Development of Electrical Excitability: Mechanisms and Roles

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This special issue of the *Journal of Neurobiology* is devoted to developmental regulation of electrical excitability. Electrical excitability is mediated by voltage-dependent ion channels, and this is a particularly advantageous time to be studying ion channels in differentiating neurons and muscle. The patch clamp technique has made a wide variety of cells from a diverse set of species amenable to electrophysiological study at the earliest stages of their differentiation. Advances in molecular cloning of ion channels have enabled identification of the molecules composing ion channels that are expressed at specific stages of development. This molecular information has also permitted the development of specific antibody probes; these immunological tools, used in combination with confocal microscopy, allow ion channel protein localization and subcellular distribution to be defined. A consistent finding is that ion channel expression involves a complex and diverse set of ion channel genes that achieve the tight regulation of emerging excitability in differentiating neurons and muscle. With respect to the roles that activity plays in these embryonic cells, imaging techniques in combination with calcium and/or voltage indicator dyes have allowed relatively noninvasive examination of spontaneous activity. Periods of spontaneous activity have been identified and consequently perturbed or abolished. Such studies have provided key information regarding the roles of excitability in embryonic neurons. The take-home message is that while ion channels are ideally designed for rapid signaling, they also participate in signaling events that occur over a longer time domain and affect programs of differentiation.

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We thank the contributors for providing articles that not only review their research areas concisely and insightfully, but also point to the new questions that have arisen from recent progress. Much of the exciting work regarding ion channel expression and function in developing cells is represented here by reference rather than by direct contribution from other groups as a result of space limitations.

We have organized the articles in two groups. One group (Mechanisms) details changes in excitability which are noted principally in embryonic cells, and, when known, the underlying mechanisms that achieve developmental regulation of excitability. Takahashi and Tanaka demonstrate that ion channel expression in neurons of ascidian embryos is triggered by cell–cell interactions and signaling events that characterize neural induction. Dryer identifies the role of cell–cell interactions and secreted factors in the regulation of ion channels during later stages of neuronal differentiation. Nerbonne focuses on regulation of potassium channels in developing heart muscle and during specific pathological states, and goes on to link specific molecular species of potassium channels to functionally distinguishable current components. Levitan reviews how transcriptionally mediated changes in potassium channel gene expression can have functional consequences in a surprisingly rapid time frame, and how changing expression of a single potassium channel subunit can have broad effects on several currents. Gan and Kaczmarek show that potassium channel genes are specifically up-regulated to satisfy the firing requirements of neurons, and Vabnick and Shrager define the localization of ion channels during development of peripheral myelinated axons.

The other group (Roles) addresses questions regarding the roles of excitability in embryonic neurons. Moody summarizes current understanding of the ways in which dynamic changes in the repertoire of channels expressed in an excitable cell can limit periods of spontaneous activity to specific developmental windows. O'Donovan, Chub, and Wenner review the origins of spontaneous activity in networks of neurons. Komuro and Rakic proceed to illuminate the mechanisms by which spontaneous activity regulates neural cell migration. Barish considers how patterned changes in intracellular calcium concentrations regulate many steps of membrane protein biosynthesis as well as membrane expansion and ion channel insertion during development. Fields analyzes the way in which action potentials regulate neural development. Finally, Finkbeiner and Greenberg review the pathways by which calcium regulation of gene expression specifies both developmental and adaptive responses in a model neuronal system. We conclude the issue with our article that summarizes studies of embryonic *Xenopus* spinal neurons, for which it is possible to examine both mechanisms and roles of developmentally regulated electrical excitability.