Channels 4:3, 1-5; May/June 2010; © 2010 Landes Bioscience

Regulation of the $K_V4.2$ complex by $Ca_V3.1$ calcium channels

Dustin Anderson, Renata Rehak, Shahid Hameed, W. Hamish Mehaffey, Gerald W. Zamponi and Ray W. Turner*

Departments of Cell Biology & Anatomy and Physiology & Pharmacology; Hotchkiss Brain Institute; University of Calgary; Calgary, AB Canada

A-type potassium current generated by the K_V4 family of channels is an important factor regulating the frequency, latency and dendritic backpropagation of spike discharge. The $K_V4.2$ complex of $K_V4.2$-KChIP3-DPP10c was recently shown to form a novel signaling complex through its association with T-type $Ca_V3.2$ or $Ca_V3.3$ calcium channel isoforms. Ca_V3-mediated calcium entry was shown to selectively right-shift the inactivation voltage of $K_V4.2$ into the physiological range to modulate cerebellar stellate cell latency and gain. We now show that $Ca_V3.1$ calcium channels can also associate with the $K_V4.2$ complex to effect similar regulation of $K_V4.2$ inactivation voltage. By comparison, no calcium-dependent shift in $K_V4.2$ inactivation properties was elicited by any of $Ca_V1.4$, $Ca_V2.1$ or $Ca_V2.3$ calcium channels coexpressed with the $K_V4.2$ complex, emphasizing the important role for low voltage-activated Ca_V3 channels in this signaling complex.

Key words: A-type, T-type, Ca_V3, K_V4, gain, first spike latency

Submitted: 03/10/10

Revised: 04/01/10

Accepted: 04/05/10

Previously published online: www.landesbioscience.com/journals/channels/article/11955

*Correspondence to:
Ray W. Turner; Email: rwturner@ucalgary.ca

Addendum to: Anderson D, Mehaffey WH, Iftinca M, Rehak R, Engbers JD, Hameed S, et al. Regulation of neuronal activity by Ca_V3-K_V4 channel signaling complexes. Nat Neurosci 2010; 13:333–7; PMID: 20154682.

Introduction

Action potential discharge is highly regulated by inward and outward currents that activate at subthreshold membrane potentials. Two currents that operate in this range arise from transiently activated A-type potassium channels of the K_V4 family and Ca_V3 T-type calcium channels. A-type currents (I_A) are known to influence first spike latency, spike frequency and the amplitude of backpropagating dendritic spikes.[1-6] T-type currents (I_T) have a wide range of functions based on their immediate depolarizing action on membrane potential as well as second messenger regulation of biochemical pathways.[7-10] We recently determined that Ca_V3 and K_V4 channels form a signaling complex that allows for calcium-dependent regulation of K_V4 inactivation.[11] Specifically, T-type mediated calcium influx in cerebellar stellate cells selectively right-shifts the inactivation profile of I_A, with no effects on parameters of activation or recovery from inactivation. The function of this complex proves to be critical in shifting the K_V4 inactivation profile into the physiological range of membrane potentials to control first spike latency and gain of stellate cell firing.[3,11]

The K_V4 complex is known to contain four K^+ Channel Interacting Proteins (KChIPs1-4) that represent members of a calcium sensor family,[5,12] as well as dipeptidyl-peptidase-like-proteins (DPLPs).[13-16] Despite a wealth of information on the structural and functional relationships between members of the K_V4 complex,[13,17,18] little progress had been made on identifying a physiological source of calcium that might modify K_V4 function. We found that $K_V4.2$ channels co-immunoprecipitate with $Ca_V3.2$ or $Ca_V3.3$ channels and are pulled down by GST fusion proteins of the $Ca_V3.2$ or $Ca_V3.3$ C-terminus.[11] Recapitulation of the stellate cell $K_V4.2$ complex in the tsA-201 expression system revealed that K_V4 modulation occurs upon co-expression of KChIP3 as a calcium sensor and $Ca_V3.2$ or $Ca_V3.3$ channels, but not with the high voltage-activated (HVA) $Ca_V2.2$ (N-type) calcium channel.[11]

The tests conducted in Anderson et al.[11] focused on a subset of proteins representative of those expressed in cerebellar stellate cells: $K_V4.2$, $Ca_V3.3$, KChIP3 and DPP10c.[19,20] However, $K_V4.2$ channels might also be subject to regulation

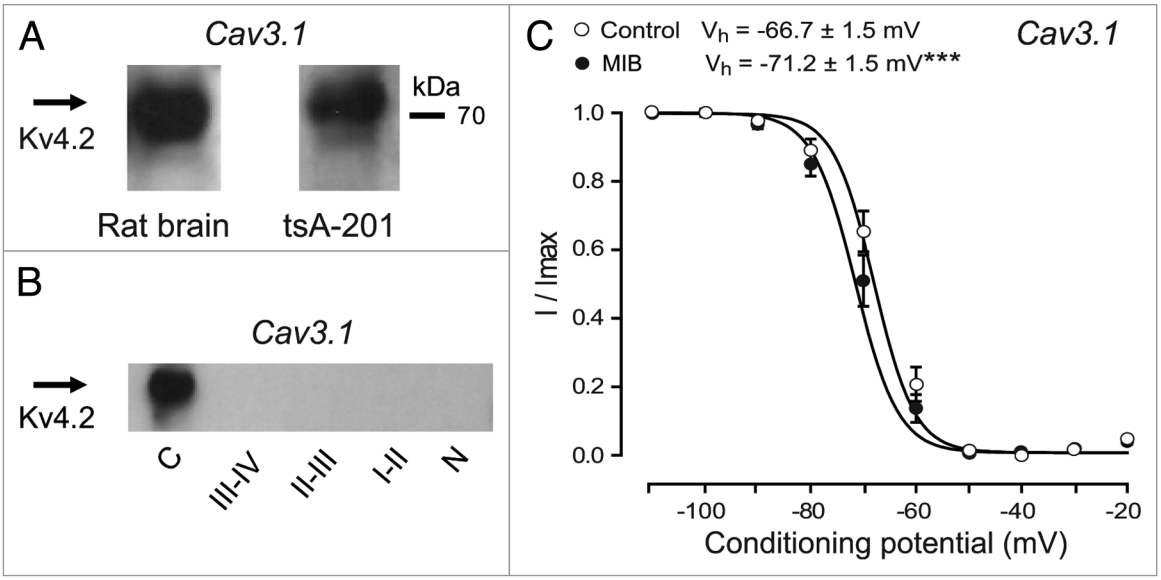

Figure 1. $Ca_V3.1$ channels link to the $K_V4.2$ channel complex to produce calcium-dependent modulation of the $K_V4.2$ inactivation profile. (A) $K_V4.2$ channels co-immunoprecipitate with $Ca_V3.1$ channels from either rat brain homogenate or lysate of tsA-201 cells co-transfected with $K_V4.2$ and $Ca_V3.1$. (B) Pulldown of $K_V4.2$ channels from whole brain homogenate with immobilized GST fusion proteins of the intracellular regions of $Ca_V3.1$ channels reveals a specific association with the $Ca_V3.1$ C-terminus. (C) The voltage-inactivation profile for $K_V4.2$ current in tsA-201 cells co-expressing $Ca_V3.1$ channels with $K_V4.2$-KChIP3-DPP10c is left-shifted upon application of 0.5 μM mibefradil to block Ca_V3 calcium influx (n = 12; $p < 0.001$).

by calcium influx through the $Ca_V3.1$ channel isoform or other HVA calcium channels. Here we extend the results of Anderson et al.[11] by presenting unpublished data on the potential for $Ca_V3.1$ and other HVA calcium channels to modulate K_V4 inactivation when co-expressed in tsA-201 cells with KChIP3 as the calcium sensor.

Results

$Ca_V3.1$ and $K_V4.2$ channels coimmunoprecipitate. We found that the $K_V4.2$ channel co-immunoprecipitated with the $Ca_V3.1$ calcium channel isoform from rat brain homogenate and from lysate of $Ca_V3.1/K_V4.2$ transfected tsA-201 cells (**Fig. 1A**). We further used GST fusion proteins of the intracellular regions of $Ca_V3.1$ channels (C-terminus, linkers I-II, II-III, III-IV and N-terminus) to perform pulldown experiments for $K_V4.2$ from rat brain homogenate. In line with our previous results, we found that the C-terminal region of $Ca_V3.1$ but none of the other regions pulled down $K_V4.2$ channels from rat brain homogenate (**Fig. 1B**). In all, these data indicate that all T-type channel family members are capable of associating with $K_V4.2$ channels.

Anderson et al.[11] showed that calcium influx through $Ca_V3.2$ or $Ca_V3.3$ calcium channels can modulate $K_V4.2$ steady-statse inactivation in tsA-201 cells providing they are co-expressed with KChIP3. Here we tested if $Ca_V3.1$ channels can regulate K_V4 inactivation in tsA-201 cells when co-expressed with $K_V4.2$, KChIP3 and DPP10c as a representative K_V4 complex. We previously determined that the half-inactivation potential (V_h) of the $K_V4.2$ complex alone is not affected by mibefradil application[11] (data not shown). However, application of the T-type channel blocker mibefradil (0.5 μM) produced a small (-4.5 mV) but significant shift in $K_V4.2$ V_h when co-expressed with $Ca_V3.1$ (from -66.7 ± 1.5 mV to -71.2 ± 1.5 mV; $p < 0.001$; n = 12) (**Fig. 1C**) without affecting $K_V4.2$ voltage for activation or rate of inactivation (data not shown).

HVA calcium influx does not alter the V_h of K_V4 channel gating. In our previous study we demonstrated that cerebellar stellate cells exhibit $Ca_V2.2$ channel immunolabel, but that calcium influx through $Ca_V2.2$ channels coexpressed in tsA-201 cells with the same representative K_V4 complex examined here did not modulate K_V4 steady-state inactivation.[11] Here we tested whether other members of the HVA families of calcium channels are capable of modulating $K_V4.2$ V_h. These tests are also relevant to cerebellar stellate cells in that immunocytochemistry revealed immunolabel for L-type ($Ca_V1.4$), P-type ($Ca_V2.1$) and R-type ($Ca_V2.3$) calcium channels (**Fig. 2A–C**). Voltage-clamp recordings were conducted on tsA-201 cells co-expressing $K_V4.2$, KChIP3, DPP10c and one of these HVA calcium channels to assess their ability to modulate K_V4 properties. The expression of HVA calcium channels in each case was confirmed by the presence of inward current during depolarizing prepotentials or following drug application to block calcium current (data not shown). Despite the expected overexpression of HVA calcium channels in this assay, application of blockers or toxins specific to each of the HVA channels produced no shift in $K_V4.2$ V_h (**Fig. 2A–C**).

Discussion

The current study extends the work of Anderson et al.[11] on the link between Ca_V3 calcium channels and the K_V4 potassium channel complex that confers calcium-dependent regulation of I_A. Here we establish that $Ca_V3.1$ channels also link to the $K_V4.2$ complex and can induce a selective

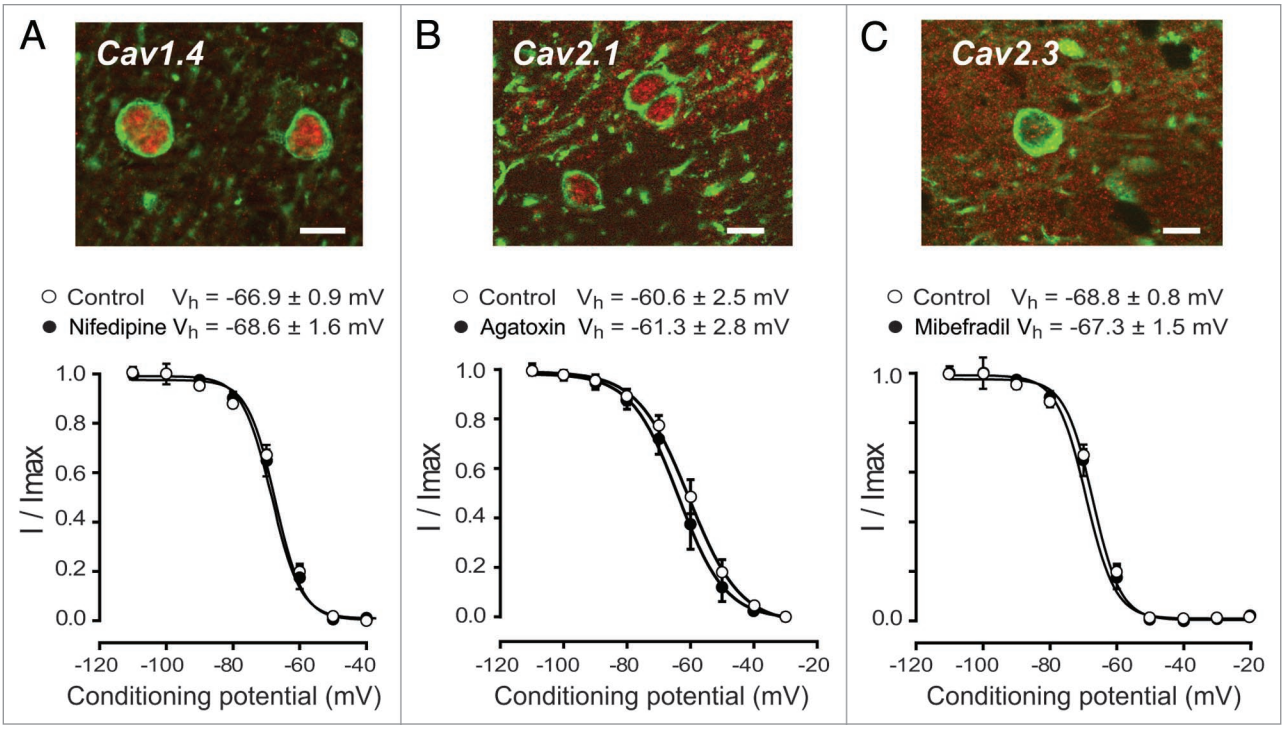

Figure 2. HVA calcium channels expressed in stellate cells do not modulate $K_V4.2$ V_h when co-expressed with a $K_V4.2$ complex in tsA-201 cells. (A–C) Shown in the top panels are stellate cells dual immunolabeled for MAP-2 (*green*) and the indicated HVA calcium channel (*red*). The lower panels illustrate the effects of specific HVA calcium channel blockers on $K_V4.2$ V_h when each HVA calcium channel is co-expressed with a combination of $K_V4.2$-KChIP3-DPP10c. No effect on $K_V4.2$ V_h was detected upon application of (A) 5 μM nifedipine to block $Ca_V1.4$ channels (L-type; $n = 6$), (B) 200 nM ω-agatoxin IVA to block $Ca_V2.1$ channels (P-type; $n = 5$), or (C) 0.5 μM mibefradil to block $Ca_V2.3$ channels (R-type; $n = 7$). Scale bars = 10 μm.

calcium-dependent shift in K_V4 V_h, indicating that this form of modulation can occur between all members of the Ca_V3 family and $K_V4.2$ channels. These data further indicate a common site for the association at the Ca_V3 C-terminus that enables calcium-dependent interaction through KChIP3 proteins. In contrast, co-expression studies now indicate that calcium influx through any of four different HVA calcium channels (L, N, P, R) cannot modulate $K_V4.2$ inactivation even when overexpressed in tsA-201 cells (**Fig. 2**).[11] The selective ability for Ca_V3 channels to modulate I_A at the nanodomain level even when each of these HVA calcium channels are also expressed in these small diameter cells supports the specificity of the association between Ca_V3 and $K_V4.2$ ion channels. Indeed, the members of this signaling complex seem well suited given the distinctive but similar activation/inactivation profiles of T-type and A-type channels, allowing calcium entry to closely match the activity of A-type potassium channels even at subthreshold potentials.

The finding that the $K_V4.2$ complex can associate with $Ca_V3.1$ channels, as well as with $Ca_V3.2$ and 3.3 isoforms, greatly increases the potential for modulation of I_A, as Ca_V3 channel isoforms are differentially distributed in CNS neurons. In situ hybridization studies first established a differential distribution for Ca_V3 mRNA expression,[21-23] while immunocytochemical studies of Ca_V3 channel isoforms indicated that most cells exhibit immunolabel for at least two if not all three of the Ca_V3 isoforms.[19,24] However, specific expression patterns can be found, with a combination of $Ca_V3.2$ and $Ca_V3.3$ but not $Ca_V3.1$ in cerebellar stellate cells.[19] This compares to a prominent $Ca_V3.1$ label in some cells (i.e., Transient Burst deep cerebellar cells, lateral habenular neurons) to cases in which only $Ca_V3.1$ immunolabel is detected (i.e., cerebellar Golgi cells).[19,24] In the case of cerebellar stellate cells, we found that the calcium-dependent shift in V_h establishes a novel voltage-first spike latency relationship.[3] Blocking I_A in these cells revealed the capacity to otherwise generate rebound frequency increases in firing, demonstrating that I_A can offset burst capability. A previous study of inhibitory interneurons of rat thalamus also reported that an I_T-driven form of burst discharge was attenuated by I_A.[25] The extent to which this might reflect a simple co-expression and activation of these opposing currents in the same cell or an active shift in I_A V_h by Ca_V3-mediated calcium current remains to be seen.

The expression pattern of $Ca_V3.1$ protein immunolabel is also interesting in showing a correlation to cells that have the ability to generate rebound bursts following membrane hyperpolarizations.[19] Burst discharge in thalamic relay cells that express $Ca_V3.1$,[21,22] is thus blocked in $Ca_V3.1$ knockout animals,[26] while all cerebellar cells that express $Ca_V3.1$ exhibit rebound bursts under normal conditions.[19] In this regard, it is interesting that the extent of the shift in the V_h of K_V4 current inactivation by $Ca_V3.1$-mediated calcium influx (4.5 mV) is approximately half of that produced by $Ca_V3.2$ and $Ca_V3.3$ (~7–9 mV).[11] It is thus possible that $Ca_V3.1$-dominated cell types experience less calcium-dependent shift in I_A V_h than

those with prominent $Ca_V3.2$ or $Ca_V3.3$ expression. We also found a pattern in the relative distribution of immunolabel for Ca_V3 channel isoforms over the soma-dendritic axis of many central neurons.[24] In general, $Ca_V3.1$ immunolabel was predominantly located near the soma, $Ca_V3.2$ immunolabel over the soma and proximal dendritic regions, and $Ca_V3.3$ over most of the soma-dendritic axis. The possibility then exists for the subcellular distribution of Ca_V3 calcium channel isoforms in somatic and dendritic regions to exert differential control of membrane excitability through I_A.[2,5]

It is important to stress that calcium-dependent modulation of I_A by this signaling complex requires the co-expression of not only Ca_V3 and $K_V4.2$ channels but also KChIP3 as the critical calcium sensor. Nevertheless, it is not currently known if co-expression of these proteins guarantees a functional association as a Ca_V3-K_V4 signaling complex. Moreover, Ca_V3 and K_V4 channels may not always be co-expressed within the same neuron. For instance, deep cerebellar nuclear neurons label differentially for $Ca_V3.1$ or $Ca_V3.3$ channels but neither express an A-type potassium current.[27] The pattern of expression for the $K_V4.2$ isoform and that of KChIP3 also exhibit greater variation than that of Ca_V3 channels.[4,20,28-31] In particular, the brain regions for which this signaling complex controls neuronal activity will presumably show a dependence on the distribution of KChIP3.

Finally, we have not assessed whether other sources of calcium influx are capable of regulating $K_V4.2$ V_h through KChIP3. Thus, it is possible that calcium influx through NMDA or CP-AMPA receptors, mGluRs, TRP channels, or calcium release from internal stores[32-36] are capable of controlling membrane excitability through the Ca_V3-K_V4 signaling complex.

Materials and Methods

Co-immunoprecipitation and GST pulldown assays. Co-immunoprecipitation and GST pulldown assays were performed as described in Anderson et al.[11]

Immunocytochemistry. Immunocytochemical sections were prepared as described in Anderson et al.[11] Polyclonal primary antibodies were rabbit polyclonal anti-$Ca_V1.4$ (1:2,000; gift of T. Snutch, Vancouver, BC), anti-$Ca_V2.1$ (1:50; Alomone, Jerusalem), and anti-$Ca_V2.3$ (1:100; Sigma-Aldrich, Oakville, ON) applied overnight at 4°C in a working solution of 3% normal donkey serum (Jackson, West Grove, PA), 0.1% TWEEN, and 1% DMSO in phosphate buffer. Anti-MAP-2 antibodies were monoclonal MAP-2 (1:1,000) or polyclonal MAP-2 (1:250) (AbCam, Cambridge, MA). Secondary antibodies (1:1,000) were Alexa Fluor-488 or -594 conjugated donkey or goat anti-rabbit or anti-mouse IgGs (Molecular Probes, Eugene, OR). Immunoreactivity was assessed using a Zeiss AxioImager microscope and Apotome grid illumination system. All immunoblot data and immunocytochemistry shown is representative of 2–3 separate experiments.

tsA-201 cell electrophysiology. cDNA for a representative K_V4 complex of $K_V4.2$, KChIP3 and DPP10c was co-transfected in tsA-201 cells as previously described.[11] cDNA (2.5 μg/μl) for $Ca_V3.1$, $Ca_V1.4$, $Ca_V2.1$, $Ca_V2.3$ and the associated β1b and α2-δ subunits were cotransfected with those of the representative K_V4 complex and $K_V4.2$ current recorded at room temperature.[11] Mibefradil (0.5 μM) and nifedipine (5 μM) were bath applied and ω-agatoxin IVA (200 nM) were focally ejected in a carrier medium containing (in mM): 120 NaCl, 3 $NaHCO_3$, 4.2 KCl, 1.2 KH_2PO_4, 1.5 $MgCl_2$, 10 D-Glucose, 10 HEPES, 1.5 $CaCl_2$. Steady-state K_V4 inactivation was determined from a holding potential of -110 mV and test potential of 0 mV (1 s) following 1 s voltage presteps from -110 mV in 10 mV increments. Slope factors ranged between 4.5 and 7 for all recordings (data not shown). The difference in slope factors was likely due to the variable expression of the various K_V4 complex members and not the co-expression of calcium channels. All values reported are mean ± s.e.m and statistical significance determined using Student's t-test.

Acknowledgements

We thank M. Kruskic and L. Chen for expert technical assistance. Research was supported by grants from the Canadian Institutes of Health Research (CIHR) (Ray W. Turner, Gerald W. Zamponi) and salary support through the Alberta Heritage Foundation for Medical Research (AHFMR) (Dustin Anderson, Renata Rehak), Natural Sciences and Engineering Research Council (Renata Rehak), and an Achiever in Medical Sciences and T. Chen Fong Scholarships (Dustin Anderson) Ray W. Turner and Gerald W. Zamponi are AHFMR Scientists and Gerald W. Zamponi is the recipient of a Canada Research Chair.

References

1. Khaliq ZM, Bean BP. Dynamic, nonlinear feedback regulation of slow pacemaking by A-type potassium current in ventral tegmental area neurons. J Neurosci 2008; 28:10905-17.
2. Johnston D, Hoffman DA, Magee JC, Poolos NP, Watanabe S, Colbert CM, et al. Dendritic potassium channels in hippocampal pyramidal neurons. J Physiol 2000; 525:75-81.
3. Molineux ML, Fernandez FR, Mehaffey WH, Turner RW. A-type and T-type currents interact to produce a novel spike latency-voltage relationship in cerebellar stellate cells. J Neurosci 2005; 25:10863-73.
4. Bourdeau ML, Morin F, Laurent CE, Azzi M, Lacaille J-C. $K_V4.3$-mediated A-type K^+ currents underlie rhythmic activity in hippocampal interneurons. J Neurosci 2007; 27:1942-53.
5. Jerng HH, Pfaffinger PJ, Covarrubias M. Molecular physiology and modulation of somatodendritic A-type potassium channels. Mol Cell Neurosci 2004; 27:343-69.
6. Connor JA, Stevens CF. Prediction of repetitive firing behaviour from voltage clamp data on an isolated neurone soma. J Physiol 1971; 213:31-53.
7. Swensen AM, Bean BP. Ionic mechanisms of burst firing in dissociated Purkinje neurons. J Neurosci 2003; 23:9650-63.
8. Yunker AM, McEnery MW. Low-voltage-activated ("T-Type") calcium channels in review. J Bioenerg Biomembr 2003; 35:533-75.
9. Iftinca MC, Zamponi GW. Regulation of neuronal T-type calcium channels. Trends Pharmacol Sci 2009; 30:32-40.
10. Huguenard JR. Low-threshold calcium currents in central nervous system neurons. Annu Rev Physiol 1996; 58:329-48.
11. Anderson D, Mehaffey WH, Iftinca M, Rehak R, Engbers JD, Hameed S, et al. Regulation of neuronal activity by Ca_V3-K_V4 channel signaling complexes. Nat Neurosci 2010; 13.
12. An WF, Bowlby MR, Betty M, Cao J, Ling HP, Mendoza G, et al. Modulation of A-type potassium channels by a family of calcium sensors. Nature 2000; 403:553-6.
13. Covarrubias M, Bhattacharji A, De Santiago-Castillo JA, Dougherty K, Kaulin YA, Na-Phuket TR, et al. The neuronal K_V4 channel complex. Neurochem Res 2008; 33:1558-67.
14. Dougherty K, Tu L, Deutsch C, Covarrubias M. The dipeptidyl-aminopeptidase-like protein 6 is an integral voltage sensor-interacting beta-subunit of neuronal K(V)4.2 channels. Channels (Austin) 2009; 3:122-8.
15. Nadal MS, Ozaita A, Amarillo Y, Vega-Saenz de Miera E, Ma Y, Mo W, et al. The CD26-related dipeptidyl aminopeptidase-like protein DPPX is a critical component of neuronal A-type K^+ channels. Neuron 2003; 37:449-61.

16. Jerng HH, Kunjilwar K, Pfaffinger PJ. Multiprotein assembly of $K_V4.2$, KChIP3 and DPP10 produces ternary channel complexes with ISA-like properties. J Physiol 2005; 568:767-88.
17. Pioletti M, Findeisen F, Hura GL, Minor DL Jr. Three-dimensional structure of the KChIP1-$K_V4.3$ T1 complex reveals a cross-shaped octamer. Nat Struct Mol Biol 2006; 13:987-95.
18. Wang H, Yan Y, Liu Q, Huang Y, Shen Y, Chen L, et al. Structural basis for modulation of K_V4 K^+ channels by auxiliary KChIP subunits. Nat Neurosci 2007; 10:32-9.
19. Molineux ML, McRory JE, McKay BE, Hamid J, Mehaffey WH, Rehak R, et al. Specific T-type calcium channel isoforms are associated with distinct burst phenotypes in deep cerebellar nuclear neurons. Proc Natl Acad Sci USA 2006; 103:5555-60.
20. Kollo M, Holderith NB, Nusser Z. Novel subcellular distribution pattern of A-type K^+ channels on neuronal surface. J Neurosci 2006; 26:2684-91.
21. Talley EM, Cribbs LL, Lee JH, Daud A, Perez-Reyes E, Bayliss DA. Differential distribution of three members of a gene family encoding low voltage-activated (T-type) calcium channels. J Neurosci 1999; 19:1895-911.
22. Craig PJ, Beattie RE, Folly EA, Banerjee MD, Reeves MB, Priestley JV, et al. Distribution of the voltage-dependent calcium channel alpha1G subunit mRNA and protein throughout the mature rat brain. Eur J Neurosci 1999; 11:2949-64.
23. Kase M, Kakimoto S, Sakuma S, Houtani T, Ohishi H, Ueyama T, et al. Distribution of neurons expressing alpha1G subunit mRNA of T-type voltage-dependent calcium channel in adult rat central nervous system. Neurosci Lett 1999; 268:77-80.
24. McKay BE, McRory JE, Molineux ML, Hamid J, Snutch TP, Zamponi GW, et al. Ca(V)3 T-type calcium channel isoforms differentially distribute to somatic and dendritic compartments in rat central neurons. Eur J Neurosci 2006; 24:2581-94.
25. Pape HC, Budde T, Mager R, Kisvarday ZF. Prevention of Ca(2+)-mediated action potentials in GABAergic local circuit neurones of rat thalamus by a transient K^+ current. J Physiol 1994; 478:403-22.
26. Kim D, Song I, Keum S, Lee T, Jeong MJ, Kim SS, et al. Lack of the burst firing of thalamocortical relay neurons and resistance to absence seizures in mice lacking alpha(1G) T-type Ca(2+) channels. Neuron 2001; 31:35-45.
27. Molineux ML, Mehaffey WH, Tadayonnejad R, Anderson D, Tennent AF, Turner RW. Ionic factors governing rebound burst phenotype in rat deep cerebellar neurons. J Neurophysiology 2008; 100:2684-701.
28. Rhodes KJ, Carroll KI, Sung MA, Doliveira LC, Monaghan MM, Burke SL, et al. KChIPs and K_V4 alpha subunits as integral components of A-type potassium channels in mammalian brain. J Neurosci 2004; 24:7903-15.
29. Menegola M, Trimmer JS. Unanticipated region- and cell-specific downregulation of individual KChIP auxiliary subunit isotypes in $K_V4.2$ knock-out mouse brain. J Neurosci 2006; 26:12137-42.
30. Alonso G, Widmer H. Clustering of $K_V4.2$ potassium channels in postsynaptic membrane of rat supraoptic neurons: an ultrastructural study. Neuroscience 1997; 77:617-21.
31. Clark BD, Kwon E, Maffie J, Jeong HY, Nadal M, Strop P, et al. DPP6 Localization in Brain Supports Function as a K_V4 Channel Associated Protein. Front Mol Neurosci 2008; 1:8.
32. 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.
33. Cueni L, Canepari M, Lujan R, Emmenegger Y, Watanabe M, Bond CT, et al. T-type Ca^{2+} channels, SK2 channels and SERCAs gate sleep-related oscillations in thalamic dendrites. Nat Neurosci 2008; 11:683-92.
34. MacDonald JF, Xiong ZG, Jackson MF. Paradox of Ca^{2+} signaling, cell death and stroke. Trends Neurosci 2006; 29:75-81.
35. Hildebrand ME, Isope P, Miyazaki T, Nakaya T, Garcia E, Feltz A, et al. Functional coupling between mGluR1 and $Ca_V3.1$ T-type calcium channels contributes to parallel fiber-induced fast calcium signaling within Purkinje cell dendritic spines. J Neurosci 2009; 29:9668-82.
36. Soler-Llavina GJ, Sabatini BL. Synapse-specific plasticity and compartmentalized signaling in cerebellar stellate cells. Nat Neurosci 2006; 9:798-806.