Classification and Function of Voltage-Gated Calcium Channels

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GENERIC PROPERTIES OF VOLTAGE-GATED CA^{2+} CHANNELS

Voltage-gated Ca^{2+} channels are members of a superfamily of voltage-gated ion channels which also includes Na^+ channels and K^+ channels. Ca^{2+} channels transduce membrane potential changes to intracellular Ca^{2+}-signals in a wide variety of cell types, including nerve, endocrine and muscle cells. Many types of Ca^{2+} channels have been characterized by pharmacological and biophysical criteria in various cell types. More recently, molecular cloning has revealed a wealth of genes encoding the subunits of native channels. Following a brief introduction to the basic properties and subunit composition of Ca^{2+} channels, we will proceed to an overview of their classification, molecular composition, and specialization for various functional roles. Details about structure-function appear in another chapter in this volume (Chapter 4) and we will confine our structural comments here to those that pertain to classification of the channels. Likewise modulation of Ca^{2+} channels is left to other authors. In addition we will not touch on several other important aspects of regulation of $[Ca^{2+}]_i$, such as Ca^{2+} channels not gated by depolarization (Putney, 1997), Ca^{2+} sequestration and extrusion, and neuropathological conditions such as stroke, epilepsy, and migraine, some involving mutations of the Ca^{2+} channels themselves.

Basic Functional Properties

Our present-day understanding of Ca^{2+} channels began with their electrophysiological isolation and description. *Gating* describes the opening and closing of channels. Typically, Ca^{2+} channels open (or *activate*) within one or a few milliseconds after the membrane is depolarized from rest, and close (*deactivate*) within a fraction of a millisecond following repolarization. Activation of Ca^{2+} channels is steeply voltage-dependent: channels open more quickly and with higher likelihood with larger depolarizations. *Inactivation*, the closing of channels during maintained or repeated depolarizations, strongly influences the cytosolic Ca^{2+} signal that arises from cellular electrical activity. While inactivation is a general property of Ca^{2+} channels, the speed of entry into and recovery from inactivation varies widely.

In addition to gating we consider two properties concerning the conduction of Ca^{2+} through the channel. *Selectivity* of voltage-gated Ca^{2+} channels for Ca^{2+} ions is remarkably high, so that Ca^{2+} is the main charge carrier even when Ca^{2+} is greatly outnumbered by other ions, as under normal physiological conditions. *Permeation* of Ca^{2+} through a single open Ca^{2+} channel can achieve rates of millions of ions per second when the electrochemical gradient is large. At driving forces reached physiologically, the flux rate is more modest, but sufficient to cause a large increase in $[Ca^{2+}]_i$ (>1 μM) in a very localized domain (~1 μm) near the mouth of the open channel.

Subunit Composition

The powerful functional capabilities of Ca^{2+} channels are rooted in their molecular architecture. Voltage-gated Ca^{2+} channels contain at their core a protein known as α_1, which is a large (200-260 kDa) transmembrane protein that contains the channel pore, the voltage-sensor and the gating machinery. Most, or possibly all, channel types additionally contain subunits known as β, α_2, δ and γ (Figure 1), that come together with the α_1 subunit to form a large macromolecular complex. The first examples of each of these subunits were originally isolated from skeletal muscle transverse tubules by biochemical techniques more than a decade ago (Catterall and Curtis, 1987; Campbell et al., 1988; Catterall et al., 1988; Glossmann and Striessnig, 1990). Each subunit has since been cloned in several forms.

Because the α_1 subunit appears to be able to form a functional Ca^{2+} channel on its own, the other subunits are sometimes referred to as auxiliary or ancillary subunits although they may dramatically affect channel gating, modulation, pharmacology, and expression. In the last few years our understanding of the relationship between the α_1 subunits and the native channel classes has become increasingly clear. While the α_1 subunit is the major determinant of channel properties, the high level of promiscuity in the association of the α_1 subunit with the various forms of the auxiliary subunits, combined with alternative splicing, can likely produce an incredible diversity of properties.

α_1

Much of the diversity of Ca^{2+} channel types seems to arise from the expression of multiple forms of the α_1 subunit, isolated by molecular cloning (e.g., Tanabe et al., 1987; Mikami et al., 1989; Mori et al., 1991; Starr et al., 1991; Dubel et al., 1992; Williams et al., 1992a; Williams et al., 1992b; Soong et al., 1993; Fisher et al., 1997; Cribbs et al., 1998; Perez-Reyes et al., 1998; Lee et al., 1999). Details of the various α_1 subunits will be examined thoroughly below.

β

All high voltage activated Ca^{2+} channels (see below) in their native state appear to contain β subunits—peripheral membrane proteins associated with the cytoplasmic aspect of the surface membrane with an apparent molecular weight of ~55-60 kDa (Glossmann et al., 1987; Takahashi et al., 1987). The β subunit of Ca^{2+} channels is not homologous to the β1 and β2 subunits of Na^+ channels, which contain putative transmembrane spanning domains and are significantly glycosylated (Isom et al., 1994). β subunits serve several important and intriguing functions: 1) They play a key role in the proper targeting of the complex of Ca^{2+} channel subunits, 2) they are subject to regulation by protein kinases, and 3) they act as modulators of the gating and pharmacological properties of α_1 subunits. In the present work we concern ourselves only with the last function. For more information on the other functions see recent reviews (Hofmann et al., 1994; Isom et al., 1994; De Waard et al., 1996; Walker and De Waard, 1998).

Four different types of β subunit are known to exist in mammals and are now known as β_1-β_4 (Birnbaumer et al., 1994). Diversity of these proteins is increased by alternative splicing (designated by lower case letters, β_{2a}, β_{2b} etc.). In general, β subunits are not found in one organ or tissue exclusively. Whereas β_1 transcripts are expressed primarily in skeletal muscle, they also appear in brain. β_2 is predominantly expressed in heart, aorta and brain, while β_3 is most abundant in brain but also present in aorta, trachea, lung, heart and skeletal muscle. β_4 mRNA is expressed almost exclusively in neuronal tissues, with the highest levels being found in the cerebellum. Because each of the β subunits appears able to partner with each of the α_1 subunits,

β subunit heterogeneity may contribute to the diversity of Ca^{2+} channels in a multiplicative manner, however it seems unlikely that β subunit differences are responsible for the differences between the major classes delineated below (L-, N-, P/Q-type, etc.).

α_2/δ

The $\alpha_2\delta$ subunit (175 kDa) is a dimer, consisting of glycosylated α_2 and δ proteins linked together by disulfide bonds, derived by posttranslational processing of a single parent polypeptide (Ellis et al., 1988; De Jongh et al., 1990; Williams et al., 1992b; Klugbauer et al., 1999). This pair of subunits has been shown to affect channel gating. The δ subunit is a transmembrane protein anchor and α_2 is entirely extracellular (Jay et al., 1991; Hofmann et al., 1994). Three α_2/δ genes have been isolated: α_2/δ-1 and α_2/δ-2 have wide tissue distribution while α_2/δ-3 is brain specific (Angelotti and Hofmann, 1996; Klugbauer et al., 1999). As with other Ca^{2+} channel subunits, α_2/δ diversity is increased by alternative splicing. The diversity of the α_2/δ genes has only recently begun to be characterized, and less is known about this subunit's effect on channel properties than that of the β subunit.

γ

A fifth subunit, known as γ (25-38 kDa), (Bosse et al., 1990; Jay et al., 1990; Eberst et al., 1997; Letts et al., 1998; Black and Lennon, 1999), has 4 transmembrane domains. Like the α_2/δ subunits, the γ subunit is now starting to receive widespread attention and little is known about its effect on channel properties, although it has been shown to promote inactivation (Eberst et al., 1997; Letts et al., 1998).

CLASSIFICATION OF NATIVE CA^{2+} CHANNELS ACCORDING TO BIOPHYSICAL, PHARMACOLOGICAL, AND MOLECULAR BIOLOGICAL PROPERTIES

Multiple types of voltage-gated Ca^{2+} channels were first distinguished by voltage- and time-dependence of channel gating, single channel conductance and pharmacology (e.g., Carbone and Lux, 1984; Nowycky et al., 1985). One physiologically relevant characteristic which varies

considerably among the different Ca^{2+} channel types is the degree of depolarization required to cause significant opening. Based on this criterion, voltage-gated Ca^{2+} channels are sometimes divided into two groups, low voltage-activated (LVA) and high voltage-activated (HVA). Use of all the criteria listed above has led to a more specific classification of native Ca^{2+} channels as T-, L- N-, P/Q- and R-type (Tsien et al., 1987; Llinás et al., 1992; Randall and Tsien, 1995).

While this classification makes good sense in view of the varied biophysical properties and functional roles of the channel types in different organ systems, the relationship of these classes to the various cloned subunits has only recently been clarified. The recent findings from molecular cloning of Ca^{2+} channel subunits have greatly increased our understanding of Ca^{2+} channel diversity. This has allowed new perspective on the familial relationships between various channel types and a more precise characterization of the pharmacological properties of individual channel types.

Molecular Biological Nomenclature

Nine different Ca^{2+} channel α_1 subunit genes have been distinguished in mammalian brain and one in skeletal muscle and have been labeled classes A through I and S (Snutch et al., 1990; Snutch and Reiner, 1992; Birnbaumer et al., 1994). α_{1S} refers to the original Ca^{2+} channel clone from skeletal muscle, first isolated by the group of the late Shosaku Numa (Tanabe et al., 1987) and the letters A-I refer to subsequently cloned channels. Based on sequence homology, the ten α_1 subunits can be assigned to various branches of a family tree as reviewed in Figure 2. This sequence homology seems to follow channel properties and functional roles quite well. Following our newfound structural and functional understanding of the Ca^{2+} channels a new naming scheme similar to that used for voltage-gated K^+ channels has been proposed (W.A. Catterall, et al., personal communication). In the following discussion we will adopt this scheme in which voltage-gated Ca^{2+} channels are designated $Ca_V S.Tx$, where S and T are numbers which refer to the subfamily and type respectively, and x is a letter which corresponds to any splice

variants. The α_1 subunits are named correspondingly as α_1S.Tx. The numbers and letters are assigned in order of discovery, thus α_{1S} becomes $\alpha_1$1.1 and so on.

Ca_V1/L-type Ca^{2+} channels

L-type channels are generally categorized with the HVA group of channels, along with N-, P/Q-, and R-type channels. However, it is important to note that L-type channels may exhibit LVA properties under certain circumstances (Avery and Johnston, 1996). L-type channels in vertebrate sensory neurons and heart cells were initially labeled as a large Ba^{2+} conductance contributing to a long-lasting current, with characteristic sensitivity to DHPs such as nifedipine or Bay K 8444 (Bean, 1985; Nilius et al., 1985; Nowycky et al., 1985). Members of this group were subsequently identified in other excitable cells such as vascular smooth muscle, uterus, and pancreatic β cells. Later, the designation of L-type was extended to refer to all channels with strong sensitivity to DHPs, including those found in skeletal muscle (Hofmann et al., 1988), even though clear-cut biophysical distinctions between skeletal and cardiac L-type channels were already known (Rosenberg et al., 1986). Thus, the category of L-type channels contains individual subtypes of considerable diversity. For example, three subtypes of L-type channel appear to co-exist in cerebellar granule neurons, two subtypes that resemble those found in heart and a third that shows prominent voltage-dependent potentiation (Forti and Pietrobon, 1993).

Three major families of α_1 subunits clearly emerge on the basis of sequence homology. The first subfamily ($\alpha_1$1) consists of 4 α_1 members. Along with the $\alpha_1$1.1 (α_{1S}) subunit from skeletal muscle, these include subunits first derived from heart muscle [$\alpha_1$1.2 (α_{1C})] (Mikami et al., 1989), neuroendocrine tissue [$\alpha_1$1.3 (α_{1D})] (Williams et al., 1992b), and retina [$\alpha_1$1.4 (α_{1F})] (Fisher et al., 1997; Bech-Hansen et al., 1998; Strom et al., 1998). These cDNAs encode HVA channels classified as "L-type" because they are responsive to DHPs. The existence of three α_1 subunits, each capable of supporting L-type channel activity, provides an obvious starting point for attempts at understanding how L-type Ca^{2+} channel diversity might be generated from specific molecular structures. However, little information is yet available to link functionally

distinct forms of L-type channel activity (e.g., Forti and Pietrobon, 1993; Kavalali and Plummer, 1994) to individual α_1 isoforms. While the $\alpha_1$1.1 subunit appears to be largely excluded from neurons according to Northern analysis and electrophysiological criteria, no sharp distinction has been made between currents generated by $\alpha_1$1.2 and $\alpha_1$1.3. Single channel recordings of expressed $\alpha_1$1.3 channels are lacking and analysis of the functional impact of various β subunits on $\alpha_1$1.2 and $\alpha_1$1.3 is not extensive.

Most of the attention to date has been focused on splice variations of $\alpha_1$1.2. These have a marked impact on channel behavior in several cases, producing 1) differences in sensitivity to DHPs in $\alpha_1$1.2 variants found in cardiac or smooth muscle (Welling et al., 1993), 2) differences in the voltage-dependence of DHP binding (Soldatov et al., 1995) and 3) differences in susceptibility to cyclic AMP-dependent phosphorylation (Hell et al., 1993b). Further analysis will be greatly facilitated by knowledge of the genomic structure of the human $\alpha_1$1.2 gene, which spans an estimated 150 kb of the human genome and is composed of 44 invariant and 6 alternative exons (Soldatov, 1994). The L-type channel in chick hair cells incorporates an $\alpha_1$1.3 subunit that differs from the $\alpha_1$1.3 subunit in brain due to expression of distinct exons at three locations (Kollmar et al., 1997). It will be interesting to see if additional splice variations can account for L-type channel activity found at the resting potential of hippocampal neurons, possibly important for setting the resting $[Ca^{2+}]_i$ (Avery and Johnston, 1996).

Ca_V2

The second α_1 subfamily consists of cDNAs which, when expressed, result in HVA channels which lack the characteristic DHP-response of L-type channels. These clones [$\alpha_1$2.1 (α_{1A}) (Mori et al., 1991), $\alpha_1$2.2 (α_{1B})(Dubel et al., 1992) and $\alpha_1$2.3 (α_{1E}) (Soong et al., 1993)] were derived from nervous tissue. Individual genes within this subfamily show ~89% identity with each other in the membrane spanning and pore forming regions but only ~53% or less with members of the $\alpha_1$1 subfamily.

$Ca_V2.2$/N-type Ca^{2+} channels

The most extensively characterized non-L-type Ca^{2+} channel was named N-type since it appeared to be largely specific to neurons as opposed to muscle cells and was clearly neither T- nor L-type (Nowycky et al., 1985). It requires relatively negative resting potentials to be available for opening, somewhat like T-type, but is high voltage-activated, like L-type. This Ca^{2+} channel is potently and specifically blocked by a peptide toxin derived from the venom of the marine snail, Conus geographus, ω-conotoxin GVIA (ω-CTx-GVIA). The N-type channel is found primarily in presynaptic nerve terminals and neuronal dendrites in addition to cell bodies (Westenbroek et al., 1992). The N-type current can be assigned with a fairly high degree of certainty to $Ca_V2.2$ (α_{1B}), which, when expressed, conducts ω-CTx-GVIA-sensitive currents with characteristics that match those of native N-type channels (Dubel et al., 1992; Williams et al., 1992a; Fujita et al., 1993).

As discussed earlier, an important source of channel heterogeneity is the association of α_1 subunits with different ancillary subunits. A good example of this is provided by the N-type Ca^{2+} channel in brain. Biochemical analysis has shown that the $\alpha_1 2.2$ subunit associates with three different isoforms of β subunit in rabbit brain (Scott et al., 1996). Antibodies against individual β subunits were each able to immunoprecipitate ω-CTx-GVIA binding activity (a marker of $Ca_V2.2$), while immunoprecipitation of $\alpha_1 2.2$ showed its association with β_{1b}, β_3 and β_4.

Different isoforms of the N-type Ca^{2+} channel subunit $\alpha_1 2.2$ have been isolated from rat sympathetic ganglia and brain by Lin *et al.* (1997). Alternative splicing determines the presence or absence of small inserts in the S3-S4 regions of domains III and IV (SFMG and ET respectively). Different combinations of inserts in these putative extracellular loop regions are dominant in central (+SFMG, ΔET) versus peripheral (ΔSFMG, +ET) nervous tissue. Most interestingly, the gating kinetics of ΔET-containing clones (as found in the central form) are significantly faster than the +ET form (Lin et al., 1999). This work provides a clear example of how alternative splicing contributes to diverse functional properties.

$Ca_V2.1$/P- and Q-type Ca^{2+} channels

Currents carried by P-type channels were originally recorded from cell bodies of cerebellar Purkinje cells (Llinás et al., 1989; Llinás et al., 1992). These channels are not blocked by DHPs or ω-CTx-GVIA, but are exquisitely sensitive to block by ω-Aga-IVA or ω-Aga-IVB, components of the venom of the funnel-web spider, Agelenopsis aperta **(Mintz et al., 1992a; Mintz et al., 1992b)**, with an IC50 of <1 nM for ω-Aga-IVA (Mintz and Bean, 1993). These channels support a current that hardly inactivates during depolarizations lasting for several seconds. They are seen in virtual isolation from other voltage-gated Ca^{2+} channels in cerebellar Purkinje neuron cell bodies, but also contribute substantially to somatic currents in many other central neurons (Mintz et al., 1992a).

Initial observations of current supported by $\alpha_1 2.1$ (α_{1A}) suggested that it corresponded to the P-type channel (Llinás et al., 1992), consistent with the strong expression of this subunit in cerebellar Purkinje cells (Mori et al., 1991, Stea, 1994 #711, Mintz Nature 92). Closer comparison of the properties of $Ca_V2.1$ expressed in Xenopus oocytes and those of P-type channels in Purkinje cells, however, revealed clear differences. P-type channels activate at relatively negative potentials and support a sustained, non-inactivating current during depolarizing pulses longer than 1 s (Llinás et al., 1992; Usowicz et al., 1992), whereas $\alpha_1 2.1$ subunits expressed in Xenopus oocytes activate at less negative potentials and exhibit marked inactivation within 100 ms (Sather et al., 1993). Furthermore, the IC_{50} for ω-Aga-IVA block of $Ca_V2.1$ expressed in oocytes (Sather et al., 1993; Stea et al., 1994) or baby hamster kidney cells (Niidome et al., 1994) is 100-200 nM. A current with these properties was characterized in the cell bodies of cerebellar granule neurons and named Q-type (Zhang et al., 1993; Randall and Tsien, 1995) since it differed from the previously defined P-type current (which was also present in the granule neurons).

Subsequently channels of intermediate type have been found in several preparations (Tottene et al., 1996; Forsythe et al., 1998; Mermelstein et al., 1999), indicating that instead of two discrete channel types, P and Q may represent points on a spectrum of channel properties.

Additionally, evidence has been mounting that both channels are encoded by the same α_1 subunit (Gillard et al., 1997; Piedras-Rentería and Tsien, 1998; Pinto et al., 1998; Jun et al., 1999), and it has been shown that differences in inactivation and toxin affinity, the basis for distinctions between these two types, can be explained in part by splice variants or subunit composition (Liu et al., 1996; Bourinet et al., 1999; Mermelstein et al., 1999). With these facts in mind, the designation P-type or P/Q-type would be appropriate to indicate current through $Ca_V2.1$ or ω-Aga-IVA/B- or ω-CTx-MVIIC-sensitive current, regardless of inactivation characteristics. P/Q-type channels have a similar distribution to N-type channels.

$Ca_V2.3$/R-type Ca^{2+} channels

R-type Ca^{2+} channel currents were identified in cerebellar granule cells as a current that remained in the presence of nimodipine, ω-CTx-GVIA, and ω-Aga-IVA, inhibitors of the L-, N-, and P/Q-type channels respectively (Ellinor et al., 1993; Zhang et al., 1993; Randall and Tsien, 1995). R-type currents have since been found in several other central nerve terminals (Meder et al., 1997; Newcomb et al., 1998; Wu et al., 1998). This predominantly HVA current decays rapidly and is at least partially responsive to low doses of Ni^{2+} and, in some preparations, SNX-482, a toxin derived from tarantula venom (Newcomb et al., 1998). Less is known about the molecular basis of R-type currents than for any of the other channel types. Of all the known α_1 subunits, $\alpha_1$2.3 (α_1E) comes the closest. Expressed $Ca_V2.3$ currents display certain attributes of R-type channels: they are readily blocked by Ni^{2+} (Soong et al., 1993; Wakamori et al., 1994; Williams et al., 1994) and the spider toxin ω-Aga-IIIA (Randall and Tsien, 1998; Rock et al., 1998), and display a single channel conductance of ~12-14 pS in 100 mM Ca^{2+}, Ba^{2+}, or Sr^{2+} (Schneider et al., 1994; Wakamori et al., 1994; Bourinet et al., 1996; Tottene et al., 1996; Tottene et al., 1999). In addition $Ca_V2.3$ antisense treatment has been shown to reduce native R-type current (Piedras-Rentería and Tsien, 1998). Some studies have found reasons to question assignment of R-type currents to $Ca_V2.3$ (Soong et al., 1993; Bourinet et al., 1996; Tottene et al., 1996; Piedras-Renteria et al., 1997; Meir and Dolphin, 1998), however some of these may be

explained by diversity in R-type currents caused by splice variants and/or auxiliary subunit differences as seen for P- vs. Q-type channels. Support for the possibility of R-type diversity comes from studies that show that SNX-482, a synthetic peptide neurotoxin, blocks R-type currents in some cell types but spares them in others (Newcomb et al., 1998) and differences in Ni^{2+} block and activation voltage in R-type current in the same cell type (Tottene et al., 1996).

Ca_V3/T-type Ca^{2+} channels

LVA Ca^{2+} channels are exemplified by T-type channels, so-named because they carry tiny unitary Ba^{2+} currents (6-8 pS with ~100 mM Ba^{2+} or Ca^{2+} as charge carrier) that occur soon after the depolarizing step, giving rise to a transient average current (Carbone and Lux, 1984; Nilius et al., 1985; Nowycky et al., 1985). Another defining characteristic of classical T-type channels is their slow deactivation following a sudden repolarization (Matteson and Armstrong, 1986). T-type channel current records also exhibit a distinctive kinetic fingerprint: the superimposed current responses cross over each other in a pattern not found with other rapidly inactivating Ca^{2+} channels such as R-type (Randall and Tsien, 1998). The kinetic properties are dominated by a strikingly voltage-dependent delay between the depolarizing step and the channel's first opening (Droogmans and Nilius, 1989). In addition to these properties, T-type channels have a unique pharmacological profile, characterized by only mild sensitivity to 1,4-dihydropyridines (DHPs), such as nifedipine or nimodipine (Cohen and McCarthy, 1987), but acute sensitivity to mibefradil (Ertel and Ertel, 1997). A newly identified antagonist, kurtoxin, has recently been shown to affect $Ca_V3.1$ (Chuang et al., 1998). Kurtoxin is an α-scorpion toxin which also affects voltage-gated sodium channels and is currently the most specific antagonist with respect to T-type *versus* other Ca^{2+} channels. Within the overall category of T-type Ca^{2+} channel, further diversity has been found, particularly with respect to kinetic characteristics and pharmacology (Akaike et al., 1989; Kostyuk and Shirokov, 1989; Huguenard and Prince, 1992). Various subtypes of T-type Ca^{2+} channel may co-exist in the same cell type and show rates of inactivation differing by as much as five-fold, while sharing similar voltage-dependence of inactivation

(Huguenard and Prince, 1992). T-type channels are found in a wide variety of central and peripheral neurons.

The Ca_V3 subfamily of T-type channels is more distantly related to the two HVA subfamilies Ca_V1 and Ca_V2 than they are to each other (Figure 2). Three genes in Ca_V3 have recently been identified, $Ca_V3.1$ (α_{1G}), $Ca_V3.2$ (α_{1H}), and $Ca_V3.3$ (α_{1I}) (Cribbs et al., 1998; Perez-Reyes et al., 1998; Lee et al., 1999). These genes encode LVA T-type channels when expressed without auxiliary subunits (Cribbs et al., 1998; Perez-Reyes et al., 1998; Lacinová et al., 1999; Lee et al., 1999). This is consistent with findings that native T-type currents are not dependent on auxiliary subunits (Lambert et al., 1997; Leuranguer et al., 1998), however there is a report that coexpression of $\alpha_2\delta$ can increase expression of native T-type current (Wyatt et al., 1998).

Note on Pharmacology

Pharmacology is the most widely used criterion when distinguishing various types of calcium currents. It should therefore be noted that antagonists discussed above are not perfectly selective. The P/Q-type blockers ω-Aga-IVA/B and ω-CTx-MVIIC all partially antagonize N-type channels at higher doses (Mintz I. M. & S. Sidach, The Society for Neuroscience abstract, 24:1021, 1998)(Hillyard et al., 1992; Grantham et al., 1994) and ω-Aga-IVA has been shown to have some effect on expressed $Ca_V2.3$ channels (Soong et al., 1993; Williams et al., 1994). In addition to the lack of complete specificity of these toxins, it should also be noted that there are occasional reports of currents that display pharmacological properties that do not fit any of the above categories. These include currents blocked by both ω-CTx-GVIA and moderate doses of ω-Aga-IVA in rat supraoptic neurons (Fisher and Bourque, 1995) and chicken forebrain synaptosomes (Lundy et al., 1994) and a current reversibly blocked by ω-CTx-GVIA (Mermelstein and Surmeier, 1997).

Evolutionary conservation of Ca^{2+} channel families

The evolutionary divergence of Ca_V1 and Ca_V2 Ca^{2+} channels occurred relatively early, as would be expected from the fairly low sequence homology between genes encoding channels

from the two subfamilies (Figure 2). This deduction can be corroborated by an examination of the distribution of Ca^{2+} channel types in organisms spread across many phyla. Both subfamilies of HVA channels are present in vertebrate species ranging from marine rays (Horne et al., 1993) to humans (Williams et al., 1992a; Williams et al., 1992b), and in many cases both are expressed within the same cells (e.g., Randall and Tsien, 1995). Amongst invertebrates, both channel types have been observed in molluscs (Edmonds et al., 1990), insects (Grabner et al., 1994; Smith et al., 1996), and nematodes (Schafer and Kenyon, 1995). Given the widespread distribution of L- and non-L-type HVA Ca^{2+} channels across the animal kingdom their bifurcation must have occurred quite early during the speciation of Animalia. Presumably LVA and HVA channels diverged even earlier. A possible descendent of an ancestral HVA channel which resembles L-type channels has been cloned from jellyfish (Jeziorski et al., 1998). A "T-like" channel has been observed in paramecium (e.g. Ehrlich et al., 1988). LVA and HVA currents have been identified in cockroaches (Grolleau and Lapied, 1996) and leech (Lu et al., 1997). Whether the various LVA currents are carried by channels with a molecular structure similar to Ca_V3 is not known.

FUNCTIONAL ROLES OF CA^{2+} CHANNELS

Introduction/Subcellular localization

The diversity of voltage-gated Ca^{2+} channels is indicative of the variety of functional roles they are called upon to serve. With the exception of $\alpha_1$1.1, which appears highly localized to skeletal muscle, α_1 subunits are broadly distributed across the spectrum of exocytotic cells. At the level of individual cells, however, the different channel types often show distinct patterns of localization to different parts of the cell.

Ca^{2+} channels of the Ca_V1 subfamily are widely distributed in muscle, nerve and endocrine cells. Their unique biophysical properties and subcellular localization put them in a good position to act as transducers linking membrane depolarization to intracellular signaling. In the brain, for example, Ca_V1 channels are found in the cell bodies and proximal dendrites of

hippocampal pyramidal cells (Westenbroek et al., 1990). $\alpha_1$1.2-containing channels were concentrated in clusters at the base of major dendrites, while Ca_V1.3 channels were more generally distributed across cell surface membrane of cell bodies and proximal dendrites (Hell et al., 1993a).

The Ca_V2 subfamily of Ca^{2+} channels is widely distributed both pre- and postsynaptically in the central and peripheral nervous systems. In most regions of the brain, antibodies against $\alpha_1$2.2 bind primarily on dendrites and nerve terminals (Westenbroek et al., 1992) whereas $\alpha_1$2.1 subunits are concentrated in presynaptic terminals and are present at lower density in the surface membrane of dendrites of most major classes of neurons (Westenbroek et al., 1995). Ca_V2.3 epitopes are found mostly on cell bodies, and in some cases in dendrites, of a broad range of central neurons (Yokoyama et al., 1995). Thus, these classes of Ca^{2+} channels seem to be well positioned to support both presynaptic Ca^{2+} influx that triggers neurotransmitter release and postsynaptic Ca^{2+} entry that helps shape the response downstream to that release.

Little is known about the subcellular distribution of the recently cloned Ca_V3 subfamily of Ca^{2+} channels. The only systematic study so far (Talley et al., 1999) contains no information regarding subcellular distribution of these proteins. In many cell types T-type currents seem to be found primarily in the dendrites as compared to somata (Karst et al., 1993; Markram and Sakmann, 1994; Magee et al., 1995; Magee and Johnston, 1995; Kavalali et al., 1997; Mouginot et al., 1997; , but see Schultz et al., 1999). This is consistent with theories about their functional roles (see below).

Excitation-contraction coupling

L-type Ca^{2+} channels play a central role in excitation-contraction coupling in skeletal, cardiac and smooth muscle, although other channel types may play a supporting role in some of these cells (Zhou and January, 1998). In skeletal muscle, L-type Ca^{2+} channels contain the $\alpha_1$1.1, β_{1a}, γ_1, and $\alpha_2\delta$-1 subunits and are largely localized to the transverse tubule system. Ca^{2+} entry through the L-type channel is not required for skeletal muscle contraction (reviewed in Miller

and Freedman, 1984), in contrast to cardiac muscle, where Ca^{2+} entry is essential for contractility (Näbauer et al., 1989). Interestingly, blockade of L-type channels in skeletal muscle by organic Ca^{2+} antagonists completely inhibits contraction (Eisenberg et al., 1983). The explanation of these findings centers on gating charge movement in the T-tubule membrane, which was known to be essential for intracellular Ca^{2+} release (Schneider and Chandler, 1973). DHPs eliminate charge movement, thereby blocking skeletal muscle contraction (Ríos and Brum, 1987). The implication of these findings was that DHP-sensitive L-type Ca^{2+} channels act as voltage sensors to link T-tubule depolarization to intracellular Ca^{2+} release.

This hypothesis was tested in elegant experiments by Tanabe, Numa, Beam and their colleagues. The cloning of the DHP receptor protein from skeletal muscle led immediately to its identification as a voltage-gated channel (Tanabe et al., 1987). Later, expression of the cloned DHP receptor in dysgenic skeletal muscle myotubes showed that it could restore electrically evoked contractility in these formerly non-responsive cells (Tanabe et al., 1988), along with L-type Ca^{2+} current (Tanabe et al., 1988; Garcia et al., 1994) and gating charge movement (Adams et al., 1990). While the skeletal DHP receptor allowed contraction even in the absence of extracellular Ca^{2+}, the cardiac L-type Ca^{2+} channel restored contractility only if Ca^{2+} entry occurred (Tanabe et al., 1990). The structural basis of the skeletal-type excitation-contraction coupling was investigated with molecular chimeras. By inserting pieces of the $\alpha_1$1.1 gene into an $\alpha_1$1.2 background, Tanabe *et al.* (1990) showed that the key domain was the intracellular loop joining repeats II and III of $\alpha_1$1.1 (see asterisk in figure 1). More recently, other groups have shown that purified II-III loop fragments can directly activate the ryanodine receptor (Lu et al., 1994; el-Hayek et al., 1995) and that this region may contain phosphorylation sites for the regulation of excitation-contraction coupling (Lu et al., 1995).

Rhythmic activity

Pacemaker

In cardiac cells, T-type Ca^{2+} channels are generally present at much lower density than L-

type channels, if at all. However, T-type channels supply a major fraction of the current recorded in cells from the sinoatrial node, the natural source of cardiac rhythms, and thus provide a significant contribution to the inward current that drives the last stages of the pacemaker depolarization (Hagiwara et al., 1988; Lei et al., 1998).

Other

T-type channels also support oscillatory activity and repetitive activity in the thalamus (Jahnsen and Llinás, 1984; McCormick and Bal, 1997). Along with an apamin-sensitive Ca^{2+}-activated K current, T-type channels in the nucleus reticularis generate rhythmic action potential bursts. In thalamocortical neurons the overlapping activation and inactivation curves of T-type currents support rebound burst firing in which a hyperpolarization is followed by a Ca^{2+} spike results in the generation of several action potentials. Interestingly, expression of T-type channels in smooth muscle fluctuates in synchrony with the cell cycle (Kuga et al., 1996), and may be associated with cell proliferation (Schmitt et al., 1995).

Excitation-secretion coupling

Generic properties

The most commonly studied role of Ca^{2+} is its ability to trigger neurotransmitter release. The importance of Ca^{2+} ions in the release of neurotransmitter has been appreciated for more than 60 years (Feng, 1936). Seminal work by Douglas (1963) and Katz (1969) and their colleagues demonstrated that Ca^{2+} ions exert their influence at the nerve terminal where they control the amount of neurotransmitter that is released. The action of Ca^{2+} ions in the regulation of neurotransmission was shown to be cooperative, requiring about four Ca^{2+} ions to bind to their receptor in order to trigger release (Dodge and Rahamimoff, 1967). The importance of Ca^{2+} action in the nerve terminal was further supported by the observation that injection of Ca^{2+} into the terminal triggered the release of transmitter at the squid giant synapse (Miledi, 1973).

Subsequently, the Ca^{2+}-sensitive protein, aequorin, was used to show that presynaptic $[Ca^{2+}]_i$ increases during neurotransmission (Llinás and Nicholson, 1975).

Studies using simultaneous voltage-clamp of the presynaptic terminal and postsynaptic axon of the squid giant synapse provided direct measurements of the Ca^{2+} currents in the presynaptic membrane that trigger the release of neurotransmitter (Llinás et al., 1981; Augustine et al., 1985). Ongoing issues include the identification of presynaptic Ca^{2+} channels and clarification of the functional consequences of their diversity (for other recent reviews, see Olivera et al., 1994; Dunlap et al., 1995; Reuter, 1996).

Ca^{2+} channels from the Ca_V2 subfamily are the primary types responsible for excitation-secretion coupling. Interestingly just as the II-III loop of the Ca_V1 channel interacts with the Ca^{2+} channel's effector for contraction, the II-III loop of the Ca_V2 channel interacts with its effector: the secretory apparatus (Sheng et al., 1994) (asterisk in figure 1). The specific type of channel involved in secretion from various cell types is discussed in greater detail below.

While the vast majority of studies of neurotransmitter release have failed to identify a role for L-type Ca^{2+} channels (Dunlap et al., 1995), this subtype has been implicated in a few specialized forms of exocytosis. For example, activation of L-type channels is required for zona pellucida-induced exocytosis from the acrosome of mammalian sperm (Florman et al., 1992). L-type channels also seem to play a role in mediating hormone release from endocrine cells. Inhibition of L-type Ca^{2+} channels reduces insulin secretion from pancreatic β cells (Ashcroft et al., 1994; Bokvist et al., 1995), oxytocin and vasopressin release from the neurohypophysis (Lemos and Nowycky, 1989), luteinizing hormone-releasing hormone release from the bovine infundibulum (Dippel et al., 1995) and catecholamine release from adrenal chromaffin cells (Lopez et al., 1994). L-type channels also seem to play an important role in supporting release of GABA from retinal bipolar cells (Maguire et al., 1989; Duarte et al., 1992), as well as dynorphin release from dendritic domains of hippocampal neurons (Simmons et al., 1995). In some cases L-type channels may function to release excitatory amino acid transmitters, in response to particular patterns of activity (Bonci et al., 1998), in cells that exhibit graded potentials (Schmitz

and Witkovsky, 1997), during extended depolarizations with high K^+, or under the experimental influence of the DHP agonist Bay K 8644 (e.g., see Sabria et al., 1995).

In addition to admitting the Ca^{2+} which directly triggers neurotransmitter release, Ca^{2+} channels regulate and are regulated by the state of the nerve terminal. Ca^{2+} entry though the same channels which trigger transmitter release, and most likely through other presynaptic channels more distant from the release site (possibly including L-type channels) affects the background level of Ca^{2+} in the terminal, which regulates endocytosis, release probability, various dynamic parameters of the vesicle pool, as well as the channels themselves (reviewed in Neher, 1998). Ca^{2+} channels also receive direct feedback about the state of the release machinery (Bezprozvanny et al., 1995; Bergsman and Tsien, 1999; Degtiar et al., 1999).

Peripheral

At the neuromuscular junction, the release of neurotransmitter is generally mediated by a single Ca^{2+} channel type, although there is variation in the type that predominates from species to species. Invertebrate motor end plates utilize primarily P/Q-type channels. In crayfish, for example, inhibitory and excitatory transmitter release onto the claw opener muscle was completely abolished by ω-Aga-IVA, while ω-CTx-GVIA and nifedipine were both ineffective (Araque et al., 1994). In locusts and houseflies, motor end plate potentials are blocked by type I and II Agatoxins, which inhibit P/Q-type channels, but not by type III Agatoxins, which potently block both L- and N-type channels (Bindokas et al., 1991). In non-mammalian vertebrates, unlike invertebrates, neurotransmitter release at the neuromuscular junction is completely blocked by ω-CTx-GVIA. This is true for frogs (Kerr and Yoshikami, 1984; Katz et al., 1995), lizards (Lindgren and Moore, 1989) and chicks (De Luca et al., 1991; Gray et al., 1992). In mammals on the other hand, ω-CTx-GVIA does not seem to have any effect on the evoked release of acetylcholine at the neuromuscular junction (Sano et al., 1987; Wessler et al., 1990; De Luca et al., 1991; Protti et al., 1991; Bowersox et al., 1995). In contrast, block of P/Q-type Ca^{2+} channels by ω-CTx-MVIIC, ω-Aga-IVA or FTx completely abolishes transmission in mice

(Protti and Uchitel, 1993; Bowersox et al., 1995; Hong and Chang, 1995) and humans (Protti et al., 1996). In all of these species, neuromuscular transmission seems to rely on a single type of channel from the Ca_V2 subfamily.

In general, sympathetic neurons contain both L- and N-type Ca^{2+} channels but not P/Q-type channels (Hirning et al., 1988; Mintz et al., 1992a; Zhu and Ikeda, 1993) (but see Namkung et al., 1998). However, only N-type Ca^{2+} channels seem to be important for the release of norepinephrine, inasmuch as ω-CTx-GVIA blocks NE secretion (Hirning et al., 1988; Fabi et al., 1993) but DHPs do not (Perney et al., 1986; Hirning et al., 1988; Koh and Hille, 1996). Along similar lines, N- but not L-type Ca^{2+} channels in sympathetic nerve terminals are susceptible to modulation of Ca^{2+} current via autoreceptors for NE or neuropeptide Y (Toth et al., 1993). Thus, sympathetic nerve endings are like motor nerve terminals in relying on a single predominant type of Ca^{2+} channel, in this case N-type, despite the sizable contribution of L-type channels to the global Ca^{2+} current. Reliance on N-type channels cannot be generalized to all autonomic terminals since P/Q-type channels play a prominent role in transmitter release in rodent urinary bladder (Frew and Lundy, 1995; Waterman, 1996) and also participate in triggering release of exocytosis from mouse sympathetic and parasympathetic nerve terminals (Waterman, 1997; Waterman et al., 1997)

Central

At central synapses, unlike synapses in the periphery, neurotransmitter release often involves more than one Ca^{2+} channel type. Central neurons appear to be richly endowed with Ca^{2+} channels, with many as five or six different types of channels in an individual nerve cell (Mintz et al., 1992a; Randall and Tsien, 1995). Several recent papers have reported that neurotransmission at specific synapses in the CNS depends upon the concerted actions of more than one type of Ca^{2+} channel (Luebke et al., 1993; Takahashi and Momiyama, 1993; Castillo et al., 1994; Regehr and Mintz, 1994; Wheeler et al., 1994; Mintz et al., 1995). The relative importance of N-, P/Q-, and R-type Ca^{2+} channels can vary from one synapse to another. Studies

of synapses in hippocampal and cerebellar slices suggest that the vast majority of single release sites are in close proximity to a mixed population of Ca^{2+} channels that jointly contribute to the local Ca^{2+} transient that triggers vesicular fusion (e.g., Mintz et al., 1995; but see also Reuter, 1995; Poncer et al., 1997; Reid et al., 1997). The synergistic effect of multiple Ca^{2+} channels arises because of limitations on the Ca^{2+} flux through individual channels under physiological conditions. Indeed, the reliance on multiple types of Ca^{2+} channels was not absolute but could be relieved by increasing the Ca^{2+} influx per channel, either by prolonging the presynaptic action potential or by increasing $[Ca^{2+}]_o$ (Wheeler et al., 1996). The reliance on more than a single Ca^{2+} channel type may offer the advantage of precise control over Ca^{2+} influx and transmitter release by allowing for differential modulation (Tsien et al., 1988; Mogul et al., 1993; Swartz et al., 1993; Mynlieff and Beam, 1994).

Postsynaptic Ca^{2+} influx

Dendritic information processing

Much of the electrical and biochemical signal processing in central neurons takes place within their dendritic trees. Ca^{2+} entry through voltage-gated channels is critical for many of these events. The idea that voltage-gated Ca^{2+} channels may contribute to electrogenesis in dendrites first arose in the interpretation of intracellular recordings from hippocampal pyramidal neurons (Spencer and Kandel, 1961). Initial intradendritic voltage recordings were conducted on the dendritic arbors of cerebellar Purkinje neurons (Llinás and Nicholson, 1971; Llinás and Hess, 1976; Llinás and Sugimori, 1980) and apical dendrites of hippocampal pyramidal neurons (Wong et al., 1979). The ability of dendrites to support Ca^{2+}-dependent action potential firing was reinforced by experiments where apical dendrites of pyramidal neurons were surgically isolated from their cell bodies in a hippocampal slice preparation (Benardo et al., 1982; Masukawa and Prince, 1984). These experiments revealed a variety of Ca^{2+}-dependent active responses in the dendrites of central neurons that could be elicited by excitatory postsynaptic potentials or injection of depolarizing current pulses.

Recent studies of the electrical properties of dendrites have been facilitated by the ability to visualize dendrites in brain slices, thus rendering dendrites accessible to patch electrodes (Stuart et al., 1993). These studies revealed that back-propagating Na^+-dependent action potentials can activate dendritic Ca^{2+} channels, thereby causing substantial increases in intradendritic free Ca^{2+} (Jaffe et al., 1992; Stuart and Sakmann, 1994; Markram et al., 1995; Schiller et al., 1995; Spruston et al., 1995). Subthreshold excitatory postsynaptic potentials can also open Ca^{2+} channels and result in more localized changes in intradendritic Ca^{2+} concentration (Markram and Sakmann, 1994; Yuste et al., 1994; Magee et al., 1995). T-type Ca^{2+} channels play a prominent role in dendritic Ca^{2+} signaling in hippocampal and cortical neurons (Magee et al., 1995), presumably due to their ability to open at relatively negative membrane potentials.

The presence of multiple types of voltage-gated Ca^{2+} channels on dendrites has been demonstrated by several techniques, including Ca^{2+} imaging (Markram et al., 1995; Watanabe et al., 1998), dendrite-attached patch clamp recordings (Usowicz et al., 1992; Magee and Johnston, 1995) and immunocytochemistry (Westenbroek et al., 1990; Westenbroek et al., 1992; Hell et al., 1993a; Westenbroek et al., 1995; Yokoyama et al., 1995). Recordings from isolated dendritic segments of acutely dissociated hippocampal neurons indicated that T-, N-, P/Q- and R-type channels all contribute to the overall Ca^{2+} current in dendrites, with T-type current particularly enhanced when compared to somata (Kavalali et al., 1997).

Excitation-expression coupling and changes in gene expression

A number of extracellular factors that influence cell growth and activity depolarize the membranes of their target cells (Hill and Treisman, 1995). Membrane depolarization opens voltage-gated Ca^{2+} channels and the resulting influx of Ca^{2+} can trigger gene transcription (for a review, see Morgan and Curran, 1989). L-type Ca^{2+} channels are thought to play a role in this cascade because agonists of these channels can induce expression of several protooncogenes in the absence of other stimuli (Morgan and Curran, 1988). Indeed the mode and location of Ca^{2+} entry may be important to how the Ca^{2+} signal is interpreted by the cell (Ghosh et al., 1994;

Rosen and Greenberg, 1994). Some recent studies have shed light on the cascade of events that follows influx of Ca^{2+} through L-type channels.

An example of a signal-transduction cascade where Ca^{2+} entry is important involves the cAMP and Ca^{2+} response element (CRE), and its nuclear binding protein (CREB) (Montminy and Bilezikjian, 1987; Hoeffler et al., 1988). The interaction of CREB with the CRE is facilitated when CREB is phosphorylated on serine-133 (Gonzalez and Montminy, 1989). The phosphorylation of CREB is catalyzed by several kinases including Ca^{2+}-calmodulin kinases II and IV, cAMP-dependent protein kinase (Greenberg et al., 1992), and others. Thus, rises in $[Ca^{2+}]_i$ can act either directly, via Ca^{2+}-calmodulin and its dependent kinases, or indirectly, by stimulating Ca^{2+}-calmodulin-sensitive adenylate cyclase leading to increased cAMP levels. Recent work has shown that Ca^{2+} entry through L-type channels can trigger CREB phosphorylation (Yoshida et al., 1995; Deisseroth et al., 1998; Rajadhyaksha et al., 1999), and that the Ca^{2+} probably binds to a target molecule within 1 μm of the point of entry (Deisseroth et al., 1996).

In addition to Ca^{2+}, Zn^{2+} influx is interesting because it regulates a wide variety of enzymes and DNA binding proteins, provides an important developmental signal, and may be involved in excitotoxicity and responses to trauma (for a review, see Smart et al., 1994). Interestingly, L-type Ca^{2+} channels can support Zn^{2+} influx into heart cells, where it can induce transcription of genes driven by a metallothionein promoter (Atar et al., 1995). Morphological studies have revealed that Zn^{2+} is highly enriched in a number of nerve fiber pathways, especially in boutons where it appears to be contained within vesicles (Smart et al., 1994). Furthermore, Zn^{2+} can be released from brain tissue during electrical or chemical stimulation (Assaf and Chung, 1984; Howell et al., 1984; Charton et al., 1985). Given that Zn^{2+} can be released by synaptic activity, and can enter cells via voltage-dependent Ca^{2+} channels, it seems likely that Zn^{2+} may play an important role in excitation-expression coupling.

CONCLUDING REMARKS

Understanding of the diversity of voltage-gated Ca^{2+} channels has greatly increased over the last decade or so as a result of several synergistic approaches. The identification of multiple types of Ca^{2+} channels on the basis of biophysical and pharmacological criteria has been complemented by studies of the biochemistry and molecular biology of their underlying subunit components. The most recent advances have been made in understanding the basis of P/Q-, R- and T-type Ca^{2+} channel activity. Considerable progress has also been made in clarifying molecular mechanisms of the structural features that distinguish individual types of Ca^{2+} channels and enable them to perform specialized functional roles or to respond to type-selective drugs. The largest area of uncertainty concerns the three-dimensional structures of Ca^{2+} channels and the structural basis of differences among channel subtypes.

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FIGURE LEGENDS

Figure 1: Structural organization of the subunits comprising a generic voltage-gated Ca^{2+} channel. Small cylinders represent α helices, large cylinders in the α_1 subunit represent 6 α helices. Asterisk marks the II-III loop of the α_1 subunit.

Figure 2: Ca^{2+} channel α_1 subunit family tree. Sequences of membrane spanning and P loop regions were aligned and matching percentages determined using CLUSTAL. Corresponding current type supported by each α_1 subunit is given, as well as tissue distribution and chromosome location of the human gene. Sequence data provided by Dr. Perez-Reyes, Department of Pharmacology, University of Virginia.

Figure 1

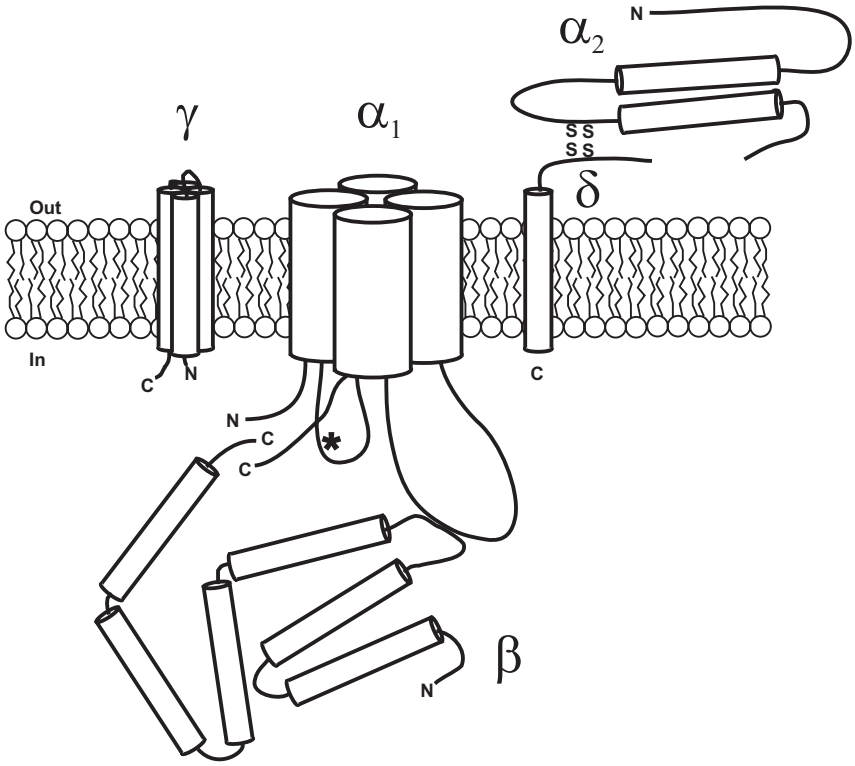
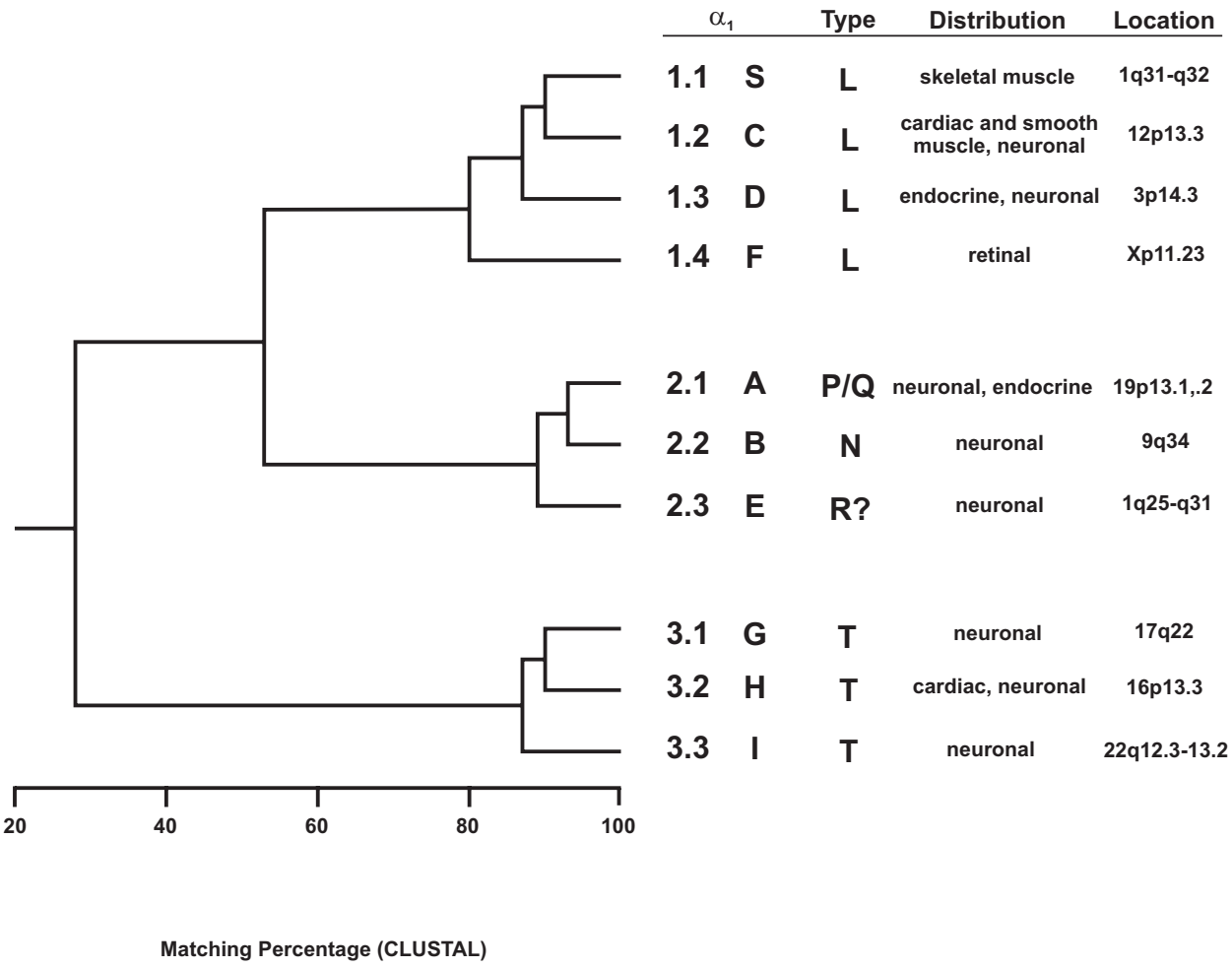


Figure 2


α1
Type
Distribution
Location
1.1 S L skeletal muscle 1q31-q32
1.2 C L cardiac and smooth muscle, neuronal 12p13.3
1.3 D L endocrine, neuronal 3p14.3
1.4 F L retinal Xp11.23
2.1 A P/Q neuronal, endocrine 19p13.1,.2
2.2 B N neuronal 9q34
2.3 E R? neuronal 1q25-q31
3.1 G T neuronal 17q22
3.2 H T cardiac, neuronal 16p13.3
3.3 I T neuronal 22q12.3-13.2
20
40
60
80
100
Matching Percentage (CLUSTAL)