A-type K^+ channels as a regulator of postsynaptic excitability in neurons

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Abstract

Since their original descriptions, information encoding and storage function of mammalian brains have been explained by revealing the cellular and molecular mechanisms of synaptic plasticities in various levels of a central nervous system, including hippocampi and cerebral cortices. The modulatory mechanisms of synaptic excitability correlated with neuronal tasks have been considered as fundamental factors to induce synaptic plasticities, which are dependent on the intracellular Ca^{2+} mediated signalings. In the present review, A-type K^+ (IA) channel, one of voltage-dependent cation channels, is issued as a key player to modulate Ca^{2+}influx though synaptic N-methyl-D-aspartic acid (NMDA) receptors and their correlated signaling pathways. The functions of IA channels previously reported indicate that they are integral parts of a synaptic complex that regulates postsynaptic processes of neurons performing memory functions and learning tasks. (J Med Life Sci 2009;6:152-157)

Key Words : Synaptic plasticity, A-type K^+ channel, Kv4.2, Long-term potentiation, Glutamate receptors, NMDA receptors, Memory mechanism

Introduction

In hippocampal neurons in mammalian brains, the outward K^+current consists of a transient or rapidly inactivating (A-type current, IA) current, which is enhanced in dendrites, and a sustained or slow/non-inactivating current expressed at a constant somatodendric density[1]. Channel proteins encoded from the shal family of K^+channels (most likely Kv4.2, voltage-dependent K^+ channel subtype) underlie the IA in CA1 hippocampal pyramidal neurons[2]. For a decade, A-type K^+ currents in cells have been studied for understanding neuronal functions to modulate dendritic signal processing, including the regulation of action potential (AP) propagation, synaptic integration, filtering of fast synaptic potentials[1-6], and in long term potentiation (LTP, a long-lasting increase of synaptic strength)[7-12]. In dendritic processes of pyramidal neurons, A-type K^+ channels (IA channels) alters dendritic Ca^{2+} influx during AP back-propagation, indicating that the regulation of backpropagation by IA channels may participate in intracellular Ca^{2+}-signaling cascades as well as dendritic transmissions of neural inputs. Interestingly, recent reports clearly demonstrate that IA channels are massively distributed in dendritic spines in which basic functions of neurons to communicate with others are performed synaptically[10, 11]. In the present paper, IA channels are reviewed with focusing on their modulatory functions restricted in active postsynaptic sites.

Typical functions of IA channels in dendrites

Transient A-type K^+ current is activating in subthreshold level (lower than -45 mV of membrane potential) and rapidly inactivating (within ~100 ms). IA was first introduced by Hagiwara et al in molluskan neurons[13]. In their typical functions, IA channels regulate AP frequency with making membrane hyperpolarization following the rising phase of APs. In heterologous expression systems, IA are mediated by Kv1.4, Kv3.4 or the Kv4 family subunits (Kv4.1-Kv4.3) that show distinct subcellular IA is comprised mainly of subunits from the Kv4 family[14-16]. Recently, direct evidence establishing Kv4.2 as the molecular identity of IA in CA1 pyramidal neurons has been shown using molecular techniques to decrease functional Kv4.2 activity followed by electrophysiological recordings to test the physiological

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effect of IA decrease[2, 9, 17].

In dendrites of hippocampal CA1 neurons, the density of IA increases with distance from the soma[1]. Moreover, in distal dendrites, IA channels have a hyperpolarization-shifted conductance of voltage curve resulting in an increased probability of channel opening at physiological voltages. Block of IA with 4-AP was demonstrated to enhance the backpropagation of dendritic APs and increase AP initiation in dendrites[1]. Recently, studies have shown that genetic down- or up-regulation of Kv4.2 alters dendritic Ca^{2+} influx during AP backpropagation[2, 9]. As $[Ca^{2+}]i$ elevation is necessary for the induction of LTP, these results indicate that the regulation of AP back-propagation by Kv4.2 maybe an important factor in the induction of synaptic plasticity. Indeed, in physiological induction protocols, which rely on AP backpropagation, LTP threshold is reduced when the activity of dendritic IA channels is reduced[5, 7, 9].

Synaptic localization of IA channels and their activity-dependence

In decades after exposing the molecular mechanisms of synaptic plasticity, glutamate receptors including N-methyl-D-aspartic acid receptors (NMDARs) and alpha-amino-3-hydroxy-5-methyl-s-isoxazolpropionic acid receptors (AMPARs) remain as the best candidate for the cellular analogue of learning and memory[18-21]. More recent reports provide evidence that synaptic strength may be determined by the regulation of synaptic surface expression of glutamate receptors[22, 23]. However, subsequent to synaptic transmission, postsynaptic potentials are subject to significant filtering in CA1 dendrites. Depending on the location and timing of synaptic input, voltage- and Ca^{2+}-gated channels located in dendritic shafts and/or spines may be activated to amplify or otherwise shape synaptic signals as they propagate toward the axon where AP threshold is lowest[24]. It is possible then that activity-dependent regulation of ion channel properties and its surface expression pattern could contribute to the expression of synaptic plasticity. Hoffman and colleagues in 1997 provided an early suggestion that IA channels might shape synaptic input[1]. Later, Ramakers and Storm confirmed a role of IA in synaptic integration in rat CA1 pyramidal cells, showing that heteropodatoxin-3 (HpTX3), a blocker of postsynaptic IA, strongly enhanced the amplitude and summation of excitatory postsynaptic responses[5].

More recently, Kim and colleagues showed that Kv4.2 subunits are localized to spines of primarily cultured hippocampal neurons. Enhanced green fluorescence protein (eGFP)-tagged Kv4.2 (Kv4.2g) fluorescence was greater in neuron spines than in dendritic shafts, suggesting Kv4.2 spine enrichment[2]. Electron microscopy confirmed that endogenous Kv4.2 is localized to spines in adult hippocampal CA1 pyramidal neurons[10]. Finally, altering the functional expression level of Kv4.2 led to changes in miniature excitatory postsynaptic current (mEPSC) amplitude[10] and in the composition of synaptic glutamate receptors[11]. Investigating the possibility that synaptically located Kv4.2 subunits are participated in synaptic plasticity, Kim and colleagues observed the activity-dependent redistribution and internalization of Kv4.2 channels[10]. Excitatory stimulation led to a clathrin-mediated endocytosis of Kv4.2 channels from the neuronal surface. This finding was confirmed by recording a decrease in IA during LTP chemically induced in young dissociated hippocampal neurons. Live imaging experiments and electrophysiological recordings showed that, as with many forms of synaptic plasticity, activity-dependent Kv4.2 internalization requires NMDA receptor activation. Furthermore, mEPSC amplitude was enhanced by stimuli that induced Kv4.2 internalization. Finally, a chemically induced LTP protocol resulted in synaptic insertion of GluR1-containing AMPA receptors along with Kv4.2 internalization.

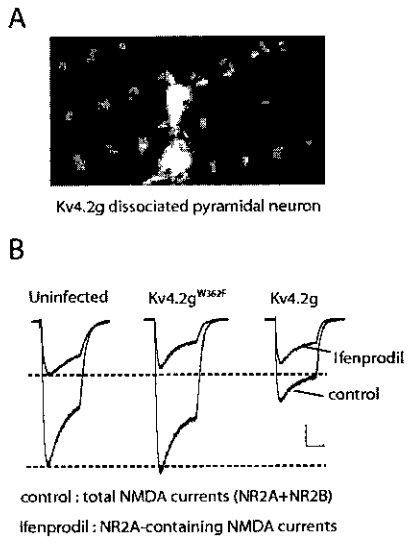
In recordings from adult CA1 hippocampal dendrites, Frick and colleagues reported that the voltage dependence of steady-state IA channel inactivation is altered after LTP induction via a hyperpolarized shift[8]. This shift decreases the proportion of channels available for activation at resting membrane potentials, enhancing dendritic excitability. These results present a novel mechanism to coordinate synaptic integration and plasticity through the activity-dependent regulation of IA channel activity. The synaptically specified distribution of IA channels can thus dramatically impact neuronal signaling through the local regulation of postsynaptic membrane excitability.

Postsynaptic regulation of I_A channels.

Why are IA channels located in spines and redistributed activity-dependently? For answering this question, we can hire the specific properties of synaptic glutamate receptors showing activity-dependent movement during synaptic plasticity. In particular, the importance of NMDARs in synaptic plasticity and memory are well described[25]. At excitatory synapses, Ca^{2+} influx occurs through both NMDARs and voltage-dependent Ca^{2+} channels[8, 26, 27].

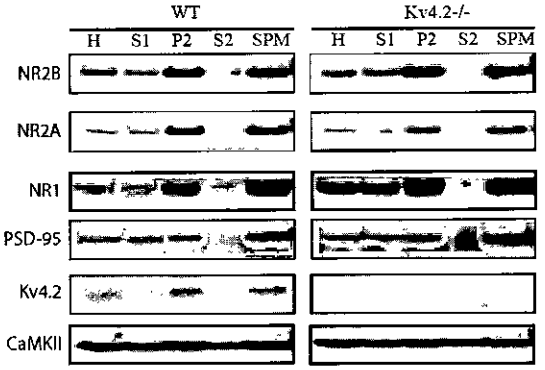
Recently, Jung and colleagues reported that IA channels controls synaptic NMDAR signaling[11]. In Fig. 1, one day after altering IA channel activity, hippocampal pyramidal neurons responded with changes in synaptic NR2 subunit composition. Increasing IA decreased the synaptic NR2B/NR2A ratio by reducing the expression of NR2B-containing NMDARs. Interestingly, this remodeling was specific to synaptic NMDARs, indicating that the modulation of NMDARs by IA channels is restricted in postsynaptic sites. Also, remodeling of NMDAR subunit composition by IA channels depends on spontaneous activities of NMDARs but not on voltage-dependent Ca^{2+} channels. Consequently, these results indicate that the activity-dependent gating properties of NMDARs are targeted by a local membrane potential of postsynaptic sites, which is modulated by the expression level of synaptic IA channels. This is also supported by other investigation showing that the spontaneous synaptic transmission (i. e. mEPSC) is regulated by IA channel expression[10].

Figure 1. NMDA subunit composition is altered by functional Kv4.2 expression level. (A) The microscopic view of a Kv4.2g (Kv4.2 overexpressing) dissociated pyramidal neuron. Puffer pipettes were located 10 mm from the soma to induce NMDA currents. (B) Sample traces of total NMDA currents ("control") and ifenprodil-insensitive currents ("ifenprodil"). To isolate the NR2A component ("ifenprodil", ifenprodil-insensitive), ifenprodil (3 mM) was added to the recording solution after recording total currents including NR2A and NR2B components (control). In this figure, the overexpressing of Kv4.2 significantly reduces total NMDA currents. However, ifenprodil-insensitive fraction shows not significant differences, indicating that the reduction of total NMDA currents in Kv4.2g neurons results from the reduction of NR2B component, ifenprodil-sensitive fraction. Scale bars : 100 pA, 1 second. (Modified from Jung et al. 2008)



Because synaptic NMDARs act as a key player to regulate postsynaptic Ca^{2+} influx, the voltage-dependence of their gating properties is a crucial factor to modulate Ca^{2+}-signaling cascades. After opening of NMDARs, the local elevation of intracellular Ca^{2+} concentration is detected by Ca^{2+}/Calmodulin-dependent kinase II (CaMKII), which is activated by Ca^{2+}/Calmodulin binding and initiates the biochemical cascade of synaptic potentiation[28]. CaMKII activated by Ca^{2+} elevation is then rapidly translocated to active synaptic sites and binds to NMDARs[29-32]. As NR2B-containing NMDAR currents have slower kinetics, allowing for greater temporal summation and Ca^{2+} influx[28, 33], Ca^{2+}-dependent synaptic potentiation potentially relies on the interaction between NR2B and a-CaMKII at postsynaptic domains. Jung and colleagues provided clear evidence that pyramidal neurons overexpressing Kv4.2 show the significant decrease of active CaMKII, while the dominant negative mutation of Kv4.2 enhances CaMKII activation[11]. Although it is still necessary to investigate why only NR2B receptors particularly respond to the changes of Ca^{2+} concentration and CaMKII activity in postsynaptic sites, higher binding affinity of NR2B receptors with CaMKII than NR2A as well as their specific functions to regulate synaptic plasticities can be candidates to explain the synaptic remodeling of NMDAR subunit compositions by IA channels[32]. Consistent with these results, knocking-out of Kv4.2 shows a distinct increase in both NR1 and NR2B (but not NR2A) proteins along with the NMDAR scaffolding protein PSD-95, demonstrating the effect of Kv4.2 deletion to increase NR2B-containing NMDARs in postsynaptic sites[11] (Fig. 2).

Figure 2. Genetic loss of Kv4.2 results in an increased synaptic NMDAR expression. Synaptic fractionation of hippocampi from wild-type and Kv4.2-/- mice revealed that expression of synaptic NR2B, NR1 and PSD95 is significantly upregulated in Kv4.2-/- mice. H, homogenate; S1, supernatant; P2, crude synaptosomal fraction; S2, supernatant; SPM, synaptic membranes. (Modified from Jung et al. 2008)



Functions of synaptic IA channels in memory and learning

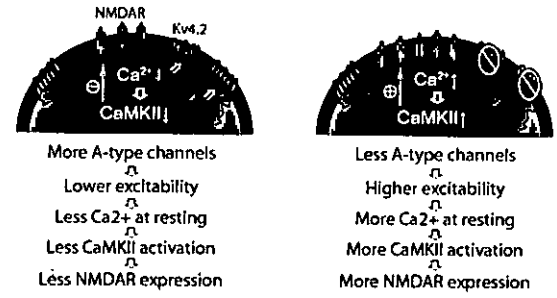
Dendritic IA channel activity, by regulating neuronal excitability and associated Ca^{2+}influx, has the potential to impact LTP on many levels[9-12]. Chen and colleagues in 2006 reported Kv4.2 to be important for the induction of LTP induced by theta-burst pairing by regulating AP backpropagation[9]. However, overexpression of Kv4.2 channels also modulate synaptic LTP induced by a pairing protocol in which it does not rely on AP backpropagation, and Kv4.2 channels would be expected to be inactivated during the pairing period (with the cell held at 0 mV)[11]. Therefore, Kv4.2 expression level affects the degree of LTP induced likely depends on secondary consequence of Kv4.2 expression rather than activity of Kv4.2 channels during induction, because sufficient NMDARs activation is required for the induction of most forms of synaptic plasticity[25] (Fig. 3). Additionally, genetic enhancement of NR2B in transgenic mice increases the synaptic potentiation and learning abilities in behavioral tasks[34], and synapses with a lower synaptic NR2B/NR2A fraction rarely induces plasticities[35], indicating that Ca^{2+} influx through NR2A receptors with lower permeability is not sufficient to induce LTP. However, there is still conflicting evidence for the role of specific NR2 subunits in synaptic plasticities[36-39].

Summary

In excitable cells such as neurons, voltage-dependent K^+ channels in membrane prevent excessive depolarization for preserving neurons from excitotoxicity and prepare neurons to make next APs. As the physiological structures of neurons determine their own functional nature, ion channels in membrane can be distinguished by their location even if they are classified as same. In the present review, the physiological functions of IA channels particularly located in spines has been described with concepts to consider IA channels as a primary regulator of postsynaptic excitability in a subthreshold range. Although revealing detail and distinctive functions of Ca^{2+} sources existing in postsynaptic sites needs further studies, the activity of IA channels is one of dominant players to regulate membrane excitability, controlling the gating properties of synaptic glutamate receptors (Fig. 3).

More sophisticated technical approaches may provide more evidence of how and why IA channels and their auxiliary subunits (DPPX, KChiPs and kinases) are targeted by neurons to control membrane excitability and secondary Ca^{2+} signaling. A number of studies on cellular and molecular mechanisms that underlie information encoding and storage are focusing on the trafficking of glutamate receptors in and out of active synapses. It is, however, important to consider voltage-dependent K^+ channels as an integral part of a synaptic complex that regulates Ca^{2+}-related postsynaptic processings, which control the expression of synaptic glutamate receptors and plasticity.

Figure 3. The function of IA channels to regulate postsynaptic excitability. The increased activity of IA channels can downregulate the membrane excitability of postsynaptic sites, which is a critical factor to control synaptic NMDARs opening. Less Ca^{2+} influx through NMDARs by IA increase, induces the downregulation of postsynaptic Ca^{2+}-mediated signaling cascades and expression of glutamate receptors.



References

1) Hoffman DA, Magee JC, Colbert CM, Johnston D. K+channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. Nature 1997:387:869-75.

2) Kim J, Wei DS, Hoffman DA. Kv4 potassium channel subunits control action potential repolarization and frequency-dependent broadening in rat hippocampal CA1 pyramidal neurones. J Physiol 2005:569:41-57.

3) Cash S, Yuste R. Input summation by cultured pyramidal neurons is linear and position-independent. J Neurosci 1998;18:10-5.

4) Schoppa NE, Westbrook GL.Regulation of synaptic timing in the olfactory bulb by an A-type potassium current. Nat Neurosci 1999:2:1106-13.

5) Ramakers GM, Storm JF.A postsynaptic transient K^+ current modulated by arachidonic acid regulates synaptic integration and threshold for LTP induction in hippocampal pyramidal cells. Proc Natl Acad Sci USA 2002:99:10144-9.

6) Goldberg JH, Tamas G, Yuste R. Ca^{2+} imaging of mouse

neocortical interneurone dendrites: Ia-type K^+ channels control action potential backpropagation. J Physiol 2003;551:49-65.

7) Watanabe S, Hoffman DA, Migliore M, Johnston D. Dendritic K^+ channels contribute to spike-timing dependent long-term potentiation in hippocampal pyramidal neurons. Proc Natl Acad Sci USA 2002;99:8366-71.

8) Frick A, Magee J, Johnston D. LTP is accompanied by an enhanced local excitability of pyramidal neuron dendrites. Nat Neurosci 2004;7:126-35.

9) Chen X, Yuan LL, Zhao C, Birnbaum SG, Frick A, Jung WE, et al. Deletion of Kv4.2 gene eliminates dendritic A-type K^+ current and enhances induction of long-term potentiation in hippocampal CA1 pyramidal neurons. J Neurosci 2006;26:12143-51.

10) Kim J, Jung SC, Clemens AM, Petralia RS, Hoffman DA.Regulation of dendritic excitability by activity-dependent trafficking of the A-type K^+ channel subunit kv4.2 in hippocampal neurons. Neuron 2007;54:933-47.

11) Jung SC, Kim J, Hoffman DA. Rapid, bidirectional remodeling of synaptic NMDA receptor subunit composition by A-type K^+ channel activity in hippocampal CA1 pyramidal neurons. Neuron 2008;60:657-71.

12) Jung SC, Hoffman DA. Biphasic somatic A-type K^+ channel downregulation mediates intrinsic plasticity in hippocampal CA1 pyramidal neurons. PLoS ONE 2009;4(8):e6549.

13) Hagiwara S, Kusano K, Saito N. Membrane changes of Onchidium nerve cell in potassium-rich media. J Physiol 1961;155:470-89.

14) Coetzee WA, Amarillo Y, Chiu J, Chow A, Lau D, McCormack T. Molecular diversity of K^+ channels. Ann N Y Acad Sci 1999;868:233-85.

15) Rudy B, McBain CJ. Kv3 channels: voltage-gated K^+ channels designed for high-frequency repetitive firing. Trends Neurosci 2001;24:517-26.

16) Song WJ. Genes responsible for native depolarization-activated K^+ currents in neurons. Neurosci Res 2002;421:7-14.

17) Lauver A, Yuan LL, Jeromin A, Nadin BM, Rodriguez JJ, Davies HA. Manipulating Kv4.2 identifies a specific component of hippocampal pyramidal neuron A-current that depends upon Kv4.2 expression. J Neurochem 2006;99:1207-23.

18) Barco A, Bailey CH, Kandel ER. Common molecular mechanisms in explicit and implicit memory. J Neurochem 2006;97:1520-33.

19) Kandel ER. The molecular biology of memory storage: a dialogue between genes and synapses. Science 2001;294:1030-8.

20) Malenka RC, Nicoll RA. NMDA-receptor-dependent synaptic plasticity: multiple forms and mechanisms. Trends Neurosci 1993;16:521-7.

21) Nicoll RA, Malenka RC. Expression mechanisms underlying NMDA receptor-dependent long-term potentiation. Ann N Y Acad Sci 1999;868:515-25.

22) Collingridge GL, Isaac JT, Wang YT. Receptor trafficking and synaptic plasticity. Nat Rev Neurosci 2004;5:952-62.

23) Malinow R, Malenka RC. AMPA receptor trafficking and synaptic plasticity. Annu Rev Neurosci 2002;25:103-26.

24) Stuart G, Spruston N, Sakmann B, Hausser M. Action potential initiation and backpropagation in neurons of the mammalian CNS. Trends Neurosci 1997;20:125-31.

25) Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron 2004;44:5-21.

26) Magee JC, Johnston D.A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. Science 1997;275:209-13.

27) Lisman J, Spruston N. Postsynaptic depolarization requirements for LTP and LTD: a critique of spike timing-dependent plasticity. Nat Neurosci 2005;8:839-41.

28) Lisman J, Schulman H, Cline H. The molecular basis of CaMKII function in synaptic and behavioural memory. Nat Rev Neurosci 2002;3:175-90.

29) Shen K, Meyer T. Dynamic control of CaMKII translocation and localization in hippocampal neurons by NMDA receptor stimulation. Science 1999;284:162-6.

30) Bayer KU, De Koninck P, Leonard AS, Hell JW, Schulman H. Interaction with the NMDA receptor locks CaMKII in an active conformation. Nature 2001;411:801-5.

31) Strack S, McNeill RB, Colbran RJ. Mechanism and regulation of calcium/calmodulin-dependent protein kinase II targeting to the NR2B subunit of the N-methyl-D-aspartate receptor. J Biol Chem 2000;275:23798-806.

32) Barria A, Malinow R. NMDA receptor subunit composition controls synaptic plasticity by regulating binding to CaMKII. Neuron 2005;48:289-301.

33) Quinlan EM, Olstein DH, Bear MF. Bidirectional, experience-dependent regulation of N-methyl-D-aspartate receptor subunit composition in the rat visual cortex during postnatal development. Proc Natl Acad Sci USA 1999;96:12876-80.

34) Tang YP, Shimizu E, Dube GR, Rampon C, Kerchner

GA, Zhuo M et al. Genetic enhancement of learning and memory in mice. Nature 1999;401:63-9.
35) Barria A, Malinow R. Subunit-specific NMDA receptor trafficking to synapses. Neuron 2002;35:345-53.
36) Berberich S, Punnakkal P, Jensen V, Pawlak V, Seeburg PH, Hvalby O, Kohr G.Lack of NMDA receptor subtype selectivity for hippocampal long-term potentiation. J Neurosci 2005;25:6907-10.
37) Liu L, Wong TP, Pozza MF, Lingenhoehl K, Wang Y, Sheng M et al. Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity. Science 2004;304:1021-4.
38) Massey PV, Johnson BE, Moult PR, Auberson YP, Brown MW, Molnar E, et al. Differential roles of NR2A and NR2B-containing NMDA receptors in cortical long-term potentiation and long-term depression. J Neurosci 2004;24:7821-8.
39) Morishita W, Lu W, Smith GB, Nicoll RA, Bear MF, Malenka RC. Activation of NR2B-containing NMDA receptors is not required for NMDA receptor-dependent long-term depression. Neuropharmacology 2007;52:71-6.