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Localization and Targeting of Voltage-Gated Ion Channels in Mammalian Central Neurons

Helene Vacher^{*,1}, Durga P. Mohapatra^{*,1}, and James S. Trimmer^{1,2}

¹Department of Neurobiology, Physiology and Behavior, College of Biological Sciences, University of California, Davis, CA 95616

²Department of Physiology and Membrane Biology, School of Medicine, University of California, Davis, CA 95616

Abstract

The intrinsic electrical properties and the synaptic input-output relationships of neurons are governed by the action of voltage-dependent ion channels. The localization of specific population of ion channels with distinct functional properties at discrete sites in neurons dramatically impacts excitability and synaptic transmission. Molecular cloning studies have revealed a large family of genes encoding voltage-dependent ion channel principal and auxiliary subunits, most of which are expressed in mammalian central neurons. Much recent effort has focused on determining which of these subunits co-assemble into native neuronal channel complexes, and the cellular and subcellular distributions of these complexes, as a crucial step in understanding the contribution of these channels to specific aspects of neuronal function. Here we review progress made on recent studies aimed at determining the cellular and subcellular distribution of specific ion channel subunits in mammalian brain neurons using *in situ* hybridization, and immunohistochemistry. We also discuss the repertoire of ion channel subunits in specific neuronal compartments and implications for neuronal physiology. Finally, we discuss the emerging mechanisms for determining the discrete subcellular distributions observed for many neuronal ion channels.

I. OVERVIEW OF MAMMALIAN BRAIN VOLTAGE-DEPENDENT ION CHANNELS

A. Introduction

Mammalian central neurons express a large repertoire of voltage-dependent ion channels (VDICs) that form selective pores in the neuronal membrane and confer diverse properties of intrinsic neuronal excitability. This allows mammalian neurons to display a richness of firing behaviors over a wide range of stimuli and firing frequencies. The complex electrical behavior of mammalian neurons is due to a huge array of VDICs with distinct ion flux rates and selectivity, although the major VDICs underlying neuronal excitability and electrical signaling are those selective for Na⁺, K⁺ and Ca²⁺ ions. Neuronal VDICs also exhibit widely differing properties of how sensitive their gating, or the opening or closing of the channels pore, is to changes in membrane potential. Different VDICs also differ in the kinetics of these gating events. Importantly in the terms of mammalian brain, different VDICs differ widely in their cellular expression and subcellular localization, impacting their relative contribution to brain

Address all correspondence to: Dr. James S. Trimmer, Department of Neurobiology, Physiology and Behavior, College of Biological Sciences, 196 Briggs Hall, University of California, One Shields Avenue, Davis, CA 95616-8519, Tel.: (530) 754-6075; Fax: (530) 754-6079, E-mail: jtrimmer@ucdavis.edu.

*these authors contributed equally to this work

function. This functional diversity is based on expression of dozens of VDIC subunits that can assemble into complicated multisubunit protein complexes with distinct properties, and their subsequent targeting to and retention at specific sites in the neuronal membrane. Molecular cloning and genomic analyses have revealed a diversity of ion channel subunits that was arguably unanticipated from previous physiological and pharmacological studies. The molecular definition of the mammalian VDIC family has led to the development of molecular tools that has allowed for studies aiming to link expression and function of specific VDIC subunits with neuronal excitability and electrical signaling in specific classes of mammalian brain neurons and neuronal networks. Such efforts find justification in leading towards a better fundamental understanding of the molecular processes that shape neuronal function, but also in identifying and validating novel targets for discovery research aimed at developing new therapeutics for CNS disorders. Here we review the findings from these studies and the implications for these goals.

B. General Structural Features of the Principal Subunits of Voltage-Dependent Ion Channels

VDICs selective for Na^+ , K^+ and Ca^{2+} are referred to as Na_v , K_v and Ca_v channels, respectively. The macromolecular proteins complexes that form these channels comprise numerous subunits with distinct structural and functional features. All mammalian VDICs contain one (Na_v , Ca_v) or four (K_v) transmembrane pore forming and voltage-sensing subunits termed α (for Na_v and K_v) or α_1 (for Ca_v). These polypeptides exist in two general forms: individual K_v channel α subunits (Fig. 1) with six transmembrane segments (termed S1-S6) that assemble posttranslationally to form tetrameric complexes, and Na_v channel α (Fig. 3) and Ca_v channel α_1 (Fig. 5) subunits that resemble four tandemly concatenated K_v α subunits and contain four internally repeated “pseudosubunit” S1-S6 domains and comprise a single 24 transmembrane segment subunit (376). These principal VDIC subunits form the major structural and functional unit of the channel and have been the focus of some of the most exciting biophysical and structural studies in all of biology in the past two decades. Much of this work has focused on the K_v channel α subunits, which from a molecular standpoint are more amenable to structure-function analyses than are the larger Na_v α and Ca_v α_1 subunits (187,207).

The picture that emerges is that the core region, containing the six transmembrane segments of the K_v α subunit (or Na_v α and Ca_v α_1 pseudosubunit), is divided into two distinct modular domains, the voltage-sensing module bounded by transmembrane segments S1-S4, and the pore module bounded by transmembrane segments S5-S6. The fourth transmembrane segment, or S4, of each subunit acts as the main voltage-sensing component of the voltage sensor module, which responds to changes in the transmembrane electrical potential and undergoes conformational changes that lead to the voltage-dependent gating of the channel (141,317). The ionic conductance pathway or pore, which is responsible for rapid and selective potassium ion flux, is formed by the close association of the last two transmembrane segments (S5 and S6) from each of the four K_v α subunits (or Na_v α and Ca_v α_1 pseudosubunits) around a central water filled cavity (79,180). Allosteric conformational changes link voltage-dependent movement of the voltage-sensor module to the opening of the channel pore, although the precise details of these movements are not yet clear (141,308). Molecular differences in structures of the voltage-sensor and pore modules account for the bulk of the functional differences between different VDICs in terms of their ion flux rate and selectivity, voltage-dependence of gating, and kinetics (376). The S1-S6 core region also contains all of the extracellular domains of the principal subunit and as such contains all of the binding sites for externally acting drugs and neurotoxins (376).

The principal subunits of VDICs also have extensive cytoplasmic domains that can profoundly affect the functional characteristics described above (268). These domains can influence the coupling between the movement of the voltage-sensor module and the opening of the channel

pore, and confer rapid inactivation. The cytoplasmic domains also mediate the interaction of the channel with the rest of the cell, acting as the target site for interacting proteins and posttranslational modifications that influence channel function (233). As discussed in detail below, the cytoplasmic domains of the principal VDIC subunits also play a major role in the intracellular trafficking, targeting and retention events that shape channel expression and localization.

C. Molecular Diversity of the Principal Subunits of Voltage-Dependent Ion Channels

The transmembrane, pore-forming and voltage-sensing α (for Na_v and K_v) or α_1 (for Ca_v) subunits of mammalian VDICs are encoded by a large and diverse family of homologous genes (374). Genes encoding the Na_v and Ca_v α/α_1 subunits arose from gene duplication and fusion of the coding regions of genes encoding six transmembrane polypeptides resembling K_v α subunits (6,97,315). Sequence homology analyses reveal that these gene-duplication and fusion events occurred after the divergence of eukaryotes and prokaryotes (6). The pore-forming and voltage-sensing functionalities of K_v channels are formed as tetrameric assemblies of four independent α subunits, while Na_v and Ca_v channels are formed by a single α/α_1 subunit (40). Diversity within the families then came about from subsequent additional gene duplication events (376). Principal α/α_1 subunits are typically associated with smaller auxiliary subunits, as detailed below, which can either be cytoplasmic, or single-, double- or tetra-span transmembrane polypeptides (109). The auxiliary subunit composition of the native channel complexes is diverse, and can dramatically influence channel function, intracellular trafficking, post-translational modification, stability and localization (333).

The complexity of the ion channel gene family, combined with a dizzying array of names given to the genes and/or cDNAs as they were isolated, have resulted in a fair degree of confusion in the molecular nomenclature of VDICs. As a response to the growing number of homegrown appellations for cloned K_v channel α subunits, Chandy (45) proposed a systematic nomenclature system that is now widely accepted. This system was later adopted for Ca_v (87) and Na_v (98) channel α subunits by consortia of involved investigators. Together, this has resulted in a clear, systematic and unambiguous nomenclature for nearly all VDICs (374). The nomenclature system is based on the chemical symbol for the principal physiologically permeant ion (K for potassium, Ca for calcium and Na for sodium), followed by the abbreviation of the ligand, which, in the case of this review, is always voltage (v). Thus we will be focusing this review on voltage-dependent potassium (K_v), calcium (Ca_v) and sodium (Na_v) channels. The nomenclature and molecular relationships within each of these families of voltage-gated channels has recently been updated in detailed compendiums; we refer the reader to these as excellent and comprehensive sources for information on K_v (107), Na_v (42) and Ca_v (43) channels.

The remainder of the nomenclature relates to the gene subfamilies within these broad ion channel families. For example, the prototypical K_v channels have been divided into twelve subfamilies (K_v1 - K_v12) based on relative sequence homology (107). K_v1 -4 channels are in one cluster, K_v7 in another, K_v5 , 6, 8, and 9 in another, and K_v10 -12 in the last (374,376). Na_v channels are primarily within the Na_v1 family, which contains all of the classical voltage-dependent sodium channels (42). The outlying second family, both in terms of sequence homology and function (termed Na_x), contains channels whose sequences share some similarity to Na_v1 sequences but have never been functionally expressed to verify their ability to function as Na_v channels (42), although genetic evidence suggests a role in sodium homeostasis in mouse brain (120). Ca_v channels have been divided into three groups based on both sequence homology and function: Ca_v1 , which comprise L-type high voltage activated channels, Ca_v2 , which form P/Q-, N- and R-type high-voltage-activated channels, and Ca_v3 , which are the T-type low-voltage activated channels (43).

A parallel nomenclature for ion channel genes has been developed by mammalian geneticists, who assigned official HUGO Human Gene Nomenclature symbols in conjunction with the human genome project (30). The K_v α subunit genes are named KCN*, with the original four gene families assigned the letters A-D (i.e. K_v1 - K_v4 =KCNA-KCND). Families K_v5 -12 have other designations as detailed below. The specific gene number is then derived from the subunit nomenclature, such that $K_v1.1$ = KCNA1, $K_v1.4$ = KCNA4, $K_v2.1$ = KCNB1, $K_v4.2$ = KCND2, etc. Similarly, $Na_v1.1$ - $Na_v1.5$ α subunit genes are simply assigned the name SCN, and the numerical designation used in the Na_v1 nomenclature followed by an A for α subunit (e.g. $Na_v1.1$ =SCN1A, $Na_v1.2$ =SCN2A, $Na_v1.3$ =SCN3A, etc.). For $Na_v1.6$ - $Kav1.9$ α subunits, the HUGO gene name is offset by two relative to the accepted α subunit nomenclature, as Nax subunits account for SCN6A and SCN7A. As such $Na_v1.6$ =SCN8A, $Na_v1.7$ =SCN9A, etc. The nomenclature for Ca_v genes is even more complex, as the names are based on the classification system that was in place before a more systematic nomenclature was adopted, such that the gene for $Ca_v1.1$ (nee α_{1S}) is CACNA1S, $Ca_v3.1$ (nee α_{1G}), is CACNA1G, etc. Thus, some knowledge of the physiological and pharmacological characteristics of the channel, as well as the history of its identification and characterization, is needed to accurately sort through the HUGO nomenclature for Ca_v genes. Throughout this review, we will predominantly use the nomenclature system developed by ion channel researchers (i.e. K_v , Ca_v and Na_v), but will refer to the HUGO system for clarification or when referring to the gene itself.

Voltage-dependent ion channel α/α_1 -subunit genes are dispersed throughout the genome, although certain highly related channel genes are found clustered in multigene complexes. Examples of ion channel gene clustering in the mammalian genome include $Na_v1.1$, $Na_v1.2$, $Na_v1.3$ and $Na_v1.7$ (the SCN1A, SCN2A, SCN3A and SCN9A loci, respectively) on 2q23-24 (14,193), $Na_v1.5$, $Na_v1.8$ and $Na_v1.9$ (the SCN5A, SCN10A, and SCN11A loci, respectively) on 3p21-24, and $K_v1.1$, $K_v1.5$ and $K_v1.6$ (KCNA1, KCNA5 and KCNA6) on 12p13 (4). These clusters presumably represent the products of gene duplication events that led to the diversity of Na_v and K_v genes observed in higher mammals (6,42,97). The genes themselves can range from the quite simple to the staggeringly complex. On the simple end of the spectrum, all six of the *Shaker*-related K_v1 α subunit genes expressed in mammalian brain ($K_v1.1$ - $K_v1.6$) are encoded by intronless open reading frames (47,107). At the opposite end of the spectrum is the CACNA1E gene (encoding the $Ca_v2.3$ channel α_1 subunit) that encodes a polypeptide of \approx 2300 amino acids in 49 exons within a gene that encompasses >388 kB of genomic sequence on human chromosome 1 (<http://www.genecards.org/cgi-bin/carddisp.pl?gene=CACNA1E>). Even genes encoding small, cytoplasmic auxiliary subunits can be quite complex. The KCNAB1 gene is over 250 kB in length, and 21 exons are used to encode the relatively small (400 amino acid, 40 kD) gene product (169) (<http://www.genecards.org/cgi-bin/carddisp.pl?gene=KCNAB1>).

D. Auxiliary Subunits of Voltage-Dependent Ion Channels

Native neuronal VDIC protein complexes also contain a variety of auxiliary subunits that are stable components of the channel complex. The subunits profoundly influence the functional properties of associated principal subunits, as well as acting as determinants of expression and localization.

Native neuronal K_v channel complexes contain both cytoplasmic and transmembrane auxiliary subunits. The best characterized of these are the cytoplasmic $K_v\beta$ subunits (Fig. 1) associated with K_v1 family members (240). The bulk of K_v1 channel complexes in mammalian brain have associated $K_v\beta$ subunits (259). Four $K_v\beta$ subunit genes exist in the human genome, and alternative splicing can generate a number of functionally distinct isoforms (240). Inclusion of the $K_v\beta1.1$ subunit in K_v channel complexes containing $K_v1.1$, or $K_v1.2$ dramatically alters the channel gating properties, converting the channels from sustained, or delayed-rectifier type,

to rapidly inactivating, or A-type (254). Moreover, the specific α and β subunit composition of native complexes can dramatically impact both the expression level and function of K_v1 channels in mammalian neurons (173,331,333). $K_v\beta$ subunits exhibit weak overall sequence similarity (198) but striking structural similarity (104) to aldo-keto reductase enzymes. Enzymatic activity of $K_v\beta$ subunits against artificial substrates has recently been demonstrated (354). As discussed in detail below, $K_v\beta$ subunits are also major determinants of K_v1 channel localization (101).

Accessory subunits for K_v4 channels have also been identified recently and are encoded by two distinct sets of proteins (139). One set is a family of cytoplasmic calcium binding proteins, called KChIPs (Fig. 1), that are members of the neuronal calcium sensor gene family (5). At least four KChIP genes have been reported to exist in mammals (5,122), and multiple alternatively spliced isoforms of each KChIP gene product have been reported (26,122,322, 341). With the exception of the KChIP4a splice variant, in heterologous expression systems all KChIP isoforms increase the surface density (302) and slow the inactivation gating and speed the kinetics of recovery from inactivation (5) of coexpressed K_v4 channels. More recently, Rudy and colleagues (217) reported the identification of a transmembrane dipeptidyl-peptidase-like protein (DPPX) as an accessory subunit of native mammalian brain K_v4 channel complexes (Fig. 1). Co-expression of different combinations of DPPX, KChIPs and K_v4 subunits gives rise to A-type currents whose diverse biophysical properties match very closely the distinct properties of native somatodendritic A-type currents in different mammalian neurons (139).

In addition to these stereotypical K_v channel auxiliary subunits, there exist in the genome genes encoding a number of “electrically silent” α subunit-like polypeptides (80). These make up the K_v5 , K_v6 , K_v8 and K_v9 subfamilies of principal or α subunits, but are to some extent analogous to auxiliary subunits in that in themselves they cannot form functional channels, but in heterologous expression systems can co-assemble with and functionally modify channels formed from *bona fide* $K_v \alpha$ subunits (234). The contribution of these subunits to native mammalian brain K_v channels has not yet been established.

Native neuronal Na_v channel complexes contain transmembrane auxiliary or $Na_v\beta$ subunits (336), of which there are four different isoforms ($Na_v\beta1$ - $Na_v\beta4$; Fig. 3). The extensive extracellular domains of these subunits are similar to those of cell adhesion molecules, suggesting a role in cell-cell interactions (252). These subunits have dramatic effects on channel function and pharmacology, and mutations in $Na_v\beta$ subunits can lead to generalized epilepsy (204).

Native neuronal Ca_v channels have a wide array of auxiliary subunits (Fig. 5). $Ca_v\beta$ subunits resemble $K_v\beta$ subunits in that they are cytoplasmic and have similar effects on intracellular trafficking (263), although a number of additional functions have recently been identified, due to the presence of MAGUK-like guanylate kinase and SH3 domains that mediate diverse protein-protein interactions (118). There exist four $Ca_v\beta$ subunits $Ca_v\beta1$ -4. $Ca_v \alpha_2$ and δ subunits are the product of a single gene whose polypeptide product is posttranslationally cleaved and then subsequently covalently linked by disulfide bonding to yield the mature transmembrane auxiliary $\alpha_2\delta$ subunit complex (67). Skeletal muscle Ca_v channels contain tetraspan $Ca_v\gamma_1$ subunits (27,136). Related proteins of the stargazin family are found in brain and interact with diverse membrane proteins (49) including AMPA-type glutamate receptors, to regulate their trafficking and function (226). A role for stargazins as auxiliary subunits of brain Ca_v channels has not been firmly established.

E. Techniques for Mapping Voltage-Dependent Ion Channel Expression in Mammalian Brain

The initial isolation of cDNA clones encoding Na_v (220), Ca_v (325), and K_v (12,144,232) α subunits initiated the molecular definition of the VDIC family that became complete with the successful completion of sequencing of the human, mouse and rat genomes. These analyses have allowed for tremendous insights into the sequences of VDIC genes, mRNAs, and the encoded polypeptides. This allowed for the generation of subtype-specific molecular probes for measuring expression levels of VDIC mRNAs in extracts of brain tissue by Northern blots, RNase protection assays, and more recently by RT-PCR. Such probes can also be used to determine cellular patterns of VDIC mRNA expression by *in situ* hybridization. These nucleotide probes can be designed with a high level of confidence as to their specificity, although the use of multiple probes targeting different regions of the target mRNA is justified (335). Detailed analyses of expression patterns have provided invaluable information as to the relative expression patterns of different VDIC mRNAs in adult brain, at different stages of brain development, in different brain regions, and in specific neuronal populations.

The isolation of cDNAs encoding VDIC subunits, and the subsequent deduction of the primary sequence of the encoded polypeptides, allowed for the efforts to generate specific antibodies targeting VDIC subunits. While this effort still continues today, there now exist extensive libraries of polyclonal and monoclonal antibodies from academic and commercial sources that can be used to identify, isolate and map cellular and subcellular expression patterns of VDIC principal and auxiliary subunits in mammalian brain. This has led to an explosion of information as to the expression and localization of specific VDICs, which combined with results from detailed physiological and pharmacological studies, can begin to yield a picture of the role of specific VDICs of defined subunit composition in mammalian central neurons. While there are numerous issues that have arisen from the use of insufficiently characterized antibodies in such studies, many of these have been addressed in a number of recent articles (262,278,279,335). While these will not be addressed in detail here, we will try throughout to provide insights into the apparent level of characterization and validation of antibodies used in studies described below, to aid in critical evaluation of any subsequent results.

II. VOLTAGE-DEPENDENT POTASSIUM CHANNEL LOCALIZATION IN MAMMALIAN BRAIN

A. Overview of Mammalian Brain Voltage-Gated Potassium Channels

K_v channels are members of a diverse gene family. The nomenclature system for K_v channel α subunits, originally proposed by Chandy and colleagues (45,107) and now widely accepted is based primarily on the relatedness of amino acid sequences between the different K_v α subunits. The remainder of the nomenclature relates to the gene families within these ion channel groups (Fig. 1). The prototypical K_v channels have been divided into four families (K_v1 - K_v4) based on the relative similarity of their amino acid sequences, and on their relatedness to their single gene orthologues in *Drosophila*: K_v1 (*Shaker*), K_v2 (*Shab*), K_v3 (*Shaw*), and K_v4 (*Shal*). More recently discovered α subunits make up the K_v5 - K_v12 subfamilies. Note that among these subfamilies, the K_v5 , K_v6 , K_v8 and K_v9 α subunits have not been shown to yield functional expression, but in heterologous cells are able to modulate the expression level and/or gating of channels comprising coexpressed *bona fide* K_v channel α subunits (107). Note that while the vast majority of publications unambiguously adhere to this nomenclature, there are still examples of ambiguity. These are noted below when appropriate to assist in accurate evaluation of the primary literature relative to the standard nomenclature, which is used exclusively here.

A parallel nomenclature for K_v channel α subunit genes has also been established by the HUGO Gene Nomenclature Committee (Fig. 1). Genes encoding the four original K_v1 - K_v4

subfamilies of α subunits are named KCN*, and assigned the letters A-D (i.e., K_v1 - K_v4 = KCNA-KCND) and the specific gene numbers following the K_v nomenclature (e.g. $K_v1.1$ = KCNA1, $K_v1.4$ = KCNA4, $K_v2.1$ = KCNB1, etc). K_v5 - K_v12 subfamilies have been assigned KCNF (K_v5), KCNG (K_v6), KCNQ (K_v7), KCVN (K_v8), KCNS (K_v9), and KCNH (K_v10 -12) gene names by HUGO.

Molecular characterization of K_v channels originally lagged behind that of Na_v and Ca_v channels. Due to the diversity of K_v channel α subunit genes, the potential for oligomerization and the complex repertoire of K_v channels in any given excitable cell, the biochemical approach of purifying Na_v channels from eel electroplax (1) and rat brain (113), and Ca_v channels from skeletal muscle (63), and that ultimately yielded success in cloning Na_v (220) and Ca_v (325) channel α subunits did not yield amounts of K_v channel subunits amenable for protein sequencing. The breakthrough for K_v channel molecular characterization came from concerted genetic and molecular analyses of potassium channel mutants in the fruit fly *Drosophila melanogaster* (133). These efforts resulted in the isolation of cDNAs encoding the K_v channel α subunit encoded at the *Shaker* gene locus (12,144,232). It was immediately clear from the deduced *Shaker* amino acid sequence that this K_v channel subunit strongly resembled one of the four internally repeated homologous pseudosubunit domains of an Na_v or Ca_v channel. This led to the proposal, initially substantiated by biophysical analyses (186) and more recently by direct visualization of cryo-electron microscopic (155,156,224,307) and crystallographic (180) structures, that K_v channels are comprised of functional tetramers of individual α subunits. In *Drosophila*, in addition to *Shaker*, four other K_v channel genes were present, named *Shab*, *Shal* and *Shaw* (2 members) (275). Subsequent genetic analyses revealed the existence of K_v7 (*KCNQ*), K_v10 (*Eag*), K_v11 (*Erg*) and K_v12 (*Elk*) genes in *Drosophila* (177).

cDNAs encoding multiple members of each of the corresponding mammalian gene families (*Shab*= K_v2 or KCNB; *Shaw*= K_v3 or KCNC; *Shal*= K_v4 or KCND; *KCNQ*= K_v7 or KCNQ; *Eag*= K_v10 =KCNH1, 5; *Erg*= K_v11 =KCNH2, 6, 7; and *Elk*= K_v12 =KCNH3, 4, 8) have now been isolated and expressed. Using the *Shaker* cDNAs as probes, Tempel and coworkers isolated the first mammalian K_v channel cDNA, $K_v1.1$ (326). In rapid succession, cDNAs encoding other K_v1 (i.e. *Shaker*-related) family members ($K_v1.2$ - $K_v1.7$, the products of the KCNA1-7 genes) were isolated [reviewed in (46)]. These different mammalian K_v1 family members had distinct functional properties when expressed alone (i.e. as homotetramers) in heterologous cells (316). Different K_v1 family members could also co-assemble into channels with mixed subunit composition, and such heterotetrameric channels exhibited functional properties intermediate between those of channels formed from homotetramers of the constituent subunits (123,129,271). Certain K_v1 channels contain strong trafficking determinants, while others do not (195). Heteromeric assembly of different subunits yields channels with intermediate trafficking characteristics (194). Thus, the subunit composition of K_v1 channels not only determines their gating and kinetic properties, but also dramatically affects their expression and localization (340).

Coincident with the identification of mammalian K_v1 α subunits, a cDNA encoding the rat brain $K_v2.1$ α subunit was isolated by expression cloning in *Xenopus* oocytes (91). The manner of cloning $K_v2.1$ is noteworthy as it reflects the high level expression of $K_v2.1$ in mammalian brain. Low stringency hybridization screening of mammalian brain cDNA libraries led to the isolation of cDNAs encoding K_v3 (184,199,270,373), K_v4 (10,266) K_v5 and K_v6 (80), and K_v10 , K_v11 and K_v12 (182,351) α subunits. The K_v8 family was identified using RT-PCR performed with degenerate primers (125), and K_v9 by *in silico* analyses of EST databases (274). The K_v7 subfamily was initially identified in human genetic analyses of genes associated with a congenital heart disorder called long QT syndrome (350).

The human genome contains a total of forty genes encoding K_v channel α subunits. Some of these genes generate messages that are subject to alternative splicing. In mammalian brain, the expression of many of these K_v channel α subunits is restricted to neurons, although glial cells may express a subset of the neuronal repertoire. In general, K_v channels exhibit subfamily-specific patterns of subcellular localization (Fig. 1), as detailed below. K_v1 channels are found predominantly on axons and nerve terminals, K_v2 channels on the soma and dendrites, K_v3 channels can be found in dendritic or axonal domains, depending on the subunit and cell type, and K_v4 channel are concentrated in somatodendritic membranes (335). K_v7 family members are predominantly on axons, although evidence also exists for somatodendritic K_v7 channels (110). Little information is available for the subcellular localization of K_v5-6 and K_v8-12 α subunits.

B. K_v1 Subfamily and Associated Auxiliary Subunits

When expressed in heterologous systems, the neuronal K_v1 α subunits can generate either transient ($K_v1.4$) or sustained ($K_v1.1-K_v1.3$, $K_v1.5-K_v1.6$) K_v currents. Moreover, heteromeric assembly with one another, and co-assembly with auxiliary $K_v\beta$ subunits can generate a diversity of function from the resultant $\alpha_4\beta_4$ channel complexes (340). In neurons K_v1 channels are found predominantly on axons and nerve terminals, although dendritic expression is also found in certain neurons (335). K_v1 family members exhibit extensive coassembly to generate heteromeric channels with distinct characteristics (239). In addition, assembly with auxiliary subunits can dramatically impact expression, localization and function of the resultant channel complexes (173). For example, inclusion of the $K_v\beta1.1$ subunit in K_v1 channel complexes containing $K_v1.1$ or $K_v1.2$ dramatically alters channel gating properties, converting the channels from sustained, or delayed-rectifier type, to rapidly inactivating, or A-type (254). The specific subunit composition of native complexes can also dramatically impact the expression level, localization and function of K_v1 channels in mammalian neurons (339).

The predominant K_v1 cellular staining pattern throughout the brain is neuronal, and subcellularly, axonal. The three most abundant K_v1 subunits expressed in mammalian brain, $K_v1.1$, $K_v1.2$ and $K_v1.4$, are found predominantly localized to axons and nerve terminals (335). In many cases, these subunits are components of heteromeric channel complexes, as $K_v1.1$, $K_v1.2$ and $K_v1.4$ exhibit precise patterns of colocalization (260), and extensive association as shown by co-purification (57,260,293). However, the subunit composition of channels containing these subunits varies across brain regions (288). The $K_v1.1$ α subunit in mammalian brain appears to be segregated into two major subpopulations: one associated with $K_v1.2$, and one associated with $K_v1.4$. $K_v1.1$ and $K_v1.2$ are found in the absence of $K_v1.4$ in cerebellar basket cell terminals (167,202,203,258,260,346,347), the juxtaparanodal membrane adjacent to axonal nodes of Ranvier (Fig. 4D) (243,245,248,249,258,260,338,346,347), and in the terminal segments of axons (73). $K_v1.1$ and $K_v1.2$ are also present at axon initial segments (72,128,342), sometimes in association with $K_v1.4$, where they control axonal action potential waveform and synaptic efficacy (160). $K_v1.1/K_v1.2$ channels also play a role in μ -opioid receptor-mediated modulation of GABAergic inputs into basolateral amygdala neurons (90) and in serotonin-modulated glutamate release from thalamocortical nerve terminals (165). Low-threshold, slowly inactivating axonal $K_v1.2$ -containing channels, presumably containing either $K_v1.4$ α or $K_v\beta1$ subunits to confer inactivation, are involved in the flexible properties of intracortical axons of layer 5 pyramidal neurons and may contribute significantly to intracortical processing (304). K_v1 -containing channels are also important in setting the firing rate of layer II/III pyramidal neurons (103). $K_v1.1$ and $K_v1.4$ are found robustly expressed in the relative absence of $K_v1.2$ within the striatal efferents in globus pallidus and pars reticulata of substantia nigra (260,297).

Within the excitatory circuitry of the hippocampus, a number of patterns for expression for these three K_v1 subunits emerge, providing a striking example of the complex heterogeneity of subunit association (260). $K_v1.1$, $K_v1.2$ and $K_v1.4$ are highly expressed in the middle third of the molecular layer of the dentate gyrus (Fig. 2A) where they are associated with axons and terminals of the medial perforant path (212,258,260,296,297,344,346,347). $K_v1.1$, $K_v1.2$ and $K_v1.4$ are also found in Schaffer collateral axons, while $K_v1.1$ and $K_v1.4$ colocalize, in the absence of $K_v1.2$, in mossy fiber axons (Fig. 2A) (61,296,297,346,347), where they regulate Ca^{2+} influx and transmitter release (96).

However, in spite of their colocalization, it is not clear that heteromeric channel complexes containing co-associated $K_v1.1$, $K_v1.2$ and $K_v1.4$ are present on perforant path and Schaffer collateral axons. Lesions in entorhinal cortex have distinct effects on the distribution of $K_v1.2$ and $K_v1.4$ in the middle third of the dentate molecular layer, suggesting that while these subunits may colocalize at the light microscope level, they may be expressed, along with $K_v1.1$, on different components of the perforant path (212). Similar results are obtained with lesions placed in other subfields. For example, in CA3 the predominant K_v1 channels appear to be composed of $K_v1.1$ with $K_v1.4$, while in the Schaffer collateral pathway, $K_v1.1$ is likely to be associated with $K_v1.2$ and $K_v1.4$ (212).

Electron microscopic immunohistochemical studies have demonstrated that $K_v1.1$, $K_v1.2$ and $K_v1.4$ are concentrated in the axonal membrane immediately preceding or within axon terminals (61,346,347). The immunoreactivity for $K_v1.1$ and $K_v1.2$ has been localized to the pre-terminal axonal membrane in *stratum (s.) radiatum* (346,347), while immunoreactivity for $K_v1.4$ has been localized to the pre-terminal extensions of mossy fiber axons (61). Activation of K_v1 channels at these sites can play a critical role in regulating nerve terminal excitability and thereby regulate neurotransmitter release, as shown by pharmacological and genetic knockdown of K_v1 function (74).

The other K_v1 α subunits appear to be expressed at lower levels in mammalian brain. $K_v1.6$ is found predominantly in interneurons, although some dendritic staining is seen throughout the brain on principal cell dendrites, which also express $K_v1.1$ and $K_v1.2$ (260), and presumably underlie the “D” current (313,378). $K_v1.3$ is highly expressed in the cerebellar cortex. The bulk of this expression is in the parallel fiber axons of cerebellar granule cells, as strong *in situ* hybridization signal is present in the granule cell layer (163), while strong immunostaining (344) and ^{125}I -margatoxin binding (specific for $K_v1.2$ and $K_v1.3$) (159) is found in the molecular layer. The molecular layer also contains high levels of staining for $K_v1.1$ (260, 344) suggesting that $K_v1.1$ and $K_v1.3$ have the opportunity to form heteromeric channels on parallel fibers. The expression of $K_v1.5$ in the brain is overall quite low (88). What $K_v1.5$ expression there is may be restricted to non-neuronal cells. For example, $K_v1.5$, and $K_v1.3$ are components of delayed rectifier currents in glia (52,150,230) and endothelial cells (206). In mammals, $K_v1.7$ is expressed in skeletal muscle, heart and pancreatic islets, but not brain (143).

In situ hybridization, immunoprecipitation and immunohistochemical analyses have also localized sites of expression of the $K_v\beta1$ and $K_v\beta2$ auxiliary subunits in mammalian brain (212,254,258-260). $K_v\beta2$ appears to be a component of many if not all K_v1 -containing channel complexes in mammalian brain, and immunoreactivity for $K_v\beta2$ is present in almost every location where immunoreactivity for K_v1 -family subunits is observed (259,260). However, there is also extensive immunostaining for $K_v\beta2$ in somata and dendrites that is not observed for K_v1 α subunits, and certain sites of intense K_v1 α subunit staining (e.g. hippocampal mossy fibers) lack robust $K_v\beta2$ immunoreactivity (212,259,260). In the hippocampus, excitotoxic lesion of distinct components of the extrinsic and intrinsic circuitry reveal that the majority of $K_v\beta2$ that is associated with K_v1 α subunits is associated with axons and presynaptic terminals

of the perforant path and Schaffer collateral pathways (212). The $K_v\beta 1$ subunit, which exerts dramatic effects on the inactivation kinetics of $K_v 1$ channels, appears to be included in $K_v 1$ channel complexes more selectively than is $K_v\beta 2$. Interestingly, the pattern of immunoreactivity for $K_v\beta 1$ closely matches the expression pattern for $K_v 1.1$ and $K_v 1.4$, in that $K_v\beta 1$ is found to co-localize with $K_v 1.4$ in the medial perforant path, mossy fiber pathway, and in striatal efferents to the globus pallidus (259,260). $K_v\beta 2$ is found in the absence of $K_v\beta 1$ at many sites that exhibit colocalized $K_v 1.1$ and $K_v 1.2$, for example in cerebellar basket cell terminals and juxtaparanodes of nodes of Ranvier (248,260). As such there exist distinct pairings of $K_v 1 \alpha$ and $K_v\beta$ subunits in heteromeric channel complexes in mammalian brain.

C. $K_v 2$ Subfamily

$K_v 2$ family members form delayed rectifier K_v channels that are prominently expressed in mammalian brain, where they are localized in the somatodendritic domain of neurons. $K_v 2.1$ was the first member of this family isolated by molecular cloning approaches, and is unique in that it was identified and isolated from an adult rat brain cDNA library by expression cloning in *Xenopus* oocytes (91), suggestive of an unusually high level expression of $K_v 2.1$ mRNA in adult rat brain. Thus it was not surprising when immunostaining revealed that $K_v 2.1$ was highly expressed, and has an extensive distribution throughout the mammalian brain (82,127,332). In fact, the cellular distribution in neurons is so broad that in many regions the cellular staining pattern of $K_v 2.1$ resembles that of a Nissl stain. However, in spite of this broad neuronal expression, within individual neurons the staining for $K_v 2.1$ is highly restricted, being present only on the somatic and proximal dendritic membrane (Fig. 2A), and absent from axons and nerve terminals (332). Immuno-electron microscopy (82) and excitotoxic lesion studies (212) have unambiguously confirmed the somatodendritic localization of $K_v 2.1$. The striking subcellular distribution is accentuated by the fact that within these domains $K_v 2.1$ is present in large clusters (82,127,190,281,332). These clusters are present on the cell surface membrane immediately facing astrocytic processes, and over subsurface cisterns underlying the plasma membrane facing astrocytes (82). The physiological basis for the highly clustered, discrete localization of $K_v 2.1$ to these specialized membrane domains is not known.

In spite of its widespread cellular distribution, there are certain cells that stand out for having especially prominent $K_v 2.1$ expression. In the cortex, pyramidal cells in layers II/III, and in layer V are especially striking for their high levels of $K_v 2.1$ expression. $K_v 2.1$ is also present in high levels throughout the hippocampus, although the levels in dentate granule cells and CA1 pyramidal cells exceed that in CA3 and CA2 pyramidal cells in both rat and mouse (Fig. 2A). However, it should be stressed that $K_v 2.1$ is found on both principal cells and interneurons (Fig. 2A) throughout the hippocampus (82). Among interneurons, $K_v 2.1$ is found in the majority of cortical and hippocampal parvalbumin, calbindin and somatostatin-containing inhibitory interneurons (82). Note that $K_v 2.1$ localization in rat brain, especially the extent of clustering, is dramatically affected by neuronal activity (209) and ischemia (208) due to changes in phosphorylation state, such that state of the subject and preparation of the sample could impact details of $K_v 2.1$ localization.

$K_v 2.2$ is expressed in many of the same cells that express $K_v 2.1$. However, unlike other K_v channels ($K_v 1$, $K_v 3$ and $K_v 4$ family members), the two members of the mammalian $K_v 2$ family apparently do not readily form heteromultimers in native neurons (although see (21)), as the subcellular localizations of $K_v 2.1$ and $K_v 2.2$ expressed in the same cells are distinct (126, 175). $K_v 2.2$ is present on dendrites, but is present uniformly and along the entire length of the dendrite. The clustered, proximal dendritic localization of $K_v 2.1$ is not observed for $K_v 2.2$. $K_v 2.2$ is present at high levels in olfactory bulb neurons, and in cortical pyramidal neurons.

D. K_v3 Subfamily

K_v3 family members have unique functional characteristics, including fast activation at voltages positive to -10 mV and very fast deactivation rates. These properties are thought to facilitate sustained high-frequency firing, and K_v3 subunits are highly expressed in fast-spiking neurons, such as neocortical and hippocampal interneurons as well as midbrain auditory neurons (269). K_v3 currents can either have sustained (K_v3.1, K_v3.2) or transient (K_v3.3, K_v3.4) characteristics, and can form hetero-oligomeric channels with intermediate gating characteristics (269). K_v3 mRNAs are somewhat unusual among K_v α subunits in that they are subjected to extensive alternative splicing to generate subunits that differ only at their cytoplasmic carboxyl termini (184). This complicates studies of localization of these subunits, as the specific nature of the *in situ* hybridization or antibody probes used can affect which K_v3 alternative splicing isoforms are detected.

Initial *in situ* hybridization analyses revealed that unlike many other K_v subunits, K_v3.1 and K_v3.2 transcripts were expressed in only a small subset of cells in the cerebral cortex and hippocampus (236,353). Interestingly, the *in situ* hybridization patterns of K_v3.1 and K_v3.2 were distinct, suggesting a strict cellular specificity to expression of these highly related K_v channel α subunits (353). Initial immunolocalization studies were performed using antibodies raised against the major splice variant of K_v3.1, termed K_v3.1b, which has a longer carboxyl terminus than the less abundant K_v3.1a variant. These and subsequent studies revealed that K_v3.1b was highly expressed in interneurons (Fig. 2B), and that expression was very low/undetectable in principal cells, such as neocortical and hippocampal pyramidal cells, and dentate granule cells (289,352). K_v3.1b is also robustly expressed in fast-spiking cells in the cochlear nucleus (236). Double labeling experiments (289) revealed that the subset of cortical cells labeled with anti-K_v3.1b antibodies corresponded to GABAergic interneurons expressing the calcium-binding protein parvalbumin, which are distinguished by their fast-spiking properties. Interestingly, K_v3.2 α subunits were found in non-fast-spiking, somatostatin- and calbindin-containing interneurons (53). Thus, the expression patterns of K_v3.1 and K_v3.2 α subunits can distinguish different populations of interneurons, raising the possibility that interneuron firing patterns rely to some extent on the subtype of K_v3 channels expressed (166,174,269). K_v3.2 is also found in the cerebellar pinceau (22), in the terminals of basket cells that synapse onto Purkinje cell axon initial segments.

Another site of prominent expression of K_v3.1b subunits is in auditory neurons (83,172,352), especially in globular bushy cells in the anterior ventral cochlear nucleus (AVCN) and principal cells in the medial nucleus of the trapezoid body (MNTB). In AVCN neurons K_v3.1b is present in somatodendritic compartments, and in MNTB neurons in presynaptic terminals (83). The expression of K_v3.1b follows a tonotopic gradient and is present in cells transmitting high frequency tones (83,172). In these cells K_v3.1b is found basally phosphorylated by protein kinase C, which suppresses K_v3.1b currents (185). Activity-dependent dephosphorylation enhances K_v3.1b currents and allows for high frequency firing at auditory synapses (309). K_v3.1b is also present at a subset of nodes of Ranvier in axons of central but peripheral neurons, and was not present at axon initial segments (70).

In the case of mammalian brain K_v3.1, alternative splicing does in fact lead to a difference in the polarized expression of K_v3.1 variants in mammalian brain (228). The initial studies of K_v3.1b localization in mammalian brain revealed staining that was present in the soma, proximal dendrites, unmyelinated axons, and axon terminals of the parvalbumin-positive interneurons (53,289,352) and neurons in the cochlear nucleus (235). In contrast, K_v3.1a proteins were prominently expressed in the axons of some of the same neuronal populations, but there was little or no K_v3.1a protein expression in somatodendritic membrane.

Studies on the exogenous expression of three different $K_v3.2$ splice variants ($K_v3.2a$, b and c) in polarized epithelial cells revealed that alternative splicing led to differences in subcellular localization. The $K_v3.2a$ variant was localized to the basolateral membrane, while the $K_v3.2b$ and $K_v3.2c$ isoforms were found apically (238). The epithelial cell:neuron analogous membrane hypothesis (77) predicts that as such, in neurons, $K_v3.2a$ would be localized to the somatodendritic domain, and $K_v3.2b$ and $K_v3.2c$ would be localized to the axon. Thus, as for the case of $Ca_v2.3$ discussed below, alternative splicing of ion channel transcripts can generate functionally similar variants of the same channel with altered subcellular distributions (228).

$K_v3.3$ α subunits are also widely expressed at the mRNA level in brain (269). In forebrain, $K_v3.3$ are coexpressed with $K_v3.1b$ and $K_v3.2$ subunits in parvalbumin-positive interneurons (48). Robust $K_v3.3$ staining is also observed in mossy fiber axons of hippocampal dentate granule cells (48). Both Purkinje cells in cerebellar cortex, and deep cerebellar nuclei contain high levels of $K_v3.3b$ message (99). Purkinje cells have $K_v3.3$ protein in axons, on somata, and in proximal and distal dendrites (48,196), where a K_v3 channel complex of $K_v3.3$ and $K_v3.4$ may play a role in shaping depolarizing events. Most brainstem auditory neurons also express $K_v3.3$ mRNA (172) and protein (48), where it may co-assemble with $K_v3.1$ in a subset of cells.

Unlike $K_v3.1$ and $K_v3.2$, in neocortex and hippocampus $K_v3.4$ is present in principal cells (256,353). Moreover, $K_v3.4$ appears to be localized to axons and nerve terminals of these cells, such that in a number of brain regions $K_v3.4$ is found co-localized with K_v1 family members. Combined *in situ* hybridization and immunohistochemistry yield a picture whereby $K_v3.4$ is found in terminals of the perforant path, as high levels of $K_v3.4$ mRNA, but not protein, are found in entorhinal cortex, and high levels of $K_v3.4$ immunostaining are present in the middle third of the molecular layer of the dentate gyrus (256,344). Intense $K_v3.4$ staining is also observed in *s. lucidum* of CA3, and appears to be associated with mossy fiber axons and/or terminals (256,344), where it may be present in heteromeric K_v3 complexes with $K_v3.3$ (48). In these regions $K_v3.4$ may be present in the same axons and terminals as $K_v1.1$ and $K_v1.4$. $K_v3.4$ is also found in cerebellar basket cell terminals, which also contain high levels of $K_v1.1$ and $K_v1.2$. Immuno-electron microscopy (167) revealed that although the localization of staining of $K_v1.1$, $K_v1.2$ and $K_v3.4$ overlaps at the light microscope level, these subunits have distinct ultrastructural localizations. $K_v1.1$ and $K_v1.2$ are present in septate-like junctions formed between basket cell terminals and Purkinje cell axons, while $K_v3.4$ is found in nonjunctional regions of the terminals (167). $K_v3.2$ is also found in basket cell terminals at sites distinct from those that contain $K_v3.4$, perhaps corresponding to active zones of the presynaptic terminals (22). These findings highlight the extent to which different highly related ion channel subunits can be precisely localized in neuronal membrane domains. It should be noted that recent data suggest that in certain fast-spiking cells $K_v3.4$ may also associate with $K_v3.1$ and/or $K_v3.2$ α subunits to generate a fast delayed rectifier current (11). However, examples of neurons in which $K_v3.4$ was found colocalized with $K_v3.1$ and $K_v3.2$ were not provided. Studies of $K_v3.1b$ (65) and $K_v3.4$ (29) localization in certain brainstem nuclei suggest that these subunits may both localize to presynaptic terminals, for example those in nucleus tractus solitarius. As noted above, Purkinje cell dendrites may contain a $K_v3.3/K_v3.4$ heteromeric channel that is important in shaping responses to certain, relatively strong depolarizing events (196).

E. K_v4 Subfamily and Associated Auxiliary Subunits

The K_v4 α subunits $K_v4.1$, $K_v4.2$ and $K_v4.3$ form transient or A-type K_v channels (139). Experimental knockdown of K_v4 α subunit expression in mammalian neurons results in suppression of A-type K_v channels (154,168,191,192,379). $K_v4.1$ is expressed at very low levels in mammalian brain (290), and what expression that can be detected in neurons does not

correlate with A current density (114). In contrast, $K_v4.2$ and $K_v4.3$ are expressed at relatively high levels (290) and the expression of these subunits correlates well with neuronal A-type current density in a number of neuronal types (114,176,303,310,330). *In situ* hybridization analyses show that the expression of $K_v4.2$ and $K_v4.3$ is widespread throughout the brain, and that while in many brain regions the cellular expression of these two K_v4 genes is reciprocal or complementary, there are numerous cell populations in which $K_v4.2$ and $K_v4.3$ are co-expressed (290).

Immunoreactivity for K_v4 subunits is concentrated primarily in the dendrites of central neurons (335). $K_v4.2$ is expressed at high levels in many principal cells, while $K_v4.3$ is found in a subset of principal cells and in many interneurons (335). In the hippocampus, dentate granule cells express high levels of $K_v4.2$ and $K_v4.3$ mRNA (290), and robust staining for both of these subunits (Fig. 2C) is present in the molecular layer (190,205,257,297). That this immunostaining is in the distal granule cell dendrites that receive input from the lateral perforant path is supported by elimination of such staining upon excitotoxic lesion of the dentate gyrus (257).

A similar colocalization of $K_v4.2$ (190,205,257,297) and $K_v4.3$ (205,257) is seen in the distal basal (in *s. oriens*) and apical dendrites (in *s. lucidum* and *s. radiatum*) of CA3 pyramidal neurons. That the staining for $K_v4.2$ and $K_v4.3$ in CA3 *s. lucidum* is to CA3 pyramidal cell dendrites, as opposed to dentate granule cell axons that form mossy fibers, is supported by the lack of an effect of excitotoxic lesions within the dentate gyrus on this staining (257). Interestingly, CA2 and CA1 pyramidal cells express $K_v4.2$ mRNA (290,297) and protein (190,205,257,297) in the absence of $K_v4.3$ mRNA (290) and protein (205,257), suggesting a unique role for $K_v4.2$ homotetramers in the distal dendrites of these cells relative to the situation in CA3. Conversely, throughout the hippocampus, $K_v4.3$ mRNA (290) and protein (205,257) is found in the absence of $K_v4.2$ in many interneurons, such as those located adjacent to the granule cell layer in dentate gyrus (Fig. 2C). Thus, different hippocampal cell types appear to have different requirements for homotetrameric and heterotetrameric $K_v4.2$ and $K_v4.3$ channels. The specific targeting of K_v4 channels to dendrites of principal cells in the hippocampus has been confirmed by excitotoxic lesion studies (257). In all cases the staining of K_v4 channels on dendrites tends to be quite uniform, with little evidence of local concentrations of clustered immunoreactivity associated with dendritic spines, postsynaptic densities or other subcellular domains.

Principal cells and interneurons in neocortex also exhibit specific patterns of $K_v4.2$ and $K_v4.3$ staining (32,257). Pyramidal cells in layer II of rat parietotemporal cortex exhibit high levels of $K_v4.3$ staining, while $K_v4.2$ staining predominates in those in layer V (257). The expression of $K_v4.2$ and $K_v4.3$ in pyramidal cell dendrites was further supported by studies in transgenic mice expressing fluorescent protein in a subset of pyramidal neurons in visual cortex (32). Clear staining for both $K_v4.2$ and $K_v4.3$ was observed in fluorescent dendrites (32). Immunoelectron microscopic studies reveal a high density of $K_v4.2$ and $K_v4.3$ immunoreactivity in distal dendrites of pyramidal neurons, and in apical tufts found in layer I (32). Interestingly, the majority of this immunostaining is associated with GABAergic and not excitatory synapses (32).

$K_v4.3$ is also found in interneurons scattered throughout layers II-VI in rat neocortex (257). $K_v4.3$ is also found in numerous GABAergic interneurons in mouse visual cortex (32). $K_v4.2$ was also found in GABAergic interneurons in mouse visual cortex, although the cellular populations are not identical to those expressing $K_v4.3$ suggesting different patterns of expression in different interneuron populations (32). K_v4 channels are also highly expressed in cerebellum. Cerebellar granule cells express both $K_v4.2$ and $K_v4.3$ mRNA (290,297) and protein (205,257,297,314). In the cerebellar granule cell layer, reciprocal gradients of mRNA

and protein expression are observed for $K_v4.2$ (anterior > posterior) versus $K_v4.3$ (posterior > anterior) (290,314).

The expression and localization of K_v4 -associated accessory cytoplasmic KChIP subunits has also been studied in some detail (205,257). Specific KChIPs exhibit distinct patterns of localization, and of colocalization, with K_v4 α subunits. The circuitry of the hippocampus is again exemplary for these patterns. For example, in hippocampus, KChIP2, KChIP3 and KChIP4 exhibit precise colocalization with $K_v4.2$ and $K_v4.3$ in dendrites of dentate granule cells, and CA3 pyramidal neurons (205,257). Interestingly, in the dendrites of CA1 pyramidal cells, which lack $K_v4.3$, KChIP3 is also not expressed, such that CA1 dendrites express $K_v4.2$, KChIP2 and KChIP4 (205,257). The distribution of KChIP1 in hippocampus is restricted to interneurons, where it is coexpressed and colocalized with $K_v4.3$ in the same subset of GABAergic cells. KChIP1 expression in neocortical and striatal interneurons also closely matches the cellular and subcellular distribution of $K_v4.3$ (257). These stereotypical K_v4 :KChIP combinations (i.e. $K_v4.2$ with KChIP2 and KChIP4, and $K_v4.3$ with KChIP1) that are found in most brain regions are not present in cerebellum. KChIP1 is more highly expressed in granule cells in anterior cerebellar cortex, which also express high levels of $K_v4.2$, than in granule cells in posterior cerebellum, which where higher levels of $K_v4.3$ are found (314). KChIP3 and KChIP4 are expressed somewhat uniformly in granule cells across the anterior-posterior gradient axis (314). In each case the expression of KChIPs in cerebellar granule cells precisely colocalizes with that of K_v4 α subunits, in the somatic plasma membrane, and in the distinct glomerular synapses that form between granule cell dendrites and afferent inputs (205,257,314).

A recent immunohistochemical study of the expression of KChIPs in the $K_v4.2$ knockout mouse provided a dramatic example of the intimate relationship between K_v4 α subunit and KChIP auxiliary subunit expression (205). Remarkably, genetic ablation of $K_v4.2$ expression precisely altered the expression of the KChIPs that exhibited colocalization with $K_v4.2$, and not other KChIPs nor $K_v4.3$. For example, in hippocampus, KChIP2 staining was virtually eliminated in the dendrites of CA1 pyramidal neurons, which normally express only $K_v4.2$. However, in dendrites of CA3 pyramids and dentate granule cells, KChIP2 staining was reduced but still present, perhaps due to the persistent expression of $K_v4.3$ in these neurons. Similar effects were observed in cerebellum, where KChIP1 expression in the $K_v4.2$ knockout mouse was dramatically diminished in granule cells in the anterior cerebellar cortex, which would normally express high levels of $K_v4.2$, versus posterior, which expresses $K_v4.3$ (205). Overall, the impact of the elimination of $K_v4.2$ expression on KChIPs was stereotypical of the extent of their colocalization with $K_v4.2$, suggesting that the expression of these subunits is coregulated, by an as yet unknown mechanism, in multiple brain regions.

While not studied in detail, the cellular expression patterns of K_v4 -associated DPP family auxiliary subunits also colocalize with those of K_v4 α subunits in mammalian brain neurons. The initial report that the DPPX isoform could be copurified with K_v4 channels from mammalian brain also provided examples of DPPX immunoreactivity precisely colocalizing with that of $K_v4.2$ in cerebellar granule cells, and specifically in somatic membranes and glomerular synapses (217). DPPX immunoreactivity in hippocampus did not provide compelling evidence for a similar colocalization with K_v4 α subunits (217). More recently, another member of the DPP family, DPP10 was found to exhibit auxiliary subunit effects on K_v4 channels in heterologous cells (140,382). *In situ* hybridization analyses revealed distinct patterns of cellular expression, and overlap with that of K_v4 α subunits, for DPPX and DPP10 (382). DPPX expression was robust in the principal cells of the hippocampus, including dentate granule cells and CA1-CA3 pyramidal cells. In contrast, DPP10 was expressed at high levels in GABAergic interneurons. This indicates that DPPX may participate in heteromeric $K_v4.2$ / $K_v4.3$ complexes (in dentate granule cells and CA3 pyramids) and homomeric $K_v4.2$

complexes (in CA1 pyramids) while DPP10 is associated with homomeric K_v4.3 complexes in interneurons. Thus, as observed previously for KChIPs, specific DPP family auxiliary subunits have distinct patterns of coexpression (and presumably subcellular colocalization) with specific K_v4 α subunits in hippocampus. Other regions of brain also exhibit distinct patterns of DPPX and DPP10 mRNA expression (382). For example, as noted above, DPPX is highly expressed in cerebellar granule cells, which have low levels of DPP10 expression, while the converse is seen in cerebellar Purkinje cells, which have high levels of DPP10 (and K_v4.3) expression, and low levels of DPPX (and K_v4.2). Together with the analyses of K_v4 α subunit and KChIP auxiliary subunit expression described above, a picture is emerging wherein different brain neurons express different combination of K_v4 α , and KChIP and DPP auxiliary subunits to form dendritic A-type with distinct functional properties (139).

F. K_v7 Subfamily

Neuronal K_v7 or KCNQ channels are the principal subunits underlying the slowly activating and non-inactivating M current that suppresses neuronal firing in many types of brain neurons (349), and suppression of M current by muscarinic modulation enhances neuronal excitability (69). Mutations in neuronal M channel principal KCNQ subunits lead to neurological diseases, the most prominent being epilepsy (60,138). The major K_v7 KCNQ subunits expressed in mammalian brain are K_v7.2 (KCNQ2), K_v7.3 (KCNQ3) and K_v7.5 (KCNQ5). For simplicity and consistency with the remainder of this section, here we shall refer to these as K_v7 subunits, although the bulk of the literature employs the KCNQ system.

K_v7.2, K_v7.3 and K_v7.5 mRNAs exhibit distinct patterns of cellular expression in mammalian brain. Initial *in situ* hybridization analyses revealed robust expression and extensive overlap of K_v7.2 and K_v7.3 mRNAs in principal cells of the hippocampus and neocortex (272,286, 328). K_v7.3 had additional expression in amygdala and thalamus (272,286). K_v7.5 mRNA is present at high levels in hippocampus, caudate putamen, and in neocortex, especially in piriform and entorhinal cortex (285). In hippocampus, expression is especially high in CA3 pyramidal neurons relative to other principal cell types (285). Northern blot analyses of regional expression patterns in human brain yield similar results, with the exception that human cerebellum, in contrast to the situation in rat, expresses high levels of K_v7.5 mRNA (285).

Immunohistochemical localization of the cellular and subcellular localization of K_v7.2 and K_v7.3 subunits in brain has revealed a predominant axonal localization. Initial reports of staining in mouse (59) and rat (267) hippocampus revealed intense staining in mossy fiber axons and their terminals (Fig. 2D), and very little or no labeling in dentate granule cells themselves. Low levels of labeling were observed in somata of principal cells in CA3-CA1 in both mouse and rat, although moderate levels of staining in neuropil of *s. oriens*, and *s. radiatum* in these regions was observed. A subpopulation of GABAergic interneurons in *s. oriens* of CA3 (Fig. 2D), and in *s. oriens*, *s. pyramidale*, and *s. radiatum* of CA1 also exhibited robust immunoreactivity for K_v7.2 (59,267), which in mouse comprised constituents of both parvalbumin-positive and -negative populations (59). In the mouse basal ganglia, strong somatic K_v7.2 staining was also observed in parvalbumin-positive neurons of the striatum, globus pallidus, and the reticular nucleus of the thalamus, dopaminergic neurons of the substantia nigra compacta and ventral tegmental area, and cholinergic neurons of the striatum and near the globus pallidus (59). In cerebellum, low levels of staining were present in granule cells, although intense labeling of a population of neurons scattered throughout the granule cell layer that presumably correspond to Golgi cells was observed (59). Staining was also seen in Purkinje cell bodies, and in the molecular layer of the cerebellar cortex, perhaps in Purkinje cell dendrites or granule cell axons (59). K_v7.2 is also present at axon initial segments of hippocampal CA3 and CA1 (Fig. 2E) pyramidal neurons and pyramidal neurons in cerebral cortex, and at nodes of Ranvier in spinal cord and optic nerve (71), in a pattern very similar to

that of Na_v channels and ankyrin-G. The localization at axon initial segments of adult rat hippocampal CA1 pyramidal neurons has been observed in independent studies using independently generated antibodies (250)

Immunohistochemical localization of K_v7.3 reveals many similarities with K_v7.2, consistent with the model whereby native M channel complexes are heteromers of K_v7.2 and K_v7.3 subunits (349). Initial immunohistochemical studies of K_v7.3 localization in rat brain yielded labeling that was cellular/nuclear and mainly present in interneurons and astrocytes (267), and did not match the cellular expression patterns predicted from previous *in situ* hybridization studies (272,286), in spite of the fact that a standard control of antibody specificity, the inclusion of immunizing peptide, eliminated all detectable staining. Subsequent reports using independently generated antibodies revealed K_v7.3 immunostaining at nodes of Ranvier (71, 229) and axon initial segments (71,229,250), consistent with localization of K_v7.2 at these sites.

The immunohistochemical analysis of the more recently identified K_v7.5 has only been performed in human brain (381). The immunostaining presented in neocortex and hippocampus was cellular in nature and closely matched the cytoarchitecture of the regions examined. This staining, while eliminated in the presence of excess immunizing peptide, did not match that observed for K_v7.3 in rodent, in spite of the fact that co-immunoprecipitation experiments revealed extensive interaction between K_v7.3 and K_v7.5 in rat brain (381). This suggests that either differences in localization of K_v7 subunits between species, or problems with tissue preservation and or antibody specificity, confound comparisons of K_v7.5 localization in human brain. A recent study of K_v7.5 localization in rat auditory system presented clear immunostaining in presynaptic terminals of the auditory nerve (34). Additional staining was observed in dendrites (34). A more comprehensive view of K_v7.5 localization in mammalian brain awaits further study.

G. K_v5, K_v6, K_v8-12 Subfamilies

The cellular and subcellular localization of members of K_v subfamilies K_v5, K_v6, K_v8-K_v12 have not been as extensively characterized as have the members of the K_v1-K_v4 and K_v7/KCNQ subfamily. For most of these K_v channel principal subunits, some information on expression in brain is available, mainly based on analyses of mRNA isolated from whole brain or from different brain regions, or on *in situ* hybridization analyses of mRNA levels in brain sections. However, immunohistochemical analyses of the subcellular localization of these subunit proteins have for the most part not been accomplished.

The single member of the K_v5 family, K_v5.1, was originally isolated from an adult rat brain cDNA library, and *in situ* hybridization analyses show strongest signals in neocortex, especially in deeper layers (80,345). K_v6.1, the product of the KCNG1 gene, is highly expressed in brain (80,345). K_v6.1 mRNA is found in each of the principal cell populations of the hippocampus, and in the granule and Purkinje cell layers in the cerebellum (80,345). Expression in neocortex is in more superficial layers than is K_v5.1 (80,345). K_v6.2 has been detected in fetal rat (387) and human (371) (387) brain, as well as other tissues. K_v6.3 is prominently expressed in adult human brain. RT-PCR analyses showed expression in adult human brain (227), although note that in this report what is now termed K_v6.3 (107) is referred to as K_v10.1. A more detailed regional analysis of human brain K_v6.3 mRNA levels by RT-PCR (277) revealed prominent expression in all brain regions examined except cerebellum (277). K_v6.4 is also present in adult human brain (227), although note that in this report K_v6.4 is referred to as K_v6.3.

K_v8.1 was originally cloned from a hamster insulinoma cell line but is also expressed in hamster brain (125). *In situ* hybridization analyses of adult hamster brain reveal strong labeling of all principal cell populations of the hippocampus, of cerebellar granule and Purkinje cells, and

throughout cerebral cortex (125). Similar findings for expression of $K_v8.1$ (termed $K_v2.3rc$ in this report) were obtained from Northern blot and *in situ* hybridization analyses of rat brain (38). In a single study on $K_v8.2$ expression (although note that is termed $K_v11.1$ in this report) no detectable expression in adult human brain was found by RT-PCR (227). $K_v8.2$ is expressed in human retina, and specifically in photoreceptors, where mutations lead to lifelong visual loss due to cone dystrophy with supernormal rod electroretinogram (367). $K_v8.2$ mRNA was also found in rat retina by RT-PCR analyses, and in human and rat photoreceptors by *in situ* hybridization (64).

K_v9 family members $K_v9.1$ and $K_v9.2$ were originally cloned from adult mouse brain, where Northern blots revealed high levels of expression in mRNA from adult mouse brain and no detectable expression in any other adult mouse tissues examined (274). Similar brain-specific expression of $K_v9.1$ was seen in Northern blots of rat tissues (312). *In situ* hybridization of adult mouse brain revealed strikingly similar patterns of cellular expression for $K_v9.1$ and $K_v9.2$ (274). High levels of expression were observed in hippocampal dentate granule cells, and in CA3-CA1 pyramidal neurons, as well as presumptive interneurons scattered through *s. oriens* and *s. radiatum* of CA3-CA1, and the hilar region of the dentate gyrus. In cerebellum, hybridization signal was observed in Purkinje cells, and in the granule cell layer, and in cerebral cortex intense signal was observed throughout all cortical layers (274). $K_v9.3$ was also found expressed in adult rat brain by RT-PCR analyses (234) and by Northern blot analyses (58, 234,312), although expression was also observed in other adult rat tissues.

The original cloning of rat $K_v10.1$ revealed expression in brain by Northern blot analysis, and *in situ* hybridization showing strong labeling in cerebellar granule cells, in hippocampal dentate granule cells and CA3 but not CA1 pyramidal neurons, and in neocortex (182). Northern blot (183,273) and RT-PCR (273) analyses of $K_v10.2$ mRNA levels showed expression in adult brain, with olfactory bulb and brainstem having much higher levels than forebrain and midbrain structures. Initial *in situ* hybridization analyses revealed strong and laminar expression in cerebral cortex, in the granule cell layer of the olfactory bulb and olfactory cortex (273). More comprehensive *in situ* hybridization analyses of the two K_v10 or Eag family members in adult rat brain (272) revealed that $K_v10.1$ (Eag1) and $K_v10.2$ (Eag2) transcripts exhibit pronounced colocalization in specific neuronal populations, although in general the expression of $K_v10.2$ was more restricted such that many neurons express only $K_v10.1$. In neocortex, prominent coexpression of both K_v10 family members was observed in layers II-VI, with most robust expression of both transcripts in layer IV. Strong signal for $K_v10.1$ but not $K_v10.2$ was observed in each of the principal cell populations of the hippocampus, with more intense labeling of CA2 and CA3 pyramids than in CA1 and dentate gyrus, and no obvious labeling of interneurons. $K_v10.1$ signal in cerebellum was present in the granule cell layer, which lacked signal for $K_v10.2$.

Two independent *in situ* hybridization analyses of the three K_v11 (Erg) family members in adult rat brain revealed primarily consistent results (231,272), although $K_v11.2$ signal was not observed in the initial study (272). The cellular patterns of expression suggested the possibility of different combinations of subunits in heteromeric channels, based on studies showing heteromeric K_v11 channel formation in heterologous cells coexpressing multiple K_v11 subunits (363,364). $K_v11.2$ (Erg2) and $K_v11.3$ (Erg3) mRNAs exhibit precise cellular colocalization in adult rat hippocampus, with expression limited to principal cells in dentate gyrus and in pyramidal layers CA3-CA1, although Saganich, Rudy and colleagues (272) observed principal cell labeling for $K_v11.1$ and $K_v11.3$ only in CA1 (Fig. 2F). In addition to labeling in principal cells, Erg1 also exhibits robust labeling of interneurons scattered in the hilar region of the dentate gyrus, and in *s. oriens* and *s. radiatum* of CA3-CA1 (Fig. 2F), some of which are also positive for parvalbumin. Labeling in *s. pyramidale* of CA3-CA1 was also more limited than observed for $K_v11.2$ and $K_v11.3$. Each of the Erg subunits displayed

extensive expression in neocortex, with especially robust expression in layer V pyramidal neurons. In the striatum, $K_v11.1$ mRNA predominated, with strong *in situ* hybridization signals in lateral and medio-dorsal compartments of the caudate-putamen, where expression was found predominantly in interneurons (272). $K_v11.1$ also dominated in the thalamus, with strong signals in anterodorsal and anteromedial nuclei, especially in reticular thalamic nucleus. All three K_v11 family members were found expressed in cerebellar Purkinje neurons. $K_v11.1$ was also expressed in cerebellar granule cells, with an especially high signal in isolated neurons scattered throughout the granule cell layer, perhaps corresponding to Golgi cells.

Immunohistochemical analyses of the cellular and subcellular localization of $K_v11.1$ in adult rat brain yielded staining that was mostly cellular in nature (231). While all observed staining was eliminated by preincubation of antibody with immunizing peptide, in most cases the staining was intracellular suggesting that the channel population relevant to control of neuronal membrane excitability was not the predominant target of the antibody. A number of consistent cellular targets of *in situ* hybridization signal (e.g. neocortical and hippocampal interneurons, cerebellar Purkinje neurons) also exhibited robust immunostaining.

In situ hybridization analyses (272) of K_v12 (Elk) subfamily members revealed little expression of $K_v12.1$ (Elk1) in adult rat brain. This was consistent with previous reports presenting either RNase protection assays that yielded positive signals for $K_v12.1$ in mRNA prepared from sympathetic ganglia but little detectable signal in that prepared from whole adult rat brain (300), and RT-PCR analyses showing low levels of $K_v12.1$ mRNA in adult brain, although levels were much higher in mRNA prepared from the brains of embryonic day 18 rats (86). $K_v12.2$ (Elk2) and $K_v12.3$ (Elk3) mRNAs were found robustly expressed in adult rat brain in both studies (86,300), as well as in a later study reporting independent isolation of $K_v12.2$ (Bec1) and $K_v12.3$ (Bec2) cDNAs from rat and human brain (210). Note that in the study of Engeland, Pongs and colleagues (86), what was later named $K_v12.3$ was referred to as Elk1, and $K_v12.1$ as Elk3. *In situ* hybridization analyses revealed expression of $K_v12.2$ in cerebellum in granule cells but not Purkinje cells, whereas detectable $K_v12.3$ signal was not found in cerebellum (272). $K_v12.3$ was expressed at high levels in the caudate putamen, consistent with earlier studies of regional expression (86). Most cells in caudate exhibited $K_v12.3$ hybridization signal, suggesting expression in principal cells (272). In neocortex, upper layers (II-III) had highest levels of both $K_v12.2$ and $K_v12.3$ mRNA. In hippocampus, hybridization signal for both $K_v12.2$ and $K_v12.3$ was prominent in CA1 pyramidal neurons and dentate granule neurons. Similar regional expression of $K_v12.2$ and $K_v12.3$ was found in human brain in studies using Northern blots (210) and quantitative RT-PCR (389).

III. VOLTAGE-DEPENDENT SODIUM CHANNEL LOCALIZATION IN MAMMALIAN BRAIN

A. Overview of Mammalian Brain Voltage-Dependent Sodium Channels

The molecular characterization of Na_v channels, and in fact of all VDICs, began with the cloning of a cDNA encoding the electric eel electroplax Na_v channel α subunit (220). The α subunit of the electroplax Na_v channel was the first subunit of a VDIC to be cloned, and early analyses of the deduced amino acid sequence led to a number of important insights into how ion channel primary structure might relate to function. Moreover, this eel Na_v channel cDNA was used to isolate, in rapid succession, cDNAs encoding rat brain Na_v channel α subunits (218). The nine mammalian Na_v channel isoforms that have been identified and functionally expressed exhibit $\geq 75\%$ pairwise amino acid identity in the transmembrane and extracellular domains. These will be referred to using the established nomenclature (42) that consists of the prefix Na_v to indicate the principal permeating ion and the principal physiological regulator, followed by a number that indicates the gene subfamily. Currently Na_v1 is the only subfamily

within the Na_v family (Fig. 3). The number following the decimal point identifies the specific channel isoform (e.g. $\text{Na}_v1.1$) and generally reflects the order in which the subunit was cloned (42). A tenth isoform exists, termed Na_x , that exhibits approximately 50 % sequence identity to mammalian Na_v channel α subunits (42). Because the Na_x α subunits have not been functionally expressed, it is possible that this gene does not encode a functional Na_v α subunit, although genetic ablation yields altered sodium homeostasis in neurons (120). Representatives of all nine isoforms and Na_x have been identified and characterized in human, mouse and rat, and representatives of some isoforms in other species.

Na_v channels (Fig. 3) consist of a highly posttranslationally modified α subunit, which is approximately 260 kD, associated with smaller auxiliary $\text{Na}_v\beta$ subunits (39). Na_v channels in the adult central nervous system and heart contain $\text{Na}_v\beta1$ - $\text{Na}_v\beta4$ subunits, whereas Na_v channels in adult skeletal muscle have only the $\text{Na}_v\beta1$ subunit (130). The pore-forming α subunit is sufficient for functional expression (219,334), but the kinetics and voltage dependence of channel gating are modified by $\text{Na}_v\beta$ subunits (130). $\text{Na}_v\beta$ subunits are also involved in channel localization and interaction with cell adhesion molecules, extracellular matrix, and intracellular cytoskeleton (130-132). Na_v α subunits are organized in four internally repeated homologous domains (I-IV), each of which contains six transmembrane segments (S1-S6) and an additional pore loop located between the S5 and S6 segments (Fig. 3). The pore loops line the outer, narrow entry to the pore, whereas the S5 and S6 segments line the inner, wider exit from the pore. The S4 segments in each domain contain positively charged amino acid residues at every third position. These residues serve as gating charges and move across the membrane to initiate channel activation in response to depolarization of the membrane. The short intracellular loop connecting homologous domains III and IV serves as the inactivation gate, folding into the channel structure and blocking the pore from the inside during sustained depolarization of the membrane (39).

At least nine of the ten Na_v1 channel α subunit genes present in the mammalian genome are expressed in the nervous system, the exception being the muscle-specific $\text{Na}_v1.4$ (334). When expressed in heterologous systems, Na_v1 α subunits generate Na_v currents whose functional properties are highly conserved (97), compared to the heterogeneity of function observed among the different Ca_v and K_v family members. Certain subtypes, such as $\text{Na}_v1.7$, $\text{Na}_v1.8$, $\text{Na}_v1.9$ and Na_x , are expressed predominantly in the peripheral nervous system and will not be discussed here. $\text{Na}_v1.4$ is the predominant Na_v channel in adult skeletal muscle, and $\text{Na}_v1.5$ in adult cardiac and embryonic skeletal muscle. The remaining four α subunits ($\text{Na}_v1.1$, $\text{Na}_v1.2$, $\text{Na}_v1.3$ and $\text{Na}_v1.6$), are expressed at high levels in brain, although in rodents $\text{Na}_v1.3$ is predominantly found in embryonic and neonatal, but not adult brain (16). In addition, Na_v1 channels are found in both neurons and glia. A number of groups have used antibodies raised against subtype-specific sequences in the intracellular inter-domain I-II linker region or the cytoplasmic C-terminus to define the localization of $\text{Na}_v1.1$, $\text{Na}_v1.2$, $\text{Na}_v1.3$ and $\text{Na}_v1.6$ in rat, mouse and human brain.

Na_v1 channels initiate and propagate action potentials in virtually all mammalian central neurons. The different subtypes exhibit different subcellular localization, as detailed below. $\text{Na}_v1.1$ and $\text{Na}_v1.3$ are predominantly localized to the neuronal soma and to proximal dendrites, where they control neuronal excitability through integration of synaptic impulses to set the threshold for action potential initiation and propagation to the dendritic and axonal compartments. $\text{Na}_v1.2$ is predominantly expressed in unmyelinated axons, where it conducts action potentials. $\text{Na}_v1.6$ is prominently found at nodes of Ranvier, the gaps in the myelin sheaths of myelinated axons, where it propagates action potentials, and at axon initial segments where action potentials initiate. Modulation of Na_v1 currents is undoubtedly important *in vivo* (37), and mutations that subtly alter Na_v1 channel function can lead to human diseases of hyperexcitability such as epilepsy (161).

B. Na_v1 subfamily

The availability of Na_v1 α subunit cDNAs allowed for the generation of subtype-specific molecular probes and led to the first studies of the regional and developmental patterns of Na_v1 gene expression in mammalian brain (15,16,19,31). The subsequent generation of isoform-specific antibodies allowed for initial analyses of the cellular and subcellular distribution of the corresponding Na_v1 α subunits in rat brain (33,100,357). These studies and many that followed are especially relevant for understanding how each isoform contributes to cellular excitability.

1. Na_v1.1—Initial studies of Na_v1.1 mRNA distribution in rat brain showed high expression in cerebellum, lower levels in the striatum, hippocampus and thalamus, and no detectable signal in cortex (19,31). Immunostaining revealed Na_v1.1 polypeptide predominantly in the cell bodies and dendrites of expressing cells (100,357). In the adult rat (Fig. 4A) and human hippocampus, strong Na_v1.1 staining was present on the soma of dentate granule cells, and of interneurons dispersed throughout the dentate hilus (100,357). Intense staining was also seen in *s. pyramidale* of all hippocampal subfields (CA1, CA2 and CA3) with staining restricted to the pyramidal cell somata and proximal dendrites (Fig. 4A). Recently, an Na_v1.1-dense subregion was observed within the axon initial segment of a subset of initial segments adjacent to or within the pyramidal cell layer of hippocampal area CA3 (342). Na_v1.1 was located at the proximal end of the axon initial segment, nearest to the soma, in this subset of CA3 neurons. Additional Na_v1.1 staining was also observed in a subpopulation of interneurons dispersed throughout *s. radiatum* and *s. oriens* (Fig. 4A). The identity of this subpopulation of interneurons has not been experimentally determined. Robust Na_v1.1 staining was also observed on the soma and apical dendrites of pyramidal cells in layer V of the cerebral cortex. In the cerebellum, studies of Na_v1.1 expression in the cerebellum are quite inconsistent. Some studies showed low level expression of Na_v1.1 in granule cells (56,343), while in other studies no Na_v1.1 expression was detected (89,225). However, cerebellar Purkinje cells have strong somatic Na_v1.1 staining, and clear staining is also seen on Purkinje cell dendrites. It should be noted that strikingly similar patterns of Na_v1.1 staining were observed in human brain (361), suggesting that this distinct pattern of localization is evolutionarily conserved and that somatodendritic targeting of Na_v1.1 is essential for normal neuronal function across species. Na_v1.1 channels are presumably involved in propagating synaptic signals from dendrites to soma, and in integration of electrical signals within the soma prior to the initiation of axonal action potentials.

2. Na_v1.2—While Na_v1.2 mRNA has a somewhat similar pattern of cellular expression to that observed for Na_v1.1 (31), the Na_v1.2 polypeptide was found specifically localized in axons and terminals (100,357). These early studies revealed that the highly related rat brain Na_v1.1 and Na_v1.2 polypeptides (\approx 88% amino acid identity) could be targeted to distinct subcellular domains (somatodendritic *versus* axonal) in rat central neurons. This localization also suggested that in central neurons, Na_v1.2 is a major component of the axonal action potential conductance mechanism, as well as a regulator of neurotransmitter release in presynaptic terminals.

High levels of Na_v1.1 and Na_v1.2 mRNA are expressed in many of the same cells. However, the subcellular staining pattern of Na_v1.2 is in many instances a reciprocal image of that for Na_v1.1. The contrasting subcellular localizations of Na_v1.1 and Na_v1.2 are especially clear in the hippocampus (Fig. 4), where the exquisitely laminar cytoarchitecture lends itself to such comparisons. In many cells expressing robust somatodendritic Na_v1.1 staining (Fig. 4A), very little if any Na_v1.2 staining is observed on the somatic or dendritic membrane (Fig. 4B). Thus the principal cell layers of the hippocampus are virtually lacking Na_v1.2 staining, while areas rich in axons and nerve terminals exhibit robust staining. In the dentate gyrus, Na_v1.2 is present

at high levels in the middle third of the molecular layer, site of termination efferents from the entorhinal cortex to the hippocampus (the so-called medial perforant path), and absent from dentate granule cell bodies (Fig. 4B). Additional strong staining is seen in *s. lucidum* of CA3, the site of densely packed mossy fiber axons of dentate granule cells, while CA3 pyramidal cell bodies are not stained (Fig. 4B). $\text{Na}_v1.2$ is also concentrated in *s. radiatum* and *s. oriens* of CA1 and appears to be associated with axons and terminals of the Schaffer collaterals (*s. radiatum*), and the commissural/associational pathway (*s. oriens*). As in other pyramidal cell layers, $\text{Na}_v1.2$ is not present on CA1 pyramidal cell bodies. In general, the staining pattern of $\text{Na}_v1.2$ (260,297) is quite similar to that of $\text{K}_v1.4$ (compare Fig. 2A and Fig. 4B), for which experimental lesions (212) and immuno-electron microscopy (61) studies have strongly supported an axonal localization. However, neither lesion studies nor immuno-electron microscopy have been utilized to verify that the $\text{Na}_v1.2$ staining is in fact localized to axons and terminals. It should be noted that in the large pyramidal cells of hippocampal CA1, and of layer V of the neocortex, some apical dendritic $\text{Na}_v1.2$ staining is apparent (100). However, this staining appears to be intracellular and presumably represents a pool of newly synthesized $\text{Na}_v1.2$ α subunits transiting through the rough endoplasmic reticulum and/or Golgi apparatus prior to subsequent trafficking to axons.

Similar contrasting localization of $\text{Na}_v1.1$ and $\text{Na}_v1.2$ is observed in the cerebellar cortex, where strong $\text{Na}_v1.1$ staining is seen in Purkinje cells, and strong $\text{Na}_v1.2$ staining on the axons of the granule cells and interneurons of the molecular layer (100,357). There are conflicting reports concerning $\text{Na}_v1.2$ expression in Purkinje cells. Some *in situ* hybridization studies detect $\text{Na}_v1.2$ mRNA (19,89) but other *in situ* hybridization and immunolocalization studies fail to detect this isoform (31,134,282). One interesting finding of a recent study is the graduated intensity of $\text{Na}_v1.2$ staining in the cerebellum, with the highest intensity found in the posterior lobes and much lower intensity in the anterior lobes (134), similar to the gradient of K_v4 channels detailed above.

3. $\text{Na}_v1.3$ and $\text{Na}_v1.5$ —In contrast to $\text{Na}_v1.1$ and $\text{Na}_v1.2$ transcripts, in rodents $\text{Na}_v1.3$ mRNA was found at highest levels in embryonic and early postnatal brain. A detailed immunohistochemical study of $\text{Na}_v1.3$ localization in brain has not been performed in the rat (although see (358)). However, recent studies of $\text{Na}_v1.3$ mRNA (360) and protein (361) in human brain have revealed that the distribution of $\text{Na}_v1.3$ in adult human brain is quite extensive. Certain human brain regions express moderate to high levels of $\text{Na}_v1.3$ staining, which in all cases, as in the rat, (358) is associated with neuronal somata and dendrites. Especially notable is staining in neocortex, where robust staining of layer III pyramidal cells is apparent (361). This strong staining extends some distance along the large apical dendrites along these layer III pyramidal cells, while in other neocortical laminae staining is less intense and restricted to somata. In rat, both layer III and layer V pyramidal cells exhibit strong $\text{Na}_v1.3$ staining extending along the length of the apical dendrites (358). In the human hippocampus, robust staining is observed to a subpopulation of interneurons scattered throughout *s. oriens* of CA1 and CA2, *s. lucidum* of CA3, and the polymorphic layer of the dentate gyrus. Less intense somatodendritic staining is also observed in pyramidal cells, but little or no staining is seen in dentate granule cells. In cerebellar cortex, moderate staining is observed in granule cells and in the molecular layer. Thus in human brain $\text{Na}_v1.3$ may act together with $\text{Na}_v1.1$ in determining the active properties of neuronal somata and dendrites. Moreover, a recent study showed a upregulation and misexpression of the $\text{Na}_v1.3$ sodium channel in neurons of the ventral posterolateral nucleus of the thalamus after a peripheral nerve injury (385). Their data document abnormal expression of the $\text{Na}_v1.3$ mRNA in the ventral posterolateral nucleus during this time of neuronal hyperresponsiveness and reduced nociceptive threshold, with no changes in the expression of other Na_v channels (e.g. $\text{Na}_v1.1$, $\text{Na}_v1.2$, or $\text{Na}_v1.6$) in ventral posterolateral neurons.

Interestingly, $\text{Na}_v1.5$, which is the predominant cardiac sodium channel, has recently been shown to be expressed at both the mRNA (112) and protein (368) level in mammalian brain. In mouse brain, $\text{Na}_v1.5$ is localized to axons (368).

4. $\text{Na}_v1.6$ —The cDNA encoding $\text{Na}_v1.6$ was originally isolated from rat brain (284), and $\text{Na}_v1.6$ mRNA is highly expressed in cerebellar granule cells and in pyramidal and granule cells of the hippocampus (282). In many central neurons, immunoreactivity for $\text{Na}_v1.6$ is found in the soma and proximal dendrites of cells expressing the corresponding mRNA (33,162). In adult neurons with myelinated axons, $\text{Na}_v1.6$ is robustly expressed at high densities at nodes of Ranvier (24,33), and axon initial segments (25), where Na_v1 channels are clustered at high densities (Fig. 4C, E). When nodes of Ranvier initially form in response to developmental myelination, $\text{Na}_v1.2$ channels are found in high densities at most if not all nodes, and $\text{Na}_v1.6$ is not found (24). However, with further maturation of the node $\text{Na}_v1.6$ becomes the predominant Na_v isoform such that $\text{Na}_v1.2$ is seen in only a small subpopulation of nodes, where it is always found in conjunction with $\text{Na}_v1.6$. In neurons such as retinal ganglion cells, where the myelinated portion of the axon within the optic nerve lies distal to extensive non-myelinated portions within the retina, it is clear that $\text{Na}_v1.2$ is highly expressed in the non-myelinated portions in the absence of $\text{Na}_v1.6$ (24). However, in the axon initial segment, $\text{Na}_v1.6$ is again found at high levels in conjunction with $\text{Na}_v1.1$ and $\text{Na}_v1.2$ (25). These findings point to the fact that a number of distinct membrane domains can exist along the length of mammalian axons. Some of these domains are defined by highly-specific cell-cell interactions, such as that which occurs between neurons and glia at the node of Ranvier of myelinated axons (as discussed below). However, intrinsic neuronal machinery must also exist to restrict the expression of Na_v isoforms to different locations in the non-myelinated portions of axons, such as axon initial segments.

$\text{Na}_v1.6$ is also robustly expressed in Purkinje cells, where it is present in the somata and throughout the dendritic arbor in rat (162) and human (361). This robust Purkinje cell staining is consistent with the finding that mutant mice lacking $\text{Na}_v1.6$ expression are missing a Purkinje cell resurgent Na_v current (242). *In situ* hybridization and immunolocalization studies demonstrated that $\text{Na}_v1.6$ is more highly expressed in the granule cells of lobules posterior to the boundary at lobules V and VI (282,283), similar to $\text{Na}_v1.2$ and K_v4 channels. Other somatodendritic $\text{Na}_v1.6$ staining is less impressive, with neurons in many brain regions, such as cortex and hippocampus, exhibiting somatodendritic staining that is somewhat intracellular in appearance (33,162). This may simply represent newly synthesized $\text{Na}_v1.6$ prior to its targeting to initial segments and/or nodes of Ranvier of myelinated axons, as opposed to a functional somatodendritic pool of $\text{Na}_v1.6$.

C. $\text{Na}_v \beta$ Auxiliary Subunits

Unlike the $\text{K}_v\beta$ and $\text{Ca}_v\beta$ auxiliary subunits, the $\text{Na}_v\beta$ subunits are transmembrane glycoproteins. Like other VDIC auxiliary subunits, $\text{Na}_v\beta$ subunits are multifunctional. They modulate channel gating and regulate the level of channel expression in the plasma membrane (130,131,241), and saxitoxin binding studies show that $\text{Na}_v\beta1$ mediates a four-fold increase in surface expression of coexpressed $\text{Na}_v1.2$ channels (132). More recently, $\text{Na}_v\beta$ subunits have been shown to function as cell adhesion molecules that mediate interaction with extracellular matrix, regulation of cell migration, cellular aggregation, and interaction with the cytoskeleton (200,311). Moreover, mutations in $\text{Na}_v\beta$ subunit cause effects on channel function and subcellular distribution that bias neurons toward hyperexcitability and epileptogenesis (204, 370). All four $\text{Na}_v\beta$ subunits, $\text{Na}_v\beta1$, $\text{Na}_v\beta2$, $\text{Na}_v\beta3$ and $\text{Na}_v\beta4$, are expressed in brain (36, 171,223,292,375). However, $\text{Na}_v\beta3$ is expressed primarily in embryonic brain, with mRNA levels decreasing around postnatal day 3, except in the hippocampus and striatum (292). $\text{Na}_v\beta3$ mRNA is highly expressed throughout the prenatal brain with a hybridization signal

temporally similar to that of both $\text{Na}_v1.2$ and $\text{Na}_v1.3$ subunits. It is possible that $\text{Na}_v\beta3$ may couple with $\text{Na}_v1.2$ and/or $\text{Na}_v1.3$ subunits during development to form a functional Na_v channel complex. In contrast, $\text{Na}_v\beta1$ and $\text{Na}_v\beta2$, while expressed in embryonic brain, only reach maximum expression levels at postnatal day 21 and expression remains elevated in adults (292). In the postnatal brain, $\text{Na}_v\beta1$ and $\text{Na}_v\beta2$ mRNA show some synchrony in their regional and temporal expression in cortex, hippocampus and cerebellum (292). $\text{Na}_v\beta1$ mRNA first appears around P3 (280) with expression increasing rapidly in most brain areas to reach a maximum by P14. $\text{Na}_v\beta2$ mRNA expression was also found to increase throughout the CNS between P3. The analyses of $\text{Na}_v\beta$ association during development, by immunoblot under non-reducing conditions, show that the association of both $\text{Na}_v1.1$ and $\text{Na}_v1.2$ with $\text{Na}_v\beta$ changes during the development of the brain (100). $\text{Na}_v\beta3$ mRNA is expressed at very high levels throughout the CNS at P1 with levels decreasing in most areas after this stage (292). $\text{Na}_v\beta3$ mRNA has a complementary distribution with $\text{Na}_v\beta1$ after P9, with distinct differences appearing by adulthood (213,292). The subcellular distribution of these $\text{Na}_v\beta$ subunits has not been extensively characterized.

The $\text{Na}_v\beta4$ mRNA is expressed in a restricted pattern throughout the cerebral cortex and present at high levels cerebellar Purkinje cells. In the hippocampal region, $\text{Na}_v\beta4$ is expressed at very low levels (375). In general, $\text{Na}_v\beta4$ protein expression was in accordance with the *in situ* hybridization data. Both $\text{Na}_v\beta2$ and $\text{Na}_v\beta4$ are coexpressed in many areas of the brain, but $\text{Na}_v\beta2$ exhibited a more widespread distribution. For example, in the hippocampus, $\text{Na}_v\beta4$ protein is found in isolated pyramidal neurons but is absent from the dentate gyrus apart from occasional hilar neurons. In contrast, $\text{Na}_v\beta2$ protein is highly expressed in hippocampal pyramidal cells and in the hilus and granule cells of the dentate gyrus (251). This complementary distribution may indicate selective association with distinct $\text{Na}_v1 \alpha$ subunits in those regions that may differentially influence Na_v channel properties or dictate differences in protein-protein interactions.

IV. VOLTAGE-DEPENDENT CALCIUM CHANNEL LOCALIZATION

A. Overview of Voltage-Dependent Calcium Channels

Ca_v channels mediate calcium influx in neuronal cells in response to membrane depolarization. Calcium entry through Ca_v channels mediates a wide range of intracellular processes such as activation of calcium-dependent enzymes, gene transcription, and neurotransmitter exocytosis/secretion (41). Their activity is an essential requirement for the coupling of electric signals in the neuronal plasma membrane to physiological events within the cells. Biochemical characterization of native brain Ca_v channels revealed that, in addition to the large principal α_1 subunit, the existence of numerous auxiliary subunits (Fig. 5), each encoded by multiple genes (41). The α_1 subunit is the largest and principal subunit, and incorporates the ion conduction pore, the membrane voltage-sensor and gating apparatus, a number of different types of which have been identified and characterized in the mammalian nervous system (Fig. 5), each with specific physiological functions and electrophysiological and pharmacological properties (41). These are classified into three families: the Ca_v1 (L-type), Ca_v2 (P/Q-, N-, and R-type), and Ca_v3 (T-type) family (43). These principal α_1 subunits, like the α subunits of Na_v channels, consist of four internally repeated homologous domains (I-IV), each with six transmembrane segments (S1-S6), wherein each S4 segment serves as the voltage sensor (Fig. 5). In addition to these principal pore-forming α_1 subunits, native functional Ca_v channels consist of auxiliary $\alpha_2\delta$, β , and γ subunits (Fig. 5), with exemplary subunit composition of many native Ca_v channels being $\alpha_1\alpha_2\delta\beta\gamma$ in a 1:1:1:1 ratio (43). Diversity among these Ca_v auxiliary subunits leads to a variety of isoform-specific effects that are crucial in determining the expression level, localization and function of the associated $\text{Ca}_v \alpha_1$ subunits (121). These different Ca_v channel subunits have distinct cellular and subcellular distributions in the mammalian brain supporting their individual physiological roles (335).

B. Ca_v1 Subfamily

The Ca_v1 family or L-type Ca_v channels play a critical role in somatodendritic calcium influx in many mammalian central neurons (43). Ca_v1 channels are involved in dendritic calcium signaling resulting from back-propagating action potentials, synaptic plasticity, and excitatory activity-dependent modulation of gene transcription in mammalian brain neurons (142). Among the four Ca_v1 family members, only Ca_v1.2 (α_{1C}), and Ca_v1.3 (α_{1D}) are expressed in mammalian central neurons. These underlie prominent somatodendritic high-voltage activated L-type Ca_v currents, as determined by specific pharmacological inhibition of channel currents by dihydropyridine inhibitors (305,335). *In situ* hybridization studies in rat brain first suggested the expression of Ca_v1.2 mRNA in olfactory bulb, hippocampus, cerebellum, and amygdala; Ca_v1.3 mRNA was also detected here as well as in cortex and habenula (181). Immunolocalization studies on brain L-type Ca_v1 channels suggested the expression of Ca_v1.2 and Ca_v1.3 in the cortex, cerebellum, and hippocampus, with distinct subcellular localization in the neuronal soma and proximal dendrites (2,116,355). In the cerebellum, initial studies with an α_2 -specific monoclonal antibody, suggested to reflect Ca_v1 expression, suggested expression and somatodendritic localization of L-type channels in the Purkinje cells and neurons in the granular and molecular layers (355). In the hippocampus Ca_v1 channels were found expressed and localized in the soma and proximal dendrites of pyramidal neurons in CA1-CA3 region, granule cells in the dentate gyrus, neurons in the subiculum and entorhinal cortex, and interneurons scattered throughout these region (85,116,355).

Subsequent Ca_v1 isoform-specific antibody staining suggested that Ca_v1.2 and Ca_v1.3 α subunits have distinct subcellular localizations in the soma and dendrites of principal cells in the hippocampus (85,116). Specific immunoreactivities of Ca_v1.2 and Ca_v1.3 were found to make up ~75% and ~20% of the total dihydropyridine binding activity in rat brain membranes respectively. Ca_v1.2 staining was consistently found associated with the soma and proximal dendrites, with a clustered localization pattern, in hippocampal pyramidal cells, cerebral cortical neurons, and cerebellar neurons (116), and closely resembled the staining pattern previously obtained with the α_2 -specific monoclonal antibody. These observations suggest that Ca_v1.2 is the major constituent of the brain L-type Ca_v channel population, whose clustering may be critical to proximal dendritic calcium entry in response to synaptic activity (85,189). Ca_v1.2 is also found on distal dendrites, especially in the molecular layer of the dentate gyrus and CA3/CA2 *s. radiatum* (116). These clusters are shown localizing at or near axosomatic and axodendritic postsynaptic regions, and are often associated with β_2 -adrenergic receptor signaling complexes (66). Subsequent immunolocalization studies on both endogenous and exogenous Ca_v1.2 in cultured mouse hippocampal neurons indicated plasma membrane expression of these channels in small clusters in the soma and apical dendrites with some expression in the axon initial segments (222). Higher resolution microscopic analyses revealed that these channel clusters are localized in both extrasynaptic as well as synaptic regions in the dendrites, the latter associated with glutamatergic synapses in dendritic spines (222). A recent ultrastructural study in hippocampus provided evidence for Cav1.2 localization on both dendrites and axon terminals in all hippocampal subfields (329).

Ca_v1.3 exhibited a staining pattern similar to Cav1.2 (Fig. 6D-F), and was found mainly in the soma and proximal dendrites but without the clustering seen for Ca_v1.2 (116). A more recent report on exogenous Ca_v1.2 and Ca_v1.3 channels in cultured rat hippocampal neurons revealed subtype-specific localization patterns, with Ca_v1.3 surface clusters less abundant, but larger in size and brighter than Ca_v1.2 clusters (383). Most of the Ca_v1.2 clusters (~80%) are located at/near synapses at the postsynaptic region, as opposed to Ca_v1.3 clusters, which are less abundant in these regions. However, co-expression of the postsynaptic adapter protein, Shank-1B, promoted synaptic localization of dendritic Ca_v1.3 clusters (383). In developing neurons Ca_v1.2 is robustly expressed in the growth cone, but upon neuronal maturation are

excluded from the distal axons and nerve terminals, suggesting that the specific targeting machinery in different neuronal compartments changes during differentiation (222).

C. Ca_v2 Subfamily

The Ca_v2 family of P/Q-, N- and R-type Ca_v channels plays critical roles in somatodendritic calcium influx, and regulates neurotransmitter release from presynaptic terminals in many mammalian central neurons. All three members of Ca_v2 α_1 subunits (Fig. 5), the P/Q-type or Ca_v2.1 (α_{1A}), the N-type or Ca_v2.2 (α_{1B}), and the Ca_v2.3 (α_{1E}) are expressed in mammalian central neurons, as determined by specific pharmacological inhibition of these isoform-specific Ca_v currents by the funnel web spider toxin ω -agatoxin-IVA, the cone snail toxin ω -GVIA-conotoxin, and the tarantula toxin SNX-482, respectively. Pharmacological studies using these toxins suggested that Ca_v2.1 and Ca_v2.2 channels constitute most of the presynaptic voltage-dependent calcium influx, which triggers neurotransmitter release from nerve terminals. In contrast to specific subcellular localization of Ca_v1 channels in the soma and dendrites, Ca_v2 family channels have both axonal as well as somatodendritic localization in mammalian brain neurons.

In situ hybridization studies in rat brain first suggested the expression of Ca_v2.1 mRNA in most regions of the brain except in habenula (181). Immunostaining of adult rat brain with a Ca_v2.1-specific antibody (Fig. 6A-C) revealed specific staining in the hippocampus, brain stem, habenula, frontal cortex, substantia nigra, molecular layer of cerebellar cortex, Purkinje cell dendrites, periglomerular cell soma and dendrites in the olfactory bulb, and deep layers of entorhinal cortex, neocortex and striatum (119). Subsequently, immunolocalization studies in rat brain using another Ca_v2.1 isoform-specific antibody suggested expression of these channels in the synaptic terminals of cerebellar molecular layer, and the mossy fiber zone of hippocampal CA3 (178,253,359). This presynaptic localization of Ca_v2.1 channels is consistent with the role of P/Q-type channels in the regulation of neurotransmitter release through interaction with release machinery (44,255). However, in cerebellar Purkinje cells, prominent somatodendritic staining of Ca_v2.1 was also observed (178,253,337,359), where staining colocalizes with that of metabotropic glutamate receptor subtype 1 receptor through a direct physical interaction (157). Immuno-electron microscopic analysis in globus pallidus neurons also suggested that in addition to prominent presynaptic expression, the Ca_v2.1 channels are also localized in the dendrites (111). Subsequently, several reports have shown dendritic localization of Ca_v2.1 channels, which are subjected to neurotransmitter regulation (85,147,179,188,214). Given that Ca_v2.1 transcripts are extensively processed by alternative splicing, it is attractive to speculate that different Ca_v2.1 splice variants are targeted to different subcellular compartments in mammalian brain neurons.

In situ hybridization studies in rat brain revealed the expression of Ca_v2.2 mRNA in most regions of the brain except in habenula (181). Localization studies on Ca_v2.2 channels using autoradiography of the Ca_v2.2-specific ¹²⁵I-labelled-GIVA-conotoxin (149) in mammalian brain revealed high-density expression in neuronal synaptic terminals in the striatum, hippocampus, cortex, and cerebellum (3,9,148,320,321). Higher resolution analyses in the hippocampus revealed intense ¹²⁵I- ω -GIVA-conotoxin-binding signals in regions rich in axons and presynaptic terminals, mainly in the CA3 *s. lucidum* where mossy fiber axons and terminals are located (9). Strong ¹²⁵I- ω -GIVA-conotoxin-binding signals were also detected in the infragranular polymorphic region of the dentate gyrus, and *s. radiatum* and *s. lacunosum moleculare* of CA1, which contains the Schaffer collateral, and lateral perforant path, axons and nerve terminals (9). Immunolocalization studies using a Ca_v2.2-specific antibody yielded similar results with strong immunoreactivity in punctate/synaptic structures in rat brain (356). Although robust Ca_v2.2 immunoreactivity was seen in the mossy fiber expansions / presynaptic terminals in the *s. lucidum* of hippocampal CA3 relative to the immunoreactivity in the

preceding axon shafts, some $Ca_v2.2$ immunoreactivity were also seen on the dendrites of pyramidal cells in the layers II/III and V of neocortex, and of layers CA1-CA3 of hippocampus (85,356). Studies in organotypic cultures of rat hippocampal CA3 revealed stronger $Ca_v2.2$ immunoreactivity associated in CA3 pyramidal cell dendrites than in mossy fiber terminals (85). Analyses of $Ca_v2.2$ localization in human hippocampus with a distinct antibody revealed less immunoreactivity in mossy fiber terminals in comparison to that in rats, although the labeling corresponded well with that for calbindin, a standard marker for CA3 mossy fiber terminals (68).

While the basis for the differences in the localization of $Ca_v2.2$ is not yet apparent, it is known that alternative splicing of $Ca_v2.2$ mRNA at the C-terminus leads to the generation of long ($Ca_v2.2a$) and short ($Ca_v2.2b$) channel isoforms (362). The long $Ca_v2.2a$ variant/isoform is specifically targeted to presynaptic terminals when expressed exogenously in cultured hippocampal neurons, whereas the short $Ca_v2.2b$ isoform is localized uniformly in the soma and dendrites (197). Such a difference in the targeting of exogenously expressed $Ca_v2.2$ splice-variants may underlie the earlier observation of nonpolarized expression of the total neuronal pool of $Ca_v2.2$ channels in mammalian brain (356). However, thorough immunolocalization studies using splice-variant-specific $Ca_v2.2$ alpha-subunit antibodies has not yet been accomplished to demonstrate the specific subcellular localization $Ca_v2.2$ alternative splice products.

In situ hybridization studies in rat brain showed the expression of $Ca_v2.3$ mRNA in almost all regions of the brain including habenula, where $Ca_v2.1$ and $Ca_v2.2$ mRNAs were not detected (181). Immunolocalization studies on $Ca_v2.3$ suggested a more prominent localization in the midbrain and hindbrain region than in forebrain structures, where $Ca_v2.1$ and $Ca_v2.2$ are more prominently localized (372). Strong immunoreactivity for $Ca_v2.3$ was observed in the soma of most cell types, however, close inspection of somatic immunoreactivity in the principal cells in neocortex and hippocampus at higher magnifications suggested perinuclear/intracellular localization of these channels, perhaps representing biosynthetic pool of inefficiently trafficked channels (372). Neurons in the globus pallidus, thalamus, anterior amygdala, subthalamic nuclei, and hypothalamus exhibited strong plasma membrane immunoreactivity in the soma and dendrites. Prominent $Ca_v2.3$ immunoreactivity was also observed in the soma and dendrites of cerebellar Purkinje neurons (372). However, subsequent immuno-electron microscopic analyses revealed that in rat globus pallidus neurons, $Ca_v2.3$ immunoreactivity was clearly present in dendritic structures as well as in a subpopulation of presynaptic boutons (111).

D. Ca_v3 Subfamily

The Ca_v3 family or T-type Ca_v channels underlie transient currents that activate at subthreshold membrane potentials, and that are crucial for the regulation of plasma membrane calcium permeability near resting membrane potentials and during action potentials. Ca_v3 family members (Fig. 5) have diverse expression patterns in the mammalian brain (323,380). Immunolocalization studies revealed that $Ca_v3.1$ channels are prominently expressed in hindbrain (cerebellum and medulla) with low-intensity immunoreactivity in forebrain and midbrain regions in human, rat, and mouse (62,323,380). In the cerebellar cortex, strong and specific $Ca_v3.1$ immunoreactivity was detected in the thick processes in the molecular layer, with or without additional immunoreactivity in Purkinje cell bodies (62,380). This immunoreactivity pattern is presumably associated with the soma and dendrites of Purkinje cells, given the high levels of $Ca_v3.1$ mRNA in rat cerebellar Purkinje cell somata (62,323), and relatively low mRNA levels in granule cells and basket cells. In the medulla, strong and specific $Ca_v3.1$ immunoreactivity was observed in the hypoglossal nucleus, the inferior olive, and the lateral reticular nucleus. Although in some neurons $Ca_v3.1$ immunoreactivity exhibited intracellular localization, in others it was present uniformly on the plasma membranes of

somatic and proximal dendritic membranes (62). A recent study on immunolocalization of $\text{Ca}_v3.1$ channels in rat brain using isoform-specific antibody revealed expression of these channels in the neocortex, thalamus, hippocampus, and cerebellum (201). Specific $\text{Ca}_v3.1$ immunostaining was observed in the soma and proximal dendrites of layers 1-4 and layer V cortical pyramidal neurons, and hippocampal CA1, CA3, and subicular pyramidal neurons (Fig. 6G). However, in hippocampal dentate granule cells, neurons in the thalamus, midline thalamic nuclei, and in cerebellar Purkinje cells $\text{Ca}_v3.1$ -specific immunostaining was more restricted to the cell somata (201).

In situ hybridization studies showed that in rat hippocampus the $\text{Ca}_v3.2$ mRNA was found at high levels in the dentate granule cells and CA pyramidal cells, as well as in olfactory bulb neurons (323). $\text{Ca}_v3.2$ immunostaining is present in the soma and medial dendrites of specific neurons in the neocortex, thalamus, hippocampus, and cerebellum (201). $\text{Ca}_v3.2$ immunostaining was found in the soma and proximal dendrites of layers 1-4 and layer V cortical pyramidal neurons. However, in hippocampal CA1, CA3, and subicular pyramidal neurons, $\text{Ca}_v3.2$ immunostaining was extended to medial dendrites, in addition to the somatic and proximal dendritic staining (Fig. 6H). $\text{Ca}_v3.2$ -specific immunostaining, like that of $\text{Ca}_v3.1$, was also restricted to neuronal somata in hippocampal dentate granule cells, neurons in the thalamus, midline thalamic nuclei, and in cerebellar Purkinje cells, (201).

Initial *in situ* hybridization and immunolocalization studies on $\text{Ca}_v3.3$ channels in mammalian brain suggested prominent localization in olfactory bulb and mid brain, distinct from that for $\text{Ca}_v3.1$ (323,380). Intense $\text{Ca}_v3.3$ immunoreactivity was also observed in the olfactory nerve layer and glomerular layer in mouse olfactory bulb (380). In hippocampus, $\text{Ca}_v3.3$ -specific immunoreactivity was observed in a subset of interneurons dispersed throughout *s. lucidum* of the dentate gyrus, CA3, and CA2, and subiculum, with the highest intensity in the CA2. In the dentate gyrus, strong immunoreactivity was seen in the inner and outer thirds of the molecular layer, which suggests localization of $\text{Ca}_v3.3$ on terminals of the associational and commissural pathways of the dentate gyrus and of the lateral perforant pathway of entorhinal cortex, respectively (380). These staining patterns might represent input-specific localization of $\text{Ca}_v3.3$ channels to specific subdomains of dentate granule cell dendrites. In rat cerebellar cortex, strong $\text{Ca}_v3.3$ immunoreactivity was seen in the molecular layer, which appeared diffuse and associated with the parallel fibers and/or their terminals (380), consistent with the observation of high levels of $\text{Ca}_v3.3$ mRNA in the granule cell layer, but not in the Purkinje cell or molecular layer (323). A recent report revealed the expression and somatodendritic localization of $\text{Ca}_v3.3$ channels in specific neuronal subtypes in the neocortex, thalamus, hippocampus, and cerebellum (201). The $\text{Ca}_v3.3$ immunostaining was restricted to the soma and proximal dendrites of layers 1-4 cortical pyramidal neurons. However, in layer V cortical pyramidal neurons, hippocampal CA1, CA3, and subicular pyramidal neurons as well as in cerebellar Purkinje cells, $\text{Ca}_v3.3$ immunostaining was seen in the soma as well as throughout the dendrites (Fig. 6I-K). Like $\text{Ca}_v3.1$ and $\text{Ca}_v3.2$, in hippocampal dentate granule cells, neurons in the thalamus and midline thalamic nuclei, $\text{Ca}_v3.2$ -specific immunostaining was restricted to somata (201).

E. Auxiliary Subunits of Ca_v Channels

Functional Ca_v channels are composed of four subunits, including the pore-forming $\text{Ca}_v \alpha_1$ subunit, and auxiliary $\text{Ca}_v \alpha_2\delta$, $\text{Ca}_v \beta$, and $\text{Ca}_v \gamma$ subunits (Fig. 5) as determined originally by biochemical purification of Ca_v channel complexes (41,145). Classification of these three subunits as *bona fide* Ca_v channels auxiliary subunits is based on their presence in purified Ca_v channel complexes, their direct interaction with the pore-forming α_1 subunit, and their ability to modulate the biophysical and/or trafficking properties of coexpressed $\text{Ca}_v \alpha_1$ subunits (8,76).

The $\text{Ca}_v\alpha_2\delta$ subunit is composed of two polypeptides ($\text{Ca}_v\alpha_2$ and $\text{Ca}_v\delta$) that are the products of the same gene and generated by the posttranslational cleavage of a single large precursor polypeptide into $\text{Ca}_v\alpha_2$, and $\text{Ca}_v\delta$ polypeptides and their subsequent covalent linkage by disulfide bonds (Fig. 5). Topologically, the $\text{Ca}_v\delta$ peptide has a single transmembrane segment, with the $\text{Ca}_v\alpha_2$ polypeptide being completely extracellular (Fig. 5). Association of $\text{Ca}_v\alpha_2\delta$ subunits enhances the membrane trafficking and current density of coexpressed $\text{Ca}_v\alpha_1$ subunits, and also modulates the channel's voltage-dependent gating (8). Some of these effects can be observed in the absence of coexpressed $\text{Ca}_v\beta$ subunits, whereas others display an absolute $\text{Ca}_v\beta$ requirement. Four distinct $\text{Ca}_v\alpha_2\delta$ subunits, (1-4) that interact with the $\text{Ca}_v\alpha_1$ subunits have been reported, of which only $\text{Ca}_v\alpha_2\delta$ -1, $\text{Ca}_v\alpha_2\delta$ -2, and $\text{Ca}_v\alpha_2\delta$ -3 have been found expressed in mammalian brain (8,106,158). However, information on the specific subcellular localization of individual $\text{Ca}_v\alpha_2\delta$ subunits (although see description of studies with a general anti- $\text{Ca}_v\alpha_2\delta$ subunit antibody described above), as well as their distribution relative to $\text{Ca}_v\alpha_1$ subunits in mammalian brain is lacking.

The $\text{Ca}_v\beta$ subunit is a product of a single gene, which subsequently gives rise to several alternatively spliced isoforms (8,75,117). Four distinct $\text{Ca}_v\beta$ subunit genes ($\text{Ca}_v\beta_1$ - $\text{Ca}_v\beta_4$) have been described. Topologically, $\text{Ca}_v\beta$ subunits are cytoplasmic polypeptides (Fig. 5), although $\text{Ca}_v\beta_{1b}$ and $\text{Ca}_v\beta_{2a}$ isoforms can associate with the plasma membrane independent of $\text{Ca}_v\alpha_1$ subunits (23,51). Interaction of $\text{Ca}_v\beta$ subunits with $\text{Ca}_v\alpha_1$ subunits promotes channel trafficking to the plasma membrane, and modulates voltage-dependent gating (18,306). *In situ* hybridization and immunolocalization studies in mammalian brain revealed that the $\text{Ca}_v\beta_{1b}$ splice variant mRNA is expressed throughout the brain, with a diffuse cytoplasmic distribution (181). The $\text{Ca}_v\beta_2$ subunit is found expressed only in specific cell types in thalamus, cerebellum and hippocampus, including cerebellar Purkinje neurons and hippocampal pyramidal neurons (17,181). Strong immunostaining of both $\text{Ca}_v\beta_3$ and $\text{Ca}_v\beta_4$ is seen in mammalian brain, with prominent $\text{Ca}_v\beta_3$ immunoreactivity in olfactory bulb, cortex, hippocampus, habenula, and cerebellum, and prominent $\text{Ca}_v\beta_4$ immunoreactivity in cerebellum, with moderate to low immunoreactivity in olfactory bulb, cortex, hippocampus, and brainstem (181). Comparative distribution studies of $\text{Ca}_v\alpha_1$ and $\text{Ca}_v\beta$ subunits indicate no exclusive association between particular pairs of these principal and auxiliary subunits. In particular, the $\text{Ca}_v\beta$ subtype associated with presynaptic Ca_v channels is not known. The only known examples of presynaptic $\text{Ca}_v\beta$ subunits are $\text{Ca}_v\beta_2$ and $\text{Ca}_v\beta_4$ subunits in cerebellum (181,359). Based on the polarized expression of exogenous $\text{Ca}_v\beta$ subunits in polarized epithelial cells (28), it is predicted that in cerebellar Purkinje neurons, the somatodendritic $\text{Ca}_v2.1\alpha_1$ subunits might be associated largely with the $\text{Ca}_v\beta_{2a}$ subunits, whereas the presynaptic $\text{Ca}_v2.1\alpha_1$ subunits might be associated with the $\text{Ca}_v\beta_4$ subunits (75). However, thorough information on the subcellular localization of specific $\text{Ca}_v\alpha_1$ - β combinations in mammalian brain is lacking.

The $\text{Ca}_v\gamma$ subunits are transmembrane proteins having four transmembrane segments and predicted intracellular amino and carboxyl termini (Fig. 5). To date eight $\text{Ca}_v\gamma$ subunits (designated $\text{Ca}_v\gamma_1$ - $\text{Ca}_v\gamma_8$) have been identified (8,20), although only $\text{Ca}_v\gamma_1$ and $\text{Ca}_v\gamma_6$ may act as auxiliary subunits of Ca_v channels (49), with all others acting as glutamate receptor auxiliary subunits (226). All, with the exception of $\text{Ca}_v\gamma_1$, have been found expressed in mammalian brain, where $\text{Ca}_v\gamma_2$, $\text{Ca}_v\gamma_3$, and $\text{Ca}_v\gamma_4$ have been found associated and colocalized with $\text{Cav}2.1$ and $\text{Cav}2.2\alpha$ subunits (294). Interestingly, unlike $\text{Ca}_v\alpha_2\delta$ and $\text{Ca}_v\beta$ subunits, $\text{Ca}_v\gamma$ subunits do not affect the trafficking and plasma membrane expression of coexpressed $\text{Ca}_v\alpha_1$ subunits, but do impact the biophysical properties of the resultant Ca_v channels (8, 20). Nonetheless, thorough information on the role of $\text{Ca}_v\gamma$ subunits in the function of specific neuronal Ca_v channels is lacking.

V. VOLTAGE-DEPENDENT ION CHANNEL REPERTOIRE OF SPECIFIC NEURONAL COMPARTMENTS

In this section, we provide selected examples of the VDIC distributions detailed above, but here organized by neuronal compartment. As different neurons can exhibit different subcellular distributions of specific VDICs, an exhaustive recapitulation of the details of VDIC expression in specific compartments of every type of neuron is well beyond the scope of even this detailed review. However, a brief summary of hallmarks of a subset of channels in well-characterized neurons is informative as to the repertoire of VDICs involved in compartment-specific functions.

A. Axons

The generation, propagation and modulation of action potentials in neurons requires the precise subcellular localization of axonal VDICs (13). Among VDICs, a restricted subset has been found expressed in the axons of mammalian brain neurons. This set includes $K_v1.1$, $K_v1.2$, $K_v1.4$ and their auxiliary $K_v\beta1$ and $K_v\beta2$ subunits, $K_v3.1b$, $K_v3.3$ and $K_v3.4$, $K_v7.2$ and $K_v7.3$, $Na_v1.1$, $Na_v1.2$ and $Na_v1.6$, and $Ca_v1.2$ (25,48,70,72,128,167,222,259,342). Two prominent examples of high density VDIC clustering in mammalian axons are the axon initial segment and the node of Ranvier. The initial segment, an axonal subdomain essential for action potential initiation, expresses high density of $Na_v1.6$, or $Na_v1.2$ at younger ages (24), and occasionally $Na_v1.1$ (342), $K_v1.1$ and $K_v1.2$ (72,128), and $K_v7.2$ and $K_v7.3$ (229,250). The node of Ranvier, characterized by regularly spaced, short 1 μm gaps in the myelin sheath, expresses high densities of clustered $Na_v1.6$, or $Na_v1.2$ in immature nodes, (24), and $K_v7.2$ and $K_v3.1b$, which generate the slowly activating (K_s) and the fast (K_f2) nodal currents, respectively (70,71). High density clustering of $K_v1.1$, $K_v1.2$ and occasionally $K_v1.4$, along with K_v2 , are found in the juxtaparanode, a 5-15 μm long axonal membrane domain adjacent to the node but peripheral to the axoglial junction of the paranode (247,259,260,346).

VDICs can be also prominently localized to unmyelinated axons. Many axons expressed high levels of $K_v1.1$, $K_v1.2$ and $K_v1.4$, and $K_v\beta1$ and $K_v\beta2$ (260). In neocortex and hippocampus, $K_v3.4$ appear to be localized to axons, frequently colocalizing with these K_v1 family members (167). Unmyelinated axons of dentate granule cells and cerebellar granule cells express $Na_v1.2$ and $Na_v1.6$ (31,100,282,284,357). $Ca_v1.2$ channels exhibit localization in axons and growth cones when exogenously expressed in cultured hippocampal neurons, but with further maturation are found in the soma and dendrites, although some localization in the axon initial segment can be observed (222).

B. Presynaptic terminals

At the presynaptic terminal, VDICs play a critical role in regulating nerve terminal excitability and controlling calcium influx which consequently regulate neurotransmitter release. $K_v1.1$, $K_v1.2$ and $K_v1.4$ are concentrated in the axonal membrane immediately preceding or within the presynaptic terminal (61,73,347). Biochemical studies demonstrate that most K_v1 channels isolated from brain synaptic membranes contain $K_v1.2$ subunits, with $K_v1.2$ homomers being prevalent (293). Studies on calyx of Held presynaptic terminals show that $K_v1.2$ is located at the transition zone between the axon and terminal but are excluded from the terminal itself (73). $K_v1.2$ located here does not influence action potentials within the terminal *per se*, but instead suppress axonal excitability, ensuring that aberrant action potentials do not invade the nerve terminal and elicit transmitter release (73). In cerebellar basket cell terminals, $K_v1.1$, $K_v1.2$ and $K_v\beta2$ and $K_v3.4$ colocalize at the level of the light microscope, but exhibit distinct ultrastructural localizations (167,260). $K_v1.1$, $K_v1.2$ and $K_v\beta2$ are present in the septate-like junctions formed between basket cell terminal and Purkinje cell axons, while $K_v3.4$ is found in nonjunctional region of basket cell terminals (167). $K_v3.2$ is also found in basket cell

terminals at sites distinct from $K_v3.4$ sites (22). $K_v3.2$ is distributed to focal regions also distinct from the septate junctions ($K_v1.1$ and $K_v1.2$), and corresponding to vesicle clusters at the terminal active zone, such that basket cell terminals possess a mosaic of K_v channel subunits (22). $Na_v1.2$ is also found concentrated near nerve terminals, such as in globus pallidus, presumably on nerve terminals of striatal afferents, and in CA3 *s. lucidum*, presumably on mossy fiber terminals (100). Specific immunolocalization of $Ca_v2.1$ and $Ca_v2.2$ has been reported in the presynaptic area of neurons in rat cerebellar molecular layer and the mossy fiber zone of hippocampal CA3 region (178,359). The long splice variant of $Ca_v2.2$ ($Ca_v2.2a$), but not the short variant/isoform $Ca_v2.2b$, is specifically targeted to presynaptic terminals when expressed exogenously in cultured hippocampal neurons (197). In rat brain globus pallidus neurons, a subset of $Ca_v2.3$ is localized in a subpopulation of presynaptic boutons, as revealed by immuno-electron microscopy (111).

C. Soma and Proximal Dendrites

In neurons the initiation of dendritic action potentials in response to excitatory postsynaptic potentials, and their subsequent active propagation to the somata, requires somatodendritic VDICs, many of which also contribute to backpropagation of action potentials from soma to dendrites (13,164). A large subset of VDICs have been found expressed in the soma and dendrites of mammalian central neurons, including $K_v1.1$, $K_v1.2$, $K_v2.1$, $K_v2.2$, $K_v3.1a$, and $K_v3.2$, $K_v4.2$, $K_v4.3$, and their auxiliary KChIP and DPP-like subunits, and $K_v7.5$ (127,216, 257,289,296,297,332,347,381). $Na_v1.1$, and to a lesser extent $Na_v1.6$ are also found in dendrites (100,282,357), $Ca_v1.2$, $Ca_v1.3$, $Ca_v2.1$, $Ca_v2.2$, $Ca_v2.3$, $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$ and their auxiliary subunits (85,116,323,372,380). In terms of specific subcellular localization of VDICs on dendrites, there exists a distinction between those found in the soma and proximal dendrites, and those on distal dendrites. In the soma and proximal dendrites, there are high levels of $K_v2.1$, $K_v2.2$, $K_v3.2a$, $K_v3.3$, and in interneurons $K_v3.1b$, $K_v3.3$ and $K_v4.3$ (53,77, 127,297,335). Among Na_v channels $Na_v1.1$ is predominantly expressed in the soma and proximal dendrites of many mammalian brain neurons, although $Na_v1.6$ is also present in certain cell types (33,357). Almost all the Ca_v channels have been found expressed in the soma and proximal dendrites, in varying degrees, and in different neurons (335). For example, although $Ca_v2.1$ and $Ca_v2.2$ are predominantly expressed in axon terminals of most central neurons, they are also expressed in the soma and proximal dendrites of cerebellar Purkinje neurons and hippocampal CA1-CA3 pyramidal neurons (85,356). $Ca_v3.1$ and $Ca_v3.2$ are also restricted to the somata of certain cell types, such as hippocampal dentate granule neurons and cerebellar Purkinje neurons (201). It should be noted when evaluating immunostaining data showing localization of VDICs on the soma and proximal dendrites that these domains contain the bulk of the neuron's rough endoplasmic reticulum and Golgi apparatus. As such, some of the immunostaining reported for VDICs may be intracellular biosynthetic pools destined for other compartments (e.g. axons), as opposed to functional plasma membrane populations. Moreover, these domains are also a major site of non-specific antibody staining (261). As such, the reported somatodendritic expression of certain VDICs may not be representative of channel pools regulating excitability of these domains.

D. Distal Dendrites

In distal dendrites of neurons, specialized expression of different VDICs is critical not only for the active propagation of dendritic action potentials from dendrites to soma, but also for controlling backpropagation of action potentials from the soma into dendrites. K_v4 channels play a crucial and dynamic role in the latter process (378), and principal and auxiliary subunits of K_v4 channels are prominently expressed in distal dendrites (205,257,297). Other K_v channels localized in the distal dendrites of mammalian brain neurons are $K_v2.2$, $K_v7.2$, $K_v7.3$, and $K_v7.5$, which are expressed in varying densities in different cell types (34,127). A subpopulation of neuronal $K_v1.1$ channels is also found in the distal dendrites of certain

mammalian brain neurons (50). $Ca_v1.2$ and $Ca_v3.3$ channels are expressed in the distal dendrites, in addition to their localization in the soma and proximal dendrites (85,201). However, in certain types of mammalian brain neurons, $Ca_v2.1$, $Ca_v2.2$ and $Ca_v2.3$ are also expressed throughout the somatodendritic region (111,119). Dynamic activity-dependent changes in the localization of $K_v4.2$ and $Ca_v1.3$ in distal dendrites, especially in relation to excitatory synapses, have recently been reported (153,383).

VI. MECHANISMS UNDERLYING VOLTAGE-DEPENDENT ION CHANNEL LOCALIZATION

A. K_v Channels

As described in detail above, among VDICs expressed in mammalian central neurons, K_v channels have among the most diverse patterns of subcellular segregation. K_v1 channels are predominantly localized in axons. Recent studies suggest a prominent role for $K_v\beta$ subunits in determining this localization. $K_v1.2 \alpha$ subunits overexpressed in cultured hippocampal neurons exhibit a somatodendritic localization, whereas cotransfection of the $K_v\beta2$ subunit, which in itself is preferentially localized to axons (35), yields a pronounced axonal localization of $K_v1.2$ (35,101). Subsequent analyses of $K_v1.2$ deletion mutants and chimeric channels revealed that the amino terminal T1 domain, which comprises the $K_v\beta$ subunit binding site (105,291, 377), is essential for axonal expression of $K_v1.2$ channels (101). Specific mutations to disrupt $K_v\beta2$ binding also disrupted axonal expression of $K_v1 \alpha$ subunits in transfected neurons, further suggesting that endogenous $K_v\beta$ subunits were contributing to the axonal K_v1 localization (101). Remarkably, when appended to single-pass transmembrane reporter proteins, the $K_v1.2$ T1 domain, but not T1 domain mutants with altered $K_v\beta$ binding, was able to direct the axonal localization of the reporter proteins when co-expressed with $K_v\beta2$ (101). Thus, cytoplasmic $K_v\beta$ subunits may affect not only early biosynthetic processing events and ER export (299), but also axonal localization (35,101), of K_v1 channels.

Recent studies have shown that axonal targeting of K_v1 channels is dependent on the direct interaction of $K_v\beta2$ with the microtubule plus-end tracking protein, EB1 (102). Analysis of $K_v\beta2$ deletion mutants revealed that disruption of the association of $K_v\beta2$ with EB1 dramatically decreases $K_v1.2$ axonal targeting (102). Suppression of endogenous EB1 expression using siRNA also impairs axonal targeting of endogenous K_v1 channels, but not of endogenous Na_v channels (102), which appear to target to axons by distinct mechanisms and motifs (94). Another recent study shows that K_v1 channel axonal targeting is not only dependent on EB1 and $K_v\beta2$, but also on the interaction of the $K_v1 \alpha$ subunit T1 domain with the kinesin KIF5B (264). The role of $K_v\beta2$, which also binds at the T1 domain, was not addressed in this study, although endogenous $K_v\beta2$ was presumably expressed in the neurons in the cultured cortical slices used in these studies (264). As such, the T1 domain of $K_v1 \alpha$ subunits mediates multiple protein-protein interactions, including tetrameric assembly of $K_v1 \alpha$ subunits, association with $K_v\beta$ subunits (and their EB-1 binding partner), and interaction with KIF5B.

Membrane-associated guanylate kinases (MAGUKs) such as PSD-95, Chapsyn-110, SAP102 and SAP97 function as scaffolding molecules to promote co-clustering of membrane receptors and ion channels (84). Mutational and structural analyses showed that the PDZ domains of PSD-95 and other MAGUKs bind to the PDZ-binding motif (S/TxV) at the carboxyl terminus of all $K_v1 \alpha$ subunits (78,151,152,327). In most mammalian central neurons, MAGUKs are found at synapses, most prominently in the postsynaptic density (295), while K_v1 channels are predominantly found on axons (335). However, MAGUKs are found as prominent components of K_v1 complexes purified from mammalian brain (287). Examples where K_v1 channels and MAGUKs, in this case PSD-95, exhibit robust colocalize in neurons, are in the colocalization

of $K_v1.1$, $K_v1.2$, and $K_v\beta2$ with PSD-95 in cerebellar basket cell terminals (151,167) and at the juxtaparanodal regions of nodes of Ranvier (247). Mutation of the *Drosophila* discs-large gene, the ortholog of PSD-95, results in failure to localize *Shaker* potassium channels to the neuromuscular junction of flies (388). However, mutation of PSD-95 in mice does not lead to altered K_v1 channel localization at juxtaparanodes and cerebellar basket cell terminals (245). At the level of the light microscope, the localization of $K_v1.1$ and $K_v1.2$ in basket cell terminals and juxtaparanodes is normal in transgenic mice expressing a truncated form of PSD-95 that is no longer expressed at these sites. Compensatory expression of other MAGUKs does not appear to be involved in maintaining K_v1 channel localization at these sites (245). However, genetic elimination of another PDZ binding protein found at the juxtaparanode, Caspr2, does lead to loss of K_v1 channels at these sites (237). While MAGUKs or other PDZ containing proteins remain attractive candidates for the interacting proteins that cluster K_v1 channels and Caspr2 at discrete plasma membrane subdomains such as juxtaparanodes of myelinated axons, axon initial segments, and near nerve terminals, the specific binding partners mediating the clustering and their regulation remain to be elucidated.

Initial studies of the polarized and clustered localization of $K_v2.1$ were performed in polarized epithelial MDCK cells. In these cells, $K_v2.1$ localizes in the basolateral membrane (281), consistent with the analogous membrane hypothesis whereby the apical and basolateral membranes of epithelial cells correspond to the axonal and somatodendritic membranes, respectively, of neurons (77). Interestingly, $K_v2.1$ is also present in large clusters in the basolateral domains of MDCK cells (281), as it is in neurons. Expression of truncation mutants that lacked relatively large portions of the cytoplasmic $K_v2.1$ carboxyl terminus revealed that an ≈ 130 amino acid segment approximately midway in the 440 amino acid carboxyl terminus of $K_v2.1$ was necessary for both polarized expression and clustering in MDCK cells (281). These findings were later extended by studies in primary cultures of hippocampal neurons (175), where further deletion analyses revealed an ≈ 25 amino acid segment that was necessary for polarized and clustered localization. This sequence is well conserved in $K_v2.2$, which has a localization distinct from $K_v2.1$, suggesting additional targeting determinants. An alanine scan through this region revealed that three of the four critical amino acids are serine residues, consistent with subsequent studies showing a role for phosphorylation in regulating $K_v2.1$ clustering (208,209).

Electron microscopic analysis has shown that plasma membrane $K_v2.1$ clusters on the somata and proximal dendrites of pyramidal neurons lie over subsurface cisternae (82), and at F-type muscarinic synapses in spinal motor neurons (215). These specialized sites where intracellular Ca^{2+} stores come into close apposition with the plasma membrane represent a specialized neuronal signaling domain that may also contain elevated levels of voltage-dependent Ca^{2+} channels (355). A functional relationship between $K_v2.1$ and dendritic $[Ca^{2+}]_i$ transients were revealed by antisense knock down of $K_v2.1$ in rat hippocampal neurons (81). Moreover, $K_v2.1$ clusters colocalize with ryanodine receptor intracellular Ca^{2+} release channels in cultured hippocampal neurons (7). These findings suggest that the clustered localization of $K_v2.1$ could affect dendritic Ca^{2+} signaling at these sites, and *vice versa*.

Some of the most exciting studies in the ion channel clustering field have recently revealed the dynamic nature of $K_v2.1$ clustering. These live cell imaging studies reveal that although $K_v2.1$ localization is restricted to clusters, within these clusters $K_v2.1$ is freely mobile (221). This has led to a perimeter fence model for $K_v2.1$ clustering, whereby $K_v2.1$ is not attached to scaffolding proteins *per se*, but is clustered through interaction with the actin-based cytoskeleton that is somehow involved in determining the perimeter of $K_v2.1$ clusters (324). It is not yet clear from this intriguing model for $K_v2.1$ clustering how point mutations in the PRC domain (175), and dephosphorylation of C-terminal $K_v2.1$ phosphorylation sites (208,

209), would eliminate clustering, and the relationship of these dynamic clusters to intracellular membranes.

The polarized expression of three different C-terminal $K_v3.2$ splice variants ($K_v3.2a$, b , and c) in polarized epithelial cells revealed that alternative splicing led to differences in subcellular localization. The $K_v3.2a$ variant was localized to the basolateral membrane, whereas the $K_v3.2b$ and $K_v3.2c$ isoforms were found apically (238). A recent report suggests that the polarized expression of $K_v3.1$ channels may also be determined by C-terminal splicing that affects interaction with ankyrin-G (369). This may be consistent with the localization of $K_v3.1b$ at nodes of Ranvier (70), which contain high levels of ankyrin-G. Is it intriguing that $K_v3.1b$ is not found at the initial segments of the same axons, as many other nodal proteins are also found here, including ankyrin-G (229,342).

As described above, K_v4 channels exhibit strict polarized somatodendritic localization in neurons (335). The determinants of dendritic targeting of K_v4 α subunits have recently been investigated using chimeras between $K_v4.2$ and axonally localized $K_v1.3$ (265). Analyses of these chimeras revealed a critical 16-amino acid dileucine-containing motif in the cytoplasmic carboxyl-terminal region of $K_v4.2$ that is conserved in all K_v4 family members from nematodes to mammals (265). Unlike the determinant for polarized localization and clustering of dendritic $K_v2.1$, the K_v4 targeting signal also targets a type 1 membrane protein reporter protein (CD8) to dendrites (265). It should be noted that these results were obtained in a neuronal background that presumably contains endogenous KChIPs and/or possibly DPPX, as such the contribution of these interacting proteins to mediating the effects of this targeting signal cannot be determined. Thus, it will be important to determine whether this trafficking signal directs polarized K_v4 targeting in an expression background lacking these proteins (e.g. MDCK cells), or whether $K_v4.2$ mutants that lack KChIP and DPP-like auxiliary subunits binding still localize to dendrites. Conversely, a direct determination of the role of auxiliary subunits in the polarized expression of K_v4 channels is needed. Dendritic targeting of K_v4 channels also appears to involve the action of the microtubule-based motor protein kinesin Kif17 (54). Knockdown of Kif17 inhibits dendritic localization of $K_v4.2$, and $K_v4.2$ and Kif17 can be copurified from brain and heterologous cells. Interestingly, Kif17 interacts with the $K_v4.2$ C-terminus outside of the motif previously defined as critical for $K_v4.2$ localization on dendrites, and knockdown of Kif17 does not affect dendritic localization of the CD8 reporter protein containing the K_v4 family dendritic localization signal (54). The authors suggest that the Kif17 motor may be the primary mechanism for $K_v4.2$ transport to dendrites, the dileucine-based motif is the primary determinant of whether this localization is maintained. The mechanism for this retention is not known.

Other proteins that interact with K_v4 α subunits in heterologous cells, such as PSD-95 and filamin, and enhance the steady-state cell surface expression level and clustering of $K_v4.2$ in non-neuronal cell lines may also play a role in the polarized localization of K_v4 channels on dendrites (366). However, it is interesting that in cultured hippocampal neurons, the obvious clusters of $K_v4.2$ and PSD-95 (as well as filamin) do not colocalize, but rather appear interdigitated along the dendrites (302). The roles of these proteins in the polarized expression of K_v4 channels remains to be elucidated.

$K_v4.2$ localization in cerebellar granule cells in organotypic culture is regulated by synapse formation and glutamatergic synaptic activity (301). Granule cells grown in the absence of synaptic contact from cerebellar mossy fiber axons have $K_v4.2$ aberrantly localized on somata. Upon mossy fiber:granule cell synapse formation $K_v4.2$ becomes clustered at/near these specialized synapses, in a process that requires ionotropic glutamate receptor activity. Stimulating glutamate receptors in the absence of synapse formation leads to translocation of $K_v4.2$ from the soma to the dendrites (301). A recent study reveals that the localization of

K_v4.2 on dendrites of hippocampal neurons is also dynamically regulated in response to glutamatergic synaptic activity through clathrin-mediated endocytosis (153). Internalization can be triggered by either glutamate receptor stimulation or paradigms that induce long term potentiation (153). Internalization of K_v4.2 increases dendritic excitability and further potentiates excitatory signaling in dendrites (153). The molecular determinants of the dynamic regulation of K_v4 localization, and whether they are intrinsic to K_v4.2, or found on KChIP or DPPX auxiliary subunits, or other interacting proteins, are as yet undefined.

The localization of K_v7 channels at axon initial segments has been the focus of recent study (55,229,250). K_v7.2 and K_v7.3 have binding motifs on their C-terminal cytoplasmic tails for interaction with the cytoskeletal associated protein ankyrin-G (229) similar to those found on Na_v channels (95,170). K_v7.2 and K_v7.3 localization at initial segments is disrupted in ankyrin-G knockout mice, and the targeting of exogenous K_v7 C-terminal fragments to the initial segments requires the ankyrin-G binding motif (55,229). Deletion of the ankyrin-G binding motif from full-length K_v7.2 and K_v7.3 also leads to loss of localization of the channel subunits at the axon initial segment (250). Interestingly, in heteromeric K_v7.2/K_v7.3 channels that form native M channels (349) the ankyrin-G binding motif of K_v7.3 appears to be dominant over that of K_v7.2 (250). This is consistent with the finding that C-terminal fragments from K_v7.3 were more effective at directing reporter proteins to initial segments than were those from K_v7.2 (55).

B. Na_v Channels

As described above, in general, Na_v channels have different subcellular distributions in mammalian brain: Na_v1.1 and Na_v1.3 are principally expressed on neuronal cell bodies, Na_v1.2 is expressed on unmyelinated axons, and Na_v1.6 is present on both dendrites and myelinated axons. The resulting compartmentalized, non-uniform distribution can dramatically impact neuronal excitability. These distinct localization patterns presumably reflect intrinsic and extrinsic mechanisms that selectively target proteins to the axonal or somatodendritic compartments. Despite the central role of Na_v channels in initiating and propagating neuronal electrical signals, the determinants of their discrete subcellular localizations in mammalian neurons are just beginning to be defined.

1. Axon initial segment determinants—The developmental expression and localization of Na_v channels at the axon initial segment (Fig. 4C, D) has mainly been studied in retinal ganglion cells, cerebellar granule cells and hippocampal neurons (24). In all cases, during early development Na_v1.2 is the predominant channel found at the axon initial segment. However, at later developmental stages Na_v1.6 is also detected at the axon initial segment together with Na_v1.2. The reason for the difference in temporal expression of the two distinct Na_v channels is unknown. Surprisingly, a recent study showed that the proximal axon initial segment of retinal ganglion cells and a subset of hippocampal CA3 neurons could also exhibit strong staining for Na_v1.1 channels (Fig. 4D), which generally has a somatodendritic distribution (342). Targeting and sequestration of Na_v channels at the axon initial segment involves a macromolecular complex of interacting proteins, including the cytoskeletal proteins ankyrin-G and βIV spectrin, the cell adhesion molecules neurofascin-186 (Nf-186) and neuron-glia related cell adhesion molecule NrCAM, and Na_vβ auxiliary subunits (137, 276, 386). The C-terminal cytoplasmic domain of the Na_v1 α subunit appears to control the polarized localization of Na_v channels in the axon (93). Appending the C-terminal cytoplasmic tail of Na_v1.2 onto a reporter protein leads to its targeting to axons (93). Deletion analyses of the Na_v1.2 C-terminus led to identification of a short sequence, CLDILFAFT that directs axonal targeting. This same sequence is also recognized by components of the endocytic pathway, suggesting that Na_v1.2 is delivered to the surface of both axons and dendrites and retrieved by endocytosis from the soma and dendrites (93). Interestingly, this sequence is 100% conserved in all neuronal Na_v

channels ($\text{Na}_v1.1$, $\text{Na}_v1.2$, $\text{Na}_v1.3$, and $\text{Na}_v1.6$) that exhibit very different subcellular localizations in mammalian brain. As such, the contribution of this signal in the establishment and maintenance of the contrasting patterns of subcellular localization of different Na_v isoforms in mammalian central neurons is unclear. However, the overall similarity of the distal C-termini of Na_v1 α subunits is low, such that differences in the overall structure of this domain could impact the activity of the axonal targeting motif. A second Na_v1 targeting determinant has been identified in the interdomain II-III linker that directs Na_v1 localization to the axon initial segment (95, 170). This determinant mediates Na_v1 interaction with the cytoskeletal scaffold ankyrin-G. However, it is important to note that this axon initial segment targeting motif is also conserved among all Na_v1 channels. This suggests that, like many of the identified targeting signals described above, there exist additional determinants that modulate activity of this conserved signal. It is important to note that a similar signal targets $\text{K}_v7.2$ and $\text{K}_v7.3$ to axon initial segments (see above).

2. Node of Ranvier determinants—Nodes of Ranvier have molecular similarities with axon initial segment (e.g. high density of Na_v channels, K_v channels, the cytoskeletal proteins ankyrin-G and βIV spectrin, the cell adhesion molecules Nf-186 and NrCAM). However, there exists a major distinction between these two domains: recruitment of proteins at nodes of Ranvier requires myelinating glia, but recruitment at the axon initial segment is neuronal autonomous (115). Although it is clear that myelinating oligodendrocytes are required for node of Ranvier formation and VDIC clustering, studies suggest that the Na_v1 channel clustering can be induced by a soluble factor released by oligodendrocytes (146), whereas other studies suggest a requirement for intact myelin (24,244,246,358). The cell adhesion molecule NF-186 is also required for the formation of CNS nodes, and mice with a neurofascin gene deletion, which appear to have intact myelination, fail to cluster Na_v1 channels (as well as NrCAM, ankyrin-G and βIV spectrin) at the node (298). Clustering of Na_v1 channels at axon initial segments, nodes of Ranvier and other sites in central neurons remains an exciting focus of much current research.

C. Ca_v Channels

Proper functioning and specific targeting of individual Ca_v channels into different subcellular compartments of neurons is crucial for the maintenance and physiological regulation of normal neuronal activity. As detailed above, different Ca_v channel subtypes exhibit different subcellular distributions in mammalian brain neurons, with $\text{Ca}_v2.1$ and $\text{Ca}_v2.2$ channels exhibiting predominantly axonal and presynaptic localization, and Ca_v1 and Ca_v3 channels mainly exhibiting somatodendritic expression.

Interaction with the $\text{Ca}_v\beta_4$ subunit has been suggested to promote the presynaptic targeting of $\text{Ca}_v2.1$ channels (28,365). This coincides with the preferential presynaptic localization of $\text{Ca}_v\beta_4$ subunits in mammalian brain neurons (365). Coexpression of the $\text{Ca}_v\beta_{1b}$ subunit in MDCK cells has also been shown to promote the targeting of $\text{Ca}_v2.1$ channels to apical membranes (28), suggesting a possible role for and $\text{Ca}_v\beta_{1b}$ in axonal targeting of $\text{Ca}_v2.1$ (75). The $\text{Ca}_v\beta$ subunits contain two conserved protein-protein interaction domains, a *src* Homology-3 (SH3) domain and a guanylate kinase (GK) domain, both of which are also found in channel clustering MAGUK scaffold proteins (108). These domains mediate the trafficking, targeting and voltage-dependent gating effects that $\text{Ca}_v\beta$ subunits exert on coexpressed $\text{Ca}_v\alpha_1$ subunits (92). A recent report suggests that the SH3 and GK domains can autonomously act to exert $\text{Ca}_v\beta$ subunit-like modulatory effects on $\text{Ca}_v\alpha_1$ trafficking and voltage-dependent gating (319). However, the precise mechanism underlying the $\text{Ca}_v\beta$ subunit-mediated targeting of $\text{Ca}_v\alpha_1$ subunits remains unclear.

Recent reports have strongly suggested the presence of a major intrinsic molecular determinant of presynaptic targeting in the Ca_v2.1 and Ca_v2.2 channels, namely a synaptic protein interaction site called the *synprint* site, which lies within the domain II - II cytoplasmic linker region (318). This domain II - III cytoplasmic linker region in Ca_v2.1 and Ca_v2.2 channels has been shown to assemble with synaptic protein such as syntaxin, SNAP-25, and synaptotagmin (135). Two Ca_v2.2 splice variants, which lack larger portions of the domain II - III cytoplasmic linker region and including the *synprint* motif exhibit axonal targeting but lack clustering in presynaptic terminals (211,318). The *synprint* motif could not direct the axonal targeting of dendritic Ca_v1.2 when inserted into the Ca_v1.2 interdomain II - III cytoplasmic linker suggested that the *synprint* site is necessary but not sufficient to direct targeting of Ca_v channels to presynaptic (318). Another study using exogenous expression of Ca_v2.2 channels in cultured rat hippocampal neurons suggested that synaptic targeting of these channels is dependent on neuronal contacts and synapse formation (197). The cytoplasmic C-terminus of Ca_v2.2 channels also contains consensus motifs for binding to PDZ and SH3 domains that are both necessary and sufficient for Ca_v2.2 axonal and synaptic targeting (197). The Ca_v2.2b splice variant lacks these motifs and does not exhibit axonal localization (197). The C-terminus of the Ca_v2.2a splice variant, which exhibits axonal and synaptic localization, contains these motifs and interacts with the adapter proteins Mint-1 and CASK, both of which are expressed in presynaptic nerve terminals. This suggests a model whereby interaction with Mint-1 and CASK promotes presynaptic recruitment of Ca_v2.2 channels in hippocampal neurons (197). However, another recent study suggested that deletion of the similar region in Ca_v2.1 does not affect presynaptic targeting, indicating possible differences in targeting of Ca_v2.1 and Ca_v2.2a channels to axon and presynaptic terminals (124). Overall, the precise molecular mechanisms underlying the axonal and presynaptic targeting of Ca_v2.1 and Ca_v2.2 channels through *synprint*-, Mint-1, CASK-mediate protein-protein interactions, as well as the involvement of these cytoplasmic C-terminal determinants are not completely defined.

Little is known of the molecular determinants and mechanisms underlying somatodendritic targeting of Ca_v1.2, Ca_v1.3 and Ca_v3 channels in mammalian neurons. One candidate is the auxiliary Ca_vβ_{2a} subunit, which in polarized epithelial cells directs the targeting of Ca_v2.1 to basolateral membranes (28,75). Ca_v1.3 colocalizes with the postsynaptic adapter protein Shank, and these proteins directly interact *via* a motif in the cytoplasmic C-terminus of Ca_v1.3 (383,384). However, the role of Shank interaction with Ca_v1.3 on its dendritic targeting is not known. Ca_v1.2 is robustly expressed in the growth cone of developing neurons, yet upon neuronal maturation is targeted to the soma and dendrites, suggesting that specific targeting machinery in different neuronal compartments changes during neuronal differentiation (222). Presumably, differential interaction of Ca_v1.2 with as yet unidentified protein(s) leads to a switch between growth cone and somatodendritic targeting of Ca_v1.2. A recent report has suggested that calcium/calmodulin binding to the cytoplasmic C-terminus of Ca_v1.2 channels regulates the activity-dependent targeting of these channels to distal dendrites, however, the precise mechanism underlying this process is not known (348). Together, these preliminary studies on somatodendritic targeting of different Ca_v channels warrants further detailed investigation and elucidation of the underlying mechanism(s).

VII. CONCLUDING REMARKS

The intrinsic electrical properties, and rapid processing and transmission of synaptic signals in mammalian neurons depend largely on the abundance and function of a large repertoire of VDICs located at specific sites in neuronal somata, dendrites and axons. The remarkable molecular complexity of VDICs principal and auxiliary subunits leads to the generation of a remarkable diversity of VDIC function critical to fine control of neuronal electrical signaling. The selective placement of specific VDIC types at precise locations in mammalian neurons, and their dynamic regulation through local signaling pathways, allows for a complexity of

neuronal function that underlies brain function. However, the molecular complexity of VDICs, the enormous cellular complexity of mammalian brain, and the extreme morphological complexity of neuronal form and poses a considerable challenge in understanding the specific role of individual VDICs in brain function, and how the specific and discrete subcellular compartmentalization of VDICs regulates signaling in mammalian neurons. Although molecular and biochemical studies have begun to define the cellular expression and subunit composition of native VDICs, defining the spatial localization of VDICs comprising specific subunit compositions remains an important challenge, for both fundamentally understanding neuronal function and validating specific VDICs as neurotherapeutic drug targets. The fundamental mechanisms that lead to the observed distributions in the neuronal membrane, and how these mechanisms are regulated during development, with aging, and in response to normal and pathological alterations in brain activity, have not yet been elucidated and remain a major topic of ongoing research.

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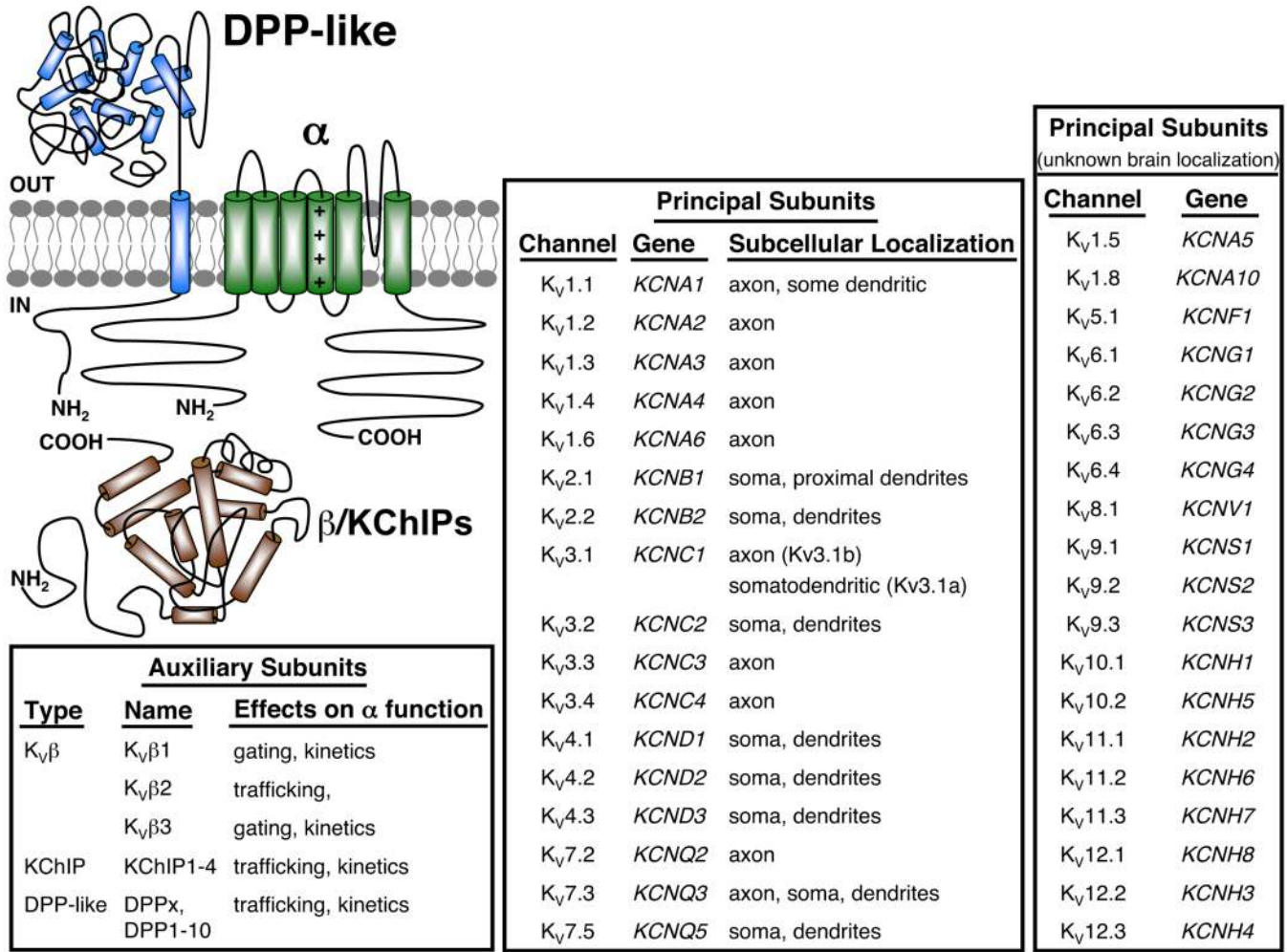


FIG. 1. Subunit composition and subcellular localization of K_v channel principal and auxiliary subunits in mammalian central neurons. Schematic representation of a single $K_v \alpha$ subunit, four of which (within the same subfamily) assemble to form functional K_v channels. Native channels also comprise auxiliary $K_v\beta$ ($K_v 1$ subfamily), or KChIP and DPP-like ($K_v 4$ family) subunits. Top middle box shows the classification, genetic nomenclature, and subcellular localization of K_v channel α subunits with well-characterized subcellular localization in mammalian central neurons. Top right box, the classification and genetic nomenclature of K_v channel principal subunits with unknown subcellular localization in mammalian brain. Bottom right box, classification of K_v channel auxiliary subunits expressed in mammalian central neurons, and their functional effects on $K_v \alpha$ subunits.

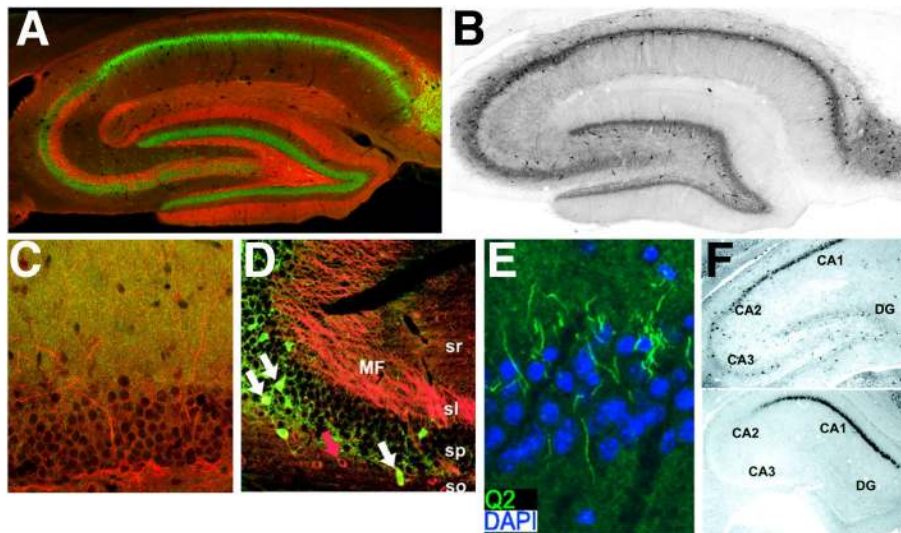
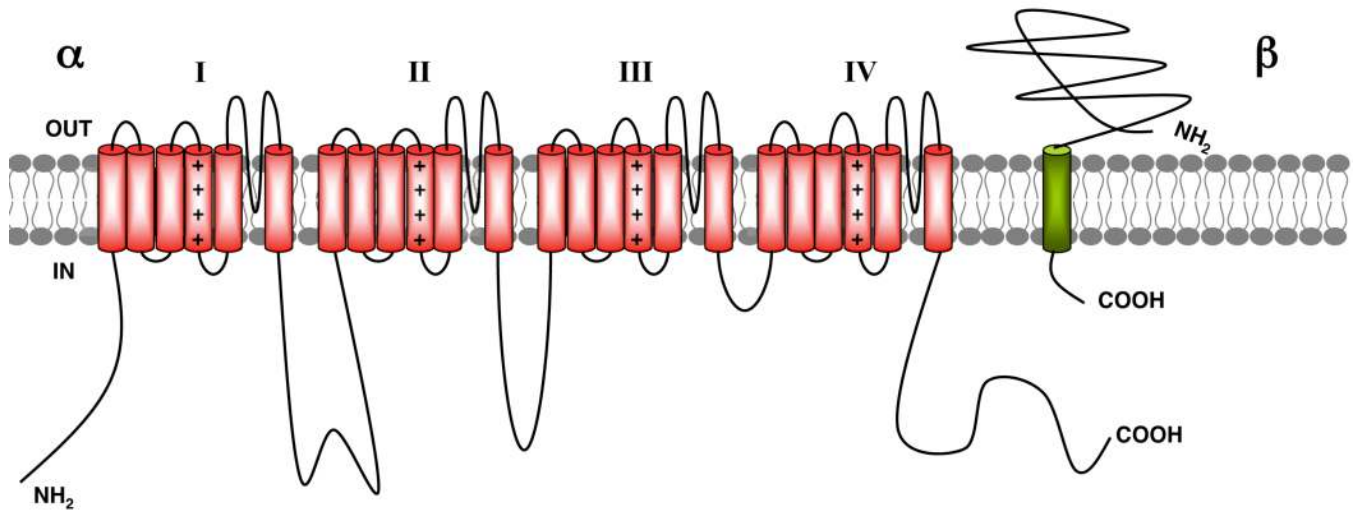


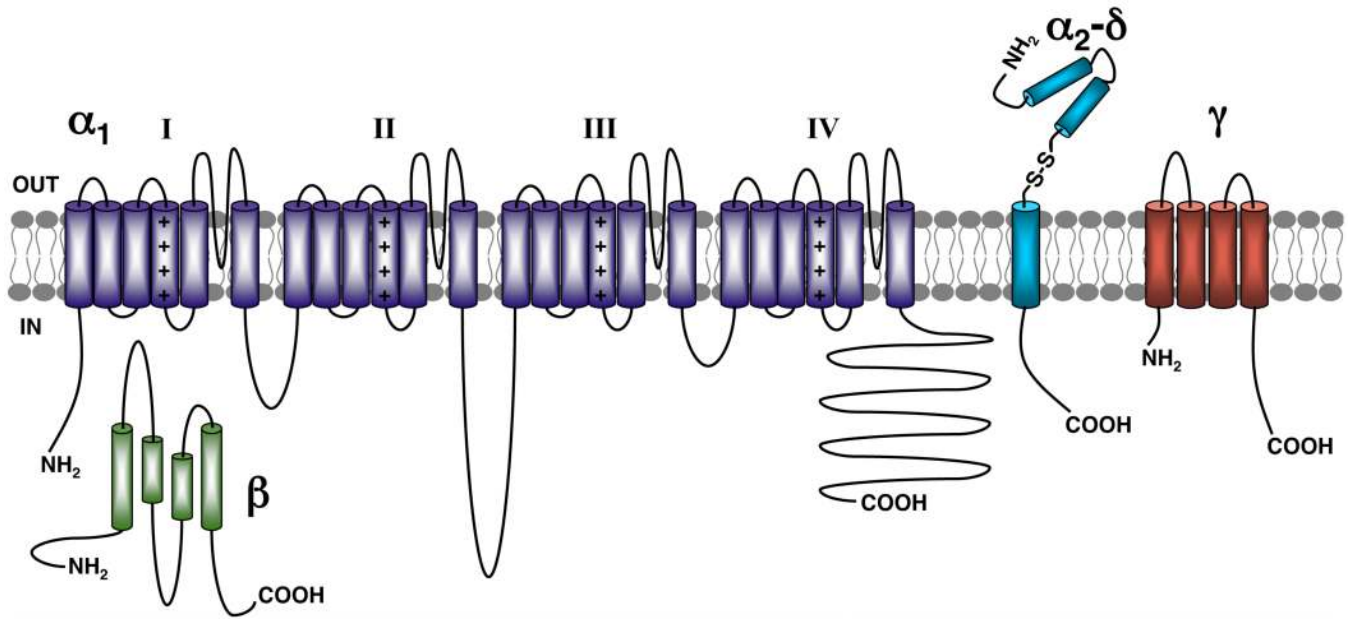
FIG. 2. Cellular and subcellular distribution of K_v channels in adult hippocampus. *A-C, F*: rat, *D-E*: mouse. *A*, Double immunofluorescence staining for $K_v1.4$ (red) and $K_v2.1$ (green). Note $K_v1.4$ staining in terminals fields of the medial perforant path in the middle molecular layer of the dentate gyrus, and mossy fiber axons and terminals in *s. lucidum* of CA3. *B*, Immunoperoxidase staining for $K_v3.1b$. *C*, Double immunofluorescence staining for $K_v4.2$ (green) and $K_v4.3$ (red) in dentate gyrus. Note uniform staining for both K_v4 α subunits in granule cell dendrites in molecular layer, and $K_v4.3$ staining in scattered interneurons. *D*, Double immunofluorescence staining for $K_v7.2$ (red) and parvalbumin (green) in CA3. White arrows depict $K_v7.2$ -negative, and red arrow $K_v7.2$ -positive neurons. MF: mossy fibers, sr: *s. radiatum*, sl: *s. lucidum*, sp: *s. pyramidale*, so: *s. oriens*. Reproduced with permission from reference (59). *E*, Double immunofluorescence staining for $K_v7.2$ (green) and DNA (DAPI, blue) in CA1. Reproduced with permission from reference (229). *F*, *In situ* hybridization of $K_v11.1$ (top panel) and $K_v11.3$ (bottom panel). DG: dentate gyrus. Reproduced with permission from reference (272).



Principal Subunits		
Name	Gene	Subcellular Localization
Na _v 1.1	<i>SCN1A</i>	soma, dendrites, some axon
Na _v 1.2	<i>SCN2A</i>	axon
Na _v 1.3	<i>SCN3A</i>	soma, dendrites
Na _v 1.6	<i>SCN8A</i>	axon, some somatodendritic

Auxiliary Subunits	
Name	Effects on α function
β_1	trafficking, gating
β_2	gating
β_3	trafficking, gating
β_4	gating

FIG. 3. Subunit composition and subcellular localization of Na_v channel principal and auxiliary subunits in mammalian central neurons. Schematic representation of a single Na_v α subunit that forms macromolecular complexes with auxiliary Na_v β subunits. Bottom left box, the classification, genetic nomenclature, and subcellular localization of mammalian brain Na_v channel principal α subunits. Bottom right box, classification of Na_v β auxiliary subunits expressed in mammalian central neurons, and their functional effects on coexpressed Na_v α subunits.



Principal Subunits					Auxiliary Subunits		
Channel	Name	α_1 -Type	Gene	Subcellular Localization	Type	Name	Effects on α_1 function
L-Type	Ca _v 1.2	α_{1C}	<i>CACNA1C</i>	soma, dendrites	Ca _v $\alpha_2\delta$	$\alpha_{2\delta-1}$	trafficking, gating, kinetics
	Ca _v 1.3	α_{1D}	<i>CACNA1D</i>	soma, proximal dendrites		$\alpha_{2\delta-2}$	current amplitude, kinetics
P/Q-Type	Ca _v 2.1	α_{1A}	<i>CACNA1A</i>	axon, some somatodendritic		$\alpha_{2\delta-3}$	trafficking, gating
N-Type	Ca _v 2.2	α_{1B}	<i>CACNA1B</i>	axon, some somatodendritic	Ca _v β	β_{1b}	trafficking, kinetics
R-Type	Ca _v 2.3	α_{1E}	<i>CACNA1E</i>	soma, dendrites		β_{2a}	trafficking, kinetics
T-Type	Ca _v 3.1	α_{1G}	<i>CACNA1G</i>	soma, proximal dendrites		β_3	trafficking, kinetics
	Ca _v 3.2	α_{1H}	<i>CACNA1H</i>	soma, proximal dendrites		β_4	trafficking, kinetics
	Ca _v 3.3	α_{1I}	<i>CACNA1I</i>	soma, dendrites	Ca _v γ	γ_2 - γ_8	current amplitude, kinetics

FIG. 4. Cellular and subcellular distribution of Na_v channels in mammalian brain and retina. *A, B:* Immunoperoxidase staining of adult rat hippocampus. Reproduced with permission from reference (100). *A,* Na_v1.1. Note staining in somata and proximal dendrites of dentate granule cells, CA3-CA1 pyramidal cells and interneurons. *B,* Na_v 1.2. Note staining in the mossy fiber pathway within CA3 *s. lucidum* and in *s. radiatum* of CA1. *C,* Double immunofluorescence staining for Na_v1 channels (red) and spectrin IV β (green) in the axonal initial segments (arrows) of pyramidal cells in human temporal neocortex. Reproduced with permission from reference (128). *D,* Double immunofluorescence staining for Na_v1.1 (red) and Na_v1.6 (green) in the axonal initial segments of retinal ganglion cells. Arrowhead denotes proximal portion of initial segment positive for Na_v1.1. Reproduced with permission from reference (342). *E,* Triple immunofluorescence staining for nodal Na_v1 channels (red), paranodal Caspr (green) and juxtaparanodal K_v1.2 (blue) in adult rat optic nerve. Image courtesy of Dr. Matthew N. Rasband.

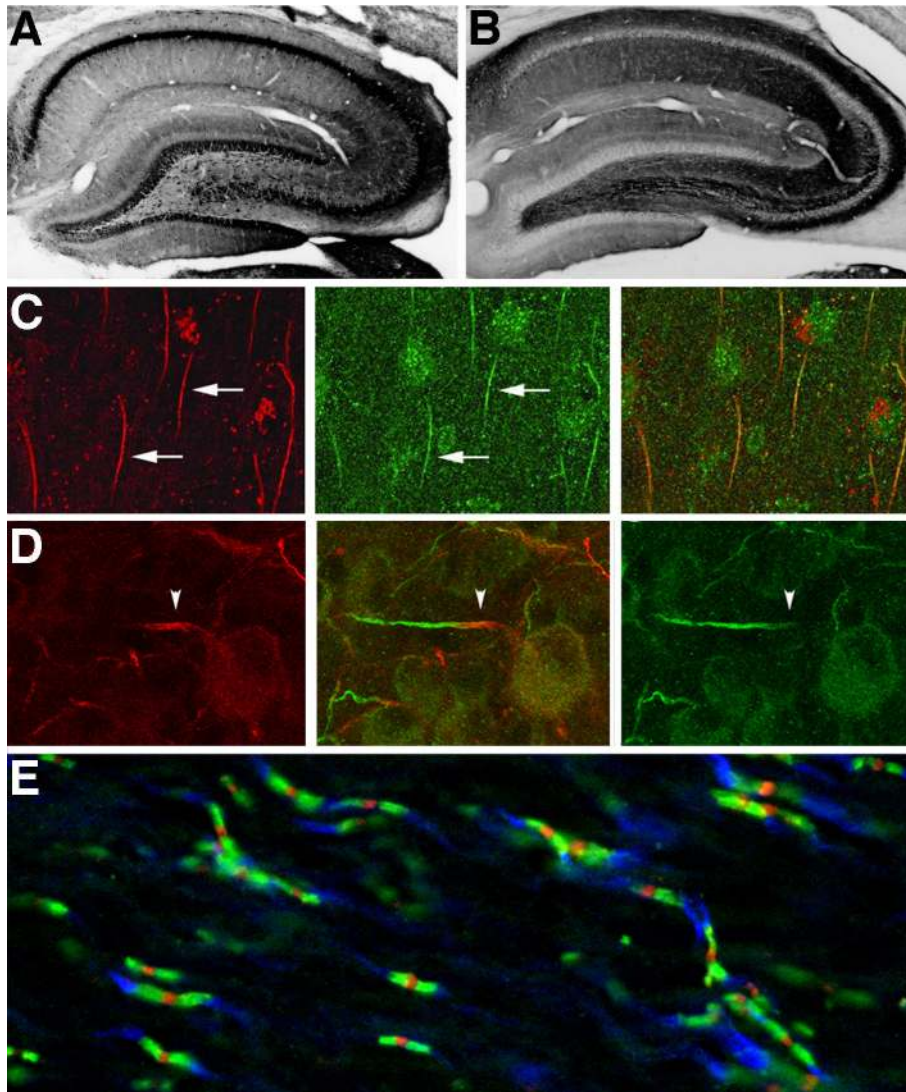


FIG. 5. Subunit composition and subcellular localization of Ca_v channel principal and auxiliary subunits in mammalian central neurons. Schematic representation of a single $\text{Ca}_v \alpha_1$ subunit that forms macromolecular complexes with auxiliary $\text{Ca}_v \beta$, $\text{Ca}_v \alpha_2 \delta$, and $\text{Ca}_v \gamma$ subunits. Bottom left box, the classification, genetic nomenclature, and subcellular localization of mammalian brain Ca_v channel principal α_1 subunits. Bottom right box, classification of $\text{Ca}_v \beta$, $\text{Ca}_v \alpha_2 \delta$, and $\text{Ca}_v \gamma$ auxiliary subunits expressed in mammalian central neurons, and their functional effects on coexpressed $\text{Na}_v \alpha$ subunits.

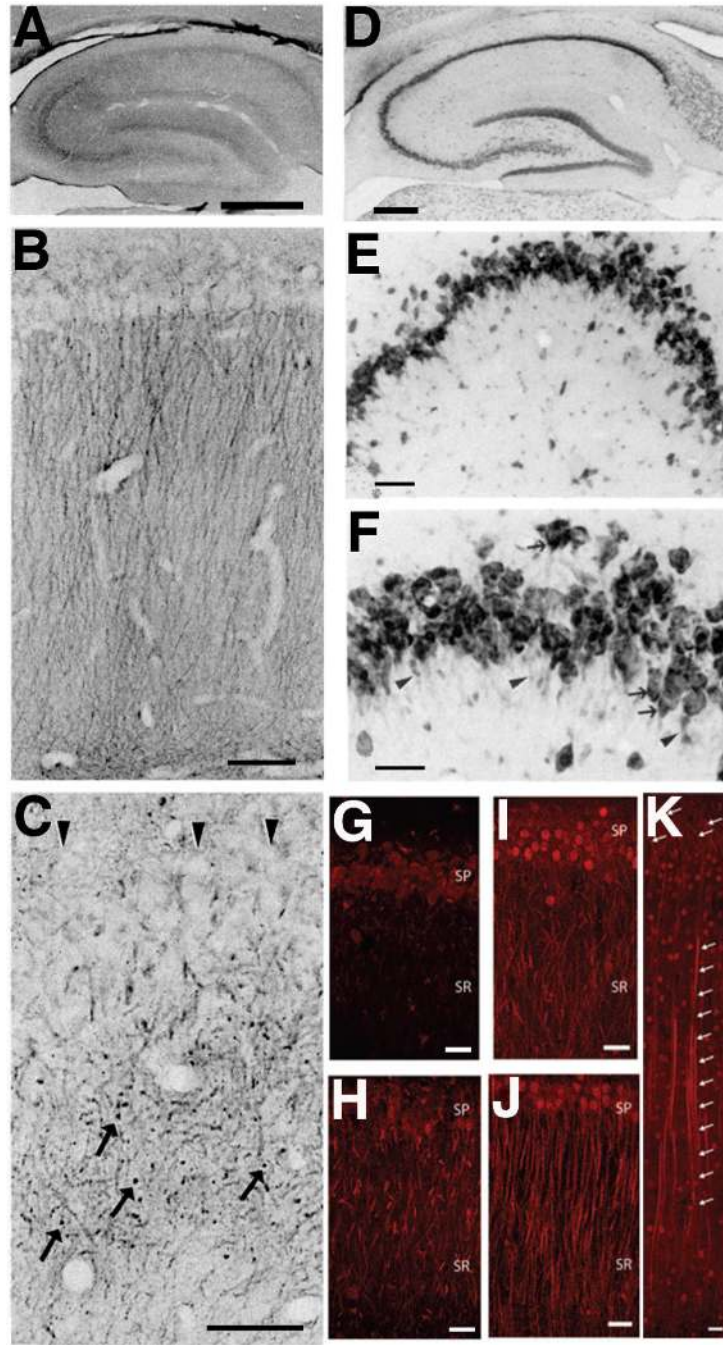


FIG. 6.

Cellular and subcellular distribution of Ca_v channels in adult rat brain. *A-F*: Immunoperoxidase staining. *G-K*, Immunofluorescence staining. *A, D-J*: Hippocampus. *B, C, K*: Neocortex. *A*, $Ca_v2.1$. Note staining in terminals fields of the medial perforant path in the middle molecular layer of the dentate gyrus, and mossy fiber axons and terminals in *s. lucidum* of CA3. *B*, Higher magnification view of $Ca_v2.1$ staining in CA1. *C*, Higher magnification view of $Ca_v2.1$ staining in CA3, arrows indicate mossy fiber terminals, and arrowheads CA3 pyramidal cell somata. *D*, $Ca_v1.3$. Note staining in somata and proximal dendrites of dentate granule cells, CA3-CA1 pyramidal cells and interneurons. *E*, Higher magnification view of $Ca_v1.3$ staining in CA3-CA2. *F*, Much higher magnification view of $Ca_v1.3$ staining in CA3-CA2. Arrows: base of

apical dendrites. Arrowheads: proximal dendrites. *G-I*: Ca_v3.1 (G), Ca_v3.2 (H), and Ca_v3.3 (I) staining in CA1. *J*, Ca_v3.3 staining in subiculum. *K*, Ca_v3.3 staining in neocortex. SP, *s. pyramidale*. SR, *s. radiatum*. Reproduced with permission from reference: *A-C*: (359); *D-F*: (116); *G-I*: (201).