysis of CaV3.2 T-type channel function and the contribution to the heart failure phenotype may be further complicated by the existence of multiple splice variants in cardiac tissue. The expression of CaV3.2 splice variants was found to be regulated during development, as well as in the LV of hypertrophic rat hearts. Furthermore, splice variants of CaV3.2 channels displayed alterations in function that could be relevant with respect to contractile performance in the diseased heart. Therefore in the future, caution must be exercised when interpreting the functional consequences of pathological expression of CaV3.2 Ca2+ channels. Splice variation has also been identified in the cardiac CaV3.1 T-type Ca2+ channel, making it possible if not likely that similar effects influence CaV3.1 channels re-expressed in the hypertrophied myocardium.

**Summary**

Although recent progress has begun to provide a better understanding of the regulatory processes involving T-type Ca2+ channel re-expression in the diseased heart, there is still much to learn about the mechanisms, and the effects these channels exert on remodeling of cardiac structure and function. A prevailing theme is that T-type channels are induced in pathological situations, where they participate in Ca2+ dependent signaling pathways in a stimulus- and isotype-specific fashion. Figure 1 provides a schematic diagram of the cardiac disease-related processes described in this article, along with signaling mechanisms that have been associated with the different stimuli. In most of these cases, T-type Ca2+ channels are regulated exclusive of effects on L-type channels, suggesting that the LVA channels are recruited...
in cardiac disease and injury for a specific purpose. In terms of signaling functions, most of the stimuli lead to enhanced T-type channel activity that is predicted to have a detrimental influence on cardiac function by stimulating hypertrophic signaling (e.g., via p38/MAPK or NFAT). Still, more studies are needed evidence to indicate impaired contractile function. The extent of functional overlap between Ca_3.2 and Ca_3.2 channels in the heart also requires further investigation, which should be facilitated by the availability of isotype-specific knockout strategies both in vivo and in vitro.

**Figure 1.** Schematic diagram of stimuli that regulate T-type Ca^{2+} channels in the heart. A schematic diagram of the cardiopulmonary circulation is shown, where normal blood flow is indicated by white arrows, via the right atrium (RA), right ventricle (RV), pulmonary artery (PA), lungs, left atrium (LA) and left ventricle (LV). Sites of LV and RV pressure overload are indicated by an asterisk (*). Environmental stress signals are indicated, along with putative signaling mechanisms in parentheses; abbreviations are as defined in the text, with the addition of GRE (glucocorticoid response element). The question mark (?) indicates that no mechanisms have been proposed for pulmonary hypertrophy associated RV hypertrophy.

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