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Dendritic ion channel trafficking and plasticity

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Abstract

Dendritic ion channels are essential for the regulation of intrinsic excitability as well as modulating the shape and integration of synaptic signals. Changes in dendritic channel function have been associated with many forms of synaptic plasticity. Recent evidence suggests that dendritic ion channel modulation and trafficking may contribute to plasticity-induced alterations in neuronal function. In this review, we discuss our current knowledge of dendritic ion channel modulation and trafficking and their relationship to cellular and synaptic plasticity. We also consider the implications for neuronal function. We argue that to gain an insight into neuronal information processing, it is essential to understand the regulation of dendritic ion channel expression and properties.

1. Dendrites and plasticity

Dendrites are extensive and elaborate processes emerging from the cell body of neurons. They occupy a large surface area and receive most synaptic inputs1. Their predominant function is in processing and transmitting synaptic signals to the cell body and axon initial segment, where, if threshold is reached, action potentials are initiated. This is an active process, as it is known that dendrites possess an abundance of ion channels that are involved in receiving, transforming and relaying information to other parts of the neuron[1]. These dendritic ion channels often differ in their biophysical properties and densities from those present in other neuronal compartments. Moreover, ion channel expression and properties may also differ within the dendritic arbor of neurons – e.g. hyperpolarization-activated cation non-selective (HCN) channels are expressed highly in the apical, but not the basal, dendritic tree of layer V cortical pyramidal neurons[2]-4. This adds an additional layer of complexity to neuronal information processing.

It is now evident that dendritic ion channel expression and properties are modulated by induction of Hebbian (including long-term potentiation (LTP) and long-term depression (LTD)) as well as homeostatic (non-Hebbian) forms of plasticity (for reviews see Refs. [5-7]). Hebbian forms of plasticity are input specific changes in synaptic strength that largely involve postsynaptic Ca^{2+} entry through voltage-sensitive N-methyl-D-aspartate receptors (NMDAR; known as NMDAR-dependent plasticity). This Ca^{2+} influx also activates intracellular signaling pathways that modify dendritic ion channel activity, local excitability and, perhaps, cell-wide excitability, or “intrinsic plasticity”[8, 9] (Figure 1). Often these activity-dependent changes in dendritic ion channel function are stabilizing and limit the extreme neuronal activity (spiking) that might otherwise result from sustained synaptic

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efficacy. This "homeostatic plasticity"[10] provides negative feedback control of Hebbian synaptic plasticity. Moreover, during synaptic plasticity altered expression and function of dendritic ion channels, through their effects on membrane polarization, may also influence the threshold for further induction of plasticity, or metaplasticity[7-9], providing a local mechanism of control over cell excitability.

Some of the activity-dependent changes in dendritic ion channel function described above are likely to be a consequence of altered post-translational modifications as well dendritic channel trafficking (Figure 1). Recent evidence suggests that selective targeting mechanisms determine the distribution and properties of dendritic ion channels[11]. Specific molecules are involved in the transport of ion channel subunits from the soma to dendrites. Additionally, mRNAs encoding ion channels can be trafficked into dendrites and locally translated, a process which may be activity-dependent[12]. Indeed, dendrites contain the necessary machinery that enables local protein synthesis[13]. Hence, expression of ion channels can be dynamically modified in dendrites in response to synaptic activity. This active modulation of ion channel function may present a sophisticated mechanism by which neurons regulate information flow and thereby, neuronal output.

Here we review recent reports on dendritic voltage-gated ion channel targeting mechanisms and plasticity, omitting ligand gated ion channel trafficking and plasticity as there have been many recent reviews on this (for example see[14, 15]). We begin by presenting an overview on how ion channels affect dendritic intrinsic excitability and synaptic integration.

2. Role of dendritic ion channels in regulating intrinsic excitability, synaptic integration and plasticity

Dendrites contain a plethora of ion channels including K^+ channels. In many central neurons, the densities of most voltage-gated potassium (K_v) channels appear to be uniform or lower in distal dendrites compared with those present at the soma[1]. One exception appears to be the K_v4 subunit. Immunohistochemical analysis first showed a predominantly dendritic localization of K_v4 channels[16] (Table 1). The K_v4 subunits form a fast activating and inactivating current in heterologous systems, reminiscent of the A-type K^+ current (I_A) in neurons[17]. Consistent with the immunohistochemical observations, electrophysiological data together with pharmacology and calcium imaging have shown that A-type K^+ channels are more efficacious in the apical[18-21], radial oblique[22,23] and basal[4,23,24] dendrites than the soma of several types of central neurons. Here, A-type K^+ channels play an important role in determining the amplitude and width of back-propagating action potentials[18,19,25]. They also limit the propagation of local dendritic spikes generated by spatially clustered and temporal synaptic input[23] and curtail dendritic Ca^{2+} signals generated by synaptic input or by back-propagating action potentials22-[24]. Thus, these channels affect forms of plasticity that depend on back-propagating action potentials or the propagation of local dendritic spikes (i.e. spike timing-dependent plasticity)[23],26. In addition, in hippocampal neurons, altering $K_v4.2$ channel expression leads to an activity-dependent remodeling of synaptic NMDAR subunit composition and consequentially the ability to induce synaptic plasticity[27], suggesting that regulation of these channels may act as a metaplasticity mechanism.

In contrast to K_v4 channels, neuronal $K_v2.1$ channels conduct delayed rectifier (I_K) currents that have a high threshold of voltage activation and slow kinetics[28]. $K_v2.1$ channels are found in many mammalian central neurons including hippocampal and cortical pyramidal cells (Table 1), where they appear to be localized to the somatodendritic compartment[28] (but see Ref. [29]). Typically delayed rectifier currents have the primary role of repolarizing the membrane after action potentials. However, the activation and inactivation properties of $K_v2.1$ suggest these channels are too slow for the regulation of single action potentials and

instead influence repetitive spiking[30]. In support of this, knockdown of $K_v2.1$ did not alter the shape of single action potentials but did cause hyperexcitability after repetitive (1 Hz) stimulation in hippocampal pyramidal cells[31]. $K_v2.1$ channels may therefore play an important role in dendritic integration, by suppressing hyperexcitability as repetitive signals approach the soma, and potentially contributing to homeostatic plasticity.

Dendrites and spines of several central neurons also contain calcium-activated potassium (K_{Ca}) channels[32-35]. Intriguingly $K_{Ca}2$ (small conductance calcium-activated potassium or SK) channels are located in close proximity to synaptic and extra-synaptic glutamate receptors, suggesting a synaptic function (Table 1). Indeed, these channels reduce dendritic integration by restricting compartmentalized Ca^{2+} spikes (plateau potentials) triggered by strong synaptic input[33]. In the hippocampus32 and the amygdala34, Ca^{2+} influx through NMDA receptors activates $K_{Ca}2$ channels, hyperpolarizing the membrane and promoting the NMDA receptor Mg^{2+} block, limiting further activation. This $K_{Ca}2$-mediated negative feedback on NMDA receptors therefore impacts the induction of Hebbian plasticity. Consistent with this model, pharmacological downregulation of $K_{Ca}2$ enhances[36], while the genetic upregulation of $K_{Ca}2$ impairs[37], hippocampal LTP induction and memory encoding.

Inwardly-rectifying K^+ (K_{ir}) channels are another group of K^+ channels that are expressed throughout the CNS including the apical dendrites of neocortical and hippocampal CA1 neurons[38-41] (Table 1). K_{ir} channels are characterized by their unidirectional inward rectification that is gated by an intracellular cation block[41]. Therefore, at membrane potentials more negative than rest, K_{ir} channels pass an inward current, returning the membrane to resting potential. However, at potentials more positive than rest, cations prevent an outward K^+ current from hyperpolarizing the cell membrane. These fundamental rectification properties of K_{ir} channels are essential in maintaining neuronal membrane potential. Of the seven K_{ir} subfamilies, $K_{ir}3.x$ channels are unique in their activation by G-protein coupled receptors (GPCRs). Specifically, G_i- or G_o-type GPCRs, such as $GABA_B$ receptors, activate $K_{ir}3$ channels[41-43]. Which particular GPCRs interact with $K_{ir}3.x$ is potentially mediated by their spatial compartmentalization. For example, γ-amino butyric acid B ($GABA_B$) receptors have been observed in close proximity to synaptic $K_{ir}3.x$ channels in spines, but less so in the dendritic shaft[44,45]. Consistent with their synaptic localization, $K_{ir}3.2$ channels mediate slow inhibitory post synaptic currents (IPSCs)[46], which are potentiated following low frequency (3 Hz) stimulation in hippocampal slices. This phenomenon is mediated by $GABA_B$ receptor activation of Kir3.2 channels, and is NMDAR- and calcium-calmodulin dependent protein kinase II (CaMKII)-dependent[44].

Clearly, K^+ channels play a significant role in shaping dendritic excitability. Dendrites, however, contain a number of other ion channels too. Interestingly, recent evidence shows that the dendrites and spines of hippocampal and cortical neurons contain an exceptionally high density of the hyperpolarization-activated cation non-selective (HCN) channels[47,48] (Table 1). Four subtypes of HCN (HCN1-4) genes exist[49], with HCN1 and HCN2 channels present predominantly in dendrites47,48. These channels have very unusual biophysical properties, in that they are permeable to both Na^+ and K^+ and are activated at potentials hyperpolarized to −50 mV. Hence, they are active at rest and are involved in maintaining the neuronal resting membrane potential (RMP). Their effects on dendritic excitability, though, are complex. Block or knockdown of HCN channels causes RMP hyperpolarization but results in significantly greater numbers of dendritic action potentials, slower excitatory post-synaptic potential (EPSP) decay and enhanced EPSP summation[50-55]. These effects are due to increased membrane resistance51,54 as well as alterations in the biophysical properties of other ion channels such as low voltage-activated Ca^{2+} channels[56] and delayed rectifier K^+ channels[57]. Hence, in spite of the RMP being hyperpolarized, a loss of I_h in distal

hippocampal dendrites gives rise to enhanced LTP[58] and elevated neural network excitability[51],[59].

In addition to HCN and K^+ channels, immunohistochemical studies have demonstrated the presence of the Na^+ channel subunits, $Na_V1.1$, $Na_V1.2$ and $Na_V1.6$ in dendrites and spines of hippocampal CA1 and cortical pyramidal neurons[60]. In agreement with this, electrophysiological studies have revealed Na^+ channels in the dendrites of these neurons[60], where they play a role in potentiating action potential back-propagation[19],[61] and generation of dendritic spikes[62] (Table 1). Action potential back-propagation and initiation of dendritic spikes are critical for the induction of some forms of Hebbian plasticity[9],[62].

The initiation and expression of many forms of plasticity also often involves Ca^{2+} entry through voltage-gated Ca^{2+} channels (VGCC). To date, ten VGCC primary subunits have been cloned[63]. Immunohistochemical as well as electrophysiological studies have revealed the presence of all subtypes of VGCC in dendrite shafts60. Further, multiple subtypes of VGCC have been found in dendritic spines in numerous cell types64 (Table 1). VGCC opening is enhanced by action potential backpropagation, synaptic potentials and action potential backpropagation, sometimes leading to the initiation of Ca^{2+} spikes and plateau potentials[60],[65],[66]. These properties allow VGCCs to regulate the induction of synaptic plasticity[60],[65],[66]. Indeed, Ca^{2+} entry through dendritic VGCC is necessary for LTD in entorhinal cortical cells[67] and hippocampal CA1 neurons[68], as well as for LTP at hippocampal CA1- perforant path synapses[66] and hippocampal CA1-schaffer collatoral synapses[69]. Moreover, Ca^{2+} influx via $Ca_V1.x$ (L-type) Ca^{2+} channels in dendritic spines contributes to induction of synapse specific NMDA receptor- dependent LTP in hippocampal neurons[70]. Hence, the presence of voltage-gated ion channels in dendrites plays a vital role in determining their intrinsic excitability as well as shaping synaptic inputs and integration and thereby induction and maintenance of plasticity.

3. Plasticity-induced post-translational modifications and membrane trafficking of dendritic ion channels

Cellular neuroplasticity has been hypothesized to underlie experience-dependent behaviours such as learning and memory and drug addiction (Figure 1). Uncovering the cellular and molecular mechanisms of the acquisition, storage and recollection of memories is a major topic of basic and translational neuroscience research, as alterations in these mechanisms may contribute to multiple disease pathologies, including autism, epilepsy, Alzheimer's and Parkinson's disease. For the most part, regulation of individual synaptic input strength (synaptic plasticity) has received the most attention with a focus on the trafficking and properties of the neurotransmitter receptors themselves (α–amino-3-hydroxyl-5-methylisoxazole-4 propionate receptors (AMPARs) and NMDARs). However, a confluence of recent evidence indicates that subsequent to receptor activation, synaptic responses are regulated by dendritic voltage-gated channels and that these channels themselves are targeted for modulation. To fully understand how these channels contribute to various forms of plasticity is it critical to determine how their biophysical properties and subcellular localization are modulated.

3.1 Post-translational modifications

Since many forms of cellular and synaptic plasticity result in altered activity of kinases and phosphatases, it is perhaps not surprising that activity-dependent changes also affect dendritic channel expression and properties (Figure 1). In distal CA1 dendrites, protein kinase A (PKA), protein kinase C (PKC) and extracellular-signal regulated kinase/mitogen-activated protein kinase (ERK/MAPK) all downregulate A-type K^+ channel activity,

resulting in enhanced action potential propagation[71,72] (Table 1). In addition, LTP induction in hippocampal slices shifts the voltage-dependence of steady-state I_A inactivation leftward [73]. These modulations both have the effect of increasing local dendritic excitability and enhancing action potential back propagation, which would lead to a change in the ability to induce subsequent potentiation (metaplasticity).

Moreover, $K_v2.1$ channels have a fascinating profile of phosphorylation-regulated activation. Not only does dephosphorylation of the channel by PP2B (protein phosphatase 2B- also known as calcineurin; Table 1) cause a hyperpolarized shift in its voltage-dependent activation[74], but it does so in a graded manner. Using a proteomics approach, 16 phosphorylation sites were identified on the $K_v2.1$ channel, 7 of which are dephosphorylated by PP2B. The more sites dephosphorylated, the greater the shift in activation, with complete dephosphorylation yielding a large (~35 mV) hyperpolarized shift[75]. With their slow kinetics, such changes in activation would likely produce more $K_v2.1$ channels being activated during repetitive stimulation, and would subsequently suppress spiking during instances of neuronal excitability, providing a mechanism of homeostatic plasticity[29].

Despite its lack of voltage-dependence, $K_{Ca}2.2$ (SK2) channel activation is also regulated through the phosphorylation state of its multiprotein complex. $K_{Ca}2.2$ channel activation occurs when Ca^{2+} binds calmodulin (CaM), which is itself constitutively bound at the channel C-terminus[76]. Also associated constitutively with $K_{Ca}2.2$ is casein kinase II (CK2) and protein phosphatase 2A (PP2A), which regulate the phosphorylation of $K_{Ca}2.2$-bound CaM[77]. While CaM phosphorylation by CK2 leads to faster channel deactivation and a reduced Ca^{2+}-sensitivity, dephosphorylation by PP2A increases Ca^{2+} sensitivity. Interestingly, phosphorylation of CaM by CK2 is Ca^{2+}- and state-dependent, only occurring when the channels are closed. The net result is a system of bidirectional modification of $K_{Ca}2.2$ channel activation, where during low activity (with infrequent Ca^{2+} signals) activation is reduced by CK2 and during repetitive stimulation or synaptic activity (with sustained Ca^{2+} signals) channel activation is enhanced by PP2A.

Similar to K_v and K_{Ca} channels, the resting state of HCN channels may also be regulated by phosphorylation. Several modulators, including 3′,5′-cyclic adenosine monophosphate (cAMP) and phosphoinositides, have been found, all of which shift the activation curves of HCN channels[49]. Hence, variation in the activity of these molecules by GPCR activity or synaptic strength would result in altered gating of these channels, leading to changes in synaptic potential shapes and integration, thereby augmenting the intrinsic excitability of neurons. Indeed, an elegant study by Wang *et al*. (2007) demonstrates that in spines of prefrontal cortical neurons, activation of α2 adrenoreceptors leads to a reduction in cAMP activity and HCN function (Table 1), thereby potentiating EPSP integration and elevating neuronal firing, eventually causing an increase in working memory[59].

Many forms of plasticity involve depolarization of dendrites leading to opening of Ca^{2+} and Na^+ channels. Na^+ channels located in dendritic trunks are present in a phosphorylated state in some neurons[78]. An altered balance of kinases and phosphatases caused by changes in GPCR activity might lead to a change in the activation and inactivation curves of these channels. This would affect the initiation and back propagation of dendritic spikes, and could thereby alter the threshold for certain types of plasticity, such as spike-timing dependent plasticity. GPCR activity may also regulate the resting state of Ca^{2+} channels. Indeed, in hippocampal spines, activation of PKA by stimulation of β2-adrenoreceptors has been demonstrated to facilitate $Ca_V1.x$ (L-type) Ca^{2+} channel activity[79], thereby priming the induction of synaptic plasticity. Interestingly, these same pathways may also cause depression of other Ca^{2+} channel subtypes and block LTP[80]. Hence, the phosphorylated

states of voltage-dependent ion channels in dendrites are critical for the generation of plasticity. This may also affect the maintenance of plasticity and thus, metaplasticity.

Throughout this section we have focused on regulation of ion channels by protein phosphorylation. However, it is likely that future research will uncover other forms of post-translational modifications (e.g. ubiquitination and palmitoylation) that contribute to dendritic ion channel sorting and localization and are therefore also potential sources of activity-dependent regulation of dendritic excitability.

3.2 Membrane trafficking – Potassium channels

In addition to post-translational modification of channel properties, active trafficking of dendritic ion channels also influences cellular and synaptic plasticity (Figure 1). For example, Kv4.2 channels are internalized from the dendritic membrane during synaptic plasticity (Figure 2). In hippocampal slices, K_V4.2 channels are internalized after LTP induction with a pairing protocol, and in cultured neurons with activation by AMPA, potassium chloride (KCl,) or glycine[81]. In this study, internalization was measured by a decrease in membrane-bound K_V4.2, a reduction in I_A, and by real-time observation of green fluorescent protein (GFP)-tagged K_V4.2 redistributing from the dendritic spine to the shaft (Figure 2B). These effects were also NMDAR-dependent, supporting the model that K_V4.2 internalization occurs during Hebbian synaptic plasticity. The mechanism of K_V4.2 internalization likely involves clathrin-mediated endocytosis, since blocking dynamin recruitment to clathrin-coated pits prevented GFP-Kv4.2 redistribution and I_A reduction.

Multiple proteins mediate K_V4.2 targeting and membrane expression, and these molecules may also play a role in its activity-dependent trafficking. The dendritic targeting of K_V4.2 subunits is dictated by a C-terminal dileucine motif [82], and K_V4.2 is transported by the motor protein Kif17, a kinesin isoform that binds to the extreme C-terminal end of the channel[83]. K_V4.2 cell surface expression is further regulated by a number of auxiliary subunits, including K_V4 channel interacting proteins (KChIPs) and dipeptidyl peptidase-like type II proteins, DPP6 and DPP10[28], which bind to the N-terminus84 and S1/S2 domains85 of K_V4.2, respectively. An intriguing avenue for future research will be to uncover how post-translational modifications and membrane expression are related. For example, PKA phosphorylation of K_V4.2 is required for activity-dependent internalization[86]. But does phosphorylation trigger internalization or is it simply required for membrane localization of the mobile pool of channels? Additionally, how do post-translational modifications interact with auxiliary subunits to affect channel complex expression and properties? Auxiliary subunits themselves could be targets for modulation. For example, it has been recently shown that K_V4.2 primary subunit phosphorylation may be required for the auxiliary protein KChIP4a to regulate channel properties[87].

Similar to K_V4.2, K_{Ca}2.2 channels are also internalized during LTP (Figure 2A, Table 1)[88]. In hippocampal slices, K_{Ca}2.2 channels are internalized after chemically-induced LTP or after physiologically-relevant LTP induction by theta burst stimulation[88]. This process also requires NMDAR activation and involves channel phosphorylation by PKA[88]. Clathrin-mediated endocytoysis of K_{Ca}2.2 subunits has also been demonstrated in lateral amygdala spines in an NMDAR- and PKA-dependent manner following LTP[89]. In this study, the authors suggest there is constitutive dynamin-dependent endocytosis of K_{Ca}2.2 channels, and PKA phosphorylation of the channel during stimulation sequesters it to the cytosolic compartment. The resulting effect is a reduction in functional synaptic K_{Ca}2.2 and enhanced LTP.

The expected consequence of reducing K^+ channel density during synaptic activity is to enhance dendritic excitability and reduce the probability of further LTP induction. But what

is the fate of $K_v4.2$ and $K_{Ca}2$ channels after activity-dependent internalization? Are they recycled back into the membrane or degraded? If the former, is reinsertion also subject to activity-dependent regulation? The spatial restriction of signaling events that trigger dendritic ion channel trafficking during plasticity is also unclear. That is, is internalization compartmentalized to the spine or could extensive spread contribute to intrinsic plasticity?[90] Recent reports show that some NMDAR-activated signalling molecules like the guanosine triphosphatase Ras spread over 10 micrometers of dendrite and invade neighbouring spines[91] whereas others, such as CaMKII, remain restricted to the activated spine [70]. Recent advancements in fluorescent protein labeling and live cell imaging techniques may soon provide answers to such questions.

Interestingly, the same neuronal activation that reduces surface expression of $K_v4.2$ and $K_{Ca}2.2$ channels increases the surface expression of K_{ir} channels (Figure 2A, Table 1). In hippocampal neurons, activation with KCl, glutamate, NMDA, or glycine reduces the surface expression of endogenous $K_{ir}3.1$ and $K_{ir}3.2$ channels[92]. This occurs through NMDAR-dependent activation of protein phosphatase 1 (PP1), which dephosphorylates $K_{ir}3.1$-2 channels, causing their insertion into the membrane from recycling endosomes[92]. This NMDAR-dependent insertion of $K_{ir}3.1$-2 channels may also regulate depotentiation of synapses, an input-specific and NMDAR-dependent form of synaptic plasticity important in maintaining bidirectional modification of synapses. In a recent study, Chung *et al*[93] demonstrate that depotentiation of hippocampal synapses requires the activation of adenosine A_1 receptors, PP1 and $K_{ir}3.1$-2 channels- suggesting that the activity-dependent insertion of $K_{ir}3.1$-2 channels into the membrane may contribute to the mechanism of depotentiation.

Together, these exciting findings raise the possibility that the input specificity of synaptic plasticity may in part be mediated by alterations in local dendritic K^+ channel expression. Regulation of local protein synthesis and lateral translocation of K_v channels are also mechanisms by which their differential expression occurs. In hippocampal neurons, local $K_v1.1$ channel translation in dendrites is upregulated upon NMDA receptor inhibition, suggesting that activity can regulate K^+ channel expression (Table 1)[94]. Moreover, in hippocampal pyramidal neurons, clustered somatodendritic $K_v2.1$ channels disperse laterally along the membrane after neuronal stimulation and dephosphorylation by PP2B (calcineurin) (Figure 2, Table 1)[74,95,96]. This dephosphorylation and translocation is accompanied by a hyperpolarizing shift in the activation and inactivation of $K_v2.1$[96,97], enhancing the influence of $K_v2.1$ during repetitive firing. Interestingly, this effect is mediated by the activation of extrasynaptic NMDARs, and may be important for the regulation of intrinsic excitability of neurons during excitotoxic events[95-97].

3.3 HCN channel targeting and plasticity

Like K^+ channels, Hebbian plasticity at selective synapses results in activity-dependent alterations in HCN channels. Induction of NMDA-receptor dependent LTP via a theta burst protocol enhances HCN expression in hippocampal CA1 neurons[98,99]. This effect is dependent on Ca^{2+} entry via NMDAR activation of CaMKII (Figure 3, Table 1)[99]. Conversely, metabotropic glutamate receptor-dependent LTD results in reduced HCN expression due to Ca^{2+} release from internal stores and activation of PKC (Figure 3, Table 1)[100]. Hence, depending on the source and possibly concentration, Ca^{2+} can bi-directionally regulate the membrane insertion of HCN channels.

One outstanding question is whether the plasticity-induced alterations in HCN function and expression involve post-translational modifications, as has been shown for LTP-induced changes in K^+ channels[81,88,89,92], modulation of auxiliary subunits or variations in local protein synthesis. All three mechanisms may occur. HCN mRNA is abundant in

dendrites[101,102] and the possibility that synaptic activity may influence local protein synthesis (as with $K_V1.1$[94]) or endocytic membrane re-cycling of HCN subunits cannot be ruled out. Excitingly though, HCN channels are actively trafficked to dendrites by binding to chaperone proteins known as TPR-containing Rab8b interacting protein (TRIP8b)[103-106]. Moreover, TRIP8b appears to be essential for membrane expression of HCN channels in hippocampal and cortical dendrites[103,105,106]. Multiple isoforms of TRIP8b have been identified, most of which enhance expression of dendritic HCN subunits[105,106]. All isoforms of TRIP8b also alter the gating of HCN channels[104-106]. TRIP8b, like HCN channels, has phosphorylation consensus sites for a number of kinases[106,107] including CaMKII and PKC, raising the prospect that alterations in the activity of these kinases could dynamically regulate expression of TRIP8b activity and thereby influence HCN channel expression and characteristics at selective synapses and dendritic locations. In keeping with this, activity-dependent loss of TRIP8b and thus HCN channel expression, has been demonstrated to occur following excessive neuronal activity[108].

Moreover, at some synapses HCN channels, and presumably TRIP8b subunits, may be located in close proximity to GPCRs. Activation of these GPCRs may additionally modulate HCN channel activity and expression and so influence the threshold of plasticity. This is certainly the case in pre-frontal cortical neurons, whereby HCN1 channels are co-localized with α2 adrenoreceptors[59]. In these neurons, activation of the α2 adrenoreceptors leads to a decrease in spine cAMP and HCN1 channel activity, resulting in enhanced LTP and working memory[59] (Table 1). This is very intriguing as neither the gating properties nor the expression profile of heterologously expressed HCN1 channels are significantly affected by acute changes in cAMP[109]. Hence, it is possible that this may be due to modulation of accessory subunits such as TRIP8b, again raising the question of whether plasticity-dependent changes of HCN channel function are due to alterations in trafficking and membrane expression of the subunits.

Additionally, there are multiple isoforms of TRIP8b, which are expressed in hippocampal and cortical neurons[105,106]. Interestingly, one of these isoforms inhibits rather than enhances HCN expression[105,106], raising the possibility that plasticity induced changes in HCN channel function may involve an altered balance in the activity of these TRIP8b isoforms. Hence, plasticity may not induce changes in TRIP8b expression *per se* but may simply result in increased activity of one isoform over the others, causing altered HCN subunit membrane expression. These are all open questions that still need to be investigated, perhaps using new tools such as isoform-specific antibodies or transgenic mice lacking selective isoforms.

4. Concluding remarks

In summary, we have discussed above how the activity and expression of dendritic ion channels can be dynamically regulated by alterations in intrinsic neuronal firing and changes in synaptic activity. Whilst enormous strides have been made in understanding how several subtypes of voltage-gated ion channels are selectively targeted to dendrites and how plasticity affects the dendritic trafficking of these channels, much less is known about others. For example, dendritic Na^+ and Ca^{2+} channel function is altered during synaptic plasticity (Table 1)[80,110] but whether these changes in function are due to variations in expression and trafficking of the subunits remains to be explored. Future studies are also required to determine how multiple trafficking events synchronize during plasticity. For instance dendritic ion channels such as $K_V4.2$ and $K_{Ca}2.2$ channels are internalized while AMPA type glutamate receptors are inserted into the membrane during LTP creating a potential traffic jam. Are these events coordinated sequentially or are they independently regulated? Related to this, do the same trafficking events that lead to plasticity-induced changes in one dendritic ion channel trigger alterations in other ion channel properties to

maintain homeostasis? Is mRNA translation co-regulated for different types of dendritic ion channels? Clearly, much remains unknown, and the answers will be especially rewarding, increasing our understanding of dendritic integration, basic biological signalling mechanisms, and cellular and synaptic plasticity.

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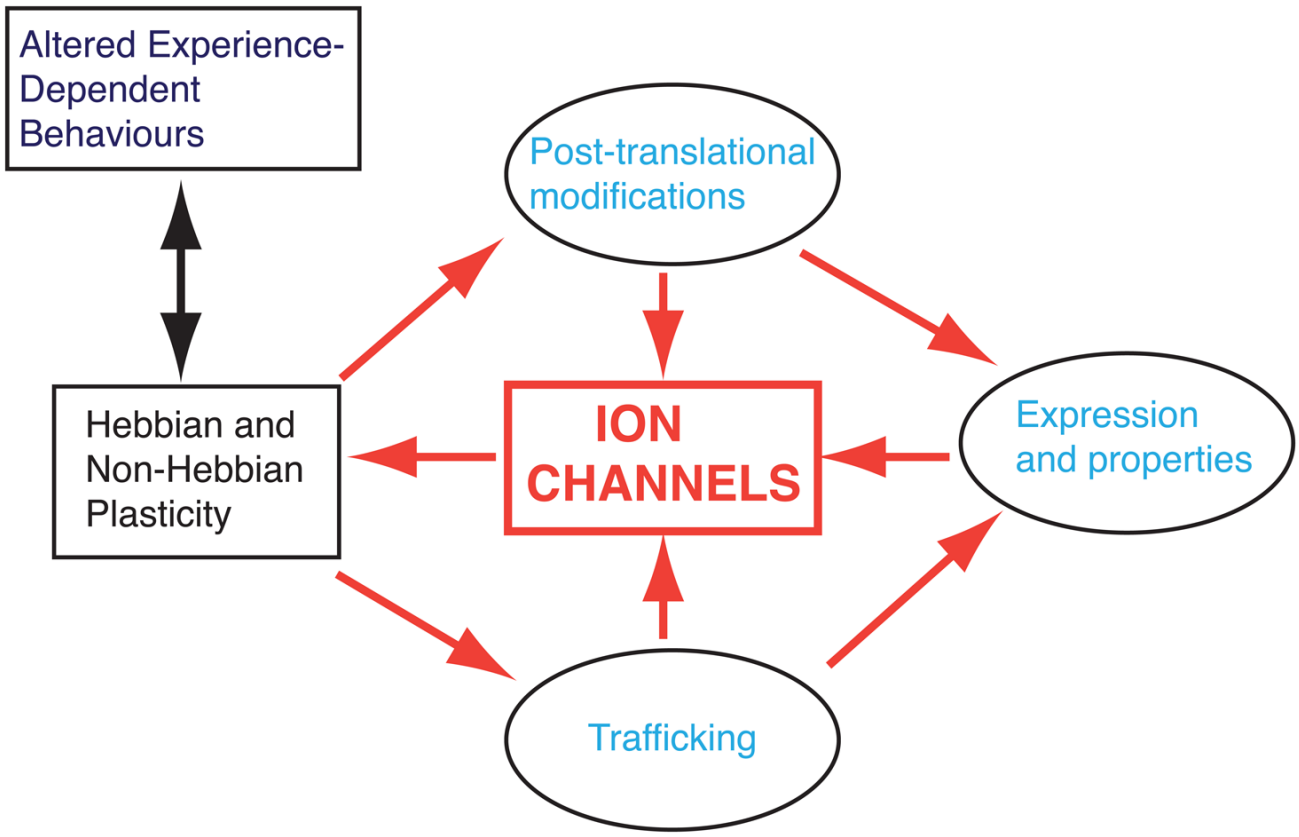

Figure 1. Diagram depicting the reciprocal relationship between ion channel modulation/ trafficking and plasticity

Schematic illustrating the possible mechanisms underlying plasticity induced changes in ion channel expression and properties. Note that dendritic trafficking mechanisms include processes such as local translation as well as endocytosis.

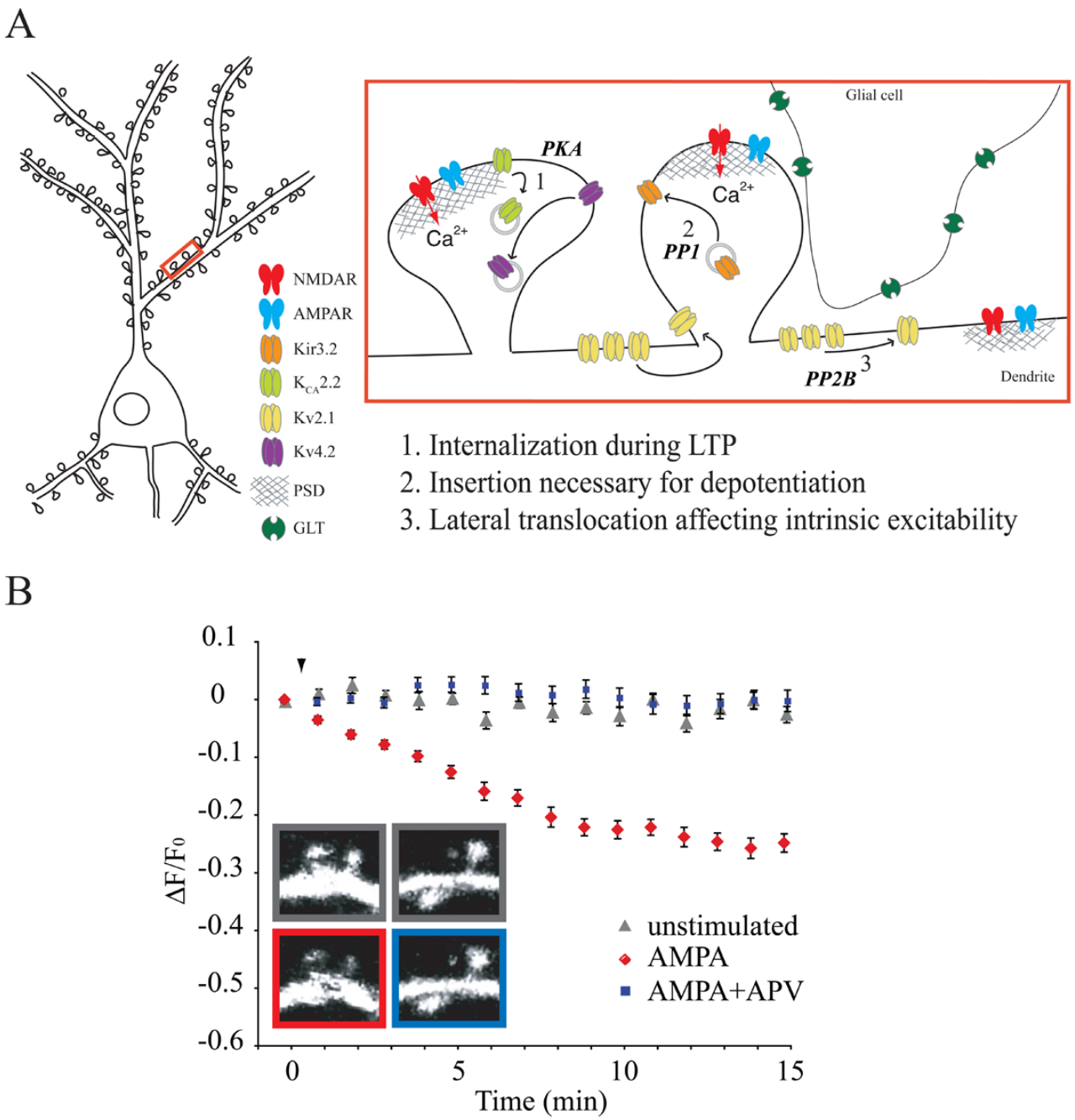

Figure 2. Activity dependent trafficking of K^+ channels

A) A) Illustration depicting the translocation of several K^+ channels in response to common forms of neuronal plasticity. Extrasynaptic $K_V4.2$ channels and $K_{Ca}2.2$ channels located near the post-synaptic density (PSD) are internalized during LTP, requiring Ca^{2+} influx and PKA activation ("1"); $K_{ir}3.2$ channels are inserted into the synapse during depotentiation via Ca^{2+} influx and protein phosphatase-1 (PP1) activation ("2"); and $K_V2.1$ channels de-cluster upon glutamate stimulation, a process dependent on Ca^{2+} influx and protein phosphatase-2B (PP2B) activation ("3"). Glial glutamate transporters (GLT) also influence Kv2.1 dephosphorylation through their regulation of extrasynaptic NMDAR-Kv2.1 channel coupling [96]. **B)** Activity-dependent internalization of the voltage-gated channel $K_V4.2$

requires NMDAR activation. Fluorescence changes are plotted from time-lapse images of spines of hippocampal neurons coexpressing EGFP-tagged $K_V4.2$ and the soluble red-fluorescent protein (tdTomato). AMPA stimulation resulted in a specific, progressive decrease of $K_V4.2$ fluorescent intensity in spines, with no significant change in tdTomato fluorescence (inset). $K_V4.2$ fluorescent intensity was not significantly changed with APV coapplication to block NMDARs. (Adapted with permission from Ref. [81]).

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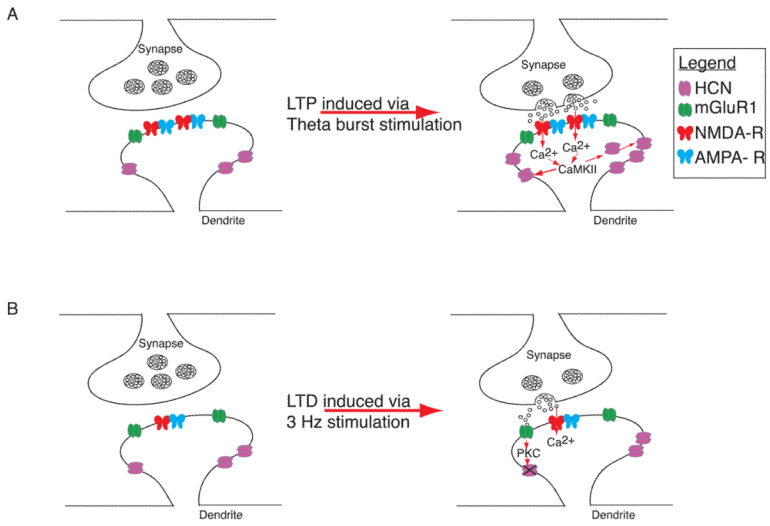

Figure 3. Plasticity induced bi-directional regulation of HCN channels

(A) Model depicting the pathways involved in upregulation of HCN channels following induction of theta-burst LTP in hippocampal neurons. (B) The converse occurs with induction of LTD and is dependent on mGluR activation and thus different intracellular signaling cascades.

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Table 1

Molecules involved in dendritic ion channel trafficking during plasticity

The known mechanisms involved in plasticity-induced changes in a variety of dendritic ion channels are summarized. Question marks indicate unknown mechanisms.

Channel Subtype	Dendritic Localization	Role in dendritic excitability	Type of Plasticity	Second Messenger Required	Trafficking Mechanism	References
$K_V4.2$	Apical, oblique and basal dendrites of several types of central neurons	Determining bAP amplitude and width; limiting propagation of dendritic spikes; curtailing Ca^{2+} influx due to bAP and synaptic potentials.	LTP; chemical neuronal activation (AMPA, KCl, glycine)	PKA activation	Clatherin-mediated endocytosis	[81]
$K_{Ca}2.2$	Apical dendrites and spines of hippocampal and amygdala lateral neurons	Maintenance of membrane potential; limiting NMDA-R activation in spines	LTP; chemical neuronal activation	PKA activation	Clatherin-mediated endocytosis	[88,89]
Kir	Hippocampal and neocortical apical dendrites and spines	Maintenance of membrane potential	Depotentiation (KCl, glutamate, NMDA, glycine)	PP1 activation	Membrane insertion via recycling endosomes	[92,93]
$K_V2.1$	Somato-dendritic compartments as well as AIS	Regulate membrane repolarization following APs	Enhanced neuronal activity	PP2B (calcineurin) activation	Lateral dispersion of subunits	[74]
$K_V1.1$	Hippocampal Dendrites	?	Reduced neuronal activity	mTOR inhibition	Enhanced local protein synthesis	[94]
HCN	Hippocampal CA1 apical dendrites and Spines	Regulation resting membrane potential, EPSP shapes and integration	LTP induced by theta burst stimulation	CaMKII activation	?	[99]
HCN	Prefrontal cortex spines	Regulation resting membrane potential, EPSP shapes and integration	α2 adrenoreceptor mediated	cAMP inhibition	?	[59]
HCN	Hippocampal CA1 apical dendrites	Regulation resting membrane potential, EPSP shapes and	LTD	PKC activation	?	[100]

Channel Subtype	Dendritic Localization	Role in dendritic excitability	Type of Plasticity	Second Messenger Required	Trafficking Mechanism	References
	and spines	integration				
$Ca_V2.3$	Hippocampal Spines	?	LTP	CaMKII activation	?	[80]
Na_V	Apical dendrites	Boosting bAPs and generation of dendritic spikes	Intrinsic Plasticity	CaMKII activation	?	[110]

(Abbreviations: bAP = back-propagating action potential; AP = action potential; EPSP = excitatory post-synaptic potential).