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Matters Arising

The Naming of Voltage-Gated Calcium Channels

Voltage-gated calcium channels are multisubunit complexes formed of a central channel-forming a, subunit and several regulatory and/or auxiliary subunits which include a β subunit and the disulfide-linked $\alpha_2\delta$ subunit. Depending on the tissue of origin, a fifth subunit, such as the skeletal muscle γ or the neuronal p95, may also form part of the channel complex. Additional subunits may still be discovered. Molecular cloning has greatly expanded the understanding of calcium channel diversity, but confusion remains in the naming of the plethora of genes that encode calcium channel α_1 and β subunits. This is further complicated by the fact that the transcripts of most subunits are subject to alternative splicing, which in some but not all cases, may be tissue specific. Table 1 compares the names of cloned α_1 genes and their mature mRNAs, their major sites of known expression, and their functional correlates as they are perceived today. Table 2 lists β subunit genes splice variants, and some sites of expression.

To simplfy matters, the undersigned propose to use a unified nomenclature based on rules that allow the description of a mature assembled heteromeric channel in terms of an $\alpha_{1X}\beta_n\gamma_n\cdot\alpha_2\delta_n$ complex, where *X* is a capital letter (S, A, B, C, D, E, etc.) that identifies the genes from which the α_1 subunit originates, and *n* is a number (1, 2, 3, etc.) that identifies the genes from which other calcium channel subunits originate. α_{1S} denotes the α_1 subunit of the skeletal muscle calcium channel, the first of theses channels to be cloned in the laboratory of the late Professor Shosaku Numa. α_{1A} through α_{1E} denote the α_1 subunits cloned subsequently, labeled with an

Table 1. Calcium Channel α1 Subunits

Gene Product			Functional Correlates	
Consensus Name(s)	Original Name(s) if Different	Sites of Expression	Current	Drug Sensitivity of Native Currents
α_{1S}	Skeletal muscle	Skeletal muscle, BC3H1	HVA L type	Sensitive to DHPs, diltiazem and verapamil
	CaCh1	cells		Insensitive to sub-μM ω-CTx-GVIA and funnel
	α_{1skm}			web spider venoms (ω-Aga-IVA, FTX)
α_{1A}	BI	Brain, cerebellum,	HVA Q type?	ω-CTx-MVIIC (>100 nM); ω-CTx-G
	CaCh4	Purkinje and granule cells, kidney,		DHP insensitive
	rbA	PC12 cells, C cells	HVA P type?	Sensitive to ω-Aga-IVA (<10nM) and low sFTX
				DHP insensitive
α_{1B}	BIII	Brain, peripheral	HVA N type	Sensitive to ω-CTx-GVIA (100-500 nM) and
	CaCh5	neurons, PC12 cells,		ω-CTx-MVIIC (>100 nM)
	rbB	C cells		DHP insensitive
α_{1C}	Cardiac	Heart, HIT cells, GH3	HVA L type	DHP sensitive
	Smooth muscle/ lung	cells, brain, aorta, lung, kidney, fibroblasts		Insensitive to low concentrations of ω-CTx-GVIA, ω-Aga-IVA, or sFTX
	CaCh2	PC12 cells, C cells		
	rbC			
$\alpha_{1C\text{-}a}$	CaCh2a	Heart		
	CaCh2-I			
$\alpha_{1C\text{-}b}$	CaCh2b	Smooth muscle, lung		
	CaCh2-II			
$\alpha_{1C\text{-}c}$	rbC	Brain		
	CaCh2-III			
α_{1D}	CaCh3	Brain, pancreas, HIT	HVA L type	DHP sensitive
	Neuroendocrine	cells, GH3 cells,		Reversibly sensitive to ω-CTx-GVIA,
	rbD	PC12 cells, C cells		ω-Aga-IVA, or FTX
α_{1E}	CaCh6	Brain, heart, C cells	HVA R type?	Sensitive to low Ni
	BII			Insensitive to DHPs or ω-CTx-MVIIC,
	rbE			or to low concentrations of ω-CTx-GVIA, ω-Aga-IVA or sFTX

This table in intended as a guide and refers only to mammalian calcium channels. Not all previously used names are listed. Vertebrate doe-1 and doe-4 α_1 subunits, cloned from the marine ray Discopyge ommata, are orthologs of mammalian α_{1E} and α_{1B}, respectively. HVA and LVA, high and low voltage activated; DHP, dihydrophyridine; ω-CTx-G and ω-CTx-M, ω-conotoxins from marine snails Conus geographus and Conus magus, respectively; Aga, agatoxin (funnel web spider Agelenopsis aperta toxin); sFTX, synthetic funnel web spider toxin. Q-type calcium channel: current in cerebellar granule cells sensitive to ω-CTx-MVIIC but insensitive to DHPs, low ω-CTx-GVIA, and low ω-Aga-IVA; R-type calcium channel: residual in cerebellar granule cells after blocking with DHP, ω-Aga-IVA, ω-CTx-GVIA, and ω-CTx_MVIIC.

Table 2. Calcium Channel β Subunits

Gene Product	Splice Variant	Other Name(s)	Proven Expression[a]	Component of
β_1	β_{1a}	β_{1M}	Skeletal muscle	DHP receptor
	β_{1b}	β_{1B2}, β_2	Brain, heart	?
	β_{1c}	β_{1B1}	Brain, heart	?
β_2	β_{2a}	β_3	Brain, heart	?
	β_{2b}		Brain, heart	?
	β_{2c}		Brain, heart	?
β_3	?		Brain, heart, aorta	ω-CTx receptor
β_4	?		Brain	?

[a]Does not exlude sites of expression.

empirical terminology developed for the calcium channels from brain, the only tissue in which all of these genes are expressed. The genes encoding regulatory/auxiliary subunits (β, $\alpha_2\delta$, γ, etc.) are numbered sequentially in approximate order of their discovery. Note that a single $\alpha_2\delta$ gene and mRNA yields two mature subunits, α_2 and δ, which are disulfide linked. Thus, the $\alpha_2\delta_1$ to $\alpha_2\delta_n$, genes are expected to encode a series of disulfide-linked subunit pairs (α_2 and δ) in the mature calcium channel protein.

Splice variants are uniformly denoted by *y*, a lowercase letter (i.e., $\alpha_{1A\text{-}a}$, $\alpha_{1A\text{-}b}$, β_{1a}, β_{1b}, $\alpha_2\delta_a$, $\alpha_2\delta_b$, etc.). If no second gene is known, such as for the $\alpha_2\delta$ subunit, the capital letter or numerical subscript is omitted. If no molecular diversity is known, such as for the γ subunit of the skeletal muscle calcium channel, subscripts are omitted. In this nomenclature, the skeletal muscle L-type calcium channel/dihydropyridine receptor has the subunit composition $\alpha_{1S}\beta_{1a}\gamma\alpha_2\delta_a$.

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