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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.

D. O. Hebb, *The Organization of Behavior,* 1949 (emphases added).

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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 (α) subunits for K^+ channels have been characterized based on the number of putative membrane-spanning alpha helices. The α 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 α 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 (or α) 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 heterotetrameric structures and associate with auxiliary or β 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

potentials above –40 mV and is sensitive to 4-aminopyridine *(8–11).* It is highly likely that Kv4.2 is a pore-forming subunit of A-type K^+ channels in CA1 pyramidal cell dendrites, as the pharmacological and kinetic properties of Kv4.2 expressed in oocytes are similar to the transient outward currents in dendrities *(9–12).* These A-type K^+ currents of CA1 pyramidal neuron dendrites have recently been shown to dynamically regulate hippocampal pyramidal-cell excitability *(12)* and to be modulated by kinase activation *(13,14).* Given these data, and the important role that phosphorylation of the α subunit, Kv4.2, or other interacting proteins, may play in the regulation of hippocampal pyramidal cells, this review will focus on those currents in the hippocampus and the molecular complex formed by the Shal-type channel, Kv4.2, and its interacting subunits.

Hippocampal Expression of the A-Type K^+ Channels

Hoffmann et al. *(12)* have recently shown that a transient A-type K^+ channel is present in high density in the dendrites of CA1 pyramidal neurons, and that the density of these channels increases linearly with distance from the cell body, being more than fivefold greater 350 μm into the apical dendrites than in the soma. Since these channels are at high density in the dendrites, where the neurons receive synaptic input, rapid activation of these channels can limit the peak of back-propagating action potentials and can modulate incoming synaptic information, exerting profound effects on hippocampal network communication.

While the exact molecular components of the current exhibited by CA1 pyramidal neurons are still unknown, as mentioned earlier, Kv4.2 is a subunit that most likely contributes to the transient K^+ channels in hippocampal dendrites. While Shal Kv4.1 and Kv4.3 are expressed at low levels in hippocampal CA1 neurons *(10,15,16),* Kv4.2 is highly expressed in hippocampal pyramidal neurons soma and dendrites *(15).* Kv1.4 is another transient channel also found in hippocampal neurons, but it is only found in axons *(10,17,18).* In addition, in magnocellular neurons of the supraoptic nucleus Kv4.2 clusters on the postsynaptic membrane directly apposed to the presynaptic terminal *(19),* suggesting the potential for a similar localization in the hippocampus. Pharmacological data shows that the Shal Kv4 subunits are inhibited by arachidonic acid *(20),* as are the transient currents recorded from CA1 somata *(21),* whereas Shaw-like Kv3 and Shaker Kv1.4 are unaffected *(20).* However, Kv4.2 channels expressed in oocytes have more negative activation and inactivation ranges and are less sensitive to TEA *(11)* compared to the transient outward current in hippocampal dendrites. This suggests that the native current in hippocampal dendrites may be a mixture of several channel types, a heteromultimer of Shal subunits, modified by an auxiliary subunit *(9,10,22,23),* or post-translationally modified by such mechanisms as phosphorylation (reviewed in ref. *[24]*). Overall, based on the available data, Kv4.2 is most likely to be the pore-forming subunit of shal-type channels in the dendrites of hippocampal pyramidal neurons, and it is subject to regulation by accessory subunits or post-translational modification. In the following sections we will outline several of these subunits and describe possible regulation mechanisms.

Beta Subunits

Functional diversity can be augmented through the formation of heteromulteric channel complexes or by association with auxiliary subunits. Auxiliary subunits interact with channels containing principal subunits and contribute to the regulation of biophysical properties and expression levels of K^+ channels, although most relevant molecular entities have not been identified. The auxiliary subunits characterized in most detail are the members of the Kvβ auxiliary subunit family. These subunits lack putative transmembrane domains and potential glycosylation sites or leader sequences, suggesting that they are

cytoplasmic proteins *(25).* Three Kvβ genes have been identified: Kvβ1, Kvβ2, and Kvβ3 *(26,27).* Several functions of the β subunits have been described including: causing an increase of the inactivation kinetics *(27)* that can convert delayed rectifiers to a rapidly inactivating current *(22,26)* or acting as chaperone proteins that promote and/or stabilize cell-surface expression of α subunits *(23,28–32).* Kvβ1 and Kvβ2 have also been shown to modulate voltage-dependence in heterologous expression systems *(33).* Another proposed role for Kvβ subunits is as a redox sensor, as they are similar to oxo-reductase enzymes *(34)* and may confer redox sensitivity to channel function. Indeed, it was previously thought that while Shal-type channels can interact with K^+ channel β1 and β2 subunits, this interaction does not appear to be physiologically relevant *(23).* Recent functional modulation of Kv4.2 by a β subunit was shown, however, in that upon association with Kvβ1.2, Kv4.2 is sensitive to redox modulation and hypoxia *(35).* Thus, while the kinetics of Kv4 channels do not appear to be altered by β subunits, there does appear to be functional modulation of Kv4 by β subunits through redox modulation (*see* below).

KChIPs

Another family of Kv4 interacting proteins, the K^+ Channel Interacting Proteins (KChIPs), has recently been described that act as chaperones for Kv4.2 and modulate the kinetic properties of Kv4 channels. Interestingly, the KChIPs are Ca^{2+} binding proteins and are homologous to a transcriptional repressor that interact solely with the Kv4 proteins. Three subtypes of KChIPs (KChIP 1, 2, and 3) have been described to date *(36).* The KChIPs colocalize and coimmunoprecipitate with brain Kv4 subunits, and are thus considered integral components of the native Kv4 channel complexes by binding to the amino-terminus of Kv4 α subunits *(36,37).* Coexpression of the KChIPs and Kv4 subunits in heterologous cells modulate the density, activation, and inactivation kinetics and rate of recovery from inactivation of the Kv channels. KChIPs 2 and 3 have been localized to the hippocampus *(38),* thus, the KChIPs are possible candidates for modulators of Kv4.2 in the hippocampus. These KChIPs have four EF-hand-like domains and bind calcium ions. The function of these Ca^{2+} binding domains is unknown; however, a Ca^{2+} dependence of transient K^+ currents has been reported *(39–41).*

The KChIPs share sequence similarity with frequenin, a calcium-binding protein that is involved in the regulation of transmitter release in Drosophila *(42),* moreover KChIPs are identical to calsenilin *(43)* and are 99% homologous with DREAM, a Ca^{2+}-regulated transcriptional repressor *(44).* Thus, phosphorylation of KChIP may have greater implications than dynamic modulation of Kv channels, possibly coupling K^+ channels to gene regulation.

Cytoskeletal Proteins

The studies showing Kv4.2 expression selectively in the somatodendritic region of neurons *(18)* and specifically in the subsynaptic regions *(19)* led to a search for the underlying mechanism for this compartmentalization. Recently Petrecca et al. *(45)* demonstrated an association between Kv4.2 and filamin, a member of the α-actinin/spectrin/dystrophin family of actin-binding protein, in neurons. Using the yeast two-hybrid system, this group demonstrated that a portion of the carboxy-terminal proline-rich region, residues 601–604, within Kv4.2 is critical for binding to filamin. Subsequent characterization studies showed that Kv4.2 and filamin colocalize in cerebellum and cultured hippocampal neurons. Furthermore, Kv4.2 is expressed in a punctate pattern in dendrites that colocalizes with the synaptic marker, synaptophysin. Electrophysiological characterization of filamin$^+$ and filamin$^-$ cells transfected with Kv4.2 suggest that the filamin/Kv4.2 interaction is functionally significant in that the transient current density is higher in the filamin$^+$ cells compared to the filamin$^-$ cells. No difference in single-channel

conductance and total Kv4.2 protein levels was observed in the filamin$^+$ and filamin$^-$ cells, suggesting that the physiological effect is due to a higher density of channels at the surface membrane. Site-directed mutagenesis of proline residues 601, 603, and 604 (P/A) within the Kv4.2 carboxy-terminus blocked the augmented transient current density observed in filamin$^+$ compared to filamin$^-$ cells, supporting the idea that this region is critical for Kv4.2 association with filamin.

Another protein that may play a role in Kv4 localization and distribution is integrin. Interaction with the cell-adhesion molecule, integrin may underlie the restricted cellular distribution of filamin *(46).* Filamin and integrin are thought to be components of the neuromuscular junction, and β-integrin plays a role in the signaling events that lead to agrin-induced clustering of ACh receptors *(47).* In addition, integrin-mediated cell anchorage is necessary for G protein-coupled receptor activation (GPCR) of ERK *(48).*

As these themes emerge, one can begin to envision a supramolecular complex of regulatory proteins including receptors and their intermediary protein kinases and downstream targets such as ion-channel subunits that are anchored to, or closely associated with the cytoskeleton. Although there are likely to be a number of modulatory events involved in the regulation of such a supramolecular complex, phosphorylation state could be one way of altering the association of the components within the complex. For example, the Kv4.2 residues critical for filamin association are in the region of an ERK phosphorylation site (S602). ERK phosphorylation at this site could alter the Kv4.2/filamin association such that Kv4.2 localization at the postsynaptic site is altered. Based on the physiological properties of Kv4.2 such a change is likely to have functional significance.

Summary

With all the various molecular components previously described, the K$^+$ channel complex has the potential to be regulated at various levels. As discussed, diversity of K$^+$ channels arises through the formation of heteromultermeric channels *(6,7)* or by the association with auxiliary subunits *(25).* These various proteins provide a multitude of molecular targets for regulation through phosphorylation, which can cause functional modulation of the channel, and perhaps even binding or unbinding of auxiliary subunits, or through regulation by redox mechanisms. In addition, the recent discovery of the KChIPs adds yet another level of complexity. While their function as Ca^{2+} binding proteins or transcriptional regulators that are coupled to K$^+$ channels are as yet unknown, one can imagine possible roles in Ca^{2+}-dependent plasticity and gene regulation. All of these interacting proteins provide multiple potential sites of modulation and amplify the mechanisms through which the function of K$^+$ channels and subsequently, neuronal excitability and synaptic plasticity can be regulated.

Regulation of A-Type K$^+$ Currents by Protein Kinases

Recent studies have indicated that phosphorylation of the K$^+$ channel, Kv4.2, or interacting subunits on the postsynaptic neuron is a very appealing target for modulation of neuronal excitability. Hoffmann and Johnston *(13)* have shown that the voltage-dependent activation of these currents (in the dendrites of CA1 pyramidal neurons) is shifted to more depolarized membrane potentials by either PKC or PKA activation *(13),* and to more hyperpolarized membrane potentials by ERK/MAPK inhibition *(49).* Functionally, this effect of PKC and PKA activation has been shown to increase the peak of back-propagating action potentials *(13)* and to be mediated by activation of β adrenergic and muscarinic receptors *(14).* Interestingly, this modulation of the back-propagating action potentials is mediated by ERK activation, as U0126, the specific MEK inhibitor, blocks the

effect of activation of β adrenergic receptors *(50),* suggesting that ERK is downstream from both PKA and PKC activation in CA1 pyramidal neuron dendrites.

Although the precise target of kinase modulation of hippocampal transient currents is not clear at this point, we have shown that the cytoplasmic domains of Kv4.2 are phosphorylated by ERK, PKA, PKC, and CaMKII. Using recombinant proteins of the amino- and carboxy-terminal cytoplasmic domains of Kv4.2 we identified two PKA sites (T38 and S552) *(51),* three ERK sites (T602, T607, S616) *(52),* two PKC sites (S447 and S537), and two CaMKII sites (S438 and S459) *(53).* Subsequently, we developed phospho-site selective antibodies that recognize the full-length channel when phosphorylated at these specific kinase sites. With these phospho-Kv4.2 antibodies, we have demonstrated that there is modulation of kinase phosphorylation of Kv4.2 in response to stimulation of upstream modulatory neurotransmitter systems that are known to impact membrane excitability. Furthermore, we have shown that there is an upregulation of ERK phosphorylation of Kv4.2 following kainate-induced seizures *(54).* These findings indicate that Kv4.2 is a substrate for a number of kinase cascades known to be involved in hippocampal plasticity.

Modulation of the properties of these channels (e.g., voltage-dependence, inactivation rate, number of channels, distribution) represents a powerful potential site for regulation of pyramidal neuron excitability in LTP. Thus, these transient outward currents (most likely composed of Kv4.2 α subunits and other α subunits or interacting proteins) appear to be ideally suited, both in terms of their biophysical properties and subcellular localization, for contributing significantly to the regulation of pyramidal neuron excitability and synaptic responsiveness. In addition, the work from Dan Johnston's lab *(12–14)* suggests that regulation of Kv4.2 by protein kinase signal-transduction cascades, particularly ERK *(50),* may be a prominent mechanism for controlling pyramidal neuron dendritic excitability.

Immunolocalization

As mentioned earlier, immunohistochemical studies show that Kv4.2 protein localizes abundantly to the hippocampus *(18),* with particular localization to the neuronal soma and dendrites at the postsynaptic density *(17,19).* Moreover, recent immunohistochemical studies with phospho-specific antibodies show specific patterns of localization of the Kv4.2 α subunit phosphorylated by different kinases *(55).* In the hippocampus specificially, CA1 labeling with an antibody that recognizes Kv4.2 when phosphorylated on the three ERK sites is localized primarily to stratum oriens and stratum radiatum, with minimal staining in stratum pyramidali, and the soma and basilar dendrites of CA3 show a striking immunoreactivity with little staining in stratum lucidum. Antibodies that recognize Kv4.2 phosphorylated by PKA show a different and distinct pattern of labeling. In general, different phospho-isoforms of Kv4.2 show localization to distinct areas of synaptic input on pyramidal neuron dendrites, suggesting that an input specificity of postsynaptic signal-transduction cascades may exist in the hippocampus, or that Kv4.2 phosphorylation may participate in targeting of channels to specific synaptic zones.

Other Potential Sites of Regulation

Structural analysis of the crystallization of the K^+ channel β subunit-2 (Kvβ2) suggests the presence of an aldoketo-reductase enzyme activity that catalyzes the transfer of a hydride anion from the nicotinamide ring of NADPH to an acceptor-substrate *(34).* The acceptor-substrate that is reduced by Kvβ2 is yet unknown and the purpose of an aldoketo-reductase in the β2 subunit is a matter of speculation. The K^+ channel β1 subunit (Kvβ1) shares 81% identical homology with the β2 subunit and by protein modeling studies is also believed to possess an aldoketo-reductase. Several studies have shown an effect of the local redox environment on the inactivation

kinetics of potassium channels. A recent report has described that Kvβ1.2, an isoform of Kvβ1, confers oxygen sensitivity when expressed with Kv4.2, in that altering the redox environment of the Kv4.2/Kvβ1.2 channel with reducing agents causes an increase in the inactivation kinetics of the current and that adding oxidizing agents reverses the effect *(35).* In a similar study of Kv3.4 in the absence of β subunits, exposure to oxidizing agents causes faster inactivation kinetics because a locally oxidized environment facilitates formation of stabilizing disulfide bonds within its own inactivation domain *(56).* Overall, it is clear that the redox environment of K^+ channels influences channel properties, but it is not known how the redox environment is created and regulated. One possible source of superoxide production may be the K^+ channel β-subunits, thus the Kvβ1 aldoketo-reductase would act as an NADH oxidoreductase that catalyzes a redox reaction with NADPH as a cofactor to generate superoxide, providing another mechanism for channel regulation.

Summary

Several lines of evidence suggest that activation of kinases may modulate K^+ channel activity through phosphorylation. We have shown that sites exist in the Kv4.2 sequence that are phosphorylated by ERK, PKA, PKC, and CaMKII, and that activation of various neuromodulatory receptors phosphorylate Kv4.2 at these sites. Phosphorylation of Kv4.2 by the individual kinases occurs at distinct areas in the hippocampus, suggesting that the activation of the postsynaptic second-messenger cascades to regulate Kv4.2 is input specific. While activation of PKA and PKC decreases the transient A-type K^+ currents in the dendrites of hippocampal pyramidal neurons, it is unknown whether this is due to phosphorylation of the primary (Kv4.2) subunits, or possibly auxiliary subunits. While phosphorylation of the K^+ channels presents one powerful mechanism for current modulation, other mechanisms exist. Indeed, we have also presented alternative mechanisms through which K^+ currents can also be dynamically regulated by redox mechanisms.

A Model of Coincidence Detection in Hebbian Plasticity K^+ Channels as Signal Integrators

As described earlier, we have found evidence that Kv4.2 is a substrate for all four kinases known to be involved in LTP: PKC, PKA, CaMKII, and ERK/MAPK. Thus, Kv4.2 may serve as a functional integrator of the actions of protein kinases by serving as a convergence point for their actions. Since PKA and PKC modulate the A-type K^+ current in hippocampal neurons through activation of ERK *(50),* and functional modulation of these currents by CaMKII has not yet been described, we will focus our discussion on the possibility that phosphorylation of Kv4.2 by ERK may play a role in neuronal excitability. For a more complete understanding of this concept, we will also discuss ERK/MAPK and the role of the ERK cascade in plasticity in the following sections.

MAPK as a Signal Integrator Controlling Kv4.2

While regulation of cell proliferation is the best-studied function of the ERK/MAPK cascade *(57,58) (59–61),* it was recently shown that hippocampal ERK/MAPK activation is critical for LTP and various forms of hippocampus-dependent memory formation *(62–69).* A wide variety of signaling mechanisms operate to control ERK activation in the hippocampus, and in this section we will focus on the capacity of the ERK cascade to potentially serve as a biochemical signal-integration system *(64).* We will draw largely from studies of hippocampal area CA1, the CNS subregion for which the most information is available.

Regulation of the ERK cascade is complex *(70).* The ERK cascade, like the other MAPK

cascades, is distinguished by a characteristic core of three kinases. The first kinase in the sequence is MAP kinase kinase kinase (MAPKKK, Raf-1 and B-Raf in the ERK cascade), which activates the second kinase, a MAP kinase kinase (MAPKK, MEK in the ERK cascade), by serine/threonine phosphorylation. MEKs are dual specificity kinases, which in turn activate a MAP kinase (p44 MAPK = ERK1, p42MAPK = ERK2) by simultaneously phosphorylating both a threonine and tyrosine. This dual phosphorylation is both necessary and sufficient for ERK activation. Despite this complexity, one simplifying feature of the cascade is that ERK (both ERK1 and ERK2) activity is exclusively regulated by MEK.

ERK/MAPK in Long-Term Potentiation

Long-term potentiation (LTP) is a robust and long-lasting form of synaptic plasticity that is a leading candidate for a cellular mechanism contributing to mammalian learning and memory. Recent advances have given us a much more detailed understanding of the signal-transduction mechanisms operating to elicit LTP, and one fact that has become clear is that ERK activation plays a critical role in LTP induction. Initial studies in this area focused on NMDA receptor-dependent LTP in area CA1, using hippocampal slices in vitro *(62,67,71,72).* In addition, recent data have shown a necessity for ERK activation in the induction of NMDA receptor-independent LTP *65–73,* LTP in the dentate gyrus *(73) (74),* LTP in vivo *(75),* and LTP at the amygdalar inputs into the insular cortex *(76).*

NMDA receptor-dependent LTP in area CA1 is generally divided into at least two phases: early LTP (E-LTP), which lasts about 60–90 min, and late LTP (L-LTP), which is longer lasting and is blocked by inhibitors of protein and RNA synthesis. This latter observation has given rise to the model that L-LTP is dependent on changes in gene expression for its induction. Given the prominent role of ERK in CREB phosphorylation and regulation of gene expression *(63,72,77–81),* it is intriguing that strong evidence exists that ERK activation is necessary for L-LTP; three structurally distinct MEK inhibitors all block late LTP *(62,63,66,67).* However, the effects of inhibitors of MAPK activation are not limited to L-LTP; E-LTP is attenuated as well.

Thus, the ERK cascade is positioned to play a key role in integrating a variety of cell-surface signals. Interestingly, the ERK cascade appears to be involved in LTP induced by repetitive stimulation, but not by a single high-frequency burst (100 Hz) *(66),* although ERK phosphorylation is induced by both theta-burst stimulation and 100 Hz stimulation *(82).* In addition, Wu et al. *(83)* showed that ERK activation in response to repetitive stimulation was necessary for the extension of new dendrite filopodia in hippocampal CA1. These data have the interesting implication that ERK has a role in long-term plasticity and anatomical rearrangement of circuits.

Pathways of ERK/MAPK Activation

Several second messenger-regulated kinases have been shown to activate the ERK cascade. Stimulation of PKC produces a robust activation of ERK2 in most cells *(84).* In the first studies of CA1 pyramidal neurons in acute hippocampal slices, this finding was reiterated: both pharmacologic NMDA receptor activation and PKC stimulation lead to ERK2 activation in this preparation *(71).* Also, activation of NMDA receptors using LTP-inducing physiologic stimulation similarly results in ERK2 activation *(71).*

More recent work demonstrated the capacity of the cAMP cascade to activate ERK in non-neuronal cells *(85),* and activation of the cAMP cascade also leads to secondary activation of ERK in hippocampal area CA1 *(86,87).* In addition, activation of β-adrenergic receptors (βARs) using isoproterenol application leads to ERK activation in area CA1, an effect attenuated by PKA inhibition *(87).* This finding is especially interesting because βARs modulate LTP induction in area CA1, and, in fact, Winder et al. *(66)* have recently observed that

the βAR modulation of LTP induction is blocked by MEK inhibitors.

The β-adrenergic receptors are not the only receptors known to activate hippocampal ERK. Metabotropic glutamate receptors, muscarinic acetylcholine receptors, DA receptors, and serotonin receptors all lead to ERK activation in the hippocampus *(87,88).* These neuromodulatory receptor agonist studies, coupled with studies indicating that both the PKA and PKC pathways can elicit hippocampal ERK activation, suggest the possibility of a broad role for the ERK cascade in the modulation of both short-term and long-term forms of hippocampal synaptic plasticity.

Moreover, regulation of ERK activation in the hippocampus is not limited to neurotransmitter receptors. One of the most widely studied activators of hippocampal ERKs is BDNF; brain-derived neurotrophic factor (BDNF) receptors couple to ERK activation in hippocampal neurons, and the ERK activation contributes to BDNF-induced synaptic plasticity in area CA1 *(89–91).* Other intriguing possible regulators of ERK in the hippocampus include a novel GTPase-activating protein, SynGAP, that potentially links CA^{2+}/calmodulin activation to ERK stimulation via CaMKII inhibition of SynGAP's GTPase-regulating activity *(92).* In addition, reactive oxygen species (ROS), including superoxide, can lead to ERK activation in the hippocampus *(93).*

A Model for n-Way Coincidence Detection

Especially intriguing is the possibility that this signal integration may not simply serve to sum up signals, but rather in some cases serve to allow synergistic effects or coincidence detection. Recent results suggest that ERK-dependent biochemical signal processing is indeed occurring in hippocampal neurons. For example, activation of several G-protein coupled receptors has been shown to cause synergistic ERK activation *(94,95).* These data suggest that multiple mechanisms for kinase activation interact to allow an amplification of subsequent effects. Of course, the activated ERKs then can phosphorylate various substrates. One intriguing candidate is Kv4.2 channels on hippocampal dendrites, which can serve as a postsynaptic activity sensor and modulate cell excitability. In the limit, the triggering of NMDA receptor-dependent synaptic plasticity in the hippocampus might depend on four signals: two modulatory neurotransmitter inputs coupled with glutamate at the synapse and the triggering of back-propagating action potentials. In this scenario the biochemistry, physiology, and cellular anatomy of hippocampal pyramidal neurons would all contribute to a capacity for sophisticated information processing.

Model for E-S Potentiation

Since transient K^+ currents are highly expressed in the dendrites of hippocampal pyramidal neurons, they most likely shape input processing, specifically regulating the propagation of the synaptic events to the cell soma. Two general physiologic effects are observed in LTP expression. The first is an increase in the amplitude of the excitatory postsynaptic potential (EPSP). A second manifestation of LTP is increased postsynaptic excitability, or E-S potentiation *(96,97).* The mechanisms underlying the LTP-associated increase in neuronal excitability are unknown. One established possibility is a reduction in inhibitory inputs to the postsynaptic neuron *(98,99).* Another intriguing possible explanation is a decrease in spike latency after LTP induction *(100–102),* a response possibly achieved by reduction of a transient outward current such as those mediated by Kv4.2. This reduction could occur through phosphorylation of the channel *(13)* or by other means described earlier. In addition, these same mechanisms are likely relevant to effects induced by direct activation of neuromodulatory receptors *(103–105).*

Back-propagating action potentials are necessary for LTP in hippocampal slices *(106),* suggesting they may play a role in learning and memory. Recent work by Quirk et al. *(107)*

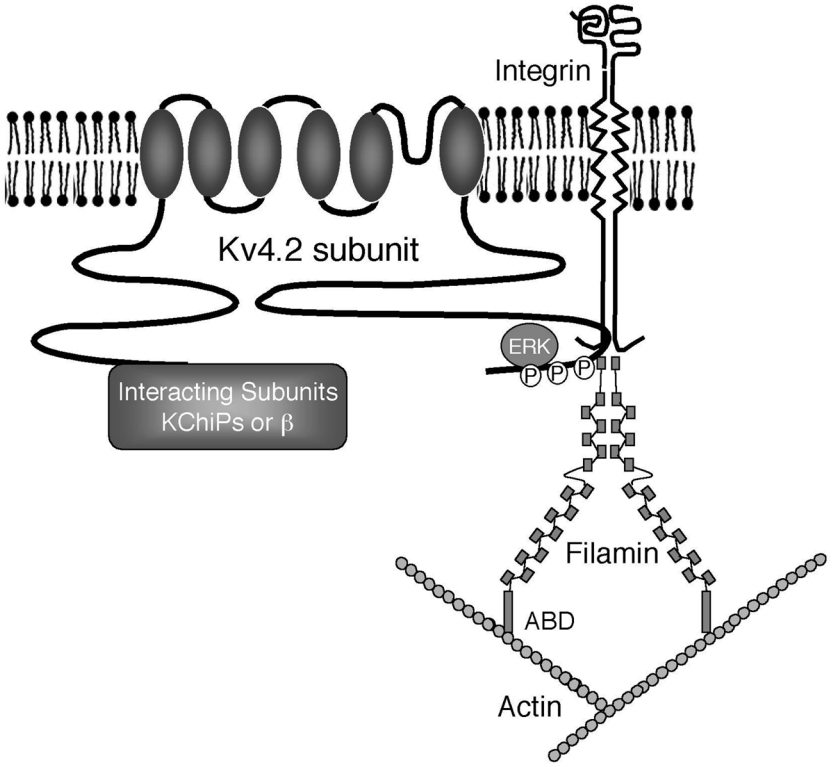

Fig. 1. Schematic diagram of proposed Kv4.2 molecular complex. One primary α subunit of Kv4.2 is shown with six transmembrane domains. The β and/or KChIP subunit interacts with the N-terminal of the α subunit. The C-terminal of the α subunit contains the three ERK phosphorylation sites and interacts with filamin. Filamin contains an actinbinding domain (ABD), which mediates binding to actin. Integrin also interacts with filamin. Integrin may be the protein that couples G-protein-coupled receptors to ERK activation.

has shown a correlation between learning behavior and back-propagating spike amplitude. They demonstrated that an experience-dependent reduction in extracellular spike amplitude during normal exploring behavior may be determined by dendritic back-propogating action potentials and that amount of attenuation is reduced with an animal's experience in an environment. Furthermore, the reductions are dependent on NMDA receptors, suggesting that the learning mechanisms during behavior are sufficient to alter the intrinsic membrane properties of hippocampal cells.

We suggest that the modulation of LTP induction by ERK activation is mediated partially through signal integration including the regulation of the dendritic transient K^+ channels and subsequently regulation of back-propagating action potentials. As mentioned earlier, the peak of back-propagating action potentials is modulated by kinase activation through regulation of transient K^+ currents in hippocampal dendrites *(13).* Particularly interesting is that in mice the activation of the ERK/MAPK cascade appears to be involved in LTP induced by repetitive stimulation but not by a single high-frequency stimulation; with prolonged high-frequency stimulation, the transient A-type current would be inactivated after the few stimuli and not recover, and thus is not expected to play a role in LTP induction. On the other hand, the current has the ability to recover from inactivation during repetitive

stimulation, and can potentially play a role in the modulation of EPSP amplitude and back-propagating action potentials and subsequent plasticity induction in this type of LTP-inducing paradigm. In this latter scenario, the ERK/MAPK signal transduction cascade may serve to "funnel" modulatory signals into Kv4.2, in order to achieve a coordinated and cohesive output at the level of membrane excitability, and thus regulate the probability of LTP induction.

Cellular Excitability and Hebb's Postulate

The 'Hebbian' synapse provides a theoretical cellular construct for triggering synaptic change *(108).* In order for increases in synaptic efficacy to occur, a "coincidence detector" that perceives the temporal correlation of pre- and postsynaptic activity is required. In this review, we have presented several potential molecular mechanisms for coincidence detection involving signal-transduction mechanisms as well as regulation at and by K^+ channels at several levels. Our overall view is that precise neuromodulation of postsynaptic dendritic excitability may be an important regulator of the likelihood of triggering Hebbian synaptic plasticity in the hippocampus.

Figure 1 is a schematic drawing of the K^+ channel complex that we propose may play an important role in signal integration in the dendritic compartment of hippocampal pyramidal neurons. Kv4.2 is shown with its interacting subunits (KChIP and β subunits) that influence channel kinetics and can be modulated by various kinases or redox regulation. In addition, Kv4.2 is associated with filamin, which anchors it to the actin cytoskeleton and integrin, which can couple activation of neurotransmitters receptors to ERK. Each element provides another level of regulation of the K^+ channel and hence, postsynaptic cell excitability. Future studies will, it is hoped allow a fuller understanding of the regulation of this complex and its role in controlling the genesis of altered synaptic function.

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