Editorial

Reexpression of T-type Ca channels after myocardial infarction: does it play a role in cardiac excitation?

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See article by Huang et al. [5] (pages 442–449) in this issue.

Cardiac Ca$^{2+}$ channels

In the heart, two types of Ca channels have been identified that are expressed on the sarcolemma of cardiomyocytes: the longlasting type of high voltage activated Ca channel ($I_{\text{Ca,L}}$) and the low voltage activated transient Ca channel ($I_{\text{Ca,T}}$). The L-type Ca current plays an important role in maintaining the plateau phase of the action potential, and providing influx of Ca ions to initiate cardiac contraction. The T-type Ca current plays a prominent role in nodal cells and embryonic cardiomyocytes and has been associated with cell growth [4–7]. However, $I_{\text{Ca,T}}$ has little effect on cardiac excitation-contraction coupling. In addition to being involved in growth and development, $I_{\text{Ca,T}}$ can modulate electrophysiological properties by providing a window current between $-60$ and $-20$ mV which will increase an inward current at the end of the plateau and may facilitate the appearance of early after depolarizations. Marked hypertrophy occurs in viable regions of myocardium after myocardial infarction, and severe left ventricular dysfunction ensues later. The prolonged action potential duration in postmyocardial infarction remodeled hypertrophied cardiomyocytes is caused by a decreased density of both slow and fast transient outward potassium currents. The decrease in current density was explained by characteristic alterations in the expression of the different voltage-gated potassium channel subunit genes. The authors of the present study [5] have shown previously that 3–4 weeks after myocardial infarction, isolated remodeled hypertrophied cardiomyocytes exhibit early and late after depolarizations.

T-type Ca$^{2+}$ channel in growth and hypertrophy

Cardiac myocytes become terminally differentiated after birth, and in adult life respond to pathologic stimuli by

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hypertrophy. Marked hypertrophy occurs in viable regions of myocardium after myocardial infarction, compromised LV function and heart failure ensues later [1–4]. During cardiac hypertrophy, cardiomyocytes dramatically change their pattern of gene expression with consequences for both mechanical and electrophysiological properties. These changes include the induction of immediate-early response genes (proto-oncogene c-fos, c-jun), the induction of fetal and neonatal genes, e.g. β-myosin heavy chain (β-MHC), L-type Ca channel and Na-K ATPase and upregulation of constitutively expressed contractile proteins. These alterations result in an increase in the production and assembly of contractile proteins into sarcomeric units and an increase in the efficiency of contraction and decrease in wall stress. Clinical studies have shown that cardiac hypertrophy is not only an adaptational state before cardiac failure, but also an independent risk factor for sudden cardiac death due to lethal ventricular tachyarrhythmias. The presence of interstitial fibrosis, areas of slow conduction and hypertrophied cardiomyocytes in the peri-infarct zone may facilitate arrhythmias based on both reentry and triggered activity. Hypertrophied cardiomyocytes show a prolonged action potential which will increase the likelihood of triggered activity.

There is a growing body of evidence that $I_{\text{Ca}, \tau}$ is associated with the development and growth processes [2–4]. The expression of T-type Ca channel protein increases in atrial myocytes from adult rats with growth hormone secreting tumors. Endothelin-1 and angiotensin II, two endogenous peptides which are able to induce cardiac hypertrophy, also enhance $I_{\text{Ca}, \tau}$ in cultured neonatal rat ventricular myocytes. Myocardial hypertrophy is characterized by reexpression of fetal and neonatal genes in the adult myocyte. The biological cascade that occurs during pathological events, such as mechanical overload, causes the cardiomyocytes to utilize the fetal genetic program. Work overload is accompanied by an induction of β-MHC causing a shift of the isomyosins. Thus, cardiac hypertrophy after myocardial infarction involves a shift in the expression of several isogenes towards a fetal program of gene expression.

**Reexpression of fetal T-type Ca$^{2+}$ channel isogenes**

The availability of recombinant T-type calcium channels for expression in cell systems and subsequently pharmacologic and biophysical characterization opens a new area of research and provides the necessary tools to unravel the ionic and molecular mechanisms of ion channel functions. The present study published in this issue of the Journal [5] shows that both alpha-1H and alpha-1G of the T-type Ca channel genes and currents are reexpressed in the rat postmyocardial infarction remodelled left ventricle which is consistent with the reemergence of fetal and neonatal isogene patterns under pathologic conditions. Native $I_{\text{Ca}, \tau}$ is always superimposed on the $I_{\text{Ca}, L}$, making detailed functional characterization of T-type Ca channel difficult. The authors of the present study have elegantly shown that both Ca channel gene and current becomes reexpressed after myocardial infarction. The physiological significance of their findings remains to be determined. Correlation of the transcript levels of T- and L-type Ca channels with electrophysiological data in the subacute phase of myocardial infarction would enhance our knowledge of the arrhythmogenesis at these stages. The consequence of selective inhibition of T-type channels on in vivo ventricular arrhythmias seen in the experimental subacute stage of myocardial infarction would be of interest. Because of the significant consequences of altered gene expression on postmyocardial infarction electrophysiological and mechanical functions of the heart, further investigation of postmyocardial infarction signal transduction pathways is needed. It is important to realize that so far, the role of T-type Ca channel has not been demonstrated in cardiomyocytes from patients with different cardiac diseases including heart failure. The T-type calcium channel blocker, mibebradil, has been used in clinical trials, however, it was soon withdrawn due to serious interactions with several other drugs.

**Post-infarction myocardial remodeling and arrhythmogenesis**

Cardiac ion channels play an important role in regulating cardiac excitable and contractile properties. Why is postinfarction heart failure associated with a specific pattern of alterations in ion channel expression and function? Are these changes adaptive or are they merely a function of reactivation of a fetal and neonatal genetic program? Alterations in mRNA expression appears to play a central role caused by transcriptional up or downregulation of gene expression. Electrophysiological and structural remodeling caused by heart failure contributes significantly to an increased risk of sudden cardiac death, especially after myocardial infarction. There is growing evidence supporting the concept that ionic remodeling is associated with structural remodeling such as hypertrophy. The physiological role of the reexpression of T-type Ca channel gene and protein in viable cardiomyocytes in the subacute phase of myocardial infarction still remains to be determined. Helicopter view of the remodeling process after myocardial infarction shows us that T-type Ca channel is one of the many components involved in the alterations leading to contractile dysfunction and arrhythmogenesis. Inherent to all research, the present study [5] leads to new questions and problems and thus goals for further research. Additional studies need to delineate the functional importance of the genetic alterations associated with post-infarction remodeling. Future experimental studies will have to show that interfering with the process of remodeling by
blocking a critical step in the regulatory process prevents
development of arrhythmogenic substrates. The fast
development in cardiac molecular physiology and genetics
will enable us to broaden our understanding of the
mechanisms of cardiac pathology and provide new tools
for intervention in the near future.

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