Minireview

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γ Subunit of Voltage-activated Calcium Channels*

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Myoung-Goo Kang‡ and Kevin P. Campbell§

From the Howard Hughes Medical Institute, Department of Physiology and Biophysics and Department of Neurology, University of Iowa College of Medicine, Iowa City, Iowa 52242

Voltage-activated Ca^{2+} channels play a major role in many fundamental physiological processes including neurotransmission, muscle contraction, intracellular signaling, hormone secretion, and development. Therefore, an understanding of the structure and regulation of Ca^{2+} channels is critical for the comprehension of these physiological phenomena. Five types of high voltage-activated Ca^{2+} channels (named L-, N-, P-, Q-, and R-type) and one type of low voltage-activated Ca^{2+} channel (known as T-type) have been identified based on the pharmacological and biophysical characteristics of native currents. Voltage-activated Ca^{2+} channels (called Ca^{2+} channel or Ca_v hereafter) consist of four subunits: α_1, β, $\alpha_2\delta$, and γ. The α_1 subunit is the main subunit responsible for ion conduction, voltage sensing, and binding of Ca^{2+} channel-specific drugs and toxins. Ten α_1 subunits have been cloned and classified as $\alpha_1$1.1 (α_{1S}), $\alpha_1$1.2 (α_{1C}), $\alpha_1$1.3 (α_{1D}), $\alpha_1$1.4 (α_{1F}), $\alpha_1$2.1 (α_{1A}), $\alpha_1$2.2 (α_{1B}), $\alpha_1$2.3 (α_{1E}), $\alpha_1$3.1 (α_{1G}), $\alpha_1$3.2 (α_{1H}), and $\alpha_1$3.3 (α_{1I}). The β and $\alpha_2\delta$ subunits are auxiliary proteins that modulate the properties of the Ca^{2+} current (1–3). Four isoforms of the β subunit (β_1, β_2, β_3, and β_4) and four isoforms of the $\alpha_2\delta$ subunit ($\alpha_2\delta$-1, $\alpha_2\delta$-2, $\alpha_2\delta$-3, and $\alpha_2\delta$-4) have been identified. An additional auxiliary subunit, γ, initially detected in skeletal muscle Ca^{2+} channels, has been recently associated with neuronal Ca^{2+} channels (4–6). The study of Ca^{2+} channel regulation by auxiliary subunits has been focused on β and $\alpha_2\delta$ subunits and demonstrated positive regulation of functional activities of Ca^{2+} channels by these proteins. The β and $\alpha_2\delta$ subunits can increase current amplitude and cause various changes in current kinetics and voltage dependence by increasing the number of channels at the plasma membrane and/or causing allosteric modulations of the α_1 subunits (7).

The skeletal γ subunit (γ_1) was first purified and characterized through biochemical studies with the other subunits of skeletal muscle Ca^{2+} channels (8, 9) followed by cloning of its cDNA (10, 11). The γ subunit has not been as extensively studied as the β and $\alpha_2\delta$ subunits. The muscle-preferential expression of γ_1 might be a reason that γ_1 has not been studied in as great detail as the other auxiliary subunits. However, recent genetic studies revealed the existence of a γ subunit isoform in the brain whose lack of expression is responsible for the epileptic and ataxic phenotype of the stargazer mouse (4). The discovery of a novel neuronal γ (γ_2) and its relevance to epilepsy and ataxia has drawn much attention to the study of Ca^{2+} channel γ subunits. Subsequently, six additional γ subunit isoforms have been identified through DNA data base searches based on sequence homology to γ_1 and γ_2 (12–16). Furthermore, mutations in Ca^{2+} channel subunits, including γ mutations, have recently been implicated in a number of human and/or animal neurological disorders, drawing even more attention to the study of Ca^{2+} channel modulation by its auxiliary subunits.

Characterization and Classification of γ Subunit Isoforms

All eight γ subunit isoforms (γ_{1-8}) are characterized by four predicted transmembrane domains, intracellular N and C termini, and the first extracellular loop that includes a signature motif (GLW*XX*C), a conserved *N*-glycosylation site, and a pair of conserved cysteine residues that may form a disulfide linkage in the first extracellular loop (Fig. 1). Phylogenetic analyses have suggested that all γ subunits are derived from a single ancestral gene through gene duplication (15, 16). Based on the phylogenetic analyses, sequence homologies, and tissue distribution, the γ subunits have been categorized into two groups: skeletal γ (γ_1 and γ_6) and neuronal γ (γ_{2-5} and γ_{7-8}) (15, 16). The γ_1 and γ_6 subunits are classified as skeletal muscle γ subunits based on their predominant expression in skeletal muscle and relatively short C terminus as well as the high sequence homology (62.5% similarity) between them. In addition, a short form of γ_6 constituted by two instead of four transmembrane domains was reported (15, 16). The γ_{2-5} and γ_{7-8} subunits are classified as neuronal γ subunits based on their predominant expression in neuronal tissues, relatively long C terminus, and the sequence homology (29.5–90.7% similarity) among them. The neuronal γ subunits can be subdivided into two groups. The γ_{2-4} and γ_8 share higher homology than γ_5 and γ_7. PDZ binding motifs at the end of C termini of the neuronal γ subunits also differentiate the two groups of neuronal γ subunits. The γ_{2-4} and γ_8 have the same PDZ binding motif (R(R/K)TTPV) at the end of C termini, which differs from the potential PDZ binding motif (S(T/S)SPC) of the γ_5 and γ_7 (16). The genes of γ_5 and γ_7 subunits share a distinct intron/exon configuration, a five-exon structure rather than the four-exon structure of the other γ genes (16, 17). In addition, γ_8 differs from the other neuronal γ subunits because of its unusual translation initiation codon (−3 A*XX*CTGG +4) and as it contains the longest C terminus (16). The N- and C-terminal regions of γ_8 also have extensive C/G nucleotide-rich regions (15).

There has been confusion about the sequences of γ_5 and γ_7. The amino acid sequence of the mouse γ_5 reported by Klugbauer *et al.* (14) was quite different from that of human γ_5 reported by Burgess *et al.* (13, 15). Chu *et al.* (16) performed a comprehensive analysis of the difference and suggested a new version of the γ_5 sequence (16). Based on the new study it seems that the mouse γ_5 reported by Klugbauer *et al.* (14) does not actually belong to the γ family and that the C-terminal sequence of human γ_5 by Burgess *et al.* (13, 15) should be modified (16). The C-terminal sequence of γ_7 was also modified as γ_5 by two recent studies (16, 17). Therefore, the new sequences of γ_5 and γ_7 genes are different from those of the original reports. The new sequences of γ_5 and γ_7 have much longer C termini than those of the originals, resulting in C-terminal length similar to that of the other neuronal γ subunits.

In addition, it has been suggested that γ may belong to the claudin family, a group of cell adhesion proteins in tight junctions (15, 18). Claudins are similar to neuronal γ subunits in that they have four predicted transmembrane domains, a C-terminal PDZ binding domain, and the first extracellular loop that includes a signature motif (GLW*XX*C) and a pair of conserved cysteine residues. On the other hand, the phylogenetic relationship of the γ subunits to claudin families is much lower compared with that among γ subunits (15). However, the possibility exists that indeed the γ family may be a subfamily of the claudin superfamily.

Expression Profile of γ Subunits at Tissue and Subcellular Levels

Tissue distribution of γ subunits has been studied mainly at the mRNA level through RT-PCR[1] or Northern blot analyses. In the case of some neuronal γ subunits, there are additional data from

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‡ Partly supported by an Epilepsy Foundation predoctoral fellowship.
§ Investigator of the Howard Hughes Medical Institute. To whom correspondence should be addressed: Howard Hughes Medical Inst., University of Iowa College of Medicine, 400 EMRB, Iowa City, IA 52242. Tel.: 319-335-7867; Fax: 319-335-6957; E-mail: kevin-campbell@uiowa.edu.

[1] The abbreviations used are: RT, reverse transcriptase; EM, electron microscopy; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate.

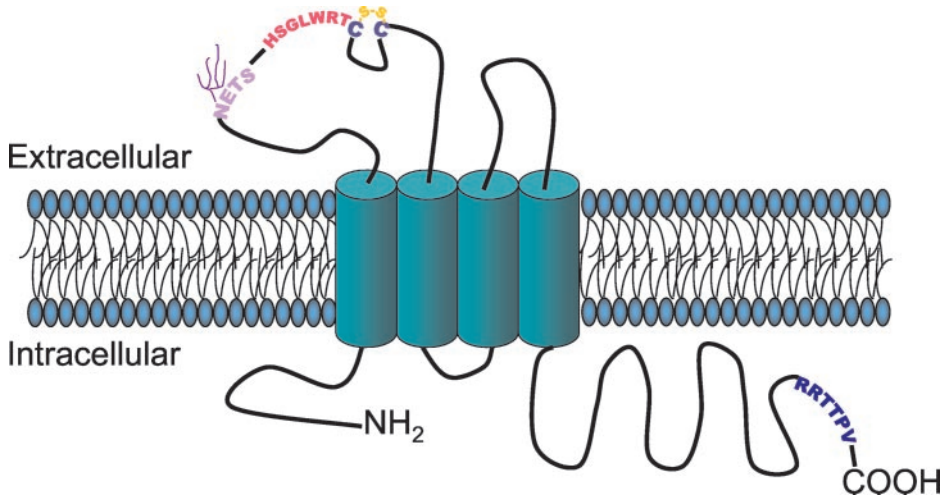

FIG. 1. **Predicted structure of γ_2 subunit and its amino acid sequence.** Predicted structural characteristics of γ_2 protein based on its primary sequence, hydropathy plot, and biochemical experiments are shown. The four transmembrane domains are presented as four cylinders (*green*). A conserved *N*-glycosylation site in the first extracellular loop is indicated by a *tree-shaped symbol* and an amino acid sequence in *purple*. The highly conserved region in the first extracellular loop is indicated by the amino acid sequence in *red*. A potential disulfide bond (-S-S- in *yellow*) between a pair of highly conserved cysteine residues (*blue C*) is in the first extracellular loop as well. The PDZ binding domain at the end of the C terminus is indicated by an amino acid sequence in *blue*. The second threonine in the PDZ binding domain is a phosphorylation site of PKA. The secondary structure in the first extracellular loop and the PDZ binding domain could be important for physical and/or functional association of γ with the Ca^{2+} channel complex and other proteins.

in situ hybridization, immunohistochemical, and Western blot analyses. In general, the expression pattern of each γ subunit varies considerably among tissues. The mRNA of γ_1 is primarily expressed in skeletal muscle (10, 11, 15, 16) although mild mRNA expression of γ_1 in other tissues has also been reported (10, 15, 16). At the protein level, γ_1 was detected in skeletal muscle but not in the brain or the heart (9, 19). Like γ_1, γ_6 also showed robust expression in skeletal muscle and mild expression in the other tissues (15, 16). In addition, RT-PCR results showed that the short form γ_6 has a different tissue distribution from that of the long form γ_6 (16). The analyses of neuronal γ subunits (γ_{2-5} and γ_{7-8}) showed predominant expression of their mRNA in the brain. However, in contrast to the brain-restricted expression of γ_3 and γ_5, the other neuronal γ subunits are expressed in various tissues (15, 16). γ_2 and γ_8 are expressed in testis whereas the expression of γ_4 is in lung and prostate tissue (15, 20). Finally, the expression of γ_7 has been detected in various tissues (16) although a recent study suggested a brain-specific expression of γ_7 (17). Similarly, Western blot data from mouse brain showed specific expression of γ_2, γ_3, and γ_4 proteins only in neuronal tissues (6).

Regional differences of neuronal γ expression within the brain have been studied at the mRNA and protein levels through RT-PCR, *in situ*, immunohistochemical, and/or Western blot analyses. The RT-PCR and *in situ* hybridization analyses of mouse brain showed highest expression of γ_2 in cerebellum (4, 14, 20). The γ_3 expression was strong in the hippocampus, cerebral cortex, amygdala, and nucleus accumbens (14, 20). In addition, γ_3 expression in cerebellum was reported by an *in situ* hybridization study (21). The γ_4 expression was high in the caudate putamen, olfactory bulb, and habenulae (14). The γ_2 and γ_4 expression in the cerebellum originates predominantly from the Purkinje cell layer and not from the granular cell layer (14). Likewise, the regional expression of the neuronal γ proteins has been analyzed through immunohistochemistry of mouse brain, and the results are consistent, to a certain degree, with the mRNA expression patterns (6). The γ_2 proteins express highest in the cerebellum and cortex. The γ_3 protein expression levels are highest in the cortex. The γ_4 proteins express highest in the cortex, midbrain, hippocampus, and striatum (6). Finally, partial purification of the Ca^{2+} channel complex from rabbit cerebellum showed that the protein expression of γ_3 in cerebellum is as strong as that of the whole brain (5).

Subcellular expression of the γ subunits has been studied through immunofluorescence and electron microscopy (EM) studies. Immunofluorescence studies showed that γ_2, γ_3, and γ_4 can go to the plasma membrane by themselves (20, 22). However, subcellular expression of γ_7 in the COS-7 cell was not associated with the plasma membrane (17). The EM study suggested predominant postsynaptic localization of γ_2, γ_3, and γ_4 and weak expression of these γ subunits at the presynapse and the soma of neurons (6, 21). A recent subcellular fractionation study also supports the EM results: dominant expression of the γ_2 and γ_3 in postsynaptic membrane and far less expression in the presynaptic membrane (23).

Protein Studies of γ Subunits

Relatively less information is available about the γ subunits at the protein level compared with the other Ca^{2+} channel subunits. The small size and high hydrophobicity of the γ protein limit the choice of peptides for the development of antibodies against a γ subunit that do not cross-react with the other γ subunits.

The γ_1 subunit was found to be a 32-kDa protein (in reduced SDS-PAGE) co-purified with Ca^{2+} channels ($Ca_v1.1$) from rabbit skeletal muscle (8). Immunoprecipitation with antibodies specific for $\alpha_1$1.1 and β subunit supports the association of γ_1 with $Ca_v1.1$ (9). Since γ_1 was co-purified with Ca^{2+} channels of skeletal muscle, there has been little doubt about the association of γ_1 with $Ca_v1.1$ in native tissue. However, because the neuronal γ subunit was not initially co-purified with $Ca_v2.2$ (24), the association of neuronal γ with Ca^{2+} channels has been controversial for several years since the finding of the γ_2 (stargazin) through the study of stargazer mice (4). However, two recent biochemical studies have shown the association of neuronal γ subunits with neuronal Ca^{2+} channels. The association of γ_2 and γ_3 with $Ca_v2.1$ and $Ca_v2.2$ was demonstrated by co-sedimentation of γ_2 and γ_3 with neuronal Ca^{2+} channel subunits and by immunoprecipitation of γ_2 and γ_3 by antibodies specific for either $\alpha_1$2.1/2 or β of Ca^{2+} channels (5). In this study, the molecular sizes of the γ_2 and γ_3 proteins in native tissue are reported as 38 and 34 kDa (in reduced SDS-PAGE), respectively (5). The association of γ_2, γ_3, and γ_4 with $\alpha_1$2.2 was also suggested by immunoprecipitation of $\alpha_1$2.2 by antibodies recognizing γ_2, γ_3, and γ_4 (6). In addition, the co-sedimentation of γ_2 and γ_3 with neuronal Ca^{2+} channel subunits (5) was demonstrated through partial purification of neuronal Ca^{2+} channels performed utilizing wheat germ agglutinin chromatography instead of heparin chromatography, which was used for initial purification of neuronal Ca^{2+} channels (24), suggesting a dissociation of γ_2 and γ_3 from the Ca^{2+} channel complex by heparin. Furthermore, a recent study with γ_1-γ_2 chimeras suggested that the first half of the γ subunit has binding domain(s) to the α_1 subunit of Ca^{2+} channels (25). The association of the other γ subunits with high voltage-activated Ca^{2+} channels has not yet been studied. No interaction between any γ subunit and low voltage-activated Ca^{2+} channels in native tissues has been reported.

Some neuronal γ subunits (γ_2, γ_3, γ_4, and γ_8) have a PDZ binding motif (R(R/K)TTPV) at the end of the C terminus (16). The binding of some PDZ domain-containing proteins to the PDZ binding motif of γ_2 has been reported (21, 26, 27). Furthermore, two of the studies suggested that the binding of PSD95 to the PDZ binding motif of the γ_2 subunit is regulated by phosphorylation of a threonine (Thr-321) in the motif (26, 27). In addition, one of these studies also suggested an interaction between the γ_2 and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors (21). On the other hand, the association of the AMPA receptor and PSD95 with Ca^{2+} channels has been demonstrated in native tissue, but γ_2 was not essential for this association (23).

It has been shown that the γ_1 subunit is glycosylated (28). The

glycosylation of some neuronal γ subunits (γ_{2-4}) has been also reported (6). The *N*-linked glycosylation site in the first extracellular loop of the γ subunit is highly conserved among all γ subunits, suggesting an important functional role of the glycosylation. The glycosylation may play an important role in the association of the γ subunit with the Ca^{2+} channel complex as shown in the study of $\alpha_2\delta$ (29), in the folding of the γ subunit, and/or in the targeting of proteins interacting with the γ subunit. On the other hand, a recent study suggested that the glycosylation is not essential for the association of the γ_1 subunit with the Ca^{2+} channel complex (25). In addition, most of the γ subunits have several potential sites for serine or threonine phosphorylation in addition to the one in the PDZ binding motif (15). Phosphorylation in these sites may be important in the function or association of the γ subunit within the Ca^{2+} channel complex or with other proteins.

Functional Studies of γ Subunits

A relatively small number of γ_1 functional assays compared with that of β and $\alpha_2\delta$ have been performed, which suggested mild changes in current amplitude, current kinetics, and/or voltage dependence of steady-state inactivation of the Ca^{2+} channels (31–35). However, it has been very difficult to reach a conclusion regarding the actions of the γ_1 subunit as the results of the functional assays have been conflicting. Furthermore, the physiological relevance of γ_1 has been difficult to estimate from the functional assays because they have been performed with cardiac α_1 ($\alpha_1$1.2) or brains α_1 ($\alpha_1$2.1) rather than skeletal muscle α_1 ($\alpha_1$1.1) due to the particularly low expression of $\alpha_1$1.1 in heterologous systems. Recently, γ_1 null mice have been generated by gene-targeting techniques, and it has been demonstrated that γ_1 has inhibitory effects on the activity of Ca^{2+} channels in skeletal muscle (36, 37). Two independent analyses of the γ_1 null mice reported an increase in current amplitude, a slowing of inactivation, and a positive shift of steady-state inactivation of Ca^{2+} channels in skeletal muscle as the main phenotype of the mice, indicating inhibitory effects of γ_1 on the functional activity of Ca^{2+} channels in skeletal muscle.

Similarly, there has been controversy about the function of the neuronal γ subunits for some time since the finding of neuronal γ subunits. However, inhibitory effects of neuronal γ subunits on Ca^{2+} channel activity have been consistently demonstrated by three recent electrophysiological studies (5, 17, 38). Electrophysiological analyses of recombinant $Ca_v2.1$ and $Ca_v2.2$ expressed in *Xenopus* oocytes showed that γ_2 co-expression significantly decreases current amplitude (37–40%) of the neuronal Ca^{2+} channels (5). Consistent with the γ_2 functional assays in the heterologous system, patch clamp analysis of stargazer mouse brain slices showed a 45% increase in the current density of high voltage-activated Ca^{2+} channels (38). Similarly, γ_7 co-expression with Ca^{2+} channels caused significant reduction in the Ca^{2+} channel currents ($Ca_v1.2$, $Ca_v2.1$, and $Ca_v2.2$).

Given that both low voltage-activated Ca^{2+} channels and the γ subunit are implicated in the etiology of epilepsy, it has been suggested that low voltage-activated Ca^{2+} channels may be modulated by the γ subunit. However, there have been only two functional assays of the γ subunit in heterologous systems that reported a change in low voltage-activated Ca^{2+} channel activity by γ subunits (14, 20). On the other hand, a recent electrophysiological study of stargazer mouse brain slices showed significant change in the current density and steady-state inactivation of low voltage-activated Ca^{2+} channels (38), suggesting that γ_2 loss could affect the activity of low voltage-activated Ca^{2+} channels as well as high voltage-activated Ca^{2+} channels *in vivo*. However, it is not clear whether the effects are direct or indirect.

As previously mentioned, the neuronal γ subunits (γ_2, γ_3, γ_4, and γ_8) have a PDZ binding motif (R(R/K)TTPV) at the end of the C terminus (16). It has been suggested that the PDZ binding motif of γ_2 subunit binds to PSD95 and that this binding is regulated by phosphorylation of a threonine (Thr-321) (26, 27). In addition, a role of the γ_2 subunits on the trafficking/clustering of AMPA receptors was reported. AMPA receptor trafficking was increased by coexpression of γ_2 in COS7 cells (21, 39). Taken together, these studies suggest that γ can increase the targeting of the AMPA receptor to the postsynapse through interaction with PSD95. Alternatively, considering the function of γ_2 in the fine-tuning of Ca^{2+} channel activity, it is possible that γ_2 modulates AMPA receptor trafficking by changing the intracellular concentration of Ca^{2+} ($[Ca^{2+}]_i$) in a local area of a neuron. It is known that the increase of postsynaptic $[Ca^{2+}]_i$ is one of the prerequisites for the long term potentiation at excitatory synapses and that AMPA receptor trafficking is one of the key components for the long term potentiation (40). Accordingly, a recent study demonstrated that the change of local $[Ca^{2+}]_i$ could regulate the lateral movement of AMPA receptors in cultured hippocampal neurons (41). Furthermore, a recent study demonstrated the association of AMPA receptors with neuronal Ca^{2+} channels in the postsynaptic membrane (23).

Considering the significant homology between γ and claudin, γ may have similar functions to claudin as a junctional protein. The claudins are cell adhesion proteins in tight junctions that are linked to membrane-associated guanylate kinase homologues (ZO-1, ZO-2, and ZO-3) through their PDZ binding domain at the end of the C terminus (42, 43). Similarly, γ may function as a cell adhesion protein at the synapse through its interaction with PDZ domain-containing proteins. In addition, a recent study of γ_4 expression during the development of chick embryo reported that the beginning of γ_4 expression in neuronal tissues such as cranial ganglia and dorsal root ganglia is observed at the stage when these neuronal tissues initiate neuronal differentiation, suggesting that the γ_4 subunit plays a role in the development of the neuronal tissues (44).

Taken as a whole, the above mentioned results suggest that the neuronal γ subunits have more than one function in the brain.

Disorders Linked to Ca^{2+} *Channels*

A number of human and murine mutations in Ca^{2+} channel subunits have been identified to be responsible for neurological disorders. In the case of human neurological disorders, mutations in the $\alpha_1$2.1 have been associated with familial hemiplegic migraine, spinocerebellar ataxia type 6, and episodic ataxia type 2 (45). The $\alpha_1$1.4 is associated with congenital stationary night blindness (45). A study reported a mutation of $\alpha_1$2.1 in a patient with epilepsy and ataxia (46). Two types of mutations in the β_4 subunit have also been reported in patients with epilepsy and/or ataxia (47). Recently, γ_1, γ_4, and γ_5 have been suggested as candidate genes for multiple sclerosis based on their loci in human chromosomes 17q23 or 17q24 (48). A recent study also reported an abnormal distribution of $Ca_v2.2$ within axons of actively demyelinating lesions of multiple sclerosis (49). In mouse models, mutations in Ca^{2+} channel subunits have been found through the positional cloning of mice models for absence epilepsy and/or ataxia. Four α_{1A} mutations have been found in tottering, leaner, rolling, and rocker mice. In the case of auxiliary subunits of Ca^{2+} channels, the lethargic mouse has a mutation in the β_4 subunit, the ducky mouse has a mutation in the $\alpha_2\delta$-2 subunit, and stargazer and waggler mice have mutations in the γ_2 subunit (45).

The discovery of the defective genes responsible for neurological disorders indicates that an understanding of Ca^{2+} channel function could lead to further comprehension of the molecular mechanisms of those neurological disorders.

Mouse Models for Study of γ Subunits

Two γ_1 null mice have been generated from two independent groups (36, 37). Although these mice are fertile and show no obvious phenotypic abnormalities, detailed electrophysiological analysis of L-type currents from isolated myotubes showed significant changes in Ca^{2+} channel activity in skeletal muscle: an increase in peak current density, a slowing of inactivation, and a positive shift of steady-state inactivation (36, 37). As previously mentioned, RT-PCR analysis suggested that γ_6 and γ_7 as well as γ_1 are highly expressed in skeletal muscle. The homology of γ_6 to γ_1 is higher than that of γ_7, and γ_6 shows higher expression than γ_7 in skeletal muscle. Therefore, γ_6 might be another skeletal muscle γ subunit compensating the γ_1 loss in the γ_1 null mice.

The stargazer mouse has been studied as a mouse model of several neurological disorders including absence epilepsy, inner ear defects, and ataxia (51). Its recurrent spike-wave seizure associated with behavioral arrest is similar to the characteristics of human absence epilepsy. Abnormal gait of the mouse is a sign of cerebellar ataxia. Head tossing and impaired conditioned eye-blink

responses are presumed to be consequences of the problem in the vestibular system and the deficit in cerebellar learning, respectively. The mutation in the stargazer mouse is the insertion of a 6-kb early transposon into the intron between exon 2 and exon 3 in the γ_2 gene (CACNG2) (4). Western blot and *in situ* hybridization analyses of stargazer brain demonstrated the absence of γ_2 protein expression in the mutant mouse (5, 6). Some studies on stargazer mice have suggested several possible molecular mechanisms. The increase of slowly activating inward current resembling the I_h has been proposed as one of components that contribute to the cortical hyperexcitability of the stargazer mouse (52). The mRNA and protein levels of brain-derived neurotrophic factor, a mediator of neuronal development and regulator of synaptic function, were reduced by 70% compared with those of wild-type mice in the cerebellum of stargazer mice (53, 54). Finally, studies on the stargazer mouse have shown a lack of functional AMPA receptors in cerebellar granule cells of the mouse (21, 55, 56).

Conclusions and Perspective

There is increasing evidence for the association of the γ subunits with the Ca^{2+} channel complex. Eight γ subunits have been identified, and phylogenical analyses have suggested that they belong to a protein family originating from a single gene. Biochemical and electrophysiological studies showing the physical and functional association of γ subunits with the Ca^{2+} channel strongly support the idea that γ is a component of the Ca^{2+} channel complex. On the other hand, the γ_2 subunit binds to PDZ domain-containing proteins and is involved in the trafficking of the AMPA receptor. Considering the number of neurological disorders in humans and/or mice linked to genes encoding Ca^{2+} channel subunits including the γ subunit, elucidation of the mechanisms of γ function will be very helpful to better understand various physiological and pathological events mediated by Ca^{2+} channels.

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