NOMENCLATURE AND STRUCTURE-FUNCTION RELATIONSHIPS OF VOLTAGE-GATED POTASSIUM CHANNELS

Lily Yeh Jan*

Departments of Physiology, Biochemistry and Biophysics
University of California, San Francisco
San Francisco, CA 94158

The author serves on the Subcommittee on Voltage-gated Potassium Channels of the Nomenclature Committee of the International Union of Pharmacology (NC-IUPHAR).

Abstract – Voltage-gated potassium channels form a large and diverse family that is evolutionarily conserved. There are 40 human voltage-gated potassium channel genes belonging to 12 subfamilies. These K_V channels display broad distributions in the nervous system and other tissues. For excitable cells such as neurons, cardiomyocytes, and muscles, K_V channels regulate the waveform and firing pattern of action potentials. K_V channels may also regulate the cell volume, proliferation, and migration of a wide range of cell types.

Voltage-gated potassium (K_V) channels belong to one of the largest and highly evolutionarily conserved ion channel families[1]. Each K_V channel contains four similar or identical pore-forming α subunits, and it may also contain auxiliary β subunits that could affect the channel function and/or localization[2,3]. Each pore-forming subunit of K_V channels contains six transmembrane segments (S1-S6), with the first four transmembrane segments (S1-S4) constituting the voltage sensor and the last two transmembrane segments flanking a pore loop (S5-P-S6) as the pore domain. In addition to the chromosome location of each K_V channel gene in human, mouse and rat, the physiological and pharmacological properties of the channel, and its tissue distribution and pathophysiology have been provided by the Ion Channel Database by the Subcommittee on Voltage-gated potassium channels of the Nomenclature Committee of the International Union of Pharmacology (NC-IUPHAR). This article presents an introduction to the diversity and functions of voltage-gated potassium channels.

Evolutionary conservation of potassium channels

The K^+-selectivity that arose in prokaryotes is conserved in a large number of potassium channels with remarkable diversity[4]. As shown in Figure 1, an evolutionary tree of the voltage-gated cation channel superfamily can be proposed based on the comparison of channel genes in the human genome with those in the genomes of other metazoans including mouse, chicken, puffer fish, tunicate, fruit fly, mosquito, nematode and sea anemone[4]. This evolutionary tree envisions a single origin of the K^+-selectivity for inwardly rectifying potassium

(Kir) channels, voltage-gated potassium (K_V) channels, and the two-pore potassium (K_{2P}) channels. It is important to note, however, that a distinct K^+-selectivity is likely associated with the evolutionarily conserved organelle K^+ channel that resides in endosomes and lysosomes[5].

Diversity of voltage-gated potassium channels

The human genome contains ~80 potassium channel genes of which 40 genes encode voltage-gated potassium channel pore-forming subunits that fall into 12 subfamilies[2] (Fig. 2). Physiologically subdivided into A-type potassium channels that display fast inactivation and delayed rectifier potassium channels without fast inactivation, these K_V channels are molecularly and functionally diverse. Fast inactivation, which may impact the action potential duration during repetitive firing, is evident in K_V1 channels containing $K_V1.4$ or $K_V\beta1$, K_V3 channels, and K_V4 channels[2]. The delayed rectifier potassium current originally characterized by Hodgkin and Huxley for its role in action potential[6] likely corresponds to the squid K_V1 channels[7] that may rely on RNA editing to achieve the flexible functional diversity as many small axons of the giant fiber lobe neurons fuse to form the squid giant axon with greater action potential conduction rate[8-10].

Remarkable diversity of K_V channels may be achieved due to the mix and match of K_V channel subunits. Within each of the K_V1, K_V2, K_V3, K_V4 and K_V7 families, homomeric and heteromeric channels may form with a range of functional properties[2,11]. K_V2 family members may also assemble with K_V5, K_V6, K_V8 or K_V9

family members with more restricted expression patterns in the nervous system and smooth muscles[12], as illustrated schematically in Fig. 3.

Functional differences in the voltage dependence and kinetics of K_V channels underlie their differential contributions to action potential modulation[11] (Fig. 4). Whereas K_V1, K_V4 and K_V7 channels require low levels of membrane depolarization for their activation, K_V2 and K_V3 channels are activated by greater depolarization. The former, low voltage activated, K_V channels may affect the threshold for action potential generation and the number of action potentials generated during depolarization or excitatory synaptic potentials. In contrast, the high voltage activated K_V channels may modulate action potential duration and firing pattern[11]. The kinetics of K_V channels also influences the ways they contribute to action potential generation. Whereas the low voltage activated K_V1 channels with fast activation may affect action potential threshold and waveform, the high voltage activated K_V3 channels and K_V2 channels can be activated sequentially during an action potential due to the difference in their activation kinetics, and K_V2 channels may have more long-lasting effects because of their slow inactivation kinetics. Moreover, K_V4 channels with fast inactivation could contribute to the difference in the action potential waveform during repetitive firing, due to suppression of the K_V4 channel activity by depolarization[11].

Potential therapeutic applications of potassium channel modulators

The ability of potassium channel modulators to alter action potential firing patterns has raised the question whether they might be of therapeutic value[13]. As indicated in Fig. 5, various neurological and psychological disorders may involve alterations in the action potential firing patterns, which could be modulated by K_V channel activators and blockers[13]. Voltage-gated potassium channels may also play a role in cell proliferation and migration; K_V channel modulators have hence been considered for potential treatments of cancer growth and metastasis[14-20]. In Fig. 6, the K_V1.2 channel structure is used schematically to illustrate that K_V channel modulators may inhibit channel activity either by occluding the channel permeation pathway, as in the case of outer-pore-blocking toxins and inner pore blockers, or via their interaction with the voltage sensor to stabilized the closed state of the channel, as in the case of gating modifier toxins. Alternatively, some small molecules act by binding to the gating machinery as gating modifiers, or by interacting with the interface between the α- and β-subunits to alter channel activity[13].

Voltage-gated potassium channel structure

The remarkable selectivity of potassium channels, which allows K^+ ions to go through the channel pore with orders of magnitude greater ease than the smaller Na^+ ions *and* with near diffusion-limited rate[1], is accounted for by the ability of the backbone carbonyls of the selectivity filter to coordinate K^+ ions that are largely stripped of their hydration shells[21,22], so that more than one K^+ ion will move

through this narrowest segment of the pore in tandem[23] (Fig. 7) – a long pore for single file K^+ ion permeation as predicated[1].

The voltage dependence of K_V channel activation[1,6] derives from their voltage sensor domains[23-25]. As shown in Fig. 8, K_V channels and related channels such as voltage-gated sodium channels and TRPV1 channels in the same superfamily have similar arrangements of their pore domains and voltage sensor domains. The voltage sensor domain of one subunit interacts with the pore domain of a neighboring subunit in a domain swap configuration, and within a voltage sensor the positively charged arginine residues on S4 may interact with negatively charged acidic residues in neighboring helices (Fig. 9).

Channelopathies linked to Voltage-gated potassium channels

Voltage-gated potassium channels are broadly expressed in a variety of tissues. In neurons, they are targeted to various subcellular compartments[3,26] (Fig. 10), and channels of different subunit compositions may be present in different subpopulations of neurons[27]. Mutations of K_V channel genes may cause neurological diseases such as episodic ataxia and epilepsies, heart diseases, and deafness[28-31]. Evolutionary conservation of K_V channel function is evident, for example, from the similar movement disorders caused by mutation of K_V1 orthologs in human, mouse, and the fruit fly[10].

Figure Legends

Figure 1. An evolutionary tree for the genesis of the voltage-gated cation channel superfamily

Based on genome-wide analyses of ion channels from cnidarians and bilateral metazoans[4], this evolutionary tree depicts a common origin for the K^+-selectivity of potassium channels (with family names in red ovals), which are related to tetrameric cyclic nucleotide-gated cation (CNG) channels, hyperpolarization-gated cation (HCN) channels and TRP channels, the dimeric TPC channels, and the monomeric Na^+, Ca^{2+}, and NALCN channels. The branch lengths do not reflect time. The gene family names at the bottom mark individual branches. Ionotropic glutamate receptors are included based on the hypothesis that they originated from an inversion of the potassium channel pore-forming domain with two transmembrane segments (red). The voltage-sensor domain has four transmembrane segments (green). A: ankryin repeats; CAM: calmodulin-binding domain; CNG: cyclic nucleotide-binding domain; PAS: Per-ARNT-Sim domain; RCK: regulator of conductance of K^+ domain; T1: tetramerization domain.

Figure 2. Phylogenetic tree for the K_V1-12 families

This phylogenetic tree is generated based on analyses of the hydrophobic domain containing the six transmembrane segments (S1-S6)[2]. Both the IUPHAR

and the HGNC (in parenthesis) names are shown, along with other commonly used names for these voltage-gated potassium channels.

Figure 3. K_V channel diversity via mix and match of pore-forming channel subunits

(A) The tetrameric K_V channels with different properties and distribution encompass homomeric K_V1, K_V2, K_V3, K_V4, and K_V7 channels, heteromeric channels formed by different members within each of these K_V channel families, and heteromeric channels formed by assembly of Kv2 family members with K_V5, K_V6, K_V8, or K_V9 family members[12]. K_V5, K_V6, K_V8 and K_V9 families give rise to homomeric channels that are electrically silent likely due to their retention in the endoplasmic reticulum[12], hence they are referred as K_VS. (B) Assembly of K_V2 and K_VS family members involve their cytoplasmic N- and C-terminal domains. (C, D) Assembly of K_V2 and K_VS family members gives rise to heteromeric channels with different voltage dependence (C) and gating mechanisms (D) as compared to homomeric channels formed by K_V2 family members[12].

Figure 4. Functional differences of Kv channels and their contributions to the action potential

(A) Different K_V channels have different voltage dependence for activation and different kinetics[11]. (B) The low voltage activated K_V1 channels with fast kinetics open as the cell is depolarized towards the threshold for action potential generation. While both K_V2 and K_V3 channels are high voltage activated, K_V3

channels open sooner than K_V2 channels during an action potential. K_V2 channels may also take longer to close following an action potential[11].

Figure 5. Potential applications of K_V channel modulators

Because abnormal action potential firing patterns have been associated with diseases such as epilepsy and multiple sclerosis, K_V channel activators and inhibitors have been considered for potential therapeutic treatments of diseases that involve alteration of neuronal excitability[13].

Figure 6. Examples of modes of action of K_V channel modulators

There are several different ways for peptide toxins and small molecules to modulate K_V channel activity. The $K_V1.2$ structure[32] is shown with the pore domains (S5-P-S6) in green, the voltage sensor domains (S1-S4) in grey, the T1 tetramerization domains in orange, and the $K_V\beta2$ auxiliary subunits in magenta[13]. Outer-pore-blocking toxins from scorpions, sea anemones, snakes, and cone snails may bind to the outer vestibule and block ion permeation. Gating modifier toxins from spiders such as hanatoxin may interact with the voltage sensor to increase the stability of the closed state, causing rightward shift of the voltage dependence curve for channel activation. There are also small molecule channel modulators that bind to the inner pore (inner pore blockers), the gating hinges (gating modifiers), or the interface between the α- and β-subunits (disinactivators)[13].

Figure 7. The pore domain of potassium channels

(a) Structure of KcsA in the conductive state (PDB: 1K4C)[21], with the outer helices in magenta, inner helices in orange, pore helices in blue, and the selectivity filter in yellow. K^+ ions are in purple while its surrounding water molecules are in red. EC: extracellular; IC: intracellular. (b, c) The selectivity filter in the boxed region of the KcsA structure is shown with K^+ ions occupying either the S2 and S4 positions (b) or the S1 and S3 positions (c), to illustrate K^+ ion permeation in single file[23].

Figure 8. The voltage sensor domain of voltage-gated potassium channels

(a) Aligning the pore domain (S5-P-S6) of different ion channels reveals that their voltage sensor domains (S1-S4) can take on a variety of orientations (viewed from the extracellular side)[23]. (b) Superimposition of the voltage sensor domain of $K_V1.2$ (PDB: 3LUT, light magenta)[33] with the voltage sensor domains of MlotiK1 (PDB: 3BEH, light brown)[34], Na_VAb (PDB: 3RVY, light green)[35], Na_VRh (PDB: 4DXW, light orange)[36] and TRPV1 (PDB: 3J5P, light blue)[37] (viewed from the membrane)[23].

Figure 9. Contacts between the pore domain and the voltage sensor domain of K_V channels

(a) The $K_V1.2$-$K_V2.1$ chimera (PDB: 2R9R)[38] with the voltage sensor domain of one subunit (light blue) contacting the pore domain of a neighboring subunit (pink). The contacts on the intracellular side involve the interaction of the S4-S5

linker with S6, and the contacts on the extracellular side involve the interaction between S1 and the pore helix[23]. Lipids (yellow) surrounding the channel and in between the pore domain and the voltage sensor domain are detectable in the crystal structure. (b) Basic residues of S4 and acidic residues in their proximity in the voltage sensor domain[23].

Figure 10. Subcellular distribution of voltage-gated potassium channels

The schematic on the top left depicts a K_V4 channel with two different auxiliary subunits. Subcellular localization of various K_V channels in mammalian central neurons is indicated in the middle box[3].

REFERENCES AND NOTES

1 Hille, B. *Ionic Channels of Excitable Membranes, 3rd, Ed.*, (Sinauer Associates Inc., 2001).

2 Gonzalez, C., Baez-Nieto, D., Valencia, I., Oyarzun, I., Rojas, P., Naranjo, D. & Latorre, R. K^+ channels: function-structural overview. *Compr Physiol* **2**, 2087-2149 (2012).

3 Vacher, H., Mohapatra, D. P. & Trimmer, J. S. Localization and targeting of voltage-dependent ion channels in mammalian central neurons. *Physiol Rev* **88**, 1407-1447 (2008).

4 Jegla, T. J., Zmasek, C. M., Batalov, S. & Nayak, S. K. Evolution of the human ion channel set. *Comb Chem High Throughput Screen* **12**, 2-23 (2009).

5 Cang, C., Aranda, K., Seo, Y. J., Gasnier, B. & Ren, D. TMEM175 Is an Organelle K^+ Channel Regulating Lysosomal Function. *Cell* **162**, 1101-1112 (2015).

6 Hodgkin, A. L. & Huxley, A. F. Currents carried by sodium and potassium ions through the membrane of the giant axon of Loligo. *J Physiol* **116**, 449-472 (1952).

7 Rosenthal, J. J., Liu, T. I. & Gilly, W. F. A family of delayed rectifier K_V1 cDNAs showing cell type-specific expression in the squid stellate ganglion/giant fiber lobe complex. *J Neurosci* **17**, 5070-5079 (1997).

8 Young, J. Z. Fused neurons and synaptic contacts in the giant nerve fibres of cephalopods. *Phil Trans R Soc Lond B* **229**, 465-503 (1939).

9 Rosenthal, J. J. & Bezanilla, F. Extensive editing of mRNAs for the squid delayed rectifier K^+ channel regulates subunit tetramerization. *Neuron* **34**, 743-757 (2002).

10 Jan, L. Y. & Jan, Y. N. Voltage-gated potassium channels and the diversity of electrical signalling. *J Physiol* **590**, 2591-2599 (2012).

11 Johnston, J., Forsythe, I. D. & Kopp-Scheinpflug, C. Going native: voltage-gated potassium channels controlling neuronal excitability. *J Physiol* **588**, 3187-3200 (2010).

12 Bocksteins, E. K_V5, K_V6, K_V8, and K_V9 subunits: No simple silent bystanders. *J Gen Physiol* **147**, 105-125 (2016).

13 Wulff, H., Castle, N. A. & Pardo, L. A. Voltage-gated potassium channels as therapeutic targets. *Nat Rev Drug Discov* **8**, 982-1001 (2009).

14 Bates, E. Ion channels in development and cancer. *Annu Rev Cell Dev Biol* **31**, 231-247 (2015).

15 Huang, X. & Jan, L. Y. Targeting potassium channels in cancer. *J Cell Biol* **206**, 151-162 (2014).

16 Huang, X., He, Y., Dubuc, A. M., Hashizume, R., Zhang, W., Reimand, J., Yang, H., Wang, T. A., Stehbens, S. J., Younger, S., Barshow, S., Zhu, S., Cooper, M. K., Peacock, J., Ramaswamy, V., Garzia, L., Wu, X., Remke, M., Forester, C. M., Kim, C. C., Weiss, W. A., James, C. D., Shuman, M. A., Bader, G. D., Mueller, S., Taylor, M. D., Jan, Y. N. & Jan, L. Y. EAG2 potassium channel with evolutionarily conserved function as a brain tumor target. *Nat Neurosci* **18**, 1236-1246 (2015).

17 Kunzelmann, K. Ion channels and cancer. *J Membr Biol* **205**, 159-173 (2005).

18 Li, M. & Xiong, Z. G. Ion channels as targets for cancer therapy. *Int J Physiol Pathophysiol Pharmacol* **3**, 156-166 (2011).

19 Pardo, L. A. Voltage-gated potassium channels in cell proliferation. *Physiology (Bethesda)* **19**, 285-292 (2004).

20 Urrego, D., Tomczak, A. P., Zahed, F., Stuhmer, W. & Pardo, L. A. Potassium channels in cell cycle and cell proliferation. *Philos Trans R Soc Lond B Biol Sci* **369**, 20130094 (2014).

21 Zhou, Y., Morais-Cabral, J. H., Kaufman, A. & MacKinnon, R. Chemistry of ion coordination and hydration revealed by a K^+ channel-Fab complex at 2.0 A resolution. *Nature* **414**, 43-48 (2001).

22 MacKinnon, R. Potassium channels. *FEBS Lett* **555**, 62-65 (2003).

23 Kuang, Q., Purhonen, P. & Hebert, H. Structure of potassium channels. *Cell Mol Life Sci* **72**, 3677-3693 (2015).

24 Isacoff, E. Y., Jan, L. Y. & Minor, D. L., Jr. Conduits of life's spark: a perspective on ion channel research since the birth of neuron. *Neuron* **80**, 658-674 (2013).

25 Swartz, K. J. Sensing voltage across lipid membranes. *Nature* **456**, 891-897 (2008).

26 Nusser, Z. Differential subcellular distribution of ion channels and the diversity of neuronal function. *Curr Opin Neurobiol* **22**, 366-371 (2012).

27 Lujan, R. Organisation of potassium channels on the neuronal surface. *J Chem Neuroanat* **40**, 1-20 (2010).

28 Abriel, H. & Zaklyazminskaya, E. V. Cardiac channelopathies: genetic and molecular mechanisms. *Gene* **517**, 1-11 (2013).

29 Kullmann, D. M. & Hanna, M. G. Neurological disorders caused by inherited ion-channel mutations. *Lancet Neurol* **1**, 157-166 (2002).

30 Lehmann-Horn, F. & Jurkat-Rott, K. Voltage-gated ion channels and hereditary disease. *Physiol Rev* **79**, 1317-1372 (1999).

31 Villa, C. & Combi, R. Potassium Channels and Human Epileptic Phenotypes: An Updated Overview. *Front Cell Neurosci* **10**, 81 (2016).

32 Long, S. B., Campbell, E. B. & Mackinnon, R. Crystal structure of a mammalian voltage-dependent Shaker family K^+ channel. *Science* **309**, 897-903 (2005).

33 Chen, X., Wang, Q., Ni, F. & Ma, J. Structure of the full-length Shaker potassium channel $K_V1.2$ by normal-mode-based X-ray crystallographic refinement. *Proc Natl Acad Sci U S A* **107**, 11352-11357 (2010).

34 Clayton, G. M., Altieri, S., Heginbotham, L., Unger, V. M. & Morais-Cabral, J. H. Structure of the transmembrane regions of a bacterial cyclic nucleotide-regulated channel. *Proc Natl Acad Sci U S A* **105**, 1511-1515 (2008).

35 Payandeh, J., Scheuer, T., Zheng, N. & Catterall, W. A. The crystal structure of a voltage-gated sodium channel. *Nature* **475**, 353-358 (2011).

36 Zhang, X., Ren, W., DeCaen, P., Yan, C., Tao, X., Tang, L., Wang, J., Hasegawa, K., Kumasaka, T., He, J., Wang, J., Clapham, D. E. & Yan, N. Crystal structure of an orthologue of the NaChBac voltage-gated sodium channel. *Nature* **486**, 130-134 (2012).

37 Liao, M., Cao, E., Julius, D. & Cheng, Y. Structure of the TRPV1 ion channel determined by electron cryo-microscopy. *Nature* **504**, 107-112 (2013).

38 Long, S. B., Tao, X., Campbell, E. B. & MacKinnon, R. Atomic structure of a voltage-dependent K^+ channel in a lipid membrane-like environment. *Nature* **450**, 376-382 (2007).

Potassium Channels

(legends for the following ten figures are included in the posted introduction to nomenclature and structure-function relationships of voltage-gated potassium channels)

Paper Discussion (Structure-Function)

Voltage Gating

Ion selectivity

K channels: $P_K/P_{Na} > 1000$ ($K^+ > Na^+$ in ion size)

Na channels: Na^+ plus H_2O can fit in the pore

Ca channels: permeation of Ca^{2+} that is of the same size as Na^+ but is orders of magnitude lower in abundance

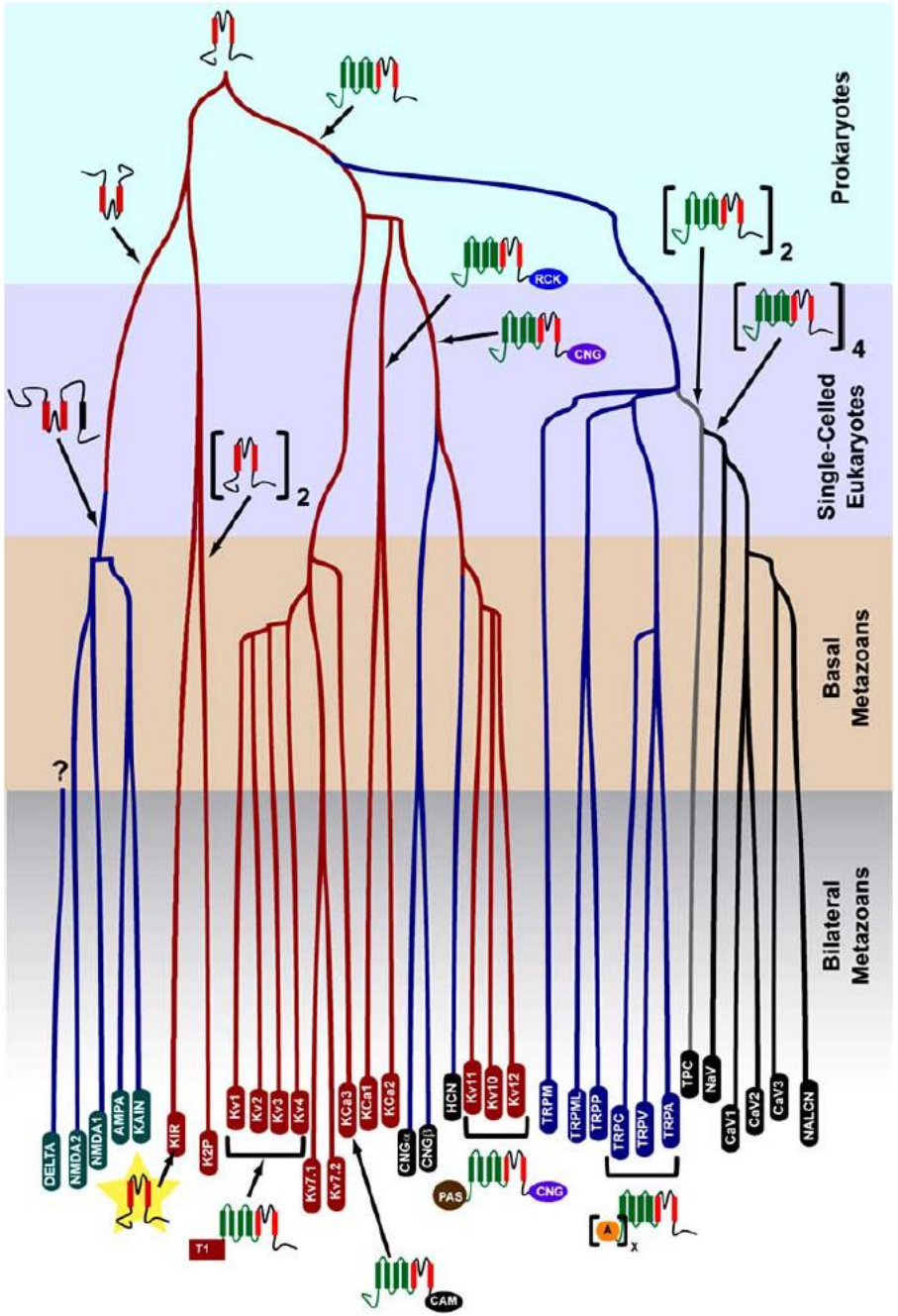


Figure 1. An evolutionary tree for the genesis of the voltage-gated cation channel superfamily

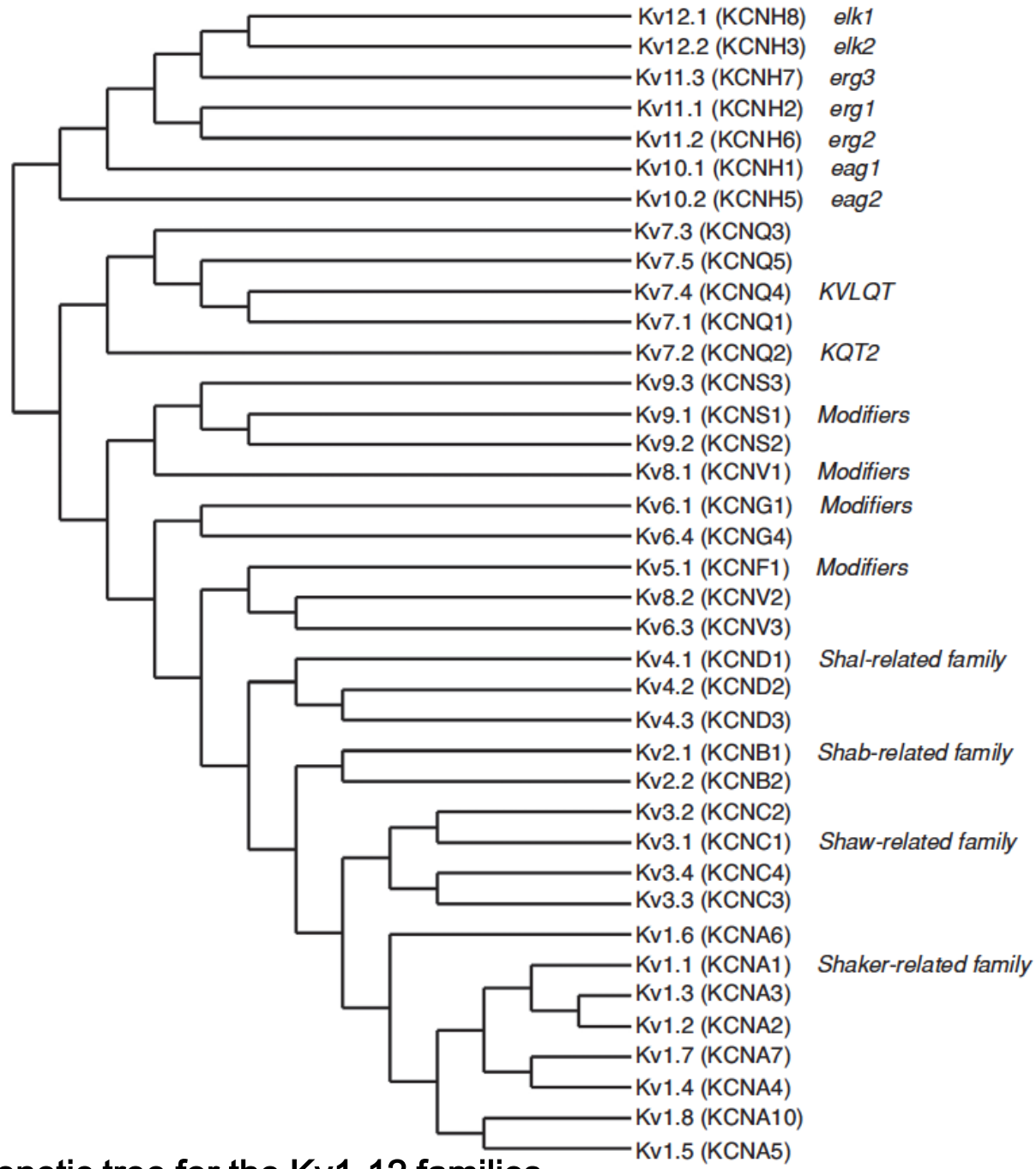


Figure 2. Phylogenetic tree for the Kv1-12 families

J Gen Physiol 147, 105-125, 2016

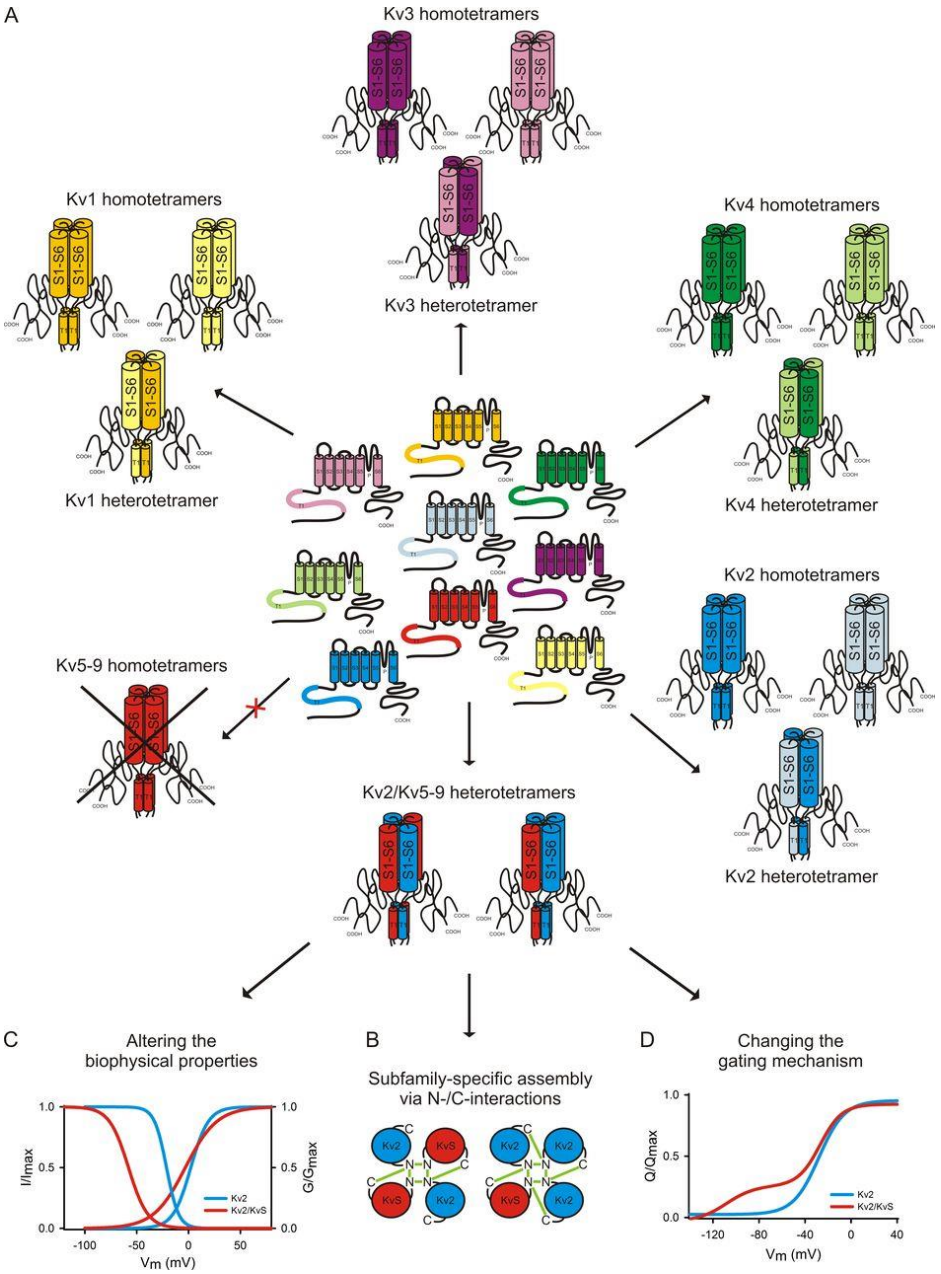


Figure 3. Kv channel diversity via mix and match of pore-forming channel subunits

Journal of Physiology 588, 3187-3200, 2010

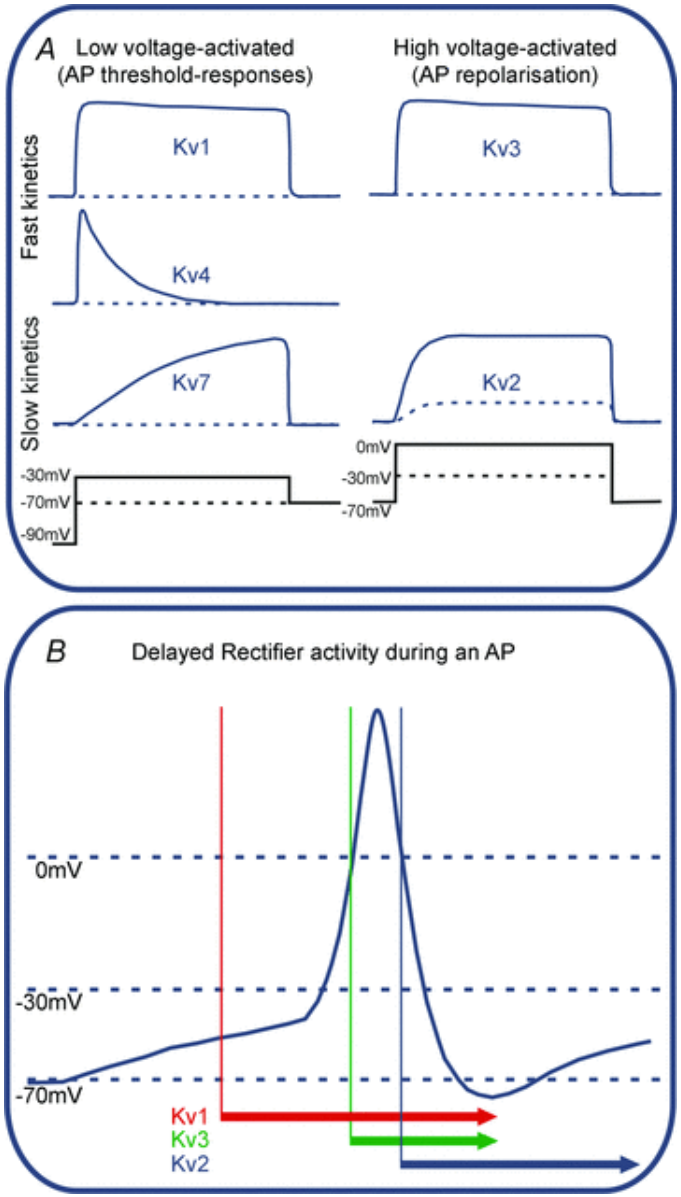


Figure 4. Functional differences of Kv channels and their contributions to the action potential

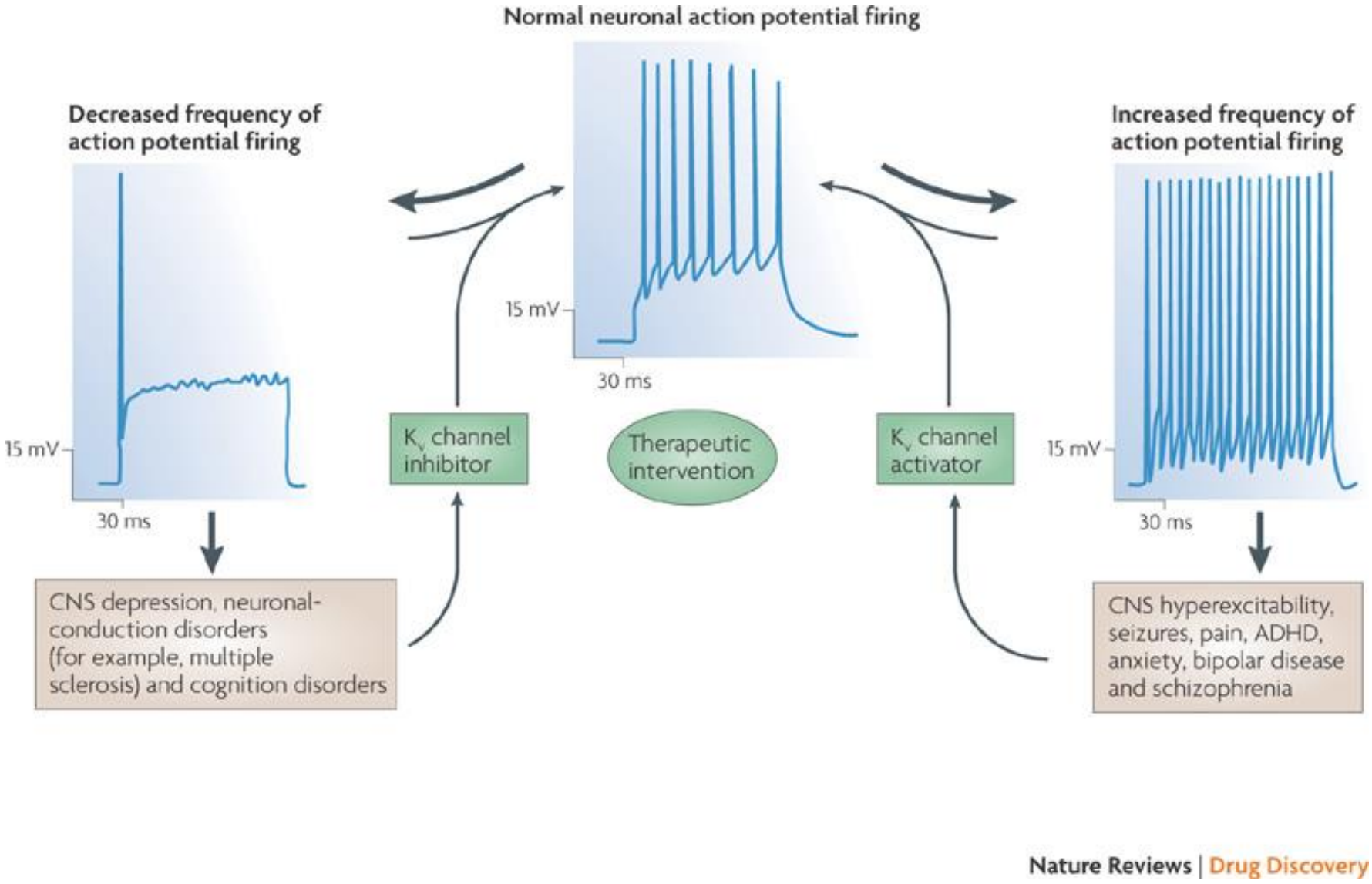


Figure 5. Potential applications of Kv channel modulators

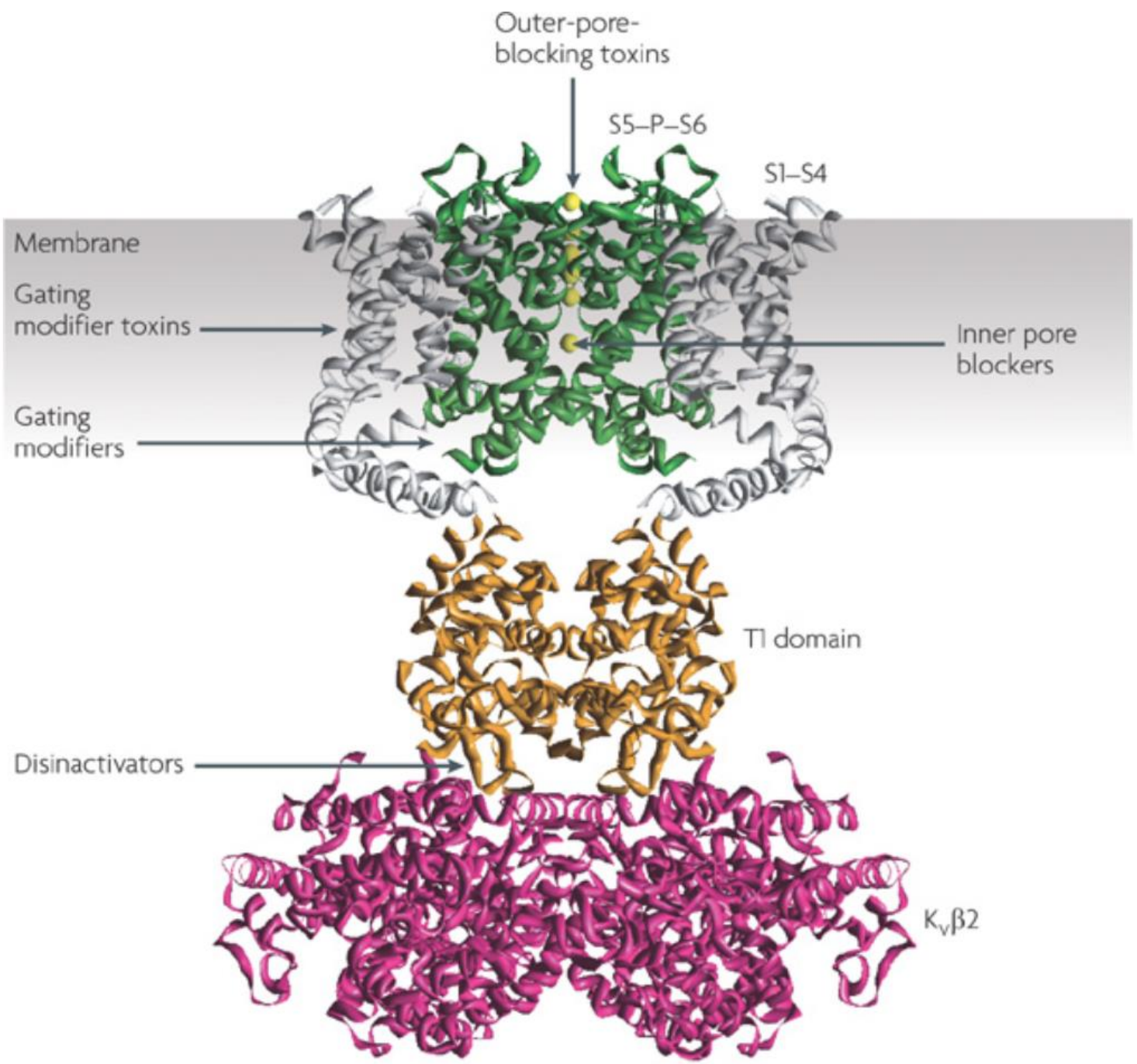


Figure 6. Examples of modes of action of Kv channel modulators

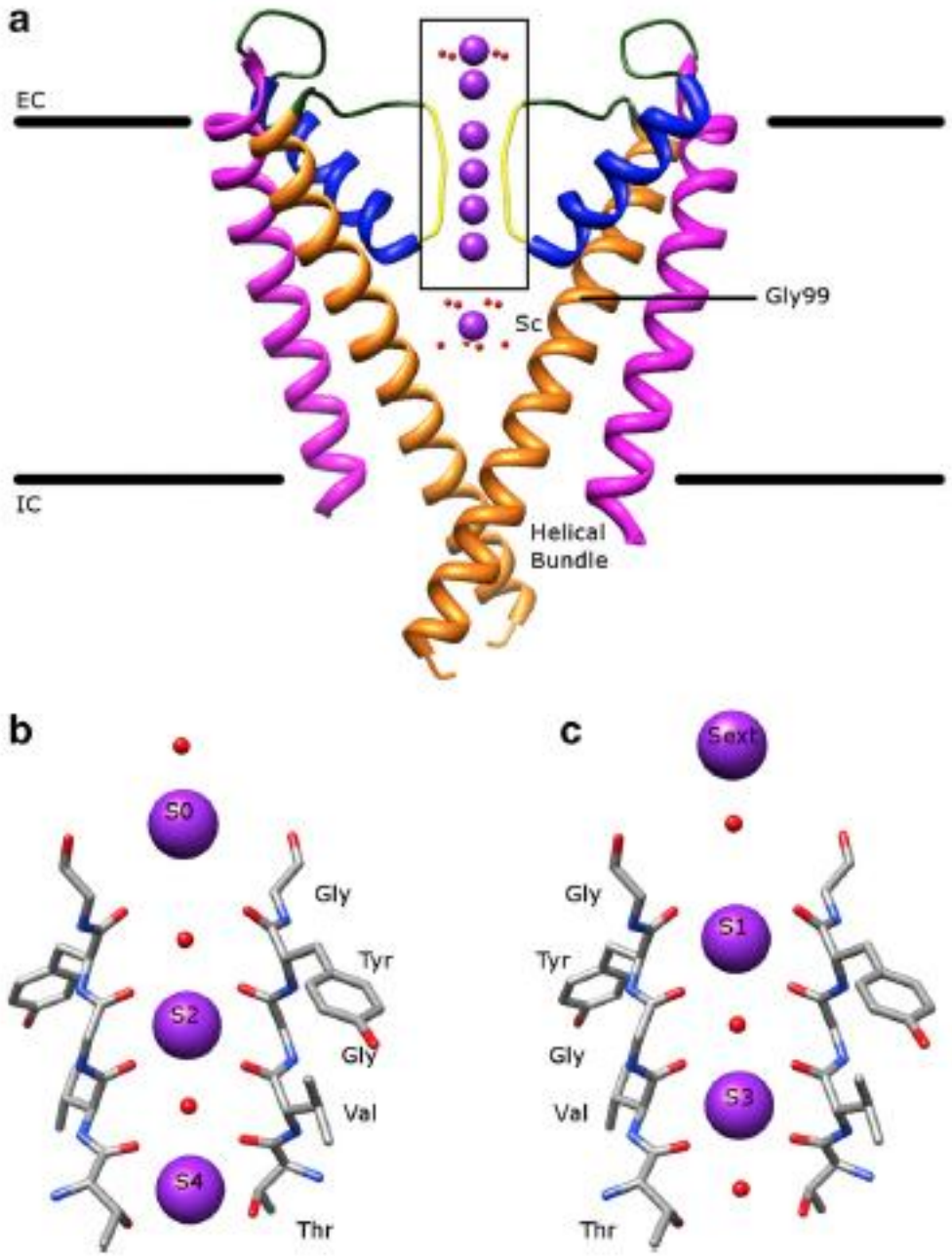


Figure 7. The pore domain of potassium channels

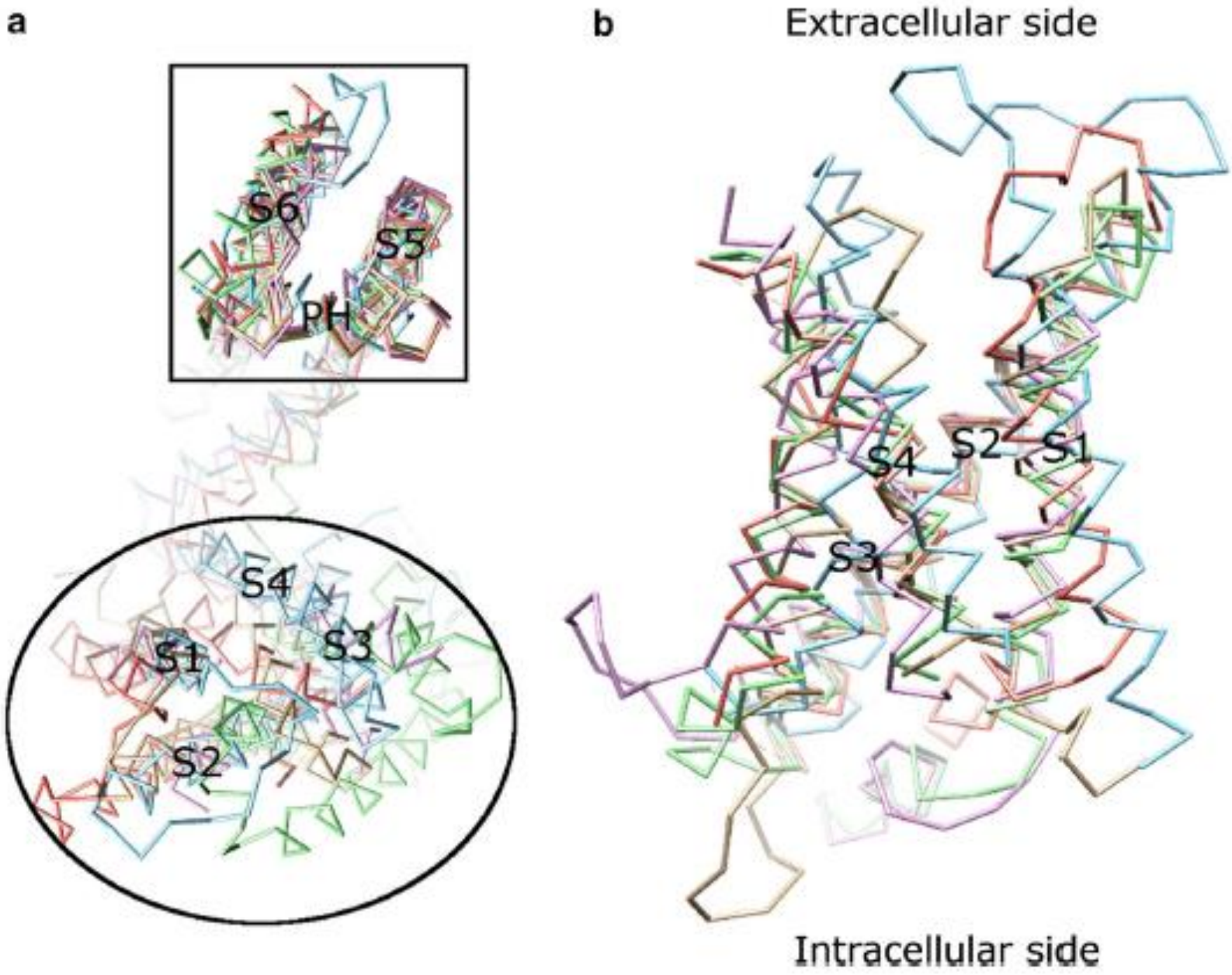


Figure 8. The voltage sensor domain of voltage-gated potassium channels

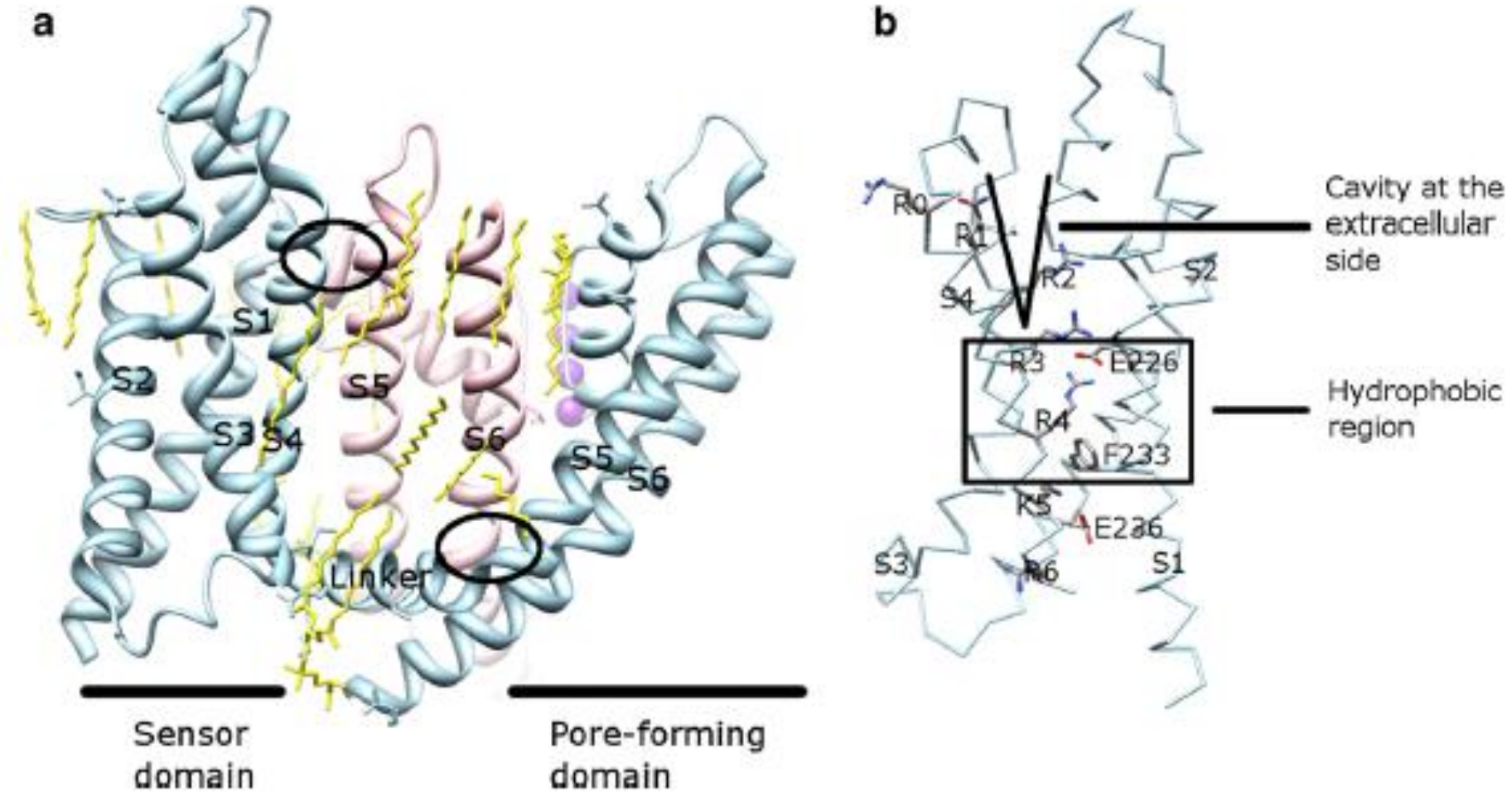
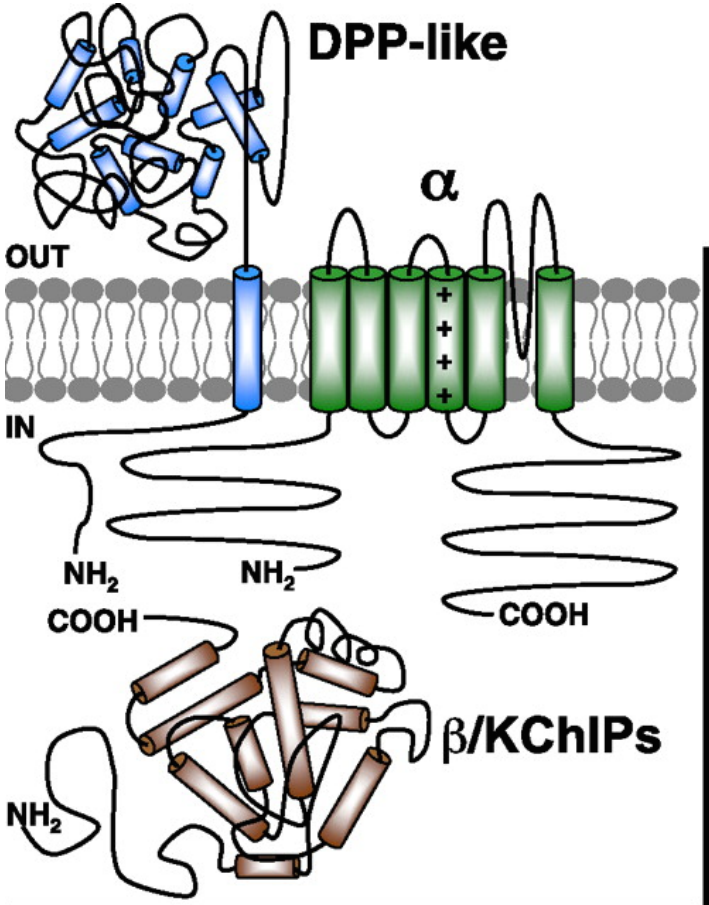


Figure 9. Contacts between the pore domain and the voltage sensor domain of Kv channels



Auxiliary Subunits

Type	Name	Effects on α function
$K_V\beta$	$K_V\beta1$	gating, kinetics
	$K_V\beta2$	trafficking,
	$K_V\beta3$	gating, kinetics
KChIP	KChIP1-4	trafficking, kinetics
DPP-like	DPPx, DPP1-10	trafficking, kinetics

Principal Subunits

Channel	Gene	Subcellular Localization
$K_V1.1$	*KCNA1*	axon, some dendritic
$K_V1.2$	*KCNA2*	axon
$K_V1.3$	*KCNA3*	axon
$K_V1.4$	*KCNA4*	axon
$K_V1.6$	*KCNA6*	axon
$K_V2.1$	*KCNB1*	soma, proximal dendrites
$K_V2.2$	*KCNB2*	soma, dendrites
$K_V3.1$	*KCNC1*	axon (Kv3.1b) somatodendritic (Kv3.1a)
$K_V3.2$	*KCNC2*	soma, dendrites
$K_V3.3$	*KCNC3*	axon
$K_V3.4$	*KCNC4*	axon
$K_V4.1$	*KCND1*	soma, dendrites
$K_V4.2$	*KCND2*	soma, dendrites
$K_V4.3$	*KCND3*	soma, dendrites
$K_V7.2$	*KCNQ2*	axon
$K_V7.3$	*KCNQ3*	axon, soma, dendrites
$K_V7.5$	*KCNQ5*	soma, dendrites

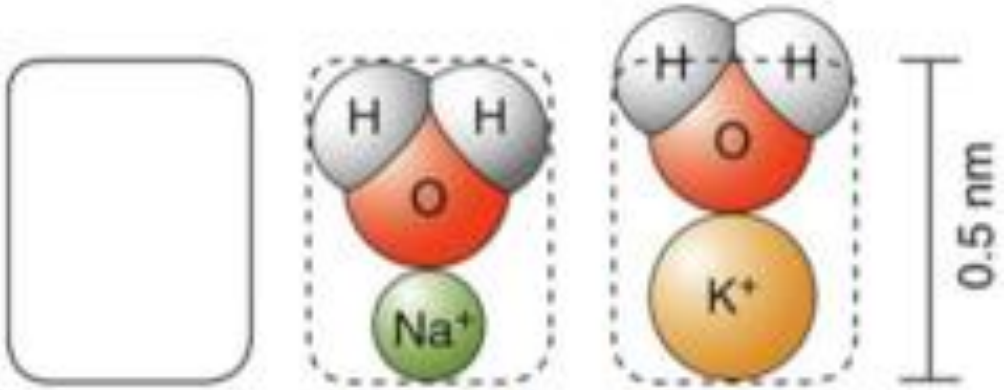
Principal Subunits
(unknown brain localization)

Channel	Gene
$K_V1.5$	*KCNA5*
$K_V1.8$	*KCNA10*
$K_V5.1$	*KCNF1*
$K_V6.1$	*KCNG1*
$K_V6.2$	*KCNG2*
$K_V6.3$	*KCNG3*
$K_V6.4$	*KCNG4*
$K_V8.1$	*KCNV1*
$K_V9.1$	*KCNS1*
$K_V9.2$	*KCNS2*
$K_V9.3$	*KCNS3*
$K_V10.1$	*KCNH1*
$K_V10.2$	*KCNH5*
$K_V11.1$	*KCNH2*
$K_V11.2$	*KCNH6*
$K_V11.3$	*KCNH7*
$K_V12.1$	*KCNH8*
$K_V12.2$	*KCNH3*
$K_V12.3$	*KCNH4*

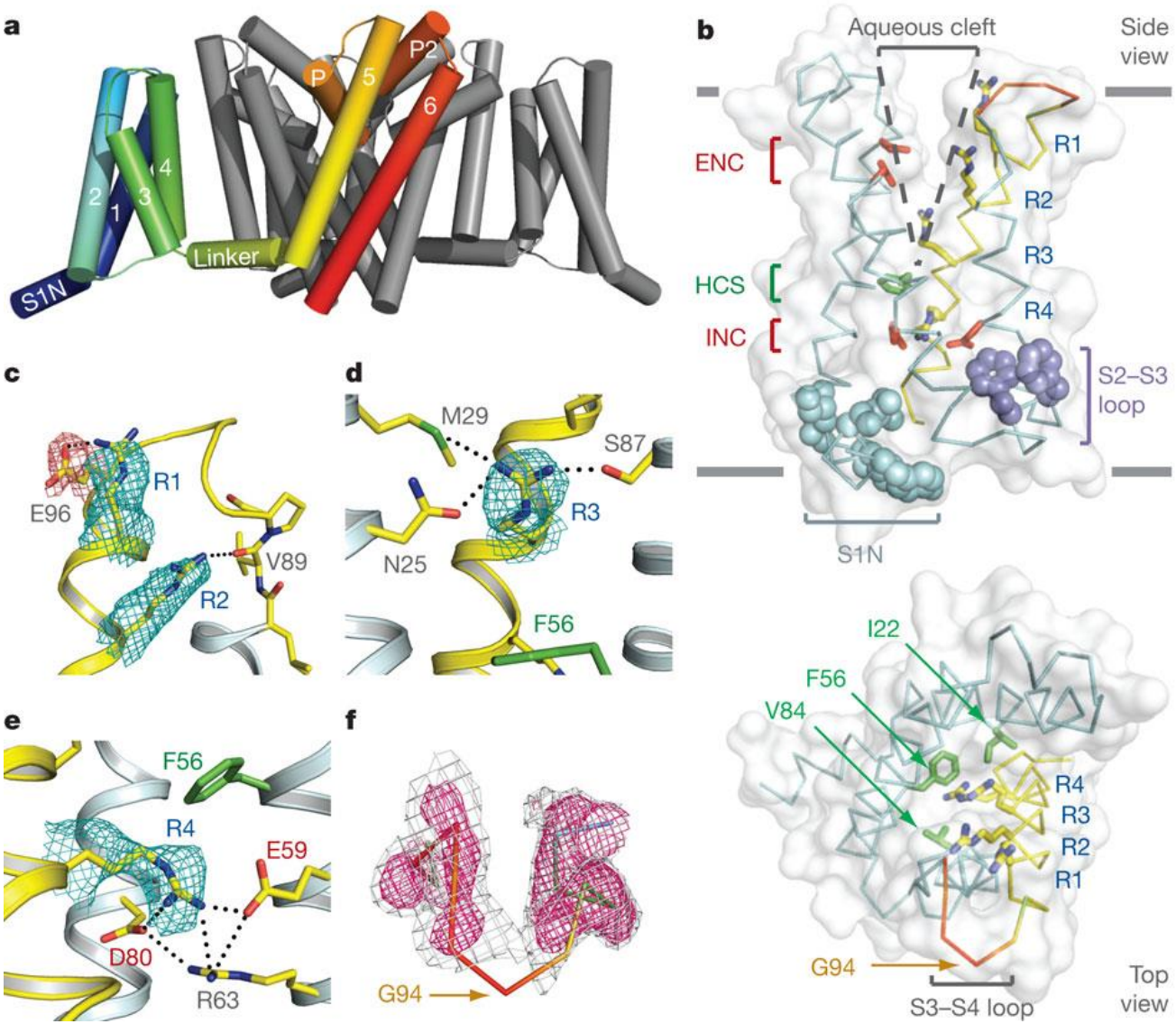
Figure 10. Subcellular distribution of voltage-gated potassium channels

Na channel has larger pore than K channel but prefers smaller Na^+ ions over larger K^+ ions

- Partially hydrated Na^+ ions can go through
- Selectivity filter can replace some waters around Na^+ ions better and hence it energetically favors dehydration of Na^+ ions over K^+ ions



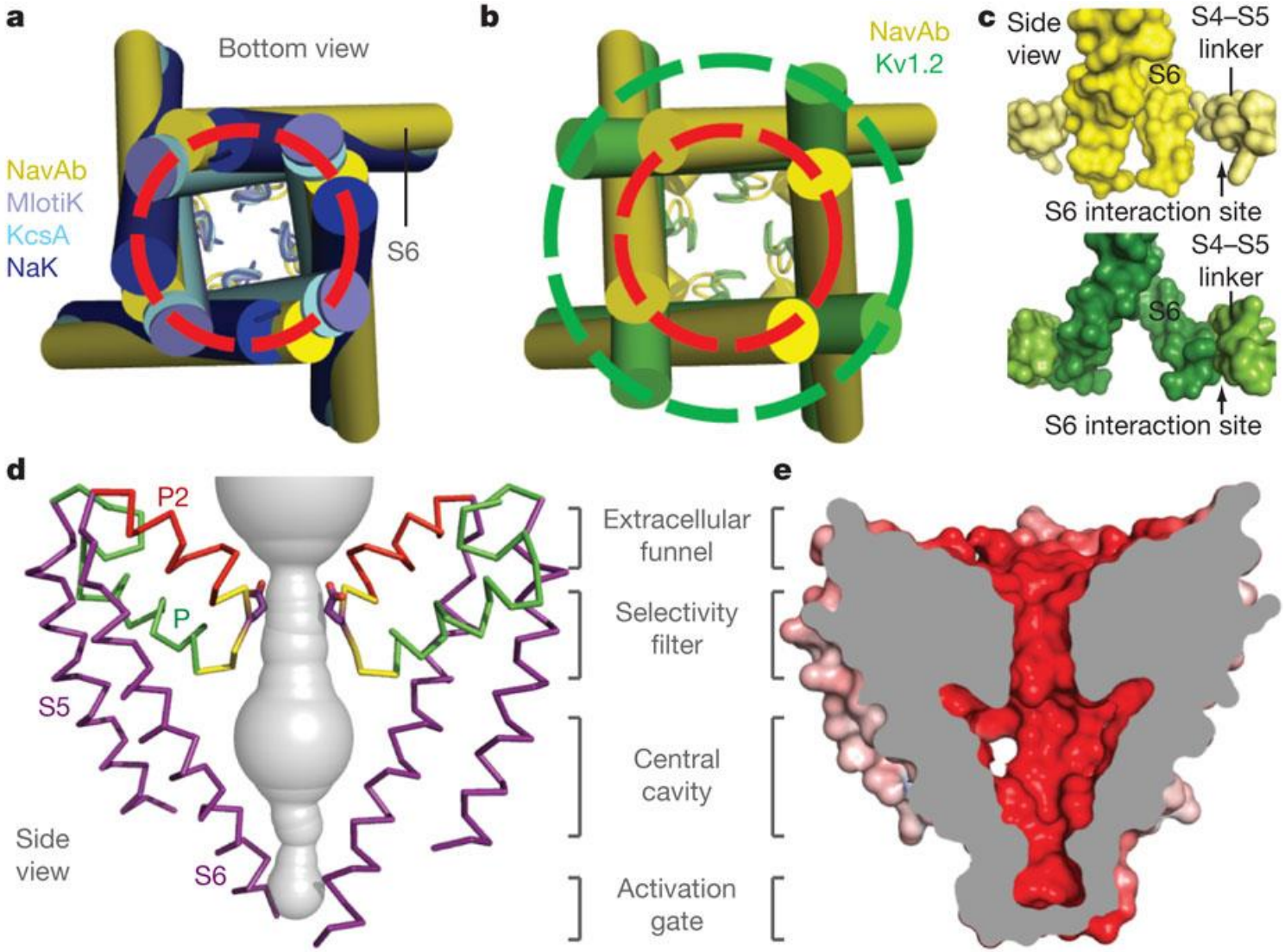
Structure of NavAb and the Activated VSD



J Payandeh *et al. Nature* (2011) doi:10.1038/nature10238

nature

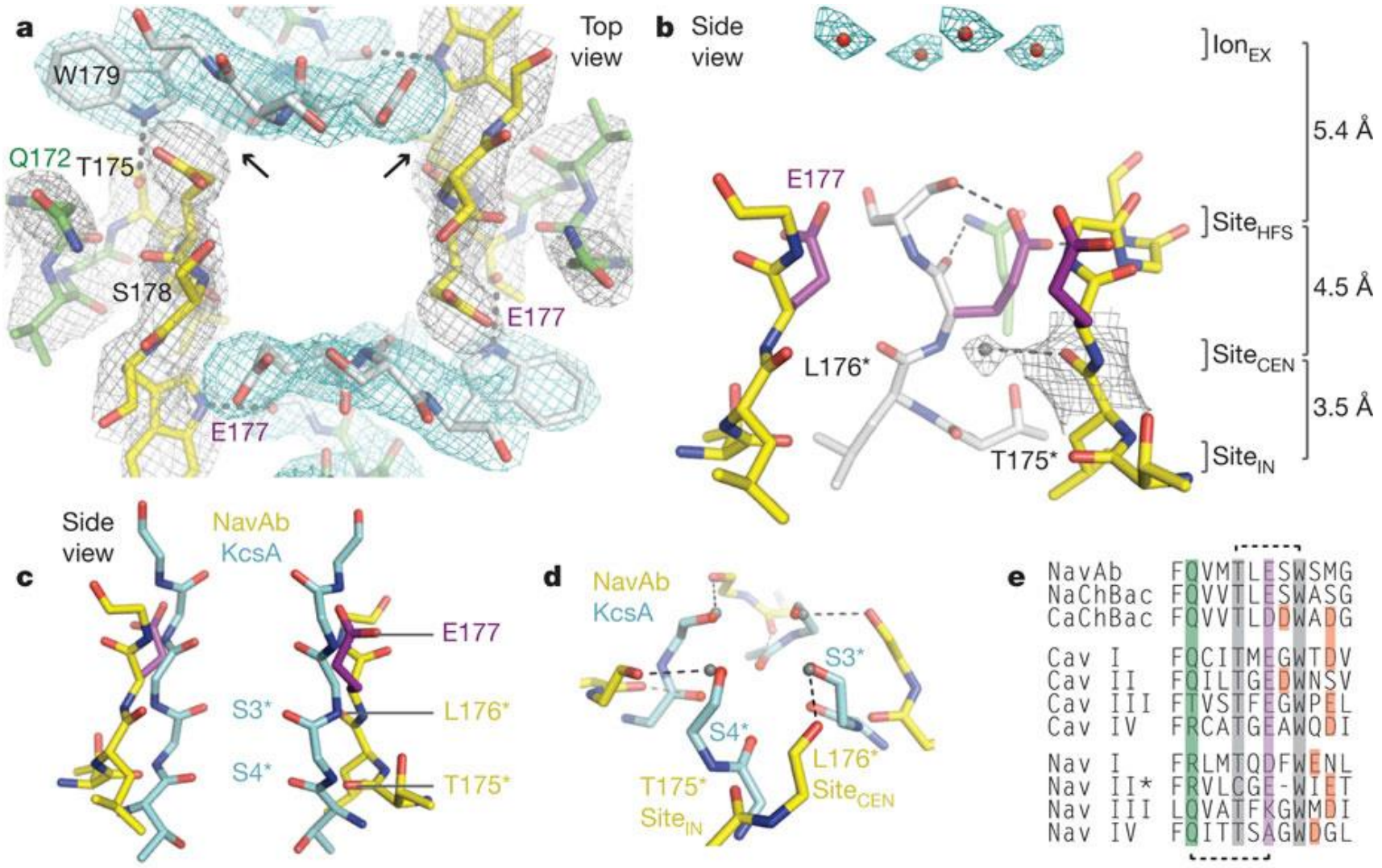
NavAb Pore Module



J Payandeh *et al. Nature* (2011) doi:10.1038/nature10238

nature

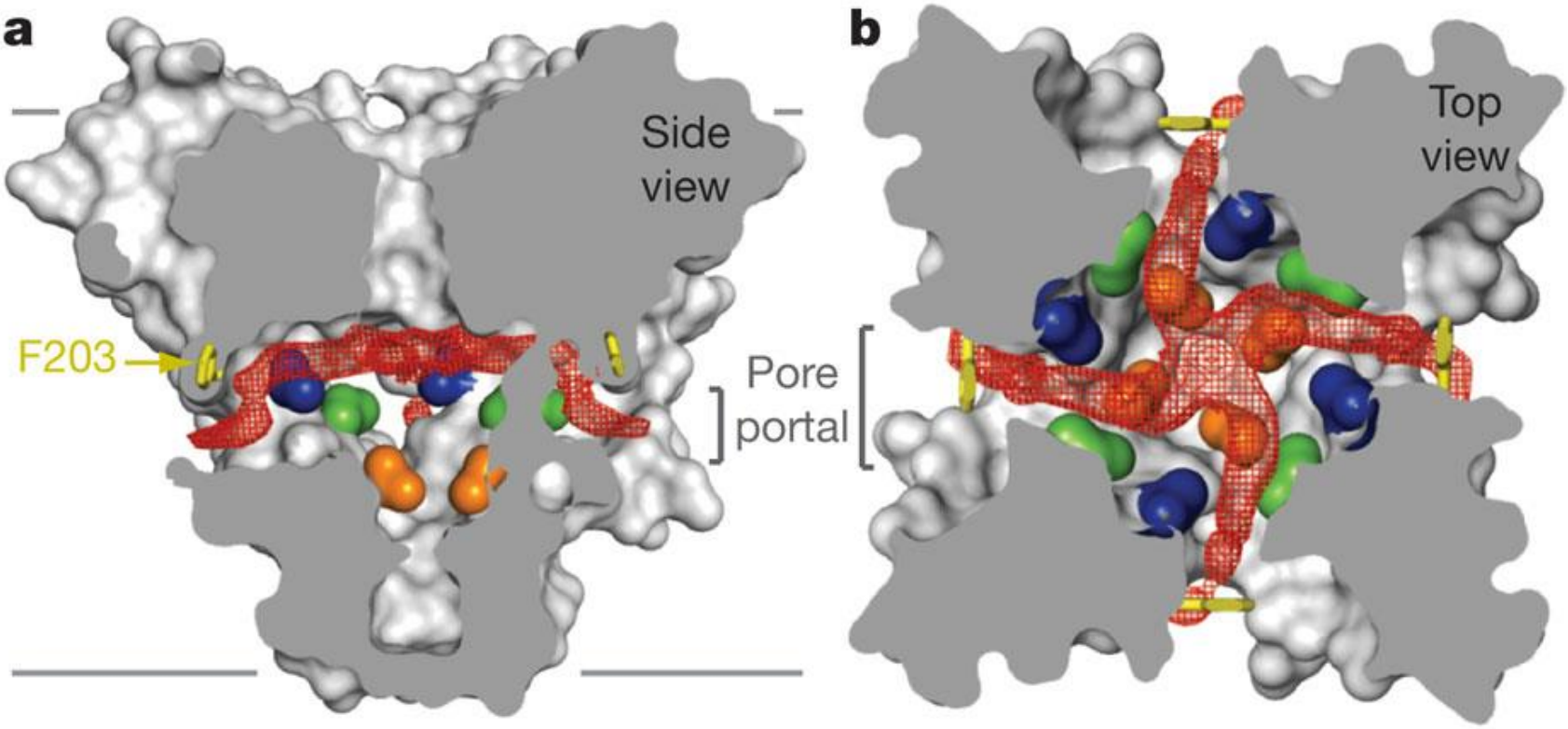
Structure of the NavAb Selectivity Filter



J Payandeh *et al. Nature* (2011) doi:10.1038/nature10238

nature

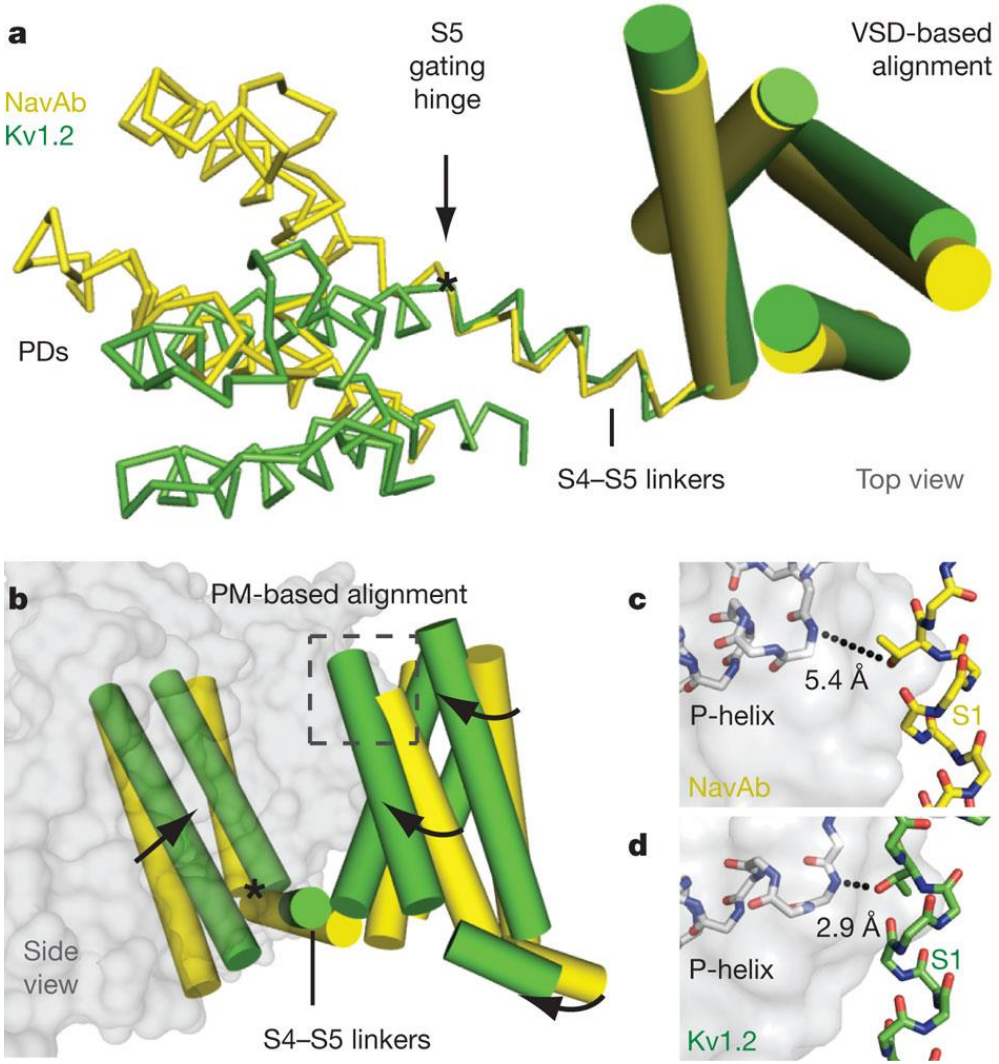
Membrane Access to the Central Cavity in NavAb



J Payandeh *et al. Nature* (2011) doi:10.1038/nature10238

nature

Model for Activation Gate Opening



J Payandeh *et al. Nature* (2011) doi:10.1038/nature10238

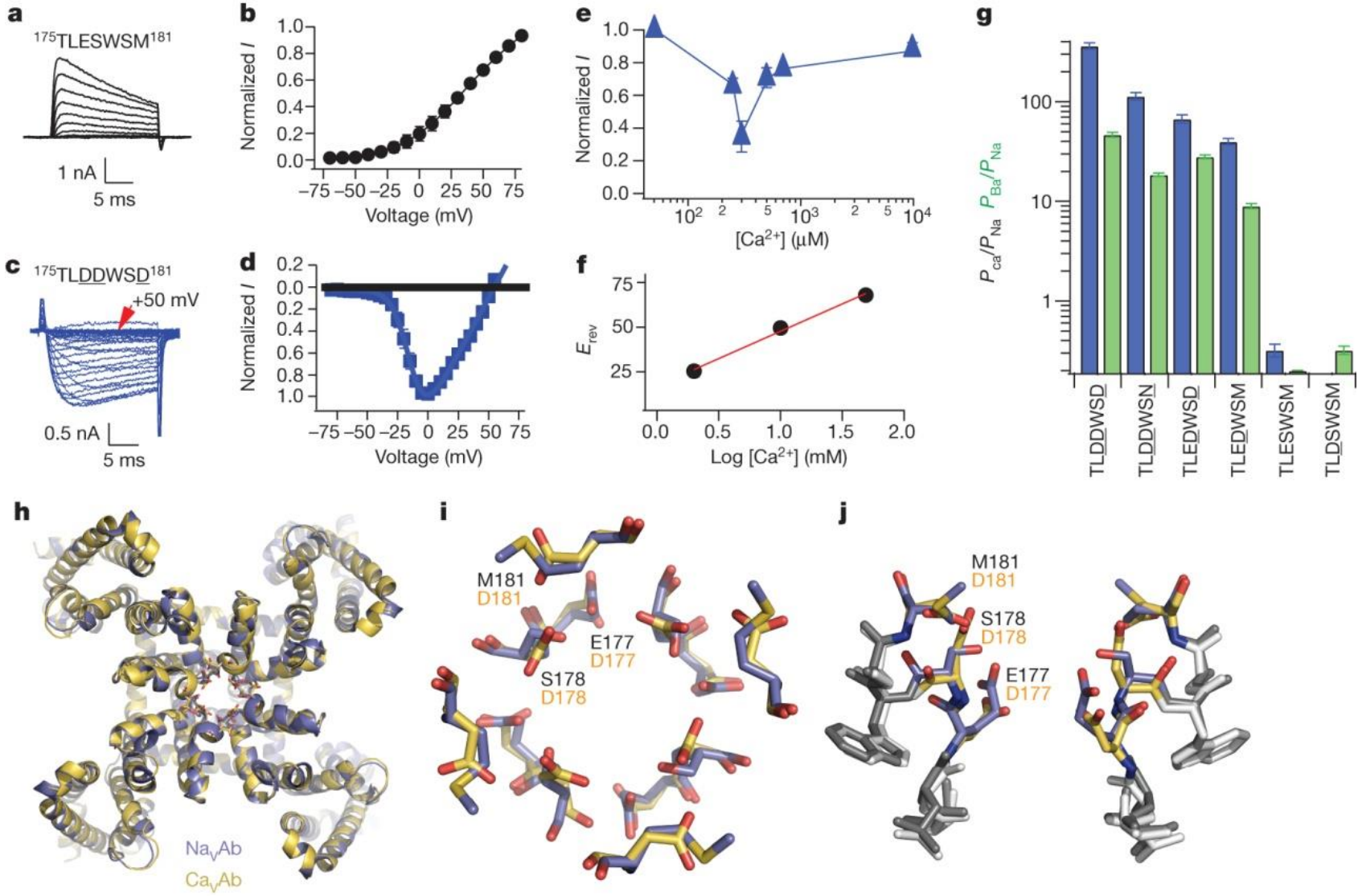
nature

How do Ca channels select for Ca^{2+} over Na^{+}?

- Ca channels permeate Na^{+} at very low [Ca^{2+}]
- Ca channels permeate neither at intermediate [Ca^{2+}]
- Ca channels have binding sites that prefer Ca^{2+}

- Na^{+} ions occupy these sites at very low [Ca^{2+}]
- Ca^{2+} ions occupy these sites at physiological [Ca^{2+}]
- Ca^{2+} ion occupies one site and blocks Na^{+} passage at intermediate [Ca^{2+}]

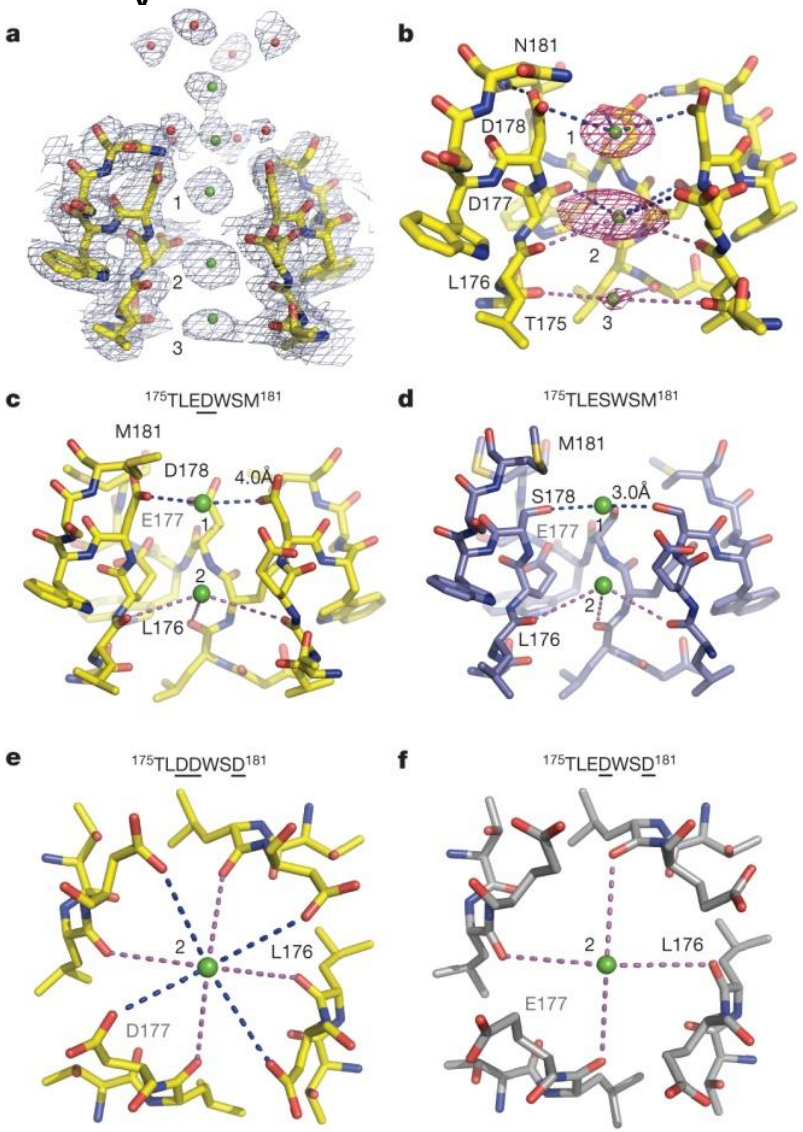
Structure and Function of the Ca_VAb Channel.



L Tang *et al. Nature* (2013) doi:10.1038/nature12775

nature

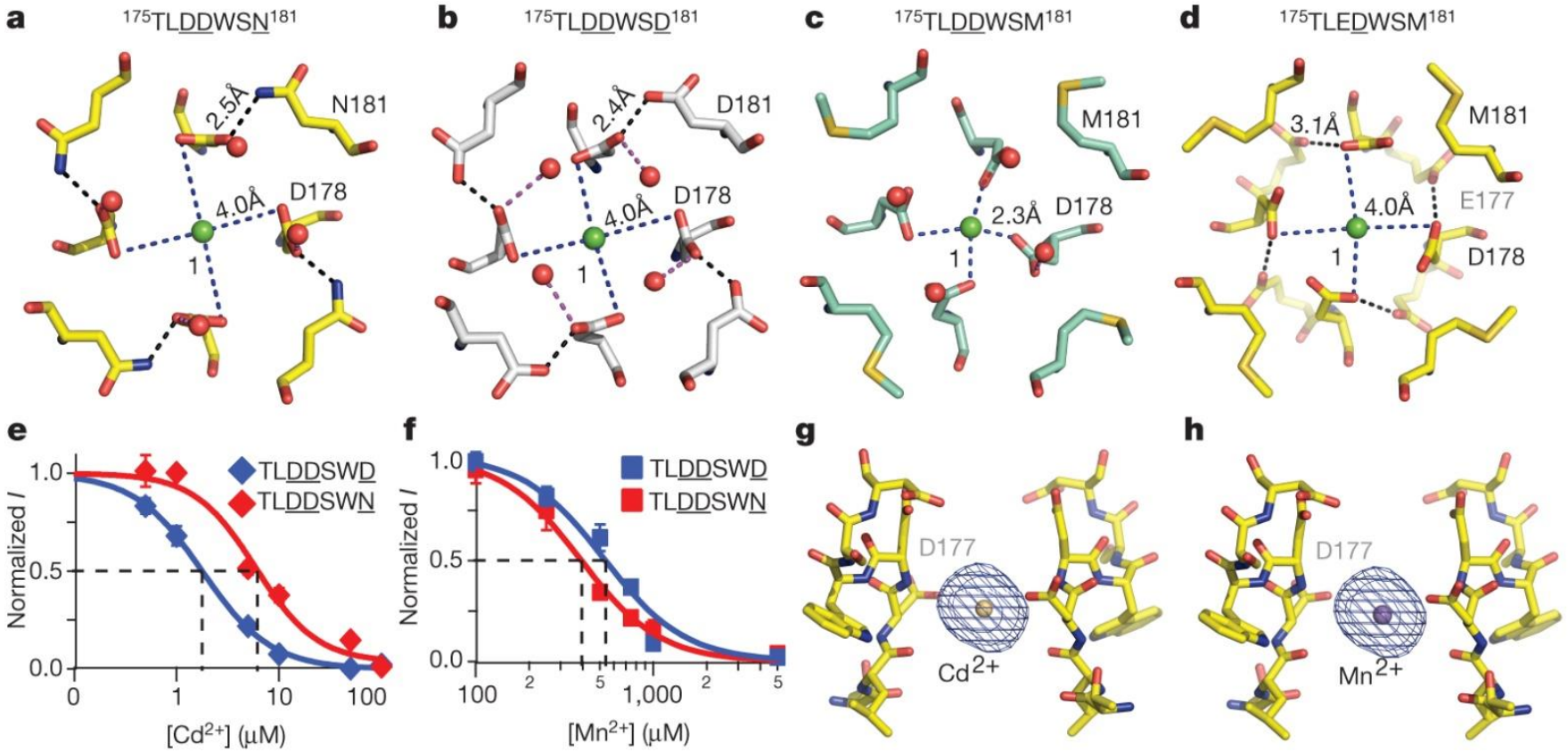
Ca^{2+}-binding Sites In and Near the Selectivity Filter of Na_VAb, Ca_VAb and Their Derivatives



L Tang *et al. Nature* (2013) doi:10.1038/nature12775

nature

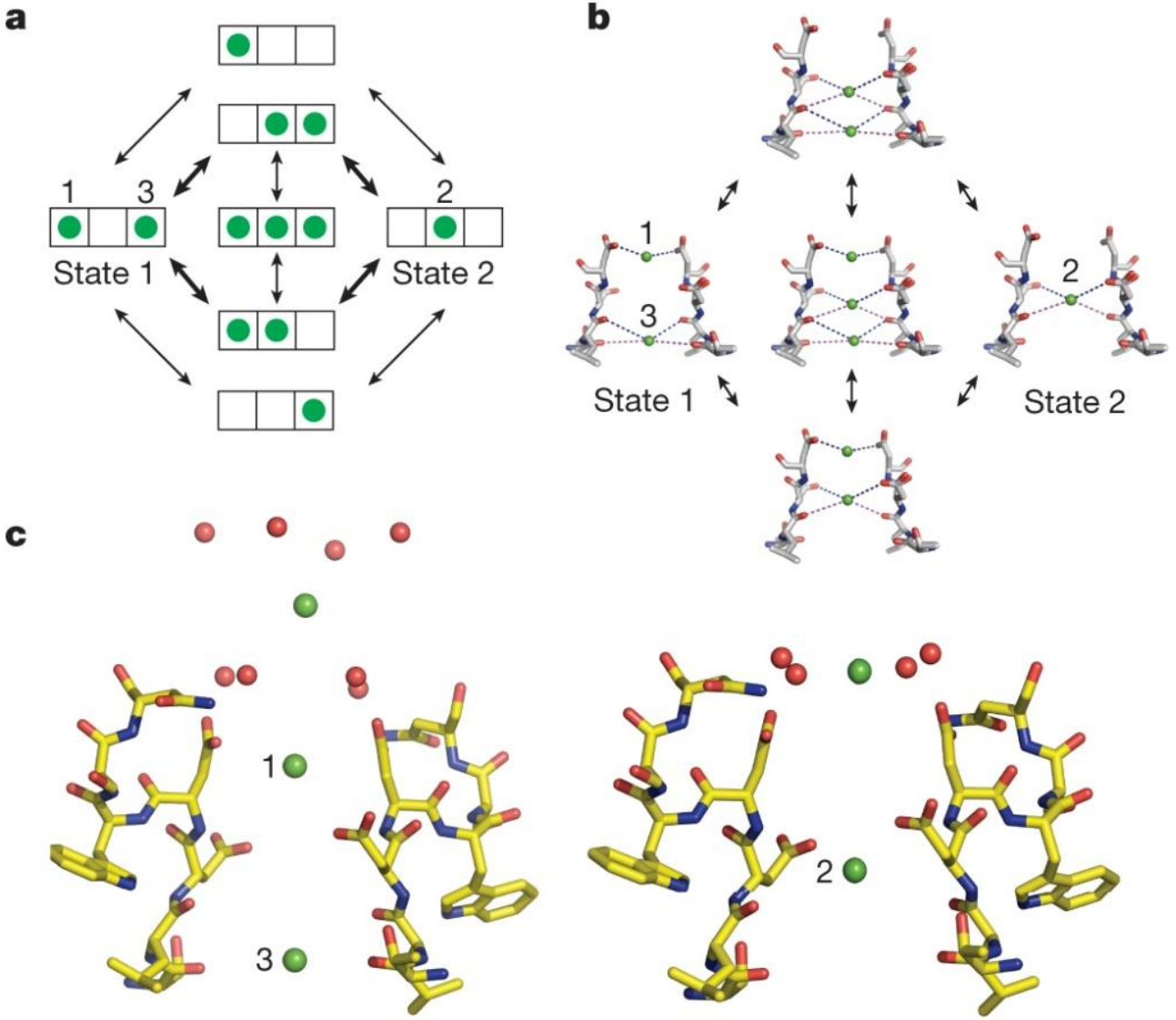
Ion Binding and Block of Ca_VAb and Its Derivatives



L Tang *et al. Nature* (2013) doi:10.1038/nature12775

nature

Catalytic Cycle for Ca^{2+} Conductance by Ca_VAb



L Tang *et al. Nature* (2013) doi:10.1038/nature12775

nature

Questions for Paper Discussion

- What indicates that the voltage sensor of NavAb is in the activated state? What might be the relevance of the aqueous cleft and the focused membrane electric field?
- How might S4 be stabilized in the membrane? What type of S4 motion is likely for channel gating?
- What is a gating pore? What can go through the gating core (and what cannot)?
- Is the pore open or closed in the NavAb structure? How might this pore conformation be reconciled with the voltage sensor placement?
- What may be the hydration state of Na^+ ion as it goes from the selectivity filter to the central cavity, then through the activation gate?
- What might be the role for the lateral fenestration of a sodium channel?
- How could the sequential gating motion and pore opening of a channel like NavAb be determined (or inferred)?
- What is different between the selectivity filter of NavAb and that of CavAb? How does it account for their different ion selectivity?
- What is different between the selectivity filter of NavAb or CavAb and that of a potassium channel? How does it account for their different ion selectivity?
- What is your general impression of these papers?