Forum Minireview

Pathophysiological Significance of T-type Ca^{2+} Channels: Preface

Kyoichi Ono^{1,*}¹Department of Pharmacology, Akita University School of Medicine, Akita 010-8543, Japan

Received August 11, 2005; Accepted October 12, 2005

Keywords: T-type Ca^{2+} channel, sinoatrial node, gene expression, cardiac hypertrophy, renal microcirculation, mibefradil, efonidipine

This Forum Minireview contains proceedings of the symposium reported at the 78th Annual Meeting of The Japanese Pharmacological Society, held on March 22 – 24, 2005, in Yokohama. The symposium aimed to summarize recent advances and trends in elucidating the pathophysiological significance of T-type Ca^{2+} channels (TCC), particularly those involved in the cardiovascular system. Although T-type Ca^{2+} current (I_{CaT}) was first recorded almost 30 years ago, studies on TCC have been impeded by the lack of selective antagonists. However, during the past 10 years, a growing body of evidence has accumulated showing important roles of TCC not only in maintaining physiological functions of various organs and tissues, but also during the progression of various diseases. Our understanding of TCC has been greatly enhanced by the identification of the pore forming subunits of TCC, and the use of drugs that differentially interact with TCC and L-type Ca^{2+} channels (LCC). A wide variety of neurotransmitters, hormones, and intracellular-signaling molecules affect endogenous I_{CaT} , and a number of pharmacological and toxicological agents suppress I_{CaT} . The use of these agents has revealed many unanticipated roles of TCC, in both normal and diseased tissues, and organs. Progresses in TCC research also extend to genetic regulation of TCC expression during development, and to some pathophysiological processes such as hypertrophy and heart failure. Spatial and temporal characterizations of TCC expression may provide important information regarding not only TCC function in normal and diseased cells, but also establish therapeutic strategies for various diseases.

Ono and Iijima described properties and functional roles of TCC in cardiac pacemaker cells. They showed

that since the activation range of TCC overlapped the pacemaker potential of sinoatrial node cells, TCC should provide an additional inward current to promote slow diastolic depolarization. However, the current density of I_{CaT} varied, and thereby, the extent of its contribution differed depending on the mammalian species and regions within the heart. At present, the existence of TCC has not been confirmed in human sinoatrial node cells. Various TCC blockers demonstrated a marked bradycardiac action, indicating that TCC plays important roles in vivo. Alternatively, it is also possible that other ionic channels, which are sensitive to TCC blockers, are crucial for generating normal heart rhythm.

Yasui et al. examined developmental changes of TCC in mouse ventricles. They showed that substantial I_{CaT} , sensitive to Ni^{2+} , was recorded at the fetal stage, whereas no current was detectable in the adult stage. $\text{Ca}_v3.2$ (α_{1H}) mRNA was expressed dominantly at the fetal stage. $\text{Ca}_v3.1$, which remained at low levels, was expressed in higher levels than $\text{Ca}_v3.2$ at the adult stage. Yasui et al. also demonstrated that TCC was expressed in hypertrophied ventricles caused by myocardial infarction (MI) and aortic banding. They found that $\text{Ca}_v3.1$ mRNA negatively correlated with brain natriuretic peptide (BNP) mRNA, and $\text{Ca}_v3.2$ mRNA positively correlated with BNP mRNA in the MI group. They suggested that $\text{Ca}_v3.2$ was the source of functional TCC in the embryonic heart and suggested that the neuron-restrictive silencer factor (NRSF) might regulate $\text{Ca}_v3.2$ expression in diseased hearts.

Kuwahara et al. described a novel mechanism for regulation of TCC expression. They previously identified a repressor element neuron-restrictive silencer element (NRSE), which controls expression of both atrial natriuretic peptide (ANP) and BNP in cardiac ventricular myocytes. A transcriptional repressor NRSF is a NRSE-binding protein and suppresses neuron-specific gene

*Corresponding author. FAX: +81-18-836-2603
E-mail: onok@med.akita-u.ac.jp

expression. The NRSE-NRSF system normally represses transcription of ANP and BNP genes in ventricular myocytes, but under pathological conditions, NRSF-mediated repression is de-repressed, leading to reactivation of ANP and BNP gene expressions. Kuwahara et al. hypothesized that a similar mechanism was involved in TCC gene expression in diseased hearts. They first found that the $Ca_v3.2$ (α_{1H}) gene contained NRSE-like sequences. Then, they created transgenic mice carrying cardiac-specific expression of a dominant-negative mutant of NRSF (dnNRSF Tg). The dnNRSF Tg mice showed dilated cardiomyopathy, ventricular arrhythmias, and died suddenly. In dnNRSF Tg mice, $Ca_v3.2$ gene expression was significantly increased, and I_{CaT} was recorded in ventricular myocytes. These findings suggested that increased expression of $Ca_v3.2$ gene by de-repression of NRSF-mediated repression might be involved in reactivation of TCC in hypertrophied ventricles and contributed to progression of cardiac dysfunction.

Tanaka and Shigenobu investigated inhibitory effects

of various drugs on I_{CaT} , in comparison to actions on I_{CaL} . Many drugs and compounds non-specifically blocked I_{CaT} . Certain dihydropyridine compounds such as efonidipine, blocked activities of both I_{CaL} and I_{CaT} . On the other hand, selective inhibition of I_{CaT} was achieved by non-hydrolyzable mibefradil or *R*(-)-efonidipine. It was anticipated that these compounds would aid in better understanding of the molecular composition and regulation of TCC as well as in the development of novel therapeutic strategies for various diseases.

Hayashi et al. investigated roles of TCC in renal microcirculation. In contrast to LCC blockers, LCC/TCC antagonists potently dilated afferent and efferent arterioles, whose effects on efferent arterioles appeared to be mediated by TCC blockade. TCC antagonists also showed various beneficial effects in renal injury such as anti-proteinuric effects and inhibition of renin/aldosterone release and proinflammatory process. Hayashi et al. suggested that various mechanisms protected against renal injury including systemic/glomerular hemodynamic actions and non-hemodynamic mechanisms.