Review

Dendritic ion channel trafficking and plasticity

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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 could 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.

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 inputs [1]. 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 because 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 can also differ within the dendritic arbor of neurons – for example, 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 (reviewed in 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 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, can 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 as of 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. In addition, mRNAs encoding ion channels can be trafficked into dendrites and locally translated, a process that could be activity-dependent [12]. Indeed, dendrites contain the necessary machinery for 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 could 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 because many recent reviews have addressed this topic (e.g. Refs [14,15]). We begin by presenting an overview on how ion channels affect dendritic intrinsic excitability and synaptic integration.

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 at the soma [1]. One exception appears to be the K_v4 subunit. Immunohistochemical analysis first showed a

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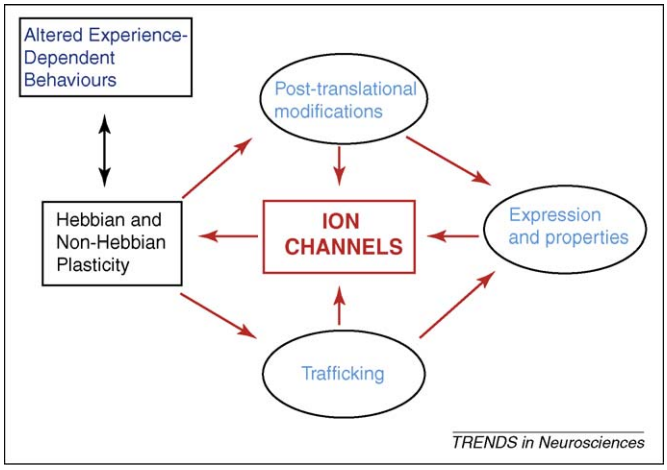

Figure 1. Schematic diagram of the reciprocal relationship between ion channel modulation/trafficking and plasticity, illustrating the possible mechanisms underlying plasticity- induced changes in ion channel expression and properties. Note that dendritic-trafficking mechanisms include processes such as local translation as well as endocytosis.

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 at the soma of several types of central neurons. 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 potentials [22–24]. 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 the regulation of these channels could 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]). Delayed rectifier currents typically have the primary role of repolarizing the membrane after action potentials. However, the activation and inactivation properties of $K_v2.1$ suggest

Table 1. Molecules involved in dendritic ion channel trafficking during plasticity

Channel Subtype	Dendritic localization	Role in dendritic excitability	Type of plasticity	Second messenger required	Trafficking mechanism	Refs
$K_V4.2$	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	Clathrin-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	Clathrin-mediated endocytosis	[88,89]
K_{ir}	Hippocampal and neocortical apical dendrites and spines	Maintenance of membrane potential	Depotentiation (KCl, glutamate, NMDA, glycine)	PP1 activation	Membrane insertion via recycling of endosomes	[92,93]
$K_V2.1$	Somatodendritic compartments as well as AIS	Regulation of 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 of resting membrane potential, EPSP shapes and integration	LTP induced by theta-burst stimulation	CaMKII activation	?	[99]
HCN	Prefrontal cortex spines	Regulation of resting membrane potential, EPSP shapes and integration	α2-adrenoreceptor-mediated	cAMP inhibition	?	[59]
HCN	Hippocampal CA1 apical dendrites and spines	Regulation of resting membrane potential, EPSP shapes and integration	LTD	PKC activation	?	[100]
$Ca_V2.3$	Hippocampal spines	?	LTP	CaMKII activation	?	[80]
Na_V	Apical dendrites	Boosting bAPs and generation of dendritic spikes	Intrinsic plasticity	CaMKII activation	?	[110]

The table summarizes known mechanisms involved in plasticity-induced changes in a variety of dendritic ion channels. Question marks indicate unknown mechanisms. Abbreviations: bAP, back-propagating action potential; AP, action potential; EPSP, excitatory postsynaptic potential.

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 of hippocampal pyramidal cells [31]. $K_v2.1$ channels could 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 hippocampus [32] and the amygdala [34], 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 on the induction of Hebbian plasticity. Consistent with this model, pharmacological downregulation of $K_{Ca}2$ enhances [36], whereas 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 γ-amino butyric acid type B ($GABA_B$) receptors, activate $K_{ir}3$ channels [41–43]. The particular GPCRs that interact with $K_{ir}3.x$ are potentially mediated by their spatial compartmentalization. For example, $GABA_B$ 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 postsynaptic currents (IPSCs) [46], that 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 both NMDAR- and calcium-calmodulin dependent protein kinase II (CaMKII)-dependent [44].

Clearly, K^+ channels play a significant role in shaping dendritic excitability. Dendrites, however, also contain a number of other ion channels. 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). There are four subtypes of HCN genes (*HCN1–4*) [49], and HCN1 and HCN2 channels are predominantly present in dendrites [47,48]. 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 postsynaptic potential (EPSP) decay and enhanced EPSP summation [50–55]. These effects are due to increased membrane resistance [51,54] as well as to 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, 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, 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 the generation of dendritic spikes [62] (Table 1). Action potential back-propagation and the initiation of dendritic spikes are crucial 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 shafts [60]. Further, multiple subtypes of VGCC have been found in dendritic spines in numerous cell types [64] (Table 1). VGCC opening is enhanced by synaptic potentials and action potential back-propagation, 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 collateral synapses [69]. Moreover, Ca^{2+} influx via $Ca_V1.x$ (L-type) Ca^{2+} channels in dendritic spines contributes to induction of synapse specific NMDAR-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 the induction and maintenance of plasticity.

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

Cellular neuroplasticity has been hypothesized to underlie experience-dependent behaviors 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 because alterations in these mechanisms could 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 different forms of plasticity is it crucial to determine how their biophysical properties and subcellular localization are modulated.

Post-translational modifications

Because 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 leftwards [73]. These modulations both have the effect of increasing local dendritic excitability and enhancing action potential back-propagation, and this 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, seven of which are dephosphorylated by PP2B. The more sites that are 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 probably lead to 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), that is itself constitutively bound at the channel C-terminus [76]. Also associated constitutively with $K_{Ca}2.2$ are casein kinase II (CK2) and protein phosphatase 2A (PP2A) that regulate the phosphorylation of $K_{Ca}2.2$-bound CaM [77]. Whereas CaM phosphorylation by CK2 leads to faster channel deactivation and 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.

As with K_v and K_{Ca} channels, the resting state of HCN channels is also likely to be regulated by phosphorylation. Several modulators including 3',5'-cyclic adenosine monophosphate (cAMP) and phosphoinositides have been found, and all 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 could 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 could 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 crucial for the generation of plasticity. This could also affect the maintenance of plasticity. and thus metaplasticity.

Throughout this section we have focused on the regulation of ion channels by protein phosphorylation. However, it is probable 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.

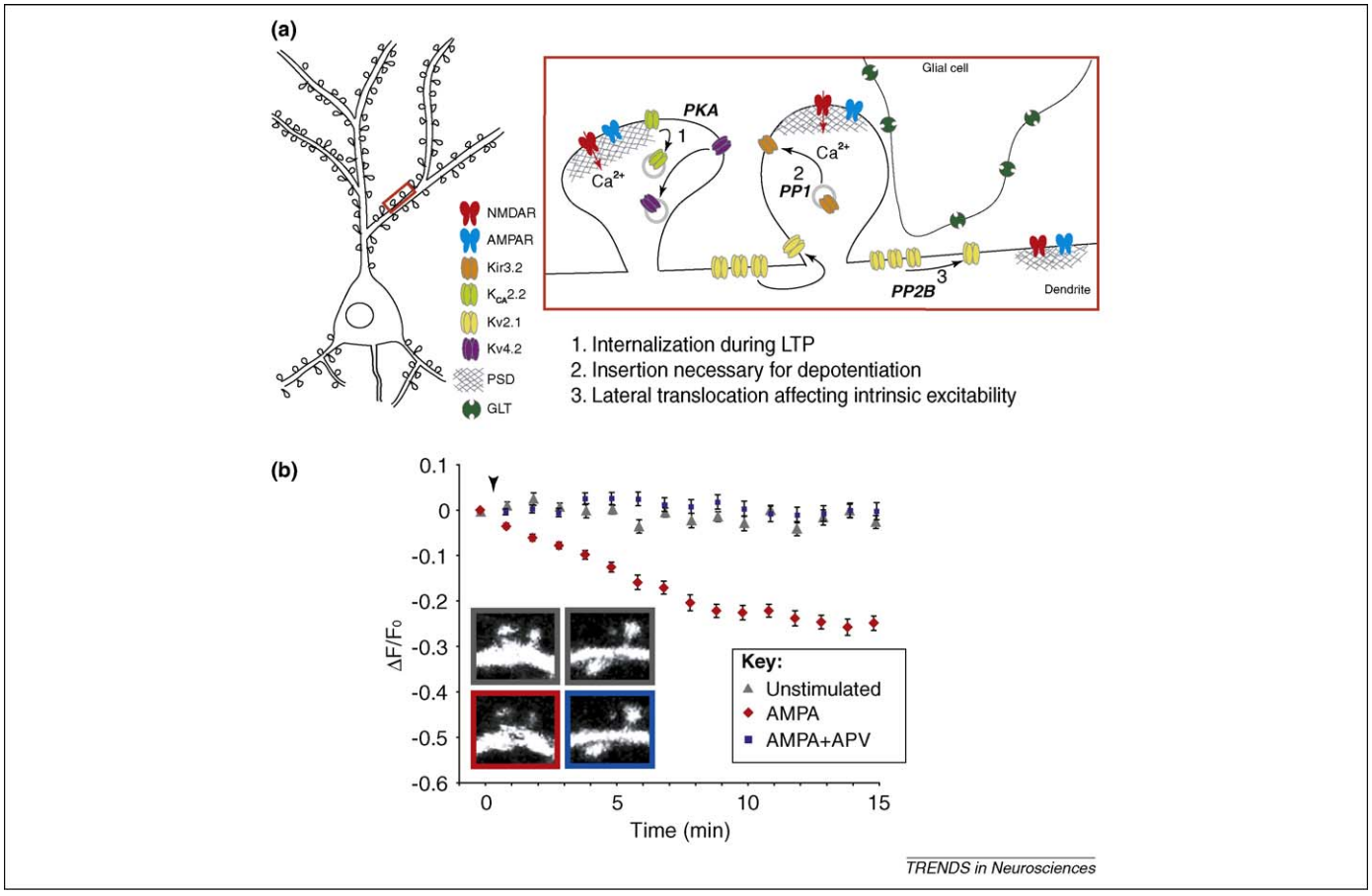

Figure 2. Activity-dependent trafficking of K^+ channels. **(a)** Illustration depicting the translocation of several K^+ channels in response to common forms of neuronal plasticity. Extrasynaptic $K_V4.2$ channels and $K_{Ca}2.2$ channels located near the postsynaptic density (PSD) are internalized 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 and progressive decrease of $K_V4.2$ fluorescence intensity in spines, with no significant change in tdTomato fluorescence (inset). $K_V4.2$ fluorescence intensity was not significantly changed by coapplication of the NMDAR inhibitor [(2*R*)-amino-5-phosphonovaleric acid] (APV) (figure adapted with permission from Ref. [81]).

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 probably involves clathrin-mediated endocytosis because 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 could 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], that bind to the N-terminus [84] and S1/S2 domains [85] 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? In addition, 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 could be required for the

auxiliary protein KChIP4a to regulate channel properties [87].

$K_{Ca}2.2$ channels, like $K_v4.2$ channels, are 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 endocytosis 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 suggested that 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 signaling molecules such as the guanosine triphosphatase Ras are 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 could 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 takes place through NMDAR-dependent activation of protein phosphatase 1 (PP1), that 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 could also regulate the depotentiation of synapses, an input-specific and NMDAR-dependent form of synaptic plasticity important for 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 might contribute to the mechanism of depotentiation.

Together, these exciting findings raise the possibility that the input specificity of synaptic plasticity could 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 takes place. 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 could be important for the regulation of intrinsic excitability of neurons during excitotoxic events [95–97].

HCN channel targeting and plasticity

As with K^+ channels, Hebbian plasticity at selective synapses results in activity-dependent alterations in HCN channels. Induction of NMDAR-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 [99] (Figure 3, Table 1). Conversely, metabotropic glutamate receptor-dependent LTD results in reduced HCN expression due to Ca^{2+} release from internal stores and activation of PKC [100] (Figure 3, Table 1). 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 could occur. HCN mRNA is abundant in dendrites [101,102], and the possibility that synaptic activity could influence local protein synthesis (as with $K_V1.1$ [94]) or endocytic membrane recycling of HCN subunits cannot be ruled out. Excitingly though, HCN channels are actively trafficked to dendrites by binding to a chaperone protein known as TPR-containing Rab8b-interacting protein (TRIP8b) [103–106]. Moreover, TRIP8b appears to be essential for the membrane expression of HCN channels in hippocampal and cortical dendrites [103,105,106]. Multiple isoforms of TRIP8b have been identified, and most of these enhance the 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 the 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 of HCN channel expression, has been demonstrated to occur following excessive neuronal activity [108].

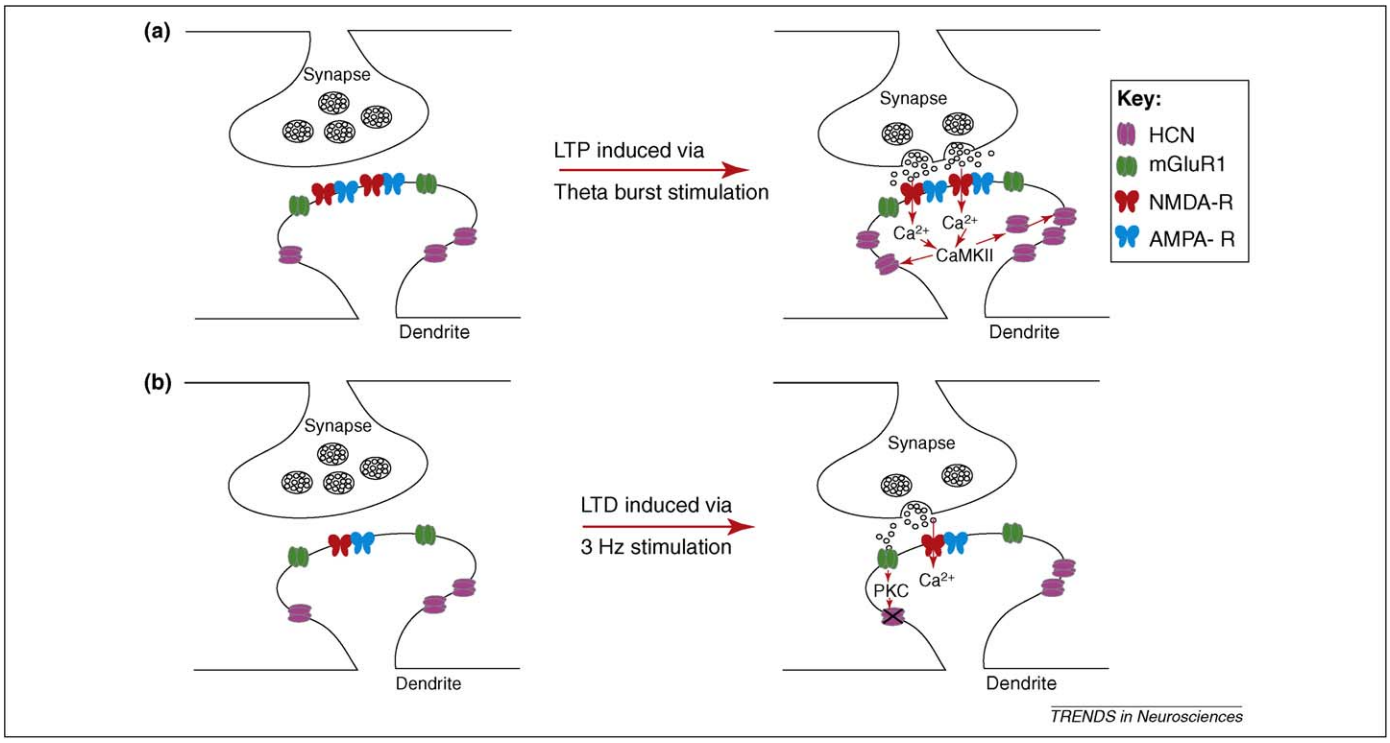

Figure 3. Plasticity induced bi-directional regulation of HCN channels. **(a)** Model depicting the pathways involved in upregulation of HCN channels following induction of theta-burst LTP in hippocampal neurons. **(b)** The converse occurs with induction of LTD and is dependent on mGluR activation and thus different intracellular signaling cascades.

Moreover, HCN channels, and presumably TRIP8b subunits, could be located in close proximity to GPCRs at some synapses. Activation of these GPCRs might also modulate HCN channel activity and expression and so influence the threshold of plasticity. This is certainly the case in prefrontal cortical neurons where HCN1 channels are co-localized with α2 adrenoreceptors [59]. In these neurons, activation of 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 because 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 could 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.

Furthermore, multiple isoforms of TRIP8b 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 could involve an altered balance in the activity of these TRIP8b isoforms. Hence, plasticity might not induce changes in TRIP8b expression *per se* but could simply result in increased activity of one isoform over the others, causing altered membrane expression of HCN subunits. 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.

Concluding remarks

In summary, we have discussed how the activity and expression of dendritic ion channels can be dynamically regulated by alterations in intrinsic neuronal firing and changes in synaptic activity. Whereas 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 [80,110] (Table 1) 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 signaling mechanisms, and cellular and synaptic plasticity.

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