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·Review·

# Roles of somatic A-type $K^+$ channels in the synaptic plasticity of hippocampal neurons

Yoon-Sil Yang[1], Kyeong-Deok Kim[1], Su-Yong Eun[1], Sung-Cherl Jung[1,2]

[1]*Department of Physiology, School of Medicine,* [2]*Institute of Medical Science, Jeju National University, Jeju 690756, Republic of Korea*

Corresponding author: Sung-Cherl Jung. E-mail: jungsc@jejunu.ac.kr



In the mammalian brain, information encoding and storage have been explained by revealing the cellular and molecular mechanisms of synaptic plasticity at various levels in the central nervous system, including the hippocampus and the cerebral cortices. The modulatory mechanisms of synaptic excitability that are correlated with neuronal tasks are fundamental factors for synaptic plasticity, and they are dependent on intracellular $Ca^{2+}$-mediated signaling. In the present review, the A-type $K^+$ ($I_A$) channel, one of the voltage-dependent cation channels, is considered as a key player in the modulation of $Ca^{2+}$ influx through synaptic NMDA receptors and their correlated signaling pathways. The cellular functions of $I_A$ channels indicate that they possibly play as integral parts of synaptic and somatic complexes, completing the initiation and stabilization of memory.

**Keywords:** A-type $K^+$ channels; intrinsic excitability; synaptic plasticity; NMDA receptors; Kv4.2

## Introduction

Synaptic plasticity is the primary candidate for memory and learning mechanisms in the mammalian brain. Because action potentials (APs), the fundamental feature of neurons, critically depend on the spatiotemporal organization of synaptic inputs, it has been hypothesized that synaptic plasticity, such as long-term potentiation and depression (LTP and LTD), is associated with changes in somatic excitability. The intrinsic excitability (IE) of neurons is defined as the ability to fire APs with given certain synaptic inputs. Furthermore, in previous studies, the relationship between the summation of excitatory postsynaptic potentials (EPSPs) and AP firing has often been found to reflect the degree of IE[1-5]. In these studies, enhanced efficiency of EPSP-AP coupling was demonstrated to be a typical property of neurons having high IE, which suggests a possible information-storage mechanism. Although major cellular changes in synaptic plasticity are likely to be restricted to active synapses[6-8], other studies have provided evidence that the induction of synaptic plasticity is accompanied by IE changes[1, 9, 10]. This correlation between synaptic plasticity and IE changes involves potential and concurrent changes in membrane factors, such as voltage-gated ion channels, to regulate the membrane potential.

In mammalian hippocampal neurons, the total outward $K^+$ current can be simply divided into two types, a transient or rapidly inactivating current (A-type current, $I_A$), which is enhanced in dendrites, and a sustained or slow/non-inactivating current expressed at a constant somatodendritic density[1]. Genetic identification in *Drosophila* has revealed that several channel proteins encoded by the *Shal* family of $K^+$ channels (Kv4 channels) underlie the major $I_A$ in the somatodendritic compartment of neurons and show a more hyperpolarized voltage-dependence of gating properties[11, 12], while *Shaker* channels (Kv1) are localized exclusively to muscle cells[13]. For a decade, the Kv subunits contributing to $I_A$ in neurons have been the focus to explain the functions that modulate dendritic signal processing, AP propagation, synaptic integration, and the filtering of fast synaptic potentials[14-19]. In particular, the NMDA-dependent synaptic LTP in hippocampal neurons

regulates the distribution of $I_A$ channels in spines and dendrites, indicating the existence of dynamic and active functions of these channels[2, 20-24]. In addition, $I_A$ channels actively alter the dendritic $Ca^{2+}$ influx during AP back-propagation for dendritic processing in hippocampal pyramidal neurons, indicating that the regulation of back-propagation may be involved in intracellular $Ca^{2+}$ signaling cascades and in the dendritic transmission of synaptic inputs[20-22].

The major functions of $I_A$ channels in dendritic processing and synaptic plasticity are dominantly based on the Kv4.2 subunit[22, 23]. In CA pyramidal neurons, Kv4.2 channels are distributed in dendrites, postsynaptic sites, and the soma, whereas Kv1.4 subunits are expressed in axon branches[25-28]. Therefore, it is possible that the somatic regulation of Kv4.2 subunits and their trafficking may exhibit patterns similar to those in dendrites, where synaptic plasticity activity-dependently regulates the redistribution of Kv4.2 channels in an activity-dependent manner. The functional expression level of Kv4.2 channels in hippocampal neurons plays an important role in the regulation of their suprathreshold excitability[2, 17]. In addition, the Kv4.2, Kv4.3, and Kv1.4 subunits have distinct regulatory properties in the firing pattern of APs in cortical neurons, which indicates that $I_A$ channels play unique regulatory roles in somatic processes under special conditions, such as plasticity or pathogenesis[2]. Therefore, $I_A$ channels expressed in somatic membranes should be considered as active modulators for the IE plasticity of neurons, although somatic signaling regarding EPSPs-AP coupling is systemically and rapidly linked to dendritic and synaptic processing.

The trafficking property of $I_A$ channels is predominantly targeted by the dendritic processes of synaptic transmission and plasticity[2, 23]. In these studies, reduced amplitude of somatic $I_A$, accompanied by enhanced IE after the induction of synaptic LTP, was found in hippocampal slices and cultured neurons. Therefore, the $I_A$-mediated somatic processes during synaptic LTP demonstrate the relations between somatic excitability and memory mechanisms, because the IE changes which accompany synaptic plasticity are associated with information storage. In the present review, three questions raised in previous studies on $I_A$ trafficking are discussed: Why is the somatic localization of $I_A$ channels regulated during synaptic plasticity? How does this regulation take place? What are the implications for learning and memory behaviors? Here, we consider that the redistribution of somatic $I_A$ channels is an important cellular process underlying memory stabilization that is triggered by synaptic plasticity.

## Regulatory Functions of $I_A$ Channels in Excitable Cells

Since the discovery of $I_A$ channels in neurons by Hagiwara and colleagues in 1961[29], their physiological functions have been pursued in myocardial cells and neurons. In both, $I_A$ channels are activated at a subthreshold level (lower than −45 mV membrane potential) and then rapidly inactivated within 100 ms to regulate the cardiac rhythm and neuronal AP firing[30]. Their suprathreshold activation after $Na^+$ channel-induced depolarization during AP firing contributes to the repolarization of the membrane potential *via* the induction of cation outflows from excitable cells, and regulates refractoriness[31, 32]. In addition to the function to regulate membrane potential, the ionic conductance and input resistances of somatic membranes are critically affected by the density of $I_A$ channels as well as hyperpolarization-activated cation channels[17, 33, 34]. Cardiac myocytes are highly sensitive to extracellular $K^+$ concentration, as chemical gradients between the intra- and extracellular compartments determine ion conductance and flow direction[35-37]. This sensitivity is due to the high density of $K^+$ channels in membrane, including $I_A$ channels and inward-rectifier channels, as well as their gating kinetics[38, 39]. In neurons, the determination of input resistance and ionic conductance by $I_A$ channels in turn determines their suprathreshold activity in response to stimuli, although these channels can be activated in the subthreshold range[17, 18, 21, 32, 40]. Virally manipulated Kv4.2 overexpression in neurons significantly delays AP onset and reduces AP frequency in CA1 neurons, while a point mutation of the Kv4.2 subunit enhances the suprathreshold excitability[17]. Interestingly, this experimental manipulation of Kv4.2 expression in cultured hippocampal neurons directly influences CaMKII activation, indicating mediation of the $Ca^{2+}$-signaling cascade[22]. Therefore, the alteration of membrane excitability by $I_A$ channels is likely to be an

important regulator of $Ca^{2+}$ influx through NMDA receptors (NMDARs) or voltage-dependent $Ca^{2+}$ channels (VDCCs) and determines neuronal functions under dynamic conditions.

## Dendritic $I_A$ Channels and Activity-dependent Synaptic Modification

As mentioned above, Kv4 families are localized particularly in dendrites and the soma of neurons in the mammalian CNS[25-28, 41, 42]. Genetic and molecular techniques to manipulate functional Kv4.2 activity have provided direct evidence for Kv4.2 as the molecular identity of $I_A$ channels in CA1 dendrites, and this has been further clarified electrophysiologically in *in-vitro* systems[17, 20, 43].

The density of $I_A$ channels in CA1 dendrites increases with distance from the soma[16]. Moreover, in distal dendrites, these channels increase the probability of channel opening at the resting membrane potential due to their hyperpolarization-shifted conductance of the inactivation curve during synaptic LTP[21]. Blocking $I_A$ channels in dendrites with 4-aminopyridine enhances the back-propagation of dendritic APs and boosts EPSPs[16]. Furthermore, the distribution and gating property of $I_A$ channels in dendrites influences the intracellular $Ca^{2+}$ levels in dendritic branches, as demonstrated by changes in dendritic $Ca^{2+}$ influx during AP back-propagation by the genetic down- or upregulation of Kv4.2[20]. Because NMDA-dependent synaptic plasticity requires $Ca^{2+}$ influx through dendritic NMDARs, the regulatory effects of $I_A$ channels (i.e. Kv4.2) on dendritic excitability are consequential keys for dendritic and synaptic processing during synaptic plasticity. The requirement of the modulatory functions of $I_A$ channels has been demonstrated by a number of studies using theta-burst stimulation protocols that rely on AP back-propagation for LTP induction[18, 20, 24]. These studies have also demonstrated that the LTP threshold is reduced by the downregulation of $I_A$ channels.

The adequate participation of glutamate receptors, including AMPARs and NMDARs, has been considered as the best candidate to support memory and learning mechanisms in mammalian brains. Based on recent evidence, synaptic strength is generally determined by regulation of the postsynaptic surface expression of glutamate receptors[44, 45]. However, the spatiotemporal properties of glutamatergic synaptic inputs determine the activation of voltage-dependent ion channels with respect to the modification of synaptic signals propagating to the axon hillock[46], and the subsequent filtering of glutamatergic transmission by the membrane conductance of dendritic shafts. This is why EPSPs are modified according to the distribution of voltage-dependent ion channels when they are transmitted through dendritic shafts. Amplified EPSPs during propagation easily reach the AP threshold in axon hillocks, while filtered and diminished signals can disappear before reaching the soma. Therefore, it is possible that the activity-dependent regulation of the gating kinetics of dendritic channels and their surface densities are major determinants of whether neurons successfully transfer or modify synaptic inputs and of whether inputs can be stored as information during the induction of memory forms. Interestingly, it has been reported that dendritic $I_A$ channels actively shape synaptic inputs and that the pharmacological blockade of $I_A$ channels strongly enhances the amplitude and summation of EPSPs[16, 18].

With respect to postsynaptic processing in synaptic plasticity, voltage-dependent ion channels located in synaptic sites are efficient targets of activity-dependent regulation, in terms of determining the postsynaptic responses to presynaptic neurotransmitter release in hippocampal neurons. Recently, it has been demonstrated that Kv4.2 subunits expressed *via* the Sindbis virus in primary hippocampal neurons, are localized to spines with higher affinity than to dendritic shafts[17]. Furthermore, electron microscopy confirmed that endogenous Kv4.2 is localized to the spines of adult hippocampal CA1 pyramidal neurons[23]. These channels located in dendritic spines seem to primarily regulate the excitability of postsynaptic membranes, as evidenced by the finding that changes in the expression level of functional Kv4.2 affect the amplitude and frequency of miniature excitatory postsynaptic currents (mEPSCs) and synaptic NMDAR composition[22, 23]. In particular, the induction of synaptic LTP contributes to the activity-dependent internalization of postsynaptic Kv4.2 channels during the insertion of GluR1 receptors into spines, indicating that the trafficking of Kv4.2 subunits in postsynaptic sites is necessary for synaptic plasticity[23]. Furthermore, the internalization of Kv4.2 from spines

is based on clathrin-mediated endocytosis, suggesting that voltage-dependent channels are also subject to the common cellular pathways responsible for regulating the expressions of membrane proteins[2, 23].

## Greater Importance of $I_A$ Channels in Spines for Synaptic Functions and Plasticity

In various types of synaptic plasticity supporting Hebbian memory theory, a common factor for synaptic potentiation is the necessity for a $Ca^{2+}$ rise in postsynaptic sites. This local $Ca^{2+}$ influx requires postsynaptic depolarization as well as the activation of NMDARs[21, 47, 48]. Because depolarization in dendritic or postsynaptic membranes is critically dependent on back-propagating APs, the high dendritic density of $I_A$ channels is considered to be a key factor in reducing the $Ca^{2+}$ influx in postsynaptic sites and dendritic shafts[16, 49]. Furthermore, Chen *et al*. reported a significant increase in dendritic $Ca^{2+}$ influx during AP back-propagation in Kv4.2 knock-out mice, compared with the wild-type[20]. And genetic deletion of the Kv4.2 subunit seems to determine the induction threshold rather than the direction or degree of synaptic plasticity, as evidenced by the lowered threshold for LTP induction in Kv4.2 knock-out CA1 neurons[20]. It has also been demonstrated that the NMDAR composition in synaptic sites is targeted by activity-dependent modulation of Kv4.2 channels, with the synaptic LTP showing increased dependence on NR2B-containing NMDARs in Kv4.2 knock-out mice after the third postnatal week[22]. Further, the functional levels of NR2B and NR2A in synaptic sites are critically higher in Kv4.2 knock-out and wild-type mice at the third postnatal week, respectively, indicating the Kv4.2-mediated remodeling of synaptic NMDAR composition. It is also important that GluR1 subunits activity-dependently replace Kv4.2 subunits in postsynaptic sites during LTP induction[23]. These findings suggest that synaptic LTP is highly dependent on Kv4.2-mediated synaptic signaling to determine both the composition and expression of glutamatergic receptors in postsynaptic sites rather than the dendritic modulations. The significance of $I_A$ channel redistribution for LTP has been experimentally established by disturbing dynamin action in endocytosis; this then abolishes the long-lasting potentiation of synaptic strength *via* blocking Kv4.2 internalization after LTP induction[2, 23].

In both immature and mature neurons of the mammalian CNS, the receptor composition in excitatory synapses is critical to the determination of neuronal functions. In maturation, the developmental replacement of receptor subunits makes silent synapses active and induces synaptic plasticity[50, 51]. Recently, upregulation of NR2B-containing NMDARs in postsynaptic sites in Kv4.2 knock-out mice has been reported to delay the maturation of silent synapses in CA1 neurons[52]. This abnormality in mature neurons is recovered by virally transfecting Kv4.2 channels that enhance NR2A-mediated maturation in the silent synapse. Kv4.2-induced remodeling of synaptic NMDAR composition indicates that these channels participate in determining synaptic function and plasticity by regulating postsynaptic excitability.

## Responses of Somatic $I_A$ Channels to Synaptic Modifications

Regarding the processing of input-output coupling in neurons, the efficiency in firing APs is dependent on the sizes, locations, and timing of synaptic inputs, which are subsequently shaped by the types and distributions of voltage-dependent ion channels in dendrites. Several studies have shown that the induction of synaptic plasticity is accompanied by IE changes, indicating the involvement of concurrent changes in voltage-dependent ion channel activity in the soma membrane[1, 9, 53]. Activity-dependent regulation of IE induced by learning tasks has been reported in various animals[5, 54, 55], and changes in the expression and/or gating kinetics of voltage-dependent ion channels in soma membranes influence IE after synaptic LTP (i.e., intrinsic plasticity)[5]. This contribution of somatic channels to IE modulation is essential for understanding how somatic excitability can be targeted by synapse-specific modifications and how ion channels participate in this cellular processing. In particular, the somatic regulatory functions of $I_A$ channels include AP repolarization, AP broadening, and back-propagation under normal conditions[16, 17]. More specifically, $I_A$ channels are rapidly activated upon depolarization, and thus can affect AP onset time, threshold, and inter-spike interval[56]. These findings indicate that $I_A$ channels are normally crucial for determining somatic excitability and then AP

firing. During synaptic plasticity, the activity-dependent trafficking of $I_A$ channels has also been noted in the soma, in a manner similar to that in dendrites[23]. The redistribution of $I_A$ channels in the somata of hippocampal neurons clearly shows activity- and NMDA-dependence, which are predominant characteristics of glutamatergic synapses for LTP induction. Electrophysiological evidence suggests that the reduction of somatic $I_A$ amplitude is directly correlated with the internalization of $I_A$ channels (Fig. 1), showing a long-lasting reduction of $I_A$ amplitude recorded in nucleated-patched CA1 neurons after LTP induction[2]. The somatic and dendritic redistribution of $I_A$ channels after LTP induction are not likely to occur independently as both are sensitive to the blockade of clathrin-mediated endocytosis[2, 23]. In addition, other homogeneous changes in somatic and dendritic $I_A$ channels are found in the voltage-dependent inactivating kinetics, which is responsible for synaptic LTP. In CA1 dendrites, LTP induction results in a hyperpolarizing shift in the voltage-dependence of the steady-state inactivation curve of $I_A$ in acute hippocampal slices[21]. A similar shift pattern in the gating kinetics of $I_A$ channels immediately following LTP induction, is found in the nucleated-patched soma[2]. This rapid and short-lasting reduction of $I_A$ *via* an inactivation curve shift during the initial period of potentiation can induce an initial and significant enhancement of excitability throughout the neuron. In fact, activity-dependent changes in somatic $I_A$ channels are not unique because various conditioning stimuli for synaptic plasticity actively influence the expression and kinetic properties of several ion channels[1, 53, 57-60]. Furthermore, it is possible that the $I_A$-mediated enhancement of somatic excitability directly affects the properties and/or expression of other voltage-dependent ion channels, and thus modifies membrane conductance and cellular signaling cascades (for review see Reyes 2001[61]).

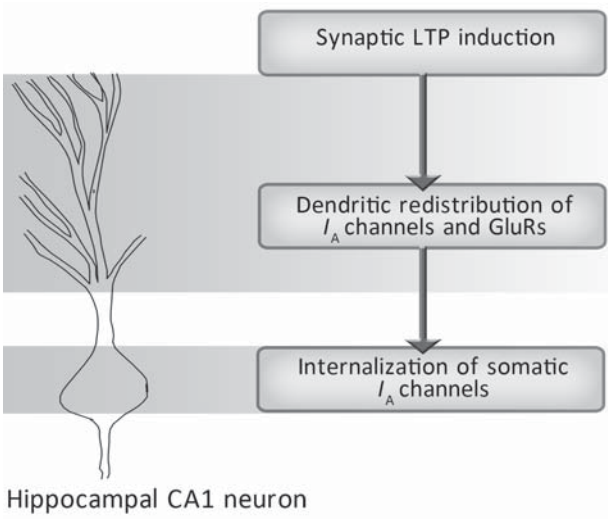


**Fig. 1. $I_A$ channel-mediated responses in dendrites and the soma of CA1 neurons after LTP induction. Synaptic LTP increases the local excitability of active synapses and dendritic branches *via* internalizing $I_A$ channels from the membrane. Somatic excitability can be also influenced after LTP induction which enhances the intrinsic ability to fire action potentials through somatic $I_A$ channel downregulation. Therefore, it seems reasonable that both synaptic and somatic regulation of $I_A$ channels may be required to complete synaptic modification for the memory mechanism.**

Then, are both changes in expression and the gating kinetics of $I_A$ channels required to complete the plastic changes in synaptic and somatic areas? According to previous studies, initial and rapid changes in the gating kinetics of $I_A$ channels are not sufficient to maintain long-term intrinsic plasticity, and blocking the endocytosis of $I_A$ channels significantly abolishes long-lasting changes in dendrites and soma under the condition of LTP[2, 23]. This indicates that the activity-dependent redistribution of $I_A$ channels is essential for completing plastic changes in neurons, while the initial kinetic changes in inactivation may play a role in lowering the threshold of LTP induction.

Although the evidence in the present review suggests $I_A$ regulation as a primary factor for intrinsic plasticity, other mechanisms could also contribute to somatic modifications. A previous study of CA1 neurons in juvenile rats found that the activation curve of voltage-gated $Na^+$ channels is hyperpolarized after LTP, acting to increase excitability[14]. However, the same study found the $Na^+$ channel inactivation curve to be hyperpolarized after LTP, thus decreasing the number of $Na^+$ channels available for activation, which would be expected to decrease excitability.

In another report, LTP induced by theta-burst pairing was shown to depress neuronal excitability *via* the upregulation of hyperpolarization-activated ($I_h$) channels in adult hippocampal CA1 neurons[58]. Subsequently, Campanac *et al*. (2008) demonstrated that $I_h$ might be up-

or down-regulated after LTP, depending on the induction method used, and determine the strength of potentiation[53]. In rat brain, the functional expression and activation of $I_h$ channels are age-dependent, and thus their modulation might be more effective in regulating the excitability of neurons in older rats[53, 58, 62]. In addition, indirect evidence suggests a possibility that the effect of an increased $I_h$ component on membrane input resistance is presumably offset by loss of $I_A$[2].

A long-lasting increase in the efficiency of EPSP-AP coupling has been considered as a memory-storage mechanism in CA1 neurons (for reviews see refs [5] and [45]). Synaptic plasticity and associated changes in dendritic processing may act to trigger changes in IE during learning tasks. Because the potentiation of synaptic strength increases local dendritic excitability and subsequent $Ca^{2+}$ influx[21], the expression level of $I_A$ channels in dendrites and synaptic sites may then be regulated by neurons to initiate secondary processing throughout neurons. This role of synaptic potentiation for intrinsic plasticity is not likely to disrupt synapse-specific mechanisms of plasticity in multiple forms of memory formation[3].

## How Are Somatic $I_A$ Channels Responsible for Synaptic Activity? – A Possible Cellular Mechanism

Answering this question would clarify the crucial roles of ion channels in the initiation and stabilization of memory formation in the mammalian brain. According to original descriptions, memory formation seems to be initiated in synaptic sites by effective and repetitive stimuli[9], and changes in IE are considered to be a mechanism of information storage (i.e. memory stabilization; for review see ref. [3]). Then, what kinds of common factors act as cellular links between memory initiation and somatic stabilization? To answer this question, we consider $I_A$ channels as potent links between soma and synapses after the induction of plasticity. Synaptic LTP-induced redistribution of $I_A$ channels in soma and dendrites has been discussed as evidence for the hypothesis that voltage-dependent ion channels are involved in the cellular processing associated with memory (Fig. 1). Synaptic events that open NMDARs induce local but sufficient $Ca^{2+}$ influx to modify glutamatergic responses in restricted postsynaptic sites in various neurons[63-68], and LTP induced in a single synapse is necessary and sufficient to change somatic excitability[2]. However, it remains unclear whether the internalization of $I_A$ channels is dependent on $Ca^{2+}$ influx through synaptic NMDARs, even though their redistribution surely requires dendritic $Ca^{2+}$ elevation[23]. On the other hand, the same paper reported that, glycine-induced chemical LTP significantly reduces the amplitude of somatic $I_A$, suggesting that cellular processing *via* synaptic NMDAR activation are involved in the internalization of $I_A$ channels. This indicates that synaptic NMDARs play a specific role in the redistribution of $I_A$ channels (Fig. 1).

Spatial isolation between active synapses and soma raises the question as to how $Ca^{2+}$ influx through synaptic NMDARs can regulate somatic $I_A$ channel trafficking. For this issue, $Ca^{2+}$-induced $Ca^{2+}$ release (CICR) through ryanodine receptors (RyRs) or IP3 receptors ($IP_3Rs$) of the endoplasmic reticulum provides a possible cellular candidate. $Ca^{2+}$ elevation in postsynaptic sites during synaptic plasticity activates CICR from intracellular $Ca^{2+}$ stores in dendrites and soma[67]. The elevation of intracellular $Ca^{2+}$ levels throughout neurons contributes to the activation of cytosolic secondary signaling cascades for plastic modification (Fig. 2)[69-72]. The involvement of RyRs in somatic modification is very reliable, because these receptors in the intracellular $Ca^{2+}$ store are responsible for multiple forms of $Ca^{2+}$-dependent plasticity[67, 69, 70]. Although it remains to be determined whether CICR through RyRs internalizes membrane $I_A$ channels or whether it affects $I_A$ channel turnover, it is possible that somatic $Ca^{2+}$ elevation by RyRs is required for the protein kinase A (PKA)-mediated trafficking of somatic $I_A$ channels[73-76], suggesting that CICR may contribute to the association between synaptic plasticity and the change of somatic excitability (Fig. 2). Previously, the involvement of PKA in $I_A$ channel trafficking had been evidenced by their ability to modulate the amplitude of APs back-propagation to dendritic branches[77]. It has recently been reported that the enhancement of PKA activity downregulates Kv4.2-mediated currents by directly phosphorylating its α-subunit and interacting with the $K^+$ channel-interacting proteins (KChIPs)[74, 75]. Because PKA phosphorylation plays multiple roles in LTP by regulating

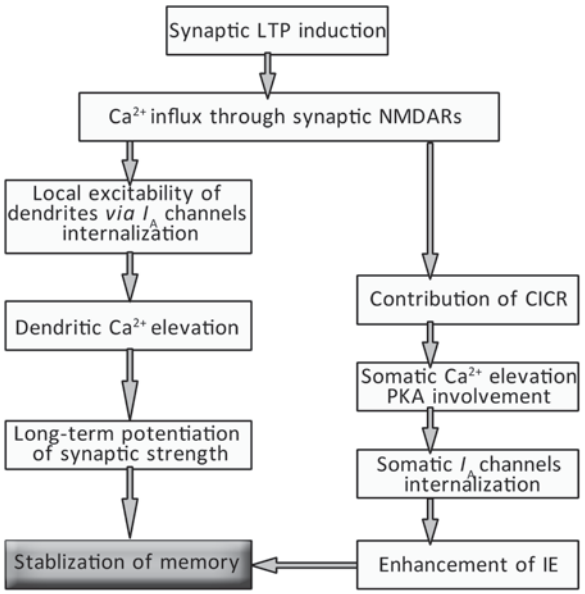


**Fig. 2. Schematic illustration showing the possible processes underlying the synaptic and somatic changes involving the trafficking of $I_A$ channels for the memory mechanism. Synaptic LTP occurs in active synaptic sites. This local processing requires $Ca^{2+}$ influx through synaptic NMDARs. Two pathways of cellular processing can be considered in CA1 neurons. One involves synaptic modification that increases the local excitability of dendrites and synapses, which requires the internalization of dendritic $I_A$ channels and glutamate receptor insertion. The other pathway concerns somatic modification. In this pathway, synaptic $Ca^{2+}$ influx activates CICR and PKA signaling, and finally induces the internalization of somatic $I_A$ channels, which enhances the IE to determine action potential firing with given synaptic inputs. It is hypothesized that both pathways are necessary for the long-lasting modification of neurons required for long-lasting memory formation. CICR, $Ca^{2+}$-induced $Ca^{2+}$ release; IE, intrinsic excitability; LTP, long-term potentiation; PKA, protein kinase A.**

protein synthesis and the expression of glutamatergic receptors in postsynaptic sites and dendritic transmission of EPSCs[78, 79], it is possible that Kv4.2 channel trafficking is one of the cellular cascades resulting from PKA-mediated signaling. Our preliminary data showed that the inhibition of PKA phosphorylation significantly increases $I_A$ amplitude in cultured hippocampal neurons, indicating that PKA phosphorylation may regulate the turnover rate of $I_A$ channels.

Although downregulation of $I_A$ channels responsible for Hebbian-type plasticity has been found in dendrites, spines, and the soma of hippocampal neurons, it is likely that synaptic inputs in peripheral branches and neuronal outputs in the soma are regulated by the subthreshold and suprathreshold gating kinetics of $I_A$ channels, respectively. Unlike the voltage-dependent $Na^+$ channels, $I_A$ channels can be activated and rapidly inactivated at subthreshold membrane potential. This subthreshold gating kinetics as well as channel density is critical to determine synaptic responses and dendritic transmission *via* regulating the local excitability in peripheral branches of neurons. However, $I_A$ channels that regulate AP firing patterns in the somatic area are mainly activated at suprathreshold membrane potentials and then determine the falling phase of each AP and hyperpolarization[2, 17]. Furthermore, various types of LTP protocols affect the inactivation properties at subthreshold potential but not the activation curve at suprathreshold potential, suggesting the existence of different modulatory signaling between dendritic and somatic $I_A$ channels[2, 21]. These reports indicate that, at suprathreshold membrane potential, the expression level rather than voltage-dependent properties of $I_A$ channels are preferentially important for the regulation of somatic excitability.

## Summary

The trafficking properties of $I_A$ channels located in dendrites and in the soma of neurons are commonly targeted by synaptic plasticity, and consequently modify membrane excitability throughout neurons. In CA1 neurons of the hippocampus, multiple forms of synaptic plasticity are considered to be cellular mechanisms of memory formation. Furthermore, the storage of information can be explained by long-lasting IE changes of the soma. Therefore, it is feasible that synaptic plasticity followed by IE changes plays a crucial role to activate cellular storage devices in the mammalian brain. At the cellular level, the linkage factors between dendritic and somatic modifications during memory formation could provide evidence to explain sequential processing from learning tasks to information storage. The functions and trafficking properties of $I_A$ channels during synaptic transmission and plasticity could act as major links between somatic and dendritic processing. Consequently, the enhancement of IE could

determine the neuronal output after memory formation. Additional to cellular and molecular mechanisms focused on the glutamatergic systems of active synapses, crucial roles of voltage-dependent ion channels in the dynamic regulation of membrane excitability should be addressed to further understand the learning and memory mechanisms.

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