Review

Mechanisms of voltage-gated ion channel regulation: from gene expression to localization

D. J. Schulz*, S. Temporal, D. M. Barry and M. L. Garcia

Division of Biological Sciences, University of Missouri-Columbia, Columbia, Missouri 65211 (USA), Fax: +1 573 884 5020, e-mail: SchulzD@missouri.edu

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Abstract. The ion channel milieu present in a neuron in large part determines the inherent excitability of a given cell and is responsible for the translation of sensory transduction and synaptic input to axonal output. Intrinsic excitability is a dynamic process subject to multiple levels of regulation from channel gene expression to post-translational modifications that influence channel activity. The goal of this review is to provide an overview of some of the mechanisms by which channels can be modified in order to influence neuronal output. We focus on four levels of regulation: channel gene transcription, alternative splicing of channel transcripts, post-translational modifications that alter channel kinetics (phosphorylation), and subcellular localization and trafficking of channel proteins.

Keywords. Ion channels, phosphorylation, channel kinetics, alternative splicing, trafficking, and neural plasticity.

Introduction

The intrinsic properties of a neuron determine the inherent excitability of a given cell and are responsible for the translation of sensory transduction and synaptic input to axonal output. It is this input-output relationship that is the heart of all nervous system activity. The excitability of any given neuron is most attributable to the proteins that are directly responsible for changes in membrane potential: the voltage-gated ion channels. These channels span the plasma membrane and generate ion-selective pores for the movement of charged particles across the membrane that ultimately results in membrane potential fluctuation in excitable cells. Thus it is the combined milieu of voltage-gated channels present, as well as the specific kinetics of the activity of these channels, that ultimately generates the response of a cell to a particular pattern of stimuli.

Intrinsic excitability is not a static state, but rather a dynamic process subject to multiple levels of regulation from channel gene expression to post-translational modifications that profoundly influence ion channel activity. This diversity of mechanisms that underlie plasticity in neuronal output is one of the core features of the malleability of the nervous system. For if the nervous system and its constituent neurons were simply static input-output devices, then dynamic processes such as learning and memory, sensory adaptation, motor coordination, and autonomic regulation of homeostatic processes would not be possible. Thus the flexibility of the individual units of the nervous system emerges to form the complex and adaptable neural networks that give rise to higher functions in all animals. Therefore, plasticity in ion
channel function is at the very foundation of nervous system function itself. The role of ion channels in the variability and plasticity of cellular phenotypes and output is due not only to flexibility in channel expression and protein function, but also as a result of the sheer diversity of ion channel subtypes present in the nervous system, or even within a single cell. Ion channels perform their roles by allowing a select group of essentially four ions across the membrane: Na\(^+\), K\(^-\), Ca\(^2+\), and Cl\(^-\). Yet the passage of K\(^-\) alone across the membrane is the result of at least 100 different K\(^-\) channel subunits [1]. There are at least 9 different genes that code for the pore forming \(\alpha\)-subunits of voltage-gated Na\(^+\) channels in humans [2], and those for the gene family encoding the primary voltage-gated calcium channels also number at least 10 [3, 4]. To this diversity add the fact that a functional channel is ultimately a combination of these \(\alpha\)-subunits with a subset of accessory subunits that also display tremendous diversity, and it is not difficult to appreciate the complexity underlying the intrinsic excitability of neurons at all levels of the nervous system.

The goal of this review is to provide an overview of some of the mechanisms by which voltage-gated ion channels can be modified in order to generate plasticity in neuronal output. We focus on four levels of regulation: channel gene transcription, alternative splicing of mRNA transcripts, post-translational modifications that alter channel kinetics (phosphorylation), and subcellular localization and trafficking of channel proteins. As discussed above, the extraordinary diversity of channel subtypes makes a comprehensive review of these topics for each channel type impossible. Rather, we have chosen to focus on general mechanisms of channel regulation rather than the details of how each individual channel is modified. Toward this end, we use the example of voltage-gated sodium channels (VGSCs) throughout each section as a device to illustrate how each level of channel regulation can influence the same channel type in order to create a diversity of neuronal output. In addition, we provide examples from other channel families to emphasize the fact that these are common mechanisms employed in generating plasticity of channel function and neuronal output.

Voltage-gated channel structure as substrates for plasticity

Voltage-gated channels consist of membrane-spanning proteins that permit the rapid influx and/or efflux of charged ions in response to changes in membrane potential. These channels are composed of a core of a single \(\alpha\)-subunit or a multimeric association of \(\alpha\)-subunits that largely make up the membrane-spanning pore of the channel complex. While these \(\alpha\)-subunits are the focus of this review, virtually all channels are heteromers of the pore-forming \(\alpha\)-subunits with accessory subunits involved in anchoring the protein to the plasma membrane or influencing channel kinetics, interactions with cytoplasmic, or cytoskeletal elements. Together these protein subunits determine the kinetics of the ion channel function, i.e. at what membrane potential and how rapidly the channel opens (‘activation’), closes (‘deactivation and inactivation’), and how much current each channel carries when it is open.

The \(\alpha\)-subunits of VGSCs are structurally representative of how most ion channels are organized (see Fig. 1) [5]. The channel proteins themselves are taxonomically described by a numerical system of the primary channel type (e.g. Na\(_{1.1}\) for VGSCs) and a numerical suffix that describes a distinct channel protein. Hence the VGSC proteins are named Na\(_{1.1–1.9}\). These VGSCs all consist of four repeat domains (D1–4), each of which is composed of six transmembrane segments (S1–S6). The transmembrane segments and the domains they make up tend to be highly conserved and are responsible for the voltage-sensing properties of the channel as well as the pore selectivity. Conversely, the portions of the protein that join together the four repeat domains are areas of diversity between channel types, and contain the majority of the residues of the protein that are involved in post-translational modification and protein-protein interactions. Therefore, it is these ‘linker’ sequences that are primarily responsible for the diversity of electrophysiological phenotypes that can be observed between different VGSC subtypes.

Transcriptional control of ion channel expression

With regard to gene expression and the functional output of any cell, the governing factors are obviously which gene is expressed, how much of this mRNA is present in the cell (the relative abundance), and how this expression is regulated. The voltage-gated ion channels are no exception, and there are myriad examples of how expression of ion channel genes differs between cell types, or under different environmental conditions, including injury. Beyond cell-type-specific differences in the abundances of which VGSC subunits are expressed, within a given cell type VGSC expression is a dynamic process as well. Indeed, with upwards of 10 different VGSC genes, it would be surprising if variability were not the norm in this situation. Expression of VGSC is known to be