The Other Half of Hebb

K⁺ Channels and the Regulation of Neuronal Excitability in the Hippocampus

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Abstract

Historically, much attention has focused on the mechanisms of activity-dependent plasticity since the description of long-term potentiation by Bliss and Lomo in the early 1970s, while extrasynaptic changes have received much less interest. However, recent work has concentrated on the role of back-propagating action potentials in hippocampal dendrites in synaptic plasticity. In this review, we focus on the modulation of back-propagating action potentials by K⁺ currents in the dendrites of hippocampal cells. We described the primary K⁺-channel subunits and their interacting subunits that most likely contribute to these currents, and how these sites can be regulated by phosphorylation and other mechanisms. In conclusion, we provide a model for an alternative form of coincidence detection through K⁺ channels in the hippocampus.

Index Entries: Hebbian; LTP; learning; memory; metaplasticity; suprasynaptic; extrasynaptic; neuromodulation; Kv4.2; shal.

“Hebb’s Postulate”—When an axon of cell A ... excites cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A’s efficiency as one of the cells firing B is increased.


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Introduction

Great progress has been made in understanding the molecular mechanisms contributing to the modulation of synaptic strength in the hippocampus; however, mechanisms contributing to extrasynaptic plasticity have received much less attention. Recent work in the hippocampus has highlighted an important role for back-propagating dendritic action potentials in the triggering of LTP in area CA1 neurons, and has suggested that $K^+$ channel regulation of dendritic-membrane excitability may be an important determinant of the probability of LTP induction. This review will highlight three themes in this context. First, we will illustrate the $K^+$ channel primary subunits, focusing on one particular subunit, and its associated proteins in the hippocampus, and the associated molecular complex that is beginning to emerge in the literature. Second, we will discuss that there is regulation of the hippocampal transient A-type $K^+$ current by protein kinase signal-transduction cascades, in particular the protein kinase A (PKA), protein kinase C (PKC), and the extracellular regulated kinase/mitogen-activated protein kinase (ERK/MAPK) cascades. Finally, we will argue that mechanisms exist whereby neurotransmitter receptors coupled to these protein kinase cascades can achieve biochemical signal integration, and, through regulation of K+ channels, potentially allow 3- and 4-way coincidence detection for gating the triggering of synaptic plasticity. This review will show that Kv4.2 and its associated accessory proteins likely form a postsynaptic $K^+$-channel supramolecular complex that can be dynamically regulated by various mechanisms. This regulation is important in order to achieve precise regulation of the channel biophysical properties and a restricted subcellular localization.

Kv4.2 Function and Structure

Potassium channels are present in eukaryotic cells throughout the animal and plant kingdoms and support highly diverse functions. Three groups of primary, pore-forming, or alpha ($\alpha$) subunits for $K^+$ channels have been characterized based on the number of putative membrane-spanning alpha helices. The $\alpha$ subunits of voltage-activated and Ca$^{2+}$-activated K$^+$ channels have six transmembrane domains, the ‘leak’ K$^+$ channels have four transmembrane domains, and the inward rectifiers have two transmembrane domains, reviewed in ref. (1). Each of these groups is divided into discrete families, based on sequence homology, which are further divided into subfamilies. The Shaker family is a group of voltage-activated K$^+$ channels with at least five different $\alpha$ subunit proteins derived from the Shaker gene by alternative splicing (2–4). Among these are the Shaker (Kv1.x), Shab (Kv 2.x), Shaw (Kv 3.x), and Shal (Kv4.x) subfamilies (1). Recent advances in the study of ion channels have shed light on the structure of K$^+$ channels. Crystallography work by Doyle et al. (5) confirmed that the primary ($\alpha$) subunits form a tetrameric K$^+$ channel structure, where each of the four subunits form the infrastructure of the channel with symmetry around the central pore. These K$^+$ channel primary subunits can assemble as homo- or heteromultimers (6,7). Thus, it is obvious that many different K$^+$ channels with diverse kinetics and functions exist. These functions include cell volume regulation, release of hormones and neurotransmitters, and the regulation of the membrane potentials of excitable cells, with each cell type exhibiting different combinations of K$^+$ channels based on its functional requirements. Diversity is also increased by their ability to form functional heterotrimeric structures and associate with auxiliary or $\beta$ subunits.

The Shal-type channels (Kv4.1-4.3) participate in the transient outward A-type current characterized in neurons throughout the central nervous system (CNS), as well as in cardiac myocytes. This current is best described as a timing mechanism to regulate action potential frequency and cell excitability. Kv4.2 specifically, is a rapidly inactivating voltage-gated K$^+$ channel that activates at membrane...