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Letter to the Editor

Nomenclature of Voltage-Gated Calcium Channels

Voltage-gated Ca^{2+} channels mediate calcium influx in response to membrane depolarization and regulate intracellular processes such as contraction, secretion, neurotransmission, and gene expression. They are members of a gene superfamily of transmembrane ion channel proteins that includes voltage-gated K^+ and Na^+ channels. The Ca^{2+} channels that have been characterized biochemically are complex proteins composed of four or five distinct subunits, which are encoded by multiple genes. The α_1 subunit of 190–250 kDa is the largest subunit, and it incorporates the conduction pore, the voltage sensor and gating apparatus, and the known sites of channel regulation by second messengers, drugs, and toxins. An intracellular β subunit and a transmembrane, disulfide-linked $\alpha_2\delta$ subunit complex are components of most types of Ca^{2+} channels. A γ subunit has also been found in skeletal muscle Ca^{2+} channels, and related subunits are expressed in heart and brain. Although these auxiliary subunits modulate the properties of the channel complex, the pharmacological and electrophysiological diversity of Ca^{2+} channels arises primarily from the existence of multiple forms of α_1 subunits. Mammalian α_1 subunits are encoded by at least ten distinct genes. Historically, various names have been given to the corresponding gene products, giving rise to distinct and sometimes confusing nomenclatures. In 1994, some of us proposed a unified nomenclature based on the most widely accepted system at the time: α_1 subunits were referred to as α_{1S} for the original skeletal muscle isoform and α_{1A} through α_{1E} for those discovered subsequently (Birnbaumer et al., 1994). Since then, four new α_1 subunits have been identified, which were named α_{1F} through α_{1I}.

Ca^{2+} currents recorded in different cell types have diverse physiological and pharmacological properties, and an alphabetical nomenclature has also evolved for the distinct classes of Ca^{2+} currents. L-type Ca^{2+} currents require a strong depolarization for activation, are long lasting, and are blocked by the organic L-type Ca^{2+} channel antagonists, including dihydropyridines, phenylalkylamines, and benzothiazepines. They are the main Ca^{2+} currents recorded in muscle and endocrine cells, where they initiate contraction and secretion. N-type, P/Q-type, and R-type Ca^{2+} currents also require strong depolarization for activation. They are unaffected by L-type Ca^{2+} antagonist drugs but are blocked by specific polypeptide toxins from snail and spider venoms. They are expressed primarily in neurons, where they initiate neurotransmission at most fast synapses. T-type Ca^{2+} currents are activated by weak depolarizations and are transient. They are resistant to both organic antagonists and to the snake and spider toxins used to define the N- and P/Q-type Ca^{2+} currents. They are expressed in a wide variety of cell types, where they are involved in shaping the action potential and controlling patterns of repetitive firing.

As new Ca^{2+} channel genes are cloned, it is apparent that these two alphabetical nomenclatures will overlap at α_{1L}, which may not mediate an L-type Ca^{2+} current and therefore may create confusion. Moreover, the present alphabetical nomenclature does not reveal the structural relationships among the α_1 subunits, which can be grouped into three families: (1) α_{1S}, α_{1C}, α_{1D}, and α_{1F}; (2) α_{1A}, α_{1B}, and α_{1E}; and (3) α_{1G}, α_{1H}, and α_{1I}. The complete amino acid sequences of these α_1 subunits are more than 70% identical within a family but less than 40% identical among families. These family relationships are illustrated for the more conserved transmembrane and pore domains in Figure 1. Division of calcium channels into these three families is phylogenetically ancient, as representatives of each are found in the *C. elegans* genome. Ideally, a nomenclature for Ca^{2+} channel α_1 subunits should provide a systematic organization based on their structural relationships and should be coordinated with nomenclatures for the other families of voltage-gated ion channels of different ionic selectivities (ie., K^+ and Na^+).

For these reasons, we wish to propose a new nomenclature of voltage-gated Ca^{2+} channels (Table 1), which is more systematic and mimics the well-defined K^+ channel nomenclature (Chandy et al., 1991). This nomenclature uses a numerical system ($K_V1.1$, $K_V2.1$, $K_V3.1$, etc.) to define families and subfamilies of K^+ channels based on similarities in amino acid sequences. In a similar manner, we propose that Ca^{2+} channels should be renamed using the chemical symbol of the principal permeating ion (Ca) with the principal physiological regulator (voltage) indicated as a subscript (Ca_V). The numerical identifier would correspond to the Ca_V channel α_1 subunit gene family (1 through 3 at present) and the order of discovery of the α_1 subunit within that family (1

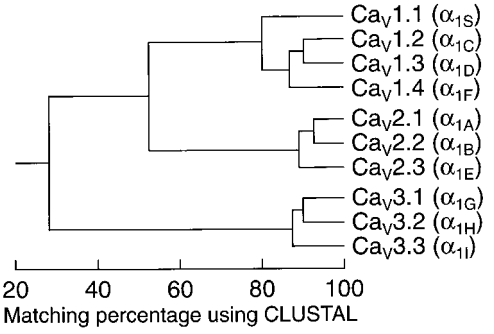

Figure 1. Phylogeny of Voltage-Gated Ca^{2+} Channel α_1 Subunits

Only the membrane-spanning segments and the pore loops (~350 amino acids) are compared. First, all sequence pairs were compared, which clearly defines three families with intrafamily sequence identities above 80% ($Ca_V1.m$, $Ca_V2.m$, $Ca_V3.m$). Then, a consensus sequence was defined for each family, and these three sequences were compared to one another, with interfamily sequence identities of ~52% ($Ca_V1.m$ versus $Ca_V2.m$) and 28% ($Ca_V3.m$ versus $Ca_V1.m$ or $Ca_V2.m$).

Table 1. Proposed Nomenclature for Cloned Voltage-Gated Ca^{2+} Channel α_1 Subunits

Name	Former Names	Accession Number	Gene Name and Human Chromosome	Splice Types	Former Names	Primary Tissues
$Ca_v1.1$ $\alpha_1 1.1$	α_{1S}, α_{1Skm}, CaCh1	X05921	CACNA1S; 1q31-32			skeletal muscle
$Ca_v1.2$	α_{1C}, rbC, CaCh2	CaCh2, X15539	CACNA1C; 12p13.3	$Ca_v1.2a$	$\alpha_{1C\text{-}a}$	heart
$\alpha_1 1.2$				$Ca_v1.2b$	$\alpha_{1C\text{-}b}$	smooth muscle
		rbC-I, M67516; rbC-II, M67515		$Ca_v1.2c$	$\alpha_{1C\text{-}b}$	brain, heart, pituitary, adrenal
$Ca_v1.3$ $\alpha_1 1.3$	α_{1D}, rbD, CaCh3	M76558	CACNA1D; 3p14.3			brain, pancreas, kidney, ovary, cochlea
$Ca_v1.4$ $\alpha_1 1.4$	α_{1F}	AJ224874	CACNA1F; Xp11.23			retina
$Ca_v2.1$ $\alpha_1 2.1$	α_{1A}, rbA, CaCh4, BI	rbA, M64373; BI-1, X57476 BI-2, X57477	CACNA1A; 19p13	$Ca_v2.1a$ $Ca_v2.1b$	BI1 BI2	brain, cochlea, pituitary brain, cochlea, pituitary
$Ca_v2.2$ $\alpha_1 2.2$	α_{1B}, rbB, CaCh5, BIII	rbB, M92905; BIII, D14157; human α_{1B}, M94172	CACNA1B; 9q34	$Ca_v2.2a$	$\alpha_{1B\text{-}1}$	brain, nervous system
				$Ca_v2.2b$	$\alpha_{1B\text{-}2}$	brain, nervous system
$Ca_v2.3$ $\alpha_1 2.3$	α_{1E}, rbE, CaCh6, BII	rbE, L15453, BII-1, X67855; human α_{1E}, L29384	CACNA1E; 1q25-31	$Ca_v2.3a$	BII	brain, cochlea, retina, heart, pituitary
				$Ca_v2.3b$	BII2	brain, cochlea, retina
$Ca_v3.1$ $\alpha_1 3.1$	α_{1G}	AF027984; AF029228	CACNA1G; 17q22	$Ca_v3.1a$		brain, nervous system
$Ca_v3.2$ $\alpha_1 3.2$	α_{1H}	AF051946; AF073931	CACNA1H; 16p13.3	$Ca_v3.2a$		brain, heart, kidney, liver
$Ca_v3.3$ $\alpha_1 3.3$	α_{1I}	AF086827	CACNA1I; 22q12.3-13-2	$Ca_v3.3a$		brain

The cloned voltage-gated Ca^{2+} channels and most widely studied alternate splice forms are presented together with the proposed nomenclature and previous nomenclatures.

through m). According to this nomenclature, the Ca_V1 family ($Ca_V1.1$ through $Ca_V1.4$) includes channels containing α_{1S}, α_{1C}, α_{1D}, and α_{1F}, which mediate L-type Ca^{2+} currents (Table 1). The Ca_V2 family ($Ca_V2.1$ through $Ca_V2.3$) includes channels containing α_{1A}, α_{1B}, and α_{1E}, which mediate P/Q-type, N-type, and R-type Ca^{2+} currents, respectively (Table 1). The Ca_V3 family ($Ca_V3.1$ through $Ca_V3.3$) includes channels containing α_{1G}, α_{1H}, and α_{1I}, which mediate T-type Ca^{2+} currents (Table 1). When specific reference to the α_1 subunit within the Ca^{2+} channel complex is intended, the designation $\alpha_1$1.m, $\alpha_1$2.m, or $\alpha_1$3.m may be used, where the numeral m represents the individual gene/protein within the family. Where applicable, lowercase letters are used to distinguish alternatively spliced variants (e.g., $Ca_V1.2a$ corresponds to channels containing the cardiac variant of the former α_{1C}). Such a systematic nomenclature has proved successful for the K_V channel proteins. Its strength resides in the rational basis derived from the structural relationships among the channel proteins and the ease and precision with which new channels can be added.

The nomenclature of the auxiliary subunits is not modified, since it already includes numbers for the gene family and lowercase letters for the splice variants. Thus, the subunit compositions of the voltage-dependent Ca^{2+} channels $Ca_Vn.mx$ may be described as α_1n.mx/βm′x′/γm′′x′′/$\alpha_2\delta$m′′′x′′′ complexes, where the number n defines a main family, the numbers m, m′, m′′, and m′′′ refer to the individual genes/proteins within the families, and the letters x, x′, x′′, and x′′′ identify the splice variants. Standard prefixes can be placed in front of the channel name to identify the species of origin. In this notation, the skeletal muscle calcium channel would be written $\alpha_1$1.1a/β1a/γ1a/$\alpha_2\delta$1a. With this new nomenclature, the Ca_V designation may also be used to identify calcium channel auxiliary subunits such as $Ca_V\beta$ or $Ca_V\gamma$ independent of their presence in a calcium channel complex.

We hope that this new nomenclature for α_1 subunits will be a stimulus to further research on voltage-gated Ca^{2+} channels by providing a common, easily accessible standard of reference for scientists working in this field. A full-length review article* is planned to present a more detailed proposal for nomenclature of the many alternate splice forms of the α_1 subunits and the auxiliary subunits of Ca^{2+} channels that have been described in cDNA cloning experiments.

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* This nomenclature has been approved by the Nomenclature Committee of the International Union of Pharmacology, and a review article giving more details of the nomenclature for calcium channel subunits and splice variants is planned for Pharmacological Reviews.

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