T-type Calcium Channels in Basic and Clinical Science

Stephen W. Schaffer • Ming Li
Editors

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Preface

It has been 30 years since the initial characterization of T-type channel current by Armstrong and Matteson (1985) and 15 years since the molecular cloning of the three subtypes of the T-type Ca^{2+} channel by Perez-Reyes et al., Cribbs et al., and Lee et al. (1998, 1999). In the last decade much has been learned regarding the biophysics, biochemistry, physiology, and pharmacology of these channels, with information being gleaned from a wide range of studies varying from structure–function relationships to therapeutic applications. In this book, recent advances in T-type Ca^{2+} channel research are reviewed, with a special emphasis on the pathological implications of the channels and the potential role of channel antagonists in clinical medicine.

Part 1 provides a relatively detailed introduction to the T-type Ca^{2+} channels, with a focus on the biophysical properties of the channels, their regulation by intercellular and intracellular signaling pathways, and current attempts to develop more selective antagonists of the channel. In Chap. 1, Drs. Senatore and Spafford review key properties of the channels and summarize their role in cellular processes, such as excitation–secretion coupling and cell cycle control. In Chap. 2, the regulation of the T-type Ca^{2+} channels by a host of modulators, including glucose, cytokines, hormones, neurohumoral agents, metals, ATP, transcription factors, and common signaling pathways is discussed by Drs. Li and Wu. In Chap. 3, a fairly comprehensive review of recent and past T-type Ca^{2+} channel antagonists and their potential clinical value has been written by Drs. Kawazu and Hashimoto.

Part 2 reviews new information gleaned on the physiological functions of the T-type Ca^{2+} channels and their role in various clinical conditions. In Chap. 4, Drs. Warnier and coworkers review the role of various T-type Ca^{2+} channel subtypes in the differentiation of neuroendocrine cells and their role in excitation–secretion coupling. The possibility that the T-type Ca^{2+} channels might play a role in neuroendocrine tumors is also discussed. Chapter 5 focuses on the role of T-type Ca^{2+} channels in the development of cardiac hypertrophy and heart failure. Drs. Schaffer and Jong discuss the controversy surrounding the regulation of cardiac hypertrophy by T-type Ca^{2+} channels and the possibility that $Ca_v3.1$ and $Ca_v3.2$ might exert opposite actions on the development of heart failure. The topic of Chap. 6 concerns one of the initially described "physiological functions" of the T-type Ca^{2+} channels, namely, their contribution to diastolic depolarization. Dr. Schaffer also discusses recent data implicating T-type Ca^{2+} channels in the

toxicity of Ca^{2+} overload related to electrical remodeling and ischemia–reperfusion injury. In Chap. 7, Drs. Chen and Parker review the convincing evidence that T-type Ca^{2+} channels play a central role in the development of absence seizures. It is anticipated that T-type Ca^{2+} channel antagonists will play a central role in the treatment of this condition. In Chap. 8, Drs. Pottle and Gray review the role of T-type Ca^{2+} channels in the regulation of cell cycling and proliferation. They introduce the novel concept that T-type Ca^{2+} channel antagonists might halt cell cycling near the G1/S checkpoint, rendering the cells more susceptible to S phase-specific chemotherapy. At the present time, this idea is being advanced to a phase Ib study in patients with recurrent high-grade glioma, a trial conducted in conjunction with the National Cancer Institute. In Chap. 9, Dr. Keyser discusses the mechanism by which T-type Ca^{2+} channels influence pain. The possibility that T-type Ca^{2+} channel antagonists might diminish both the sensation of pain and the progression of diseases, such as diabetic neuropathy, is discussed. In Chap. 10, the complex relationship between hyperglycemia, T-type Ca^{2+} channel activity, and insulin secretion is discussed. Dr. Li suggests that the T-type Ca^{2+} channels might provide a new target for the treatment of type 2 diabetes mellitus.

Skeptics maintain that potential adverse side effects of the T-type Ca^{2+} channel blockers will hamper wide acceptance of these therapeutic agents. They point out that the T-type Ca^{2+} channels are broadly distributed in a variety of human tissues, but in particular in vital organs, such as heart and thalamic neurons, where they exert important functions. However, at least three subtypes of the T-type Ca^{2+} channels are present in humans, where they serve different functions. Some of these subtype-specific actions are discussed in Part 2. It is likely that the development of subtype-specific antagonists will improve the efficacy while diminishing the toxicity of the newly developed antagonists.

The T-type Ca^{2+} channels, like all voltage-gated Ca^{2+} channels, conduct extracellular Ca^{2+} into the cytosol. Nevertheless, T-type Ca^{2+} channels, unlike the L-type Ca^{2+} channels, only carry a "transient and tiny" current. Yet, irregular expression of T-type Ca^{2+} channels has been implicated in a number of disease conditions, including cardiac hypertrophy (Chap. 5), ischemia–reperfusion injury (Chap. 6), absence seizures (Chap. 7), tumor cell proliferation (Chap. 8), and hyperinsulinemia (Chap. 10). Thus, there is an adequate therapeutic index window for T-type Ca^{2+} channel blockers to suppress pathological conditions while retaining the physiological function of the channels in normal tissue. In concluding remarks, Drs. Senatore and Spafford in Chap. 1 state that "new T-type channel drugs on the horizon have potential for disease treatment. The newer and more specific drugs will also contribute to a clearer understanding of how T-type channels function in normal cellular physiology, as well as in pathological conditions." We feel that the future of the T-type Ca^{2+} channel is bright.

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