Journal of Bioenergetics and Biomembranes, Vol. 35, No. 6, December 2003 (© 2003)

Modulation and Pharmacology of Low Voltage-Activated ("T-Type") Calcium Channels

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Although T-type calcium channel currents were observed almost 30 years ago, the genes that encode the pore-forming subunits have only been recently reported. When expressed in heterologous systems, three distinct alpha1 subunits (alpha1G ($Ca_v3.1$), alpha1H ($Ca_v3.2$), and alpha1I ($Ca_v3.3$)) conduct T-type currents with insert similar but not identical electrophysiological characteristics that. Alpha1G, alpha1H, and alpha1I transcripts are found throughout neural and nonneural tissues, suggesting multiple types of T-type channels (also called low voltage-activated calcium channels (LVAs)) are coexpressed by many tissues. The study of endogenous LVAs has been hampered by a lack of highly selective antagonists that differentiate between LVA subtypes. Furthermore, many pharmacological agents attenuate currents conducted by LVA and high voltage-activated calcium channels (HVAs). At least 15 classes of pharmacological agents affect T-type currents, and the therapeutic use of many of these drugs has implicated LVAs in the etiology of a variety of diseases. Comparison of the responses of recombinant and native LVAs to pharmacological agents and endogenous modulatory molecules will lead to a better understanding of LVAs in normal and diseased cells.

KEY WORDS: T-type; review; alpha1G ($Ca_v3.1$); alpha1H ($Ca_v3.2$); alpha1I ($Ca_v3.3$); epilepsy; cardiac; vascular; pharmacology.

INTRODUCTION

Our understanding of voltage-dependent calcium channels (VDCCs) has been greatly enhanced by the use of drugs that differentially interact with one or more types of VDCCs. Although VDCCs are roughly categorized by their electrophysiological properties into high voltage-activated (HVAs) and low voltage-activated (LVAs) calcium channel families (reviewed in Catterall, 2000), further discrimination of a single channel type within a family has been facilitated by the use of toxins, cations, and pharmacological agents that preferentially affect one type of channel. This is especially true for HVAs, as multiple HVA currents (P-/Q-, L-, N-, and R-types) can be recorded from individual neurons, and many of these currents have similar biophysical properties (reviewed in Jones, 1998). The application of selective blockers such as ω-agatoxin IVA, ω-conotoxin GVIA, and dihydropyridines is used frequently to define P-/Q-, N-, and L-type currents, respectively, and use of these blockers has been crucial in assessing the contribution of each current to specific calcium-dependent intracellular events such as neurotransmission and regulation of gene expression (reviewed in Doering and Zamponi, 2003). Selective blockers have also been important in establishing the molecular identity of HVA pore-forming subunits (Hui *et al.*, 1991; Mikami *et al.*, 1989; Mori *et al.*, 1991; Seino *et al.*, 1992; Tanabe *et al.*, 1987; Williams *et al.*, 1992a,b), and their use has permitted purification and biochemical analyses of HVAs (Curtis and Catterall, 1984; Flockerzi *et al.*, 1986; Haase *et al.*, 1991; Leung *et al.*, 1987; Liu *et al.*, 1996; Martin-Moutot *et al.*, 1995; McEnery, 1993; McEnery *et al.*, 1991; Schneider and Hofmann, 1988; Sharp *et al.*, 1987; Sieber *et al.*, 1987; Striessnig *et al.*, 1987; Witcher *et al.*, 1993).

Although T-type currents were first recorded almost 30 years ago (Hagiwara *et al.*, 1975), the study of LVAs has been impeded by the absence of a panel of selective

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0145-479X/03/1200-0577/0

channel blockers that have been of paramount importance in analyses of HVAs. The study of LVAs has been further complicated by the discovery that T-type currents recorded from a variety of cell types have differing voltage-dependent kinetics (reviewed in Huguenard, 1996) and sensitivities to inhibition by cations and dihydropyridines (see below) when compared to each other, suggesting the potential for heterogeneity in both the identity of LVA alpha1 pore-forming subunits and their association with modulatory auxiliary subunits. This insight has recently been validated by the molecular cloning of three alpha1 pore-forming LVA subunits (alpha1G ($Ca_v3.1$), alpha1H ($Ca_v3.2$), and alpha1I ($Ca_v3.3$)) (Cribbs *et al.*, 1998; Klugbauer *et al.*, 1999; Lee *et al.*, 1999a; McRory *et al.*, 2001; Mittman *et al.*, 1999a,b; Monteil *et al.*, 2000a,b; Perez-Reyes *et al.*, 1998; Williams *et al.*, 1999; Zhuang *et al.*, 2000; reviewed in Yunker and McEnery, 2003). T-type currents recorded from recombinant channels formed by alpha1G, alpha1H, and alpha1I can differ in their biophysical properties (Chemin *et al.*, 2002; Klöckner *et al.*, 1999; Kozlov *et al.*, 1999; Lee *et al.*, 1999a,b; McRory *et al.*, 2001), sensitivities to channel blockers, and modulation by exogenous molecules and second messengers (see below). However, T-type currents conducted by these three alpha1 subunits also have a number of biophysical and pharmacological similarities, and the task of defining the molecular identity of endogenous LVAs by comparison of endogenous and recombinant T-type currents has been arduous. A wide variety of neurotransmitters, hormones, and intracellular-signaling molecules affect endogenous T-type currents, and more than 15 classes of pharmacological and toxicological agents attenuate T-type currents expressed throughout neural and nonneural tissues. The use of these agents has revealed many unanticipated roles of T-type currents in both normal and diseased cells, (reviewed in Yunker, 2003). It is anticipated that the further discovery of more selective drugs will aid in our understanding of the molecular composition and regulation of T-type channels.

Functional Evidence for Exogenous and Endogenous Modulators of LVA Alpha1 (Ca_v3) Subunits

A wide variety of exogenous neurotransmitters (Kawai *et al.*, 1999; Lenglet *et al.*, 2002; Pemberton *et al.*, 2000; Pfeiffer-Linn and Lasater, 1998; reviewed in Anwyl, 1991) and hormones (Barrett *et al.*, 1991a; Cohen *et al.*, 1988; McCarthy *et al.*, 1993; Ritchie, 1993; Xu and Best, 1990) have been reported to affect endogenous T-type currents recorded from neurons, endocrine cells, and cardiac myocytes (Table I). Although some of the cellular pathways for modulation have been elucidated (Table I), the mechanisms by which many of these molecules affect endogenous T-type channels have not been demonstrated. Many intracellular molecules can modulate endogenous T-type currents, including GTP (Scott *et al.*, 1990), cGMP-dependent protein kinase (Kawai and Miyachi, 2001b), protein kinase A (Alvarez *et al.*, 1996; Kawai *et al.*, 1999; Lenglet *et al.*, 2002; Pemberton *et al.*, 2000; Pfeiffer-Linn and Lasater, 1993), protein kinase C (Rossier *et al.*, 1995; Schroeder *et al.*, 1990), calcium- and/or calmodulin-dependent protein kinase II (Barrett *et al.*, 2000; Fern *et al.*, 1995; Lu *et al.*, 1994; Wolfe *et al.*, 2002), and protein tyrosine kinases (Arnoult *et al.*, 1997; Morikawa *et al.*, 1998), suggesting activation of many pathways can alter T-type currents (Table I). However, it should be noted that there is a great deal of heterogeneity in the responses of T-type channels to many of these hormones and neurotransmitters. For example, T-type currents may be increased, decreased, or not affected by the beta-adrenergic receptor agonists norephinephrine and isoproterenol (Table I). Similarly, GABA, substance P, and serotonin can either attenuate or potentiate T-type currents recorded in a variety of neurons (Table I). Although the explanation for these heterogeneous responses is not known, it is possible that some of the differences in responses to hormones and neurotransmitters may reflect diversity in the molecular identity of LVA alpha1 pore-forming subunits. As sequence analyses of alpha1G-, alpha1H-, and alpha1I-predicted proteins reveal a wide number of differences in the presence of consensus sites for phosphorylation and binding of G proteins (see later), it is plausable that channels formed by different LVA alpha1 subunits may be differentially affected by exogenous and endogenous molecules.

At this time, it is unclear if T-type channel modulation by hormones and neurotransmitters is a common physiological event. However, multiple lines of evidence suggest that the presence of intracellular molecules can modulate the function and/or expression of T-type currents in the absence of exogenous neurotransmitters or hormones. Strong depolarization or high-frequency stimulation enhances T-type currents (Alvarez *et al.*, 1996; Arnoult *et al.*, 1997; Ganitkevich and Isenberg, 1991; Publicover *et al.*, 1995). Manipulation of G protein activation prevents this potentiation in some cells (Alvarez *et al.*, 1996), suggesting that modulatory intracellular molecules can potentiate T-type currents in the absence of exogenous factors. Manipulation of kinase levels can also directly affect T-type currents (Table I; see later). For example, tyrosine kinase inhibitors increase T-type currents in the absence of exogenous molecules, suggesting that tyrosine kinase inhibits basal T-type channel activity (Arnoult *et al.*, 1997).

Table I. Many Extracellular and Intracellular Molecules Modulate T-Type Currents

Ligand/Receptor	Second messenger(s)	Tissue or recombinant channel subtype	T-type current (I_T) response	Reference
n/a[a]	Calcium/calmodulin-dependent protein kinase II (γ_c)	Alpha1H; not alpha1G	Increases I_T	Barrett *et al.*, 2000; Lu *et al.*, 1994; Wolfe *et al.*, 2002
n/a	Guanosine 5′-*O*-(3-thio) triphosphate	Rat dorsal root ganglion neurons	Low concentrations increase I_T density; high concentrations decrease I_T	Scott *et al.*, 1990
		Rat nodose ganglion neurons	Attenuates I_T	Gross *et al.*, 1990
n/a	Protein kinase A	Bass horizontal cells	Attenuates I_T	Pfeiffer-Linn and Lasater, 1998
n/a	Protein kinase C	Rat dorsal root ganglion neurons	Attenuates I_T	Schroeder *et al.*, 1990
		Bass horizontal cells		Pfeiffer-Linn and Lasater, 1998
		Rat ventricular myocytes	Increases I_T	Furukawa *et al.*, 1992
		Canine ventricular myocytes and Purkinje cells	Attenuates I_T	Tseng and Boyden, 1991
n/a	Protein tyrosine kinase	NG108-15 neuroblastoma cells	Maintains or increases I_T	Morikawa *et al.*, 1998
n/a	Protein tyrosine kinase	Mouse spermogenic cells	Attenuates I_T	Arnoult *et al.*, 1997
n/a	Tyrosine phosphatase	Mouse spermogenic cells	Maintains or increase I_T	Arnoult *et al.*, 1997
Acetylcholine		Hen granulosa cells	Attenuates I_T	Wan *et al.*, 1996
		Guinea pig CA3 hippocampal neurons	Increases I_T	Fisher and Johnston, 1990
		Rat lacunosum molecular hippocampal neurons	Increases I_T	Fraser and MacVicar, 1991
Acetylcholine/m3, m5 muscarinic receptor	cAMP, protein kinase A	3T3 fibroblasts	Increases I_T amplitude	Pemberton *et al.*, 2000
Adrenocorticotrophic hormone		Rat zona fasciculata cells	Increases I_T	Barbara and Takeda, 1995
Anandamide (endocannabinoid)	Direct effect	Alpha1H > alpha1I > alpha1G NG198-15 cells	Attenuates I_T	Chemin *et al.*, 2001c
Aldosterone	Induces T-type expression	H295 human adrenocarcinoma cell line	Increases I_T	Lesouhaitier *et al.*, 2001
Angiotensin II/type I receptor	G_i	Adrenal glomerulosa cells	Increases I_T	Lu *et al.*, 1996
Angiotensin II/type II receptor	G protein; phosphotyrosine phosphatase	NG108-15 cells	Attenuates I_T	Buisson *et al.*, 1992, 1995
Angiotensin II	Calmodulin-dependent protein kinase II	Adrenal glomerulosa cells	Increases I_T	Barrett *et al.*, 2000; Cohen *et al.*, 1988; McCarthy *et al.*, 1993
		Rat adrenal glomerulosa cells	No effect	Drolet *et al.*, 1997
	Protein kinase C	Adrenal glomerulosa cells	Attenuates I_T	Rossier *et al.*, 1995, 1998
Arachidonic acid		Alpha1H	Attenuates I_T	Zhang *et al.*, 2000
Atrial natriuretic factor	cGMP	Bovine adrenal glomerulosa cells	Attenuates I_T	Barrrett *et al.*, 1991a,b
ATP		Frog atrial cardiomyocyte	Increases I_T	Alvarez and Vassort, 1992

Table I. (*Continued*)

Ligand/Receptor	Second messenger(s)	Tissue or recombinant channel subtype	T-type current (I_T) response	Reference
Baclofen		Rat lacunosum molecular hippocampal neurons	Attenuates I_T	Fraser and MacVicar, 1991
		Rat dorsal root ganglion neurons	Increases I_T (low concentrations); attenuates I_T (high concentrations)	Scott *et al.*, 1990
Bradykinin		ND7-23 dorsal root ganglion cell line	Attenuates I_T	Kobrinsky *et al.*, 1994
L-cysteine		Rat dorsal root ganglion neurons; alpha1H	Increases I_T	Todorovic *et al.*, 2001
Dopamine	Beta/gamma G-protein; PKA	Adrenal glomerulosa	Attenuates I_T	Drolet *et al.*, 1997
		Chick dorsal root ganglion neurons	Attenuates I_T	Marchetti *et al.*, 1986
		Rat pituitary melanotrophs	Attenuates I_T	Keji *et al.*, 1992
		Rat pituitary pars intermedia	Attenuates I_T	Nussinovitch and Kleinhaus, 1992
Dopamine/D1 receptors	PKA, PKC	Bass horizontal cells	Attenuates I_T	Pfeiffer-Linn and Lasater, 1998
Dopamine/D2 receptors	G_o alpha	Rat anterior pituitary	Attenuates I_T	Lledo *et al.*, 1990
DTNB (oxidizing agent)		Rat dorsal root ganglion neurons; alpha1H	Attenuates I_T	Todorovic *et al.*, 2001
DTT (reducing agent)		Rat dorsal root ganglion neurons; alpha1H	Increases I_T	Todorovic *et al.*, 2001
Endothelin	PKC	Rat ventricular myocytes	Increases I_T	Furukawa *et al.*, 1992
		Guinea pig portal vein smooth muscle cells	Increases I_T	Inoue *et al.*, 1990
Enkephalin		NG108-15 neuroblastoma cells	Attenuates I_T	Kasai *et al.*, 1992
Epinephrine	PKA	Newt olfactory receptor cells	Attenuates I_T	Kawai *et al.*, 1999
Erythropoietin		SK-N-MC neuroblastoma cells	Increases I_T	Assandri *et al.*, 1999
Estradiol		Spermatogenic cells	Attenuates I_T	Espinosa *et al.*, 2000
Estrogen	Requires protein synthesis	GH3 anterior pituitary cells	Increases I_T density	Ritchie, 1993
Farnesol		Retinal Muller cells	Attenuates I_T	Bringmann *et al.*, 2000
$GABA_B$	G proteins	Dorsal root ganglia	Low concentrations increases I_T; high concerntrations attenuates I_T	Dolphin *et al.*, 1989; Scott and Dolphin, 1990
Glutathione, reduced		Alpha1H	Enhances I_T	Fearon *et al.*, 2000
cGMP		Newt olfactory receptor cells	Enhances I_T	Kawai and Miyachi, 2001b
Growth hormone-producing tumor		Adult rat atrial myocytes	Increases I_T density	Xu and Best, 1990
Growth hormone-releasing hormone	cAMP/protein kinase A	Pituitary somatotrophs	Increases I_T	Chen *et al.*, 2000
Hydrogen ions		Alpha1H	Increases I_T	Delisle and Satin, 2000
Hypoxia		Alpha1H > alpha1I	Attenuates I_T	Fearon *et al.*, 2000
Insulin-like growth factor		Atrial myocytes	Increases I_T	Chen and Best, 1996

Table I. (*Continued*)

Ligand/Receptor	Second messenger(s)	Tissue or recombinant channel subtype	T-type current (I_T) response	Reference
Isoproterenol		Frog atrial myocytes	Increases I_T	Alvarez *et al.*, 1996
		Guinea pig ventricular myocytes	Increases I_T	Mitra and Morad, 1986; Zhang *et al.*, 2002
		Canine atrial myotyes	No effect	Bean, 1985
		Rabbit sinoatrial cells	No effect	Hagiwara *et al.*, 1988
		Canine cardiac Purkinje cells	No effect	Hirano *et al.*, 1989
		Guinea pig ventricular myocytes	No effect	Tytgat *et al.*, 1988
		Guinea pig CA3 hippocampal neurons	No effect	Fisher and Johnston, 1990
Morphine		N1E115 neuroblastoma cells	Attenuates I_T	Yang *et al.*, 2000
Neurotensin		Rat nucleaus basalis neurons	Attenuates I_T	Margeta-Mitrovic *et al.*, 1997
		Trigeminal ganglion neurons	No effect	Borgland *et al.*, 2001
Nociceptin/kappa3 opioid receptor		Dorsal root ganglion neurons	Attenuates I_T	Abdulla and Smith, 1997
Norepinephrine		Rat portal vein myocytes	Increases I_T	Pacaud *et al.*, 1987
		Chick sensory neurons	Attenuates I_T	Bean, 1989
		Canine Purkinje cells	Variable response	Tseng and Boyden, 2002
p21ras		Chick dorsal root ganglion neurons	Increases I_T	Hahnel *et al.*, 1992
Serotonin		*Xenopus* larvae sensory neurons	Attenuates I_T	Sun and Dale, 1998
		Rat spinal motoneurons	Increases I_T	Berger and Takahashi, 1990
		Rat hippocampal lacunosum molecular neurons	Increases I_T	Fraser and MacVicar, 1991
Serotonin/5-HT(7) receptor	$G_s$alpha cAMP PKA	Rat adrenal glomerulosa cells	Increases I_T	Lenglet *et al.*, 2002
Somatostatin		Rat somatotrophs	Attenuates I_T	Buisson *et al.*, 1995
		neuroblastoma cells	No effect	Bean, 1989
Substance P		Rat dorsal horn neurons	Increases and attenuates I_T	Ryu and Randic, 1990
		Rat nucleus basalis neurons	Attenuates I_T	Margeta-Mitrovic *et al.*, 1997
Vasoactive intestinal polypeptide		Rat zona fasciculata cells	Increases I_T	Barbara and Takeda, 1995

Note. The sensitivities of T-type channels formed by recombinant LVA alpha1 subunit proteins are indicated when available.
[a] n/a, not available.

Finally, the biophysical properties of recombinant T-type channels differ from those of endogenous T-type currents (Williams *et al.*, 1999), and the biophysical properties of recombinant alpha1I channels are markedly different when translated in different expression systems (Chemin *et al.*, 2001b; Lee *et al.*, 1999a; McRory *et al.*, 2001), implying that differences in the intracellular environment can influence T-type currents.

Functional Evidence That T-Type Channels Are Regulated by Second Messengers

G Proteins

As described in the preceding sections, a number of neurotransmitters and hormones activate G-protein-coupled receptors to either attenuate or potentiate T-type

currents (Table I). Although receptor stimulation can lead to activation of a variety of kinases that may phosphorylate T-type channels directly (Table I and see later), there is some evidence that T-type channels may be directly modulated by G proteins. GTPγS activates all G proteins, and release of low concentrations of GTPγS from a caged precursor potentiates T-type currents in dorsal root ganglion neurons (Scott *et al.*, 1990). In contrast, high concentrations of GTPγS attenuate T-type currents (Kobrinsky *et al.*, 1994; Scott *et al.*, 1990), consistent with association of G proteins with T-type channels. This effect is inhibited by pertussis toxin, suggesting G_o/G_i may bind to T-type channels. Similarly, GTPγS inhibits some T-type currents in rat nodose ganglia in a pertussis-sensitive manner (Gross *et al.*, 1990), and both G_i and G_s have been suggested to modulate T-type channels in bullfrog atrial cells (Alvarez *et al.*, 1996). Furthermore, antibodies against $G_o\alpha$ reduce the ability of dopamine to attenuate T-type currents in anterior pituitary cells (Lledo *et al.*, 1992), and antibodies against $G_i\alpha$ reduce T-type current potentiation by angiotensin II in adrenal glomerulosa cells (Lu *et al.*, 1996). Finally, it has been suggested that G$\beta\gamma$ may directly bind to T-type channels in rat adrenal glomerulosa to inhibit T-type channel activity (Drolet *et al.*, 1997). Although alpha1G and alpha1I LVA alpha1 subunits do not have consensus binding sites in the II–III intracellular loop for binding G$\beta\gamma$ (see Yunker and McEnery, 2003), this sequence (QXXER; Chen *et al.*, 1995) is found in cloned alpha1H sequences (Williams *et al.*, 1999), suggesting that channels formed by alpha1H, but not alpha1G or alpha1I, may be modulated by G proteins. Additional studies are needed to determine the molecular identity of T-type channels affected by manipulation of G proteins, and if either Gα or G$\beta\gamma$ can bind to LVA alpha1 subunits to modulate T-type channel activity.

Phosphorylation

Phosphorylation is an important mechanism for regulation of HVAs, as members of the Ca_v1 group of HVAs, such as alpha1S and alpha1C, are directly regulated by phosphorylation. In contrast, members of the HVA Ca_v2 group, such as alpha1A and alpha1B, directly bind G proteins, which themselves could be sites for phosphorylation (reviewed in Catterall, 2000). Numerous studies of HVA alpha1 subunits demonstrate the presence of multiple phosphorylation consensus sites (De Jongh *et al.*, 1991; Hell *et al.*, 1994). Furthermore, as differential phosphorylation of unique splice variants can result in marked alterations in the biophysical properties of the channel (Hell *et al.*, 1993, 1994; Lai *et al.*, 1990), phosphorylation of VDCCs may be an important mechanism for channel regulation.

Accumulating evidence suggests that channels formed by LVA alpha1 subunits may be regulated by phosphorylation. Sequence analyses of cloned LVA alpha1 subunits reveal that LVA alphal subunits harbor many consensus sites for a variety of kinases. For example, at least eight phosphorylation sites for cAMP- and cGMP-dependent protein kinases have been identified in predicted murine alpha1G protein (Klugbauer *et al.*, 1999), and over 30 phosphorylation sites for protein kinase A, protein kinase C, tyrosine kinase, and casein kinase II (CKII) have been identified in predicted human alpha1G protein (Mittman *et al.*, 1999a). The other LVA alpha1 subunits also harbor consensus phosphorylation sites for kinases, as human alpha1I protein contains over 20 potential phosphorylation sites for the aforementioned kinases (Lee *et al.*, 1999a; Mittman *et al.*, 1999b). In contrast, human alpha1H protein (AF051946; Cribbs *et al.*, 1998) contains over 40 consensus sites for phosphorylation by protein kinase A (R/K-R/K-X-S/T or R/K-R/K-X-X-S/T; reviewed in Lee *et al.*, 1999a), protein kinase C (S/T-X-R/K), and tyrosine kinase (R/X-X-X-X-D-X-X-Y). Interestingly, analysis of predicted alpha1G protein reveals that at least five of the consensus phosphorylation sites for PKA, PKC, and CKII lie in regions subjected to alternative splicing (Mittman *et al.*, 1999a). This observation implies that presentation of novel phosphorylation sites by alternative splicing may yield channels with markedly different biophysical properties or sensitivities to endogenous modulators such as neurotransmitters and hormones (Table I).

Although some HVA subfamilies such as L-type channels are primarily regulated through direct phosphorylation by second messenger-activated kinase pathways (reviewed in Catterall, 2000), it is unclear if such mechanisms are important regulators of endogenous channels formed by alpha1G, alpha1H, and alpha1I. Unlike HVA currents, neither endogenous nor recombinant T-type channels display metabolic rundown (Carbone and Lux, 1984; Hagiwara *et al.*, 1975). Furthermore, the catalytic subunit of cAMP-dependent protein kinase does not alter T-type currents (Gross *et al.*, 1990), suggesting that T-type channels are not dependent on cAMP-dependent protein kinase-induced phosphorylation for maintenance of activity. In contrast, a large number of papers demonstrates that protein kinase A, protein kinase C, and tyrosine kinase affect T-type currents in a variety of cell types (Table I), and at least some neurotransmitters and hormones alter the amplitude of T-type currents through activation of kinases (Table I). Although the action of

hormones and neurotransmitters on T-type current may be influenced by both the cell type and the molecular identity of the T-type channel, activation of protein kinase A frequently attenuates T-type current amplitudes, although potentiation of T-type currents is also observed (Table I). Similarly, activation of either protein kinase C or tyrosine kinase can increase or decrease T-type current amplitudes (Table I). Finally, as phosphorylation of specific amino acid residues can be important for regulating binding of SNARE proteins and G proteins (reviewed in Catterall, 2000), phosphorylation of T-type channels may alter interactions of LVA alpha1 subunits with other molecules. Alternatively, phosphorylation may directly alter the electrophysiological properties of the channel, resulting in modulation of T-type currents by neurotransmitters and hormones.

Calcium

Calcium can regulate expression and biophysical properties of VDCCs. For example, calcium can bind to EF hand regions in the carboxyl tail of some HVAs to influence inactivation and facilitation (Babitch, 1990). Although cloned LVA alpha1 subunits have been reported to lack calcium-binding motifs (Perez-Reyes, 1998), recombinant alpha1H, but not alpha1G or alpha1I, channels exhibit slower activation and inactivation in the presence of 10-mM calcium compared to barium, suggesting that alpha1H may be uniquely modulated by calcium (Klöckner *et al.*, 1999). Interestingly, alpha1H is highly expressed in the adrenal gland (Schrier *et al.*, 2001), and increasing concentrations of extracellular calcium potentiate T-type currents in adrenal glomerulosa cells (Lu *et al.*, 1994). This potentiation depends on activation of calcium/calmodulin-dependent protein kinase II (Barrett *et al.*, 2000; Fern *et al.*, 1995). KN-62, a specific organic inhibitor of calcium/calmodulin kinase II, prevents potentiation of T-type currents by calcium, potentially by competing with calmodulin at its binding site (Lu *et al.*, 1994). Furthermore, recombinant calmodulin kinase II gamma$_c$ increases T-type currents conducted by recombinant alpha1H, but not alpha1G (Wolfe *et al.*, 2002). These data suggest only some LVA alpha1 subunits have a consensus site for phosphorylation by this kinase, thus providing a tentative explanation for differential regulation of recombinant LVA alpha1 channels by calcium.

Antagonists of T-Type Channels

Members of over 15 classes of drugs have been reported to reduce endogenous T-type currents in situ. Although some of the classes (inorganic divalent and trivalent cations and small peptides) are not useful therapeutic agents, members of many other classes (dihydropyridines, succinimide derivatives, diphenylbutylpiperidine derivatives, benzodiazepines, and anesthetics) are currently used to treat a variety of neural and cardiovascular diseases. Whereas none of the drugs discussed later are absolutely selective for T-type channels, some of them allow discrimination between T-type and HVA currents within a range of concentrations. However, for every class of drugs investigated, almost all of them can also have effects on ion channels and/or enzymes besides VDCCs, thus requiring caution when interpreting in vivo or in situ pharmacological data. Although most of the drug classes do not allow differentiation between T-type channels formed by different LVA alpha1 subunits, use of many of these drugs have permitted insights into the physiological significance of T-type channels in both normal and diseased cells (reviewed in Yunker and McEnery, 2003). It is anticipated that the future generation and characterization of specific T-type channel blockers will be crucial for both the further study of T-type channels and treatment of a number of neural and cardiovascular diseases.

Polyvalent Cations

Inorganic divalent and trivalent cations were some of the first chemicals used to block T-type currents (Burlhis and Aghajanian, 1987; Hagiwara *et al.*, 1975; Llinás and Yarom, 1981, 1982; Narahashi *et al.*, 1987). Comparison of the concentrations of drugs necessary to inhibit half-maximal T-type currents suggested heterogeneity in endogenous T-type channels, as different rank orders of inhibition were observed in a tissue-dependent manner. The inhibition profile obtained from hypothalamic neurons (Akaike *et al.*, 1989b), hippocampal neurons (Takahashi and Akaike, 1991), thyroid C cell line (Enyeart *et al.*, 1992), dorsal root ganglia (Todorovic and Lingle, 1998), and smooth muscle cells (Akaike *et al.*, 1989a) ($La^{3+} > Zn^{2+} > Cd^{2+} > Ni^{2+} > Co^{2+}$) was different than that recorded from skeletal muscle cells ($La^{3+} > Ni^{2+} > Cd^{2+} > Co^{2+}$) (Satoh *et al.*, 1991), amygdala neurons ($La^{3+} > Ni^{2+} > Zn^{2+} = Cd^{2+}$) (Kaneda and Akaike, 1989), or cortical neurons ($La^{3+} > Cd^{2+} > Zn^{2+} > Ni^{2+}$) (Ye and Akaike, 1993) (Table II). Additional support for T-type channel heterogeneity comes from comparison of the concentration of individual polyvalent cations necessary to block T-type channels. For example, whereas some T-type channels are sensitive to nickel or cadmium, T-type channels from other brain regions can require over 10-fold greater cation concentration to attenuate T-type currents

Table II. Comparison of the Concentration of Polyvalent Cations Necessary to Inhibit 50% of T-Type or High Voltage-Activated (HVA)-Type Currents Recorded From Endogenous and Recombinant Calcium Channels in the Presence of Varying Concentrations of Calcium or Barium as the Charge Carrier

	T-type										
	Mouse neuroblastoma (50 mM Ba^{2+})	Rat hypothalamus (10 mM Ca^{2+})	Rat amygdala (10 mM Ca^{2+})	Rat hippocampus (10 mM Ca^{2+})	Rat frontal cortex (2 mM Ca^{2+})	Rat aorta smooth muscle (20 mM Ca^{2+})	Chick skeletal muscle (50 mM Ba^{2+})	Guinea pig atrial myocytes (5 mM Ca^{2+})	Recombinant LVA alpha1 channels		
									Alpha1G	Alpha1H	Alpha 1I
La^{3+}	1.5	0.7	1.8	1	1	0.6	14.7	n/a	n/a	n/a	n/a
Zn^{2+}	n/a	100	650	20	84	30	n/a	n/a	n/a	n/a	n/a
Cd^{2+}	160	300	650	80	15	400	51.2	66	162 (Ba^{2+})[a]	218[b]	n/a
									658 (Ca^{2+})[a]	n/a	n/a
Ni^{2+}	47	600	30	230	260	600	20.7	23	167[c]	5.7[c]	87[c]
									250[d]	12[d]	216[d]
									470 (20 mM Ba^{2+})[a]	10[b]	n/a
									1130 (20 mM Ca^{2+})[a]	n/a	n/a
Co^{2+}	160	3000	n/a	760	n/a	n/a	912	n/a	n/a	n/a	n/a
	HVA-type										
La^{3+}	0.9	n/a	n/a	n/a	1.2	0.08	29	n/a	n/a	n/a	n/a
Zn^{2+}	n/a	n/a	n/a	n/a	100	30	n/a	n/a	n/a	n/a	n/a
Cd^{2+}	7	n/a	n/a	n/a	3.8	6	7	n/a	n/a	n/a	n/a
Ni^{2+}	280	n/a	n/a	n/a	440	10	280	n/a	n/a	n/a	n/a
Co^{2+}	560	n/a	n/a	n/a	n/a	n/a	560	n/a	n/a	n/a	n/a
	Narahashi *et al.*, 1987	Akaike *et al.*, 1989b	Kaneda and Akaike, 1989	Takahashi and Akaike, 1991	Ye and Akaike 1993	Akaike *et al.*, 1989a	Satoh *et al.*, 1991	Perchenet *et al.*, 2000			

Note. All data are presented as micromolar concentrations. It should be noted that comparison of T-type channel blockade by polyvalent cations in different tissues is complicated by the recording conditions used. Some polyvalent cations have a wide range of kinetic effects on VDCC (Doehring and Zamponi; Lacinová *et al.*, 2000; Zamponi *et al.*, 1996, 2003) and both the concentration (Akaike *et al.*, 1989a) and the molecular identity of the charge carrier (Lacinová *et al.*, 2000) can affect the concentration–response relationship.

[a]HEK-293 cells, 20 mM Ba^{2+} or Ca^{2+} (Lacinová *et al.*, 2000).

[b]HEK-293 cells, 5 mM Ca^{2+} (Perchenet *et al.*, 2000).

[c]*Xenopus* oocytes, 10 mM Ba^{2+} (Lee *et al.*, 1999b).

[d]HEK-293 cells, 10 mM Ba^{2+} (Lee *et al.*, 1999b).

(reviewed in Huguenard, 1996) (Table II), suggesting the molecular identity of the T-type channel and/or presence of modulating molecules greatly influences channel pharmacology.

Most polyvalent cations have limited use as T-type channel antagonists. Many cations attenuate calcium currents conducted by both T-type and HVAs (Burlhis and Aghajanian, 1987; Coulter *et al.*, 1989a; Narahashi *et al.*, 1987; Pfrieger *et al.*, 1992; Satoh *et al.*, 1991). Comparison of the pharmacological profiles of polyvalent cations reveals that some polyvalent cations have similar concentrations for half-maximal blockade of T-type and HVA currents (Akaike *et al.*, 1989a; Narahashi *et al.*, 1987; Ye and Akaike, 1993) (Table II). In contrast, other cations are able to differentiate between LVAs and HVAs in a tissue dependent manner. For example, 50-μM cadmium abolishes N- and L-type currents recorded from dorsal root ganglia, but only reduces T-type currents by $\sim$50% (Nowycky *et al.*, 1985). In contrast, 100-μM cadmium abolishes LVA and HVA currents in cultured rat hippocampal neurons (Yaari *et al.*, 1987). Taken together, these data suggest that a lack of effect does not equate to the absence of T-type channels, and the presence of inhibition does not guarantee that the current in question is conducted by T-type channels.

Similar to other polyvalent cations, nickel can attenuate both T- and L-type currents depending on the tissue examined (Table II). However, unlike responses to other polyvalent cations, T-type currents are usually more sensitive to nickel than currents conducted by HVAs (Table II). For example, approximately 80% of T-type currents in the lateral geniculate nucleus of the thalamus are attenuated by 500-μM nickel, but L-type currents are only reduced by 12% (Suzuki and Rogawski, 1989). Variability in the nickel sensitivity of endogenous T-type channels is observed (Table II), and studies of recombinant T-type channels demonstrate that nickel is over ten fold more potent at inhibiting T-type currents conducted by alpha1H than currents conducted by alpha1G or alpha1I in two expression systems (*Xenopus* oocytes and HEK-293 cells) (Lee *et al.*, 1999b) (Table II). Interesting, the nickel sensitivity of currents conducted by alpha1I recombinant channels is influenced by the expression system (Lee *et al.*, 1999b), implying factors other than the molecular identity of the pore-forming subunit may modulate T-type channel sensitivity to polyvalent cations. Additional studies are needed to prove that nickel-sensitive endogenous T-type channels are composed of alpha1H, and to determine if heterogeneity in T-type channel responsiveness to polyvalent cations solely reflects differences in the molecular identity of the alpha1 subunit.

Dihydropyridines

The dihydropyridine class of small organic molecules has been paramount in the study of L-type channels and treatment of cardiovascular diseases (reviewed in Triggle, 1998). T-type channels were first believed to be insensitive to activation by dihydropyridine agonists (Fox *et al.*, 1987; reviewed in Akaike *et al.*, 1989a; Ertel *et al.*, 1997; Formenti *et al.*, 1993). However, the dihydropyridine agonist Bay K 8644 reduces T-type currents in rat hypothalamic neurons (Akaike *et al.*, 1989b) and avian dorsal root ganglia (Boll and Lux, 1985), suggesting this drug is not specific for L-type channels.

In contrast to many early studies that suggested neural and cardiac T-type currents were insensitive to organic calcium antagonists (Boll and Lux, 1985; Fedulova *et al.*, 1985; Fox *et al.*, 1987; Nilius *et al.*, 1985; reviewed in Akaike *et al.*, 1989a), later studies demonstrated that endogenous T-type channels are antagonized by dihydropyridines (Table III). Comparison of rank order values for inhibition of T-type currents in hypothalamic and aortic smooth muscle cells demonstrates that some dihydropyridines are more potent than others (nicardipine $>$ nifedipine $>$ nimodipine) (Akaike *et al.*, 1989a,b) (Table III). Similar to the pharmacological profile of polyvalent cations, T-type channel sensitivity to dihydropyridines is not straight forward, as T-type channel responsiveness to individual agents appears dependent on the tissue examined, potentially indicating channel heterogeneity. For example, nifedipine does not antagonize T-type currents in chick skeletal muscle (Satoh *et al.*, 1991), and nitrendipine, niludipine, and nimodipine do not affect T-type currents in dorsal root ganglia neurons (Kostyuk and Shirokov, 1989), although these agents can attenuate T-type currents in other neural tissues (Akaike *et al.*, 1989b; Takahashi and Akaike, 1991) (Table III). Variability in endogenous T-type channel sensitivity to dihydropyridines is also seen within the same tissue. Whereas some investigators report that nimodipine is ineffective in reducing T-type currents in dorsal root ganglia (Formenti *et al.*, 1993), nimodipine can increase, decrease, or have no effect on T-type currents recorded from dorsal root ganglia (Kostyuk and Shirokov, 1989).

The most obvious difficulty with dihydropyridines is that both T- and L-type currents can be blocked by a single concentration of a given dihydropyridine. Many tissues coexpress functional T- and L-type channels and dihydropyridines including CD392 (Hirakawa *et al.*, 1994), efondipine (Tanaka and Shigenobu, 2002), elgodipine (Galan *et al.*, 1998), flunarizine (Tytgat *et al.*, 1996), nifedipine (Hirakawa *et al.*, 1994), niguldipine (Romanin

Table III. Many Classes of Drugs Attenuate T-Type Currents[a]

Pharmacological agent	Tissue	IC50 (μM)		Cation concentration	Reference
		T-type	HVA-type		
I. *Dihydropyridines*					
Amlodipine	Atrial myocytes	5.7	0.5	5 mM Ca^{2+}	Perchenet *et al.*, 2000
	Heterologous expression	31 (alpha1H)	n/a	5 mM Ca^{2+}	Perchenet *et al.*, 2000
CD832	Aortic smooth muscle	0.3	1.1 (L-type)	20 mM Ca^{2+}	Hirakawa *et al.*, 1994
Efondipine	Ventricular myocytes	10	0.1 (L-type)	5.4 mM Ca^{2+} (T-type); 1.8 mM Ca^{2+} (L-type)	Masumiya *et al.*, 1998
Elgodipine	Portal vein myocytes	32	2.3 (L-type)	5 mM Ba^{2+}	Lepretre *et al.*, 1994
	Neonatal ventricular myocytes	2.2	0.3	5.4 mM Ca^{2+}	Galan *et al.*, 1998
Felodipine	Thyroid carcinoma cell line	0.2	n/a	10 mM Ca^{2+}	Enyeart *et al.*, 1990
	Adrenal zona fasciculata	3.8	n/a	10 mM Ca^{2+}	Enyeart *et al.*, 1993
Nicardipine	Amygdala	2.5	n/a	10 mM Ca^{2+}	Kaneda and Akaike, 1989
	Hippocampus	1.6	n/a	10 mM Ca^{2+}	Takahashi and Akaike, 1991
	Hypothalamus	3.5	n/a	10 mM Ca^{2+}	Akaike *et al.*, 1989b
	Aortic smooth muscle	0.8	0.2 (L-type)	20 mM Ca^{2+}	Akaike *et al.*, 1989a
		0.6	0.1 (L-type)	20 mM Ca^{2+}	Kuga *et al.*, 1990
Nifedipine	Hypothalamus	5	n/a	10 mM Ca^{2+}	Akaike *et al.*, 1989b
	GH3 pituitary	50	n/a	10 mM Ca^{2+}	Herrington and Lingle, 1992
	Thalamus	2.6	n/a	2 mM Ca^{2+}	Tarasenko *et al.*, 1997
	Aortic smooth muscle	0.04	2.7 (L-type)	20 mM Ca^{2+}	Hirakawa *et al.*, 1994
	Skeletal muscle	No effect	3.3	50 mM Ba^{2+}	Satoh *et al.*, 1991
	Heterologous expression	100 (alpha 1G)	0.2 (alpha 1C)	5 mM Ba^{2+}	Kumar *et al.*, 2002
Niguldipine	Aortic smooth muscle	3	Ran down	20 mM Ca^{2+}	Akaike *et al.*, 1989a
	Atrial myocytes	0.18	n/a	2 mM Ca^{2+}	Romanin *et al.*, 1992
Nimodipine	Hypothalamus	5	n/a	10 mM Ca^{2+}	Akaike *et al.*, 1989b
	Adrenal zona fasciculata	3.5	n/a	10 mM Ca^{2+}	Enyeart *et al.*, 1993
Oxodipine	Ventricular myocytes	0.41	0.24	5.4 mM Ca^{2+}	Galan *et al.*, 1998
PN200-110	Spermatogenic cells	0.040	n/a	10 mM Ca^{2+}	Arnoult *et al.*, 1998
PPK-5	Heterologous expression	~2.5 (alpha 1G)	~70 (alpha 1C)	5 mM Ba^{2+}	Kumar *et al.*, 2002
II. *Succinimide derivatives*					
Alpha-methyl-alpha-phenyl-succinimide (MPS) (50–200 μM, therapeutic plasma range; reviewed in Coulter *et al.*, 1989b)	Dorsal root ganglia	190	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
		170	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	Ventrobasal thalamic relay neurons	1100	n/a	1 mM Ca^{2+}	Coulter *et al.*, 1990
	Heterologous expression	1700 (alpha 1G)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
		1950 (alpha 1G)	n/a	5 mM Ca^{2+}	Gomora *et al.*, 2001
		2300 (alpha 1H)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
		3000 (alpha 1H)	n/a	5 mM Ca^{2+}	Gomora *et al.*, 2001
		1820 (alpha 1I)	n/a	5 mM Ca^{2+}	Gomora *et al.*, 2001
Ethosuximide 300–700 μM, therapeutic plasma range; reviewed in Coulter *et al.*, 1989b	Ventrobasal thalamic relay neurons	200	n/a	1 mM Ca^{2+}	Coulter *et al.*, 1990
	Dorsal root ganglia	7	15 (L-type)	1.8 mM Ca^{2+}	Kostyuk *et al.*, 1992
		23700	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	Heterologous expression	14000 (alpha 1G)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
		12000 (alpha 1G)	n/a	5 mM Ca^{2+}	Gomora *et al.*, 2001
		10000 (alpha 1G)	n/a	10 mM Ba^{2+}	Gomora *et al.*, 2001
		22000 (alpha 1H)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
Methsuximide (50–200 μM, therapeutic plasma range; reviewed in Coulter *et al.*, 1989b)	Ventrobasal thalamic relay neurons	1100	n/a	1 mM Ca^{2+}	Coulter *et al.*, 1990
III. *Alkyl-substituted Thiobutyrolactones* (200–400 μM; reviewed in Gross *et al.*, 1997)					
Alpha-EMTBL	Dorsal root ganglia	75	300	5 mM Ca^{2+}	Gross *et al.*, 1997
Beta-EMTBL	Dorsal root ganglia	350	400	5 mM Ca^{2+}	Gross *et al.*, 1997

Table III. (*Continued*)

Pharmacological agent	Tissue	IC50 (μM) T-type	IC50 (μM) HVA-type	Cation concentration	Reference
IV. *Phenytoin* (4–8 μM; reviewed in Todorovic and Lingle, 1998)					
	Hippocampus	~100	n/a	10 mM Ca^{2+}	Yaari *et al.*, 1987
	Dorsal root ganglia	7.3	n/a	10 mM Ba^{2+}	Todorvic and Lingle, 1998
		7.8	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
	Heterologous expression	74 (alpha1G)	n/a	20 mM Ba^{2+}	Lacinová *et al.*, 2000
		140 (alpha1G)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
		8.3 (alpha1H)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
		192 (alpha1H)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
V. *Diphenylbutylpiperidine (DPBP) derivatives*					
Flunarizine	Hippocampus	1.2	n/a	10 mM Ca^{2+}	Takahashi and Akaike, 1991
	Hypothalamus	0.7	n/a	10 mM Ca^{2+}	Akaike *et al.*, 1989b
	Amygdala	1.1	n/a	10 mM Ca^{2+}	Kaneda and Akaike, 1989
	Thyroid carcinoma	10	n/a	10 mM Ca^{2+}	Enyeart *et al.*, 1992
	Aortic smooth muscle	0.2	0.1 (L-type)	20 mM Ca^{2+}	Akaike *et al.*, 1989a
		0.1	0.1 (L-type)	20 mM Ca^{2+}	Kuga *et al.*, 1990
	Ventricular myocytes	4.6	3.3–5.2 (L-type)	1.8 or 5.4 mM Ca^{2+}	Tytgat *et al.*, 1996
	Heterologous expression	0.53 (alpha1G)	n/a	2 mM Ca^{2+} or,	Santi *et al.*, 2002
		3.5 (alpha1H)		2 mM Ba^{2+}	
		0.84 (alpha1I)			
Penfluridol	Adrenal zona fasciculata	0.3	n/a	10 mM Ca^{2+}	Enyeart *et al.*, 1993
	Thyroid carcinoma	0.25	0.5	10 mM Ca^{2+}	Enyeart *et al.*, 1992
	Heterologous expression	0.11 (alpha1G)	n/a	2 mM Ca^{2+} or	Santi *et al.*, 2002
		0.07 (alpha1H)		2 mM Ba^{2+}	
		0.10 (alpha1I)			
Pimozide	Adrenal zona fasciculata	0.5	n/a	10 mM Ca^{2+}	Enyeart J.J. *et al.*, 1993
	Spermatogenic cells	0.46	n/a	10 mM Ca^{2+}	Arnoult *et al.*, 1998
	Heterologous expression	0.04 (alpha1G)	n/a	2 mM Ca^{2+} or	Santi *et al.*, 2002
		0.06 (alpha1H)		2 mM Ba^{2+}	
		0.04 (alpha1I)			
VI. *Non-DPBP* neuroleptics					
Chlorpromazine	N1E-115 neuroblastoma cells	15	15	50 mM Ba^{2+}	Ogata and Narahashi, 1990
Haloperidol	Heterologous expression	1.2 (alpha1G)	n/a	2 mM Ca^{2+} or	Santi *et al.*, 2002
		1.4 (alpha1H)		2 mM Ba^{2+}	
		1.3 (alpha1I)			
VII. *Anesthetics*					
Etomidate	Dorsal root ganglia	205	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	Heterologous expression	161 (alpha1G)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
Halothane	GH3 pituitary cells	1300	n/a	10 mM Ca^{2+}	Herrington and Lingle, 1992
(310 μM)	Dorsal root ganglia	655	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
		100	1500	10 mM Ca^{2+}	Takenoshita and Steinbach, 1991
Isoflurane	GH3 pituitary cells	1300	0.85	10 mM Ca^{2+}	Herrington and Lingle, 1992
(400 μM)	Dorsal root ganglia	303	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	Atrial myocytes	230	340 (L-type)	2 mM Ca^{2+}	Camara *et al.*, 2001
	Alpha1G	277	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
Ketamine	Dorsal root ganglia	2500	n/a	10 mM Ba^{2+}	Todorvic and Lingle, 1998
	Alpha1G	1200	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
Methoxyflurane	GH3 pituitary cells	1410	n/a	10 mM Ca^{2+}	Herrington and Lingle, 1992
Nitrous oxide	Dorsal root ganglia	45%	No effect (L-type)	5–10 mM Ba^{2+}	Todorovic *et al.*, 2001
(20–50%)	Heterologous expression	No effect (alpha1G)	n/a	5–10 mM Ba^{2+}	Todorovic *et al.*, 2001
		58% (alpha1H)	n/a	5–10 mM Ba^{2+}	Todorovic *et al.*, 2001
Octanol	Dorsal root ganglia	122	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	GH3 pituitary cells	244	n/a	10 mM Ca^{2+}	Herrington and Lingle, 1992
	Heterologous expression	160 (alpha1G)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
		219 (alpha1H)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
Propofol	Dorsal root ganglia	13	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	Heterologous expression	21 (alpha1G)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
		27 (alpha1H)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000

Table III. (*Continued*)

Pharmacological agent	Tissue	IC50 (μM) T-type	IC50 (μM) HVA-type	Cation concentration	Reference
VIII. *Barbiturates*					
Methohexital	Dorsal root ganglia	502	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
Pentobarbital (50 μM; reviewed in Todorovic and Lingle, 1998)	Dorsal root ganglia	334	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	GH3 cells	985	n/a	10 mM Ca^{2+}	Herrington and Lingle, 1992
	Heterologous expression	310 (alpha1G)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
		345 (alpha1H)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
Phenobarbital	Dorsal root ganglia	1700	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	Heterologous expression	1540 (alpha1G)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
Thiopental	Dorsal root ganglia	153	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	Heterologous expression	280 (alpha1G)	n/a	2 mM Ca^{2+}	Todorovic *et al.*, 2000
IX. *Neurosteroid agonists*					
(+)-ACN	Dorsal root ganglia	0.4	5–20	10 mM Ba^{2+}	Todorovic *et al.*, 1998
Alphaxalone (6–13 μM)	Dorsal root ganglia	1.3	n/a	10 mM Ba^{2+}	Todorovic *et al.*, 1998
(+)-ECN	Dorsal root ganglia	0.3	9	10 mM Ba^{2+}	Todorovic *et al.*, 1998
X. *Phenylalkylamines*					
D600	Amygdala	65	n/a	10 mM Ca^{2+}	Kaneda and Akaike, 1989
	Hippocampus	120	n/a	10 mM Ca^{2+}	Takahashi and Akaike, 1991
	Hypothalamus	50	n/a	10 mM Ca^{2+}	Akaike *et al.*, 1989b
	Cerebellar Purkinje cells	44	n/a	2.5 mM Ca^{2+}	Kaneda and Akaike, 1989
	GH3 pituitary cells	51	n/a	10 mM Ca^{2+}	Herrington and Lingle, 1992
	Skeletal muscle	No effect	9.2	50 mM Ba^{2+}	Satoh *et al.*, 1991
Verapamil	Aortic smooth muscle cells	70	0.9	20 mM Ca^{2+}	Akaike *et al.*, 1989a
		30	0.6	20 mM Ca^{2+}	Kuga *et al.*, 1990
	Spermatogenic cells	70	n/a	10 mM Ca^{2+}	Arnoult *et al.*, 1998
XI. *Benzodiazepines*					
Chlorodiazepoxide (1–5 μM; reviewed in Reuveny *et al.*, 1993)	N1E-115 neuroblastoma cells	311	398 (L-type)	50 mM Ba^{2+}	Reuveny *et al.*, 1993
Medazepam	Dorsal root ganglia	77	77	5 mM Ca^{2+}	Yang *et al.*, 1987
XII. *Amiloride*					
	Neuroblastoma	30	<20% block (L-type)	5 mM Ca^{2+}	Tang *et al.*, 1988
	Dorsal root ganglia	30	<20% block (L-type)	5 mM Ca^{2+}	Tang *et al.*, 1988
		76	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	GH3 pituitary cells	1550	n/a	10 mM Ca^{2+}	Herrington and Lingle, 1992
	Cardiac myocytes	233	n/a	5.4 mM Ca^{2+}	Tytgat *et al.*, 1996
	Skeletal muscle fiber	5.4	n/a	10 mM Ca^{2+}	Berthier *et al.*, 2002
	Spermatogenic cells	245	n/a	10 mM Ca^{2+}	Arnoult *et al.*, 1998
	Heterologous expression	38% block at 5000 (alpha 1G)	n/a	20 mM Ca^{2+} or Ba^{2+}	Lacinová *et al.*, 2000
		>5000 (alpha1H)	n/a	20 mM Ca^{2+} or Ba^{2+}	Lacinová *et al.*, 2000
		167 (alpha1H)	n/a	15 mM Ca^{2+} or Ba^{2+}	Williams *et al.*, 1999
XIII. *Miberfradil*					
	Cerebellar granule cells	1.1	n/a	2 mM Ca^{2+}	Randall and Tsien, 1997
	Cerebellar Purkinje cells	0.02	3 (P-type)	5 mM Ba^{2+}	McDonough and Bean, 1998
	Dorsal root ganglion cells	3	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1988
	Spinal motoneurons	~1	~1	5 mM Ba^{2+}	Viana *et al.*, 1997
	Thyroid carcinoma and heterologous expression	2.7	19 (L-type)	30 mM Ba^{2+}	Mehrke *et al.*, 1994
	Azygos vein smooth muscle cells	0.1	1 (L-type)	20 mM Ca^{2+}	Mishra and Hermsmeyer, 1994
	Atrial myocytes	1.5	28 (L-type)	5 mM Ca^{2+}	Perchenet *et al.*, 2000
	Skeletal muscle myocytes	0.7	2 (L-type)	10 mM Ba^{2+}	Liu *et al.*, 1999
	Spermatogenic cells	4.7	n/a	10 mM Ca^{2+}	Arnoult *et al.*, 1998

Table III. (*Continued*)

Pharmacological agent	Tissue	IC50 (μM) T-type	IC50 (μM) HVA-type	Cation concentration	Reference
	Heterologous expression	0.39 (alpha1G)	n/a	20 mM Ba^{2+}	Klugbauer *et al.*, 1999
		1 (alpha1G)	n/a	2 mM Ca^{2+}	Monteil *et al.*, 2000b
		2.3 (alpha1I)			
		1.1 (alpha1G)	12.9 (alpha 1C)	10 mM Ba^{2+}	Martin *et al.*, 2000
		1.2 (alpha1H)			
		1.5 (alpha1I)			
		0.27 (alpha1G)	n/a	2 mM Ca^{2+}	Martin *et al.*, 2000
		0.14 (alpha1H)			
		1.2 (alpha1H)	n/a	5 mM Ca^{2+}	Perchenet *et al.*, 2000
		n/a	8 (alpha1A)	5 mM Ca^{2+}	Bezprozvanny and Tsien, 1995
			3 (alpha1B)		
			22 (alpha1C)		
			7 (alpha1E)		
XIV. *Zonisamide*					
	Cerebral cortex	~500	n/a	7 mM Ca^{2+}	Suzuki *et al.*, 1992
XV. *Invertebrate toxins*					
Kurtoxin	Heterologous expression	0.02	n/a	5 mM Ba^{2+}	Chuang *et al.*, 1998
	Thalamic neurons	0.049	0.07 (L-type)	5 mM Ba^{2+}	Sidach and Mintz, 2002
	Cerebellar Purkinje neurons	n/a	0.01 (P-type)	5 mM Ba^{2+}	Sidach and Mintz, 2002
	Sympathetic neurons	n/a	0.46 (N-type)	5 mM Ba^{2+}	Sidach and Mintz, 2002
	Dorsal root ganglia	0.01	3	2 mM Ca^{2+}	Scott *et al.*, 1992
	Heterologous expression	0.02 (alpha 1G)	n/a	5 mM Ba^{2+}	Chuang *et al.*, 1998
Arginine polyamine	Dorsal root ganglia	0.01	3	2 mM Ca^{2+}	Scott *et al.*, 1992
XVI. *Benzothiazepines*					
Diltiazem (0.47 μM)	Hippocampus	210	n/a	10 mM Ca^{2+}	Takahashi and Akaike, 1991
	Hypothalamus	70	n/a	10 mM Ca^{2+}	Akaike *et al.*, 1989b
	Amygdala	120	n/a	10 mM Ca^{2+}	Kaneda and Akaike, 1989
	Cerebellar Purkinje cell	82	n/a	2.5 mM Ca^{2+}	Kaneda *et al.*, 1990
	GH3 pituitary cells	131	n/a	10 mM Ca^{2+}	Herrington and Lingle, 1992
	Aortic smooth muscle cells	0.3	3	20 mM Ca^{2+}	Akaike *et al.*, 1989a
		30	3	20 mM Ca^{2+}	Kuga *et al.*, 1990
XVII. *Miscellaneous anti-epileptic drugs*					
Carbamazepine	Dorsal root ganglia	No effect	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
Valproate (6–200 μM; reviewed in Todorovic and Lingle, 1998)	Dorsal root ganglia	330	n/a	10 mM Ba^{2+}	Todorovic and Lingle, 1998
	Alpha1G	No effect	n/a	20 mM Ca^{2+} or Ba^{2+}	Lacinová *et al.*, 2000

[a] All data are presented as the concentration of drug (μM) necessary to inhibit 50% of T-type or high voltage-activated (HVA)-type current recorded from endogenous or recombinant calcium channels. It should be noted that many of these drugs only partially antagonize T-type currents (reviewed in Herrington and Lingle, 1992). Furthermore, the potency of many T-type blockers is dependent on the state of the channel, the voltage protocols used to study the channels, and the concentration and identity of ions used as the charge carrier. Finally, almost none of these drugs exclusively block VDCCs (see text for details). Where listed, concentration ranges in the left column represent human therapeutic concentrations.

et al., 1992), and oxodipine (Galan *et al.*, 1998) can reduce both T- and L-type calcium currents recorded from the same cell, although with different potencies (Table III). Interestingly, some dihydropyridines such as CD832, nifedipine, and PPK-5 are more potent at inhibiting T-type currents compared to L-type currents in smooth muscle cells (Table III), implying that calcium influx through T-type channels expressed by smooth muscle cells may contribute to the development and/or maintenance of high blood pressure (see Yunker and McEnery, 2003).

Succinimide Derivatives

The drugs ethosuximide, trimethadione, and methsuximide are clinically useful in the treatment of generalized (petit mal) absence seizures (reviewed in Coulter *et al.*, 1989b). As T-type channels are implicated

in the generation of spike and wave discharges (see Yunker and McEnery, 2003), T-type channels may be the site of action for this class of antiepileptic drugs. Investigations into the cellular mechanism of action for succinimides have provided some evidence that these compounds block both endogenous T-type channels (Coulter *et al.*, 1989b, 1990; Gomora *et al.*, 2001; Huguenard and Prince, 1994; Todorovic *et al.*, 2000) and recombinant alpha1G, alpha1H, and alpha1I T-type channels (Gomora *et al.*, 2001; Lacinová *et al.*, 2000; Todorovic *et al.*, 2000). For example, succinimide derivatives including ethosuximide, dimethadione (the active metabolite of trimethadione), and alpha-methyl-alpha-phenyl succinimide (MPS) reduce endogenous T-type currents in ventrobasal thalamic neurons (Coulter *et al.*, 1989b, 1990; but see Leresche *et al.*, 1998; Pfieger *et al.*, 1992) and dorsal root ganglia (Kostyuk *et al.*, 1992; Todorovic *et al.*, 2000). In contrast, succinimide, the clinically inactive base structure, and tetramethylsuccinimide, a convulsant, do not attenuate T-type calcium currents (Coulter *et al.*, 1989b, 1990; Todorovic and Lingle, 1998; but see Gomora *et al.*, 2001).

Analyses of endogenous and recombinant T-type channels suggest that T-type channels may not be the primary site of action for succinimide derivatives, as succinimides are neither potent nor selective blockers of T-type channels. For example, an ethosuximide concentration near the upper limit of the therapeutic plasma level (1 mM) reduces ~75% of ventrobasal thalamic T-type currents by a maximum of ~40% (Coulter *et al.*, 1989b). Similarly, the ethosuximide IC50 value for attenuation of T-type currents conducted by recombinant alpha1G, alpha1H, and alpha1I channels is ~10-fold greater (Gomora *et al.*, 2001) than therapeutic plasma levels (reviewed in Coulter *et al.*, 1989b). Interestingly, many studies have failed to observe an effect of ethosuximide on T-type currents recorded from thalamic (Leresche *et al.*, 1998; Pfrieger *et al.*, 1992; but see Huguenard and Prince, 1994), neocortical (Sayer *et al.*, 1993; Tsakiridou *et al.*, 1995), neostriatal (Hoehn *et al.*, 1993), or hippocampal (Thompson and Wong, 1991) neurons, although it must be noted that T-type current blockade by succinimide derivatives is both voltage-dependent (Coulter *et al.*, 1990; Gomora *et al.*, 2001; Lacinová *et al.*, 2000) and state-dependent (Gomora *et al.*, 2001). Finally, ethosuximide also inhibits HVA currents (Coulter *et al.*, 1989b; but see Leresche *et al.*, 1998), noninactivating sodium currents, and calcium-activated potassium currents (Leresche *et al.*, 1998), and affects responses to exogenous GABA (Coulter *et al.*, 1990). As a similar lack of potency and specificity is observed for MPS (Coulter *et al.*, 1989b, 1990; Todorovic *et al.*, 2000), these results suggest that succinimides act at multiple cellular sites of action to prevent spike and wave discharges.

Alkyl-Substituted Thiobutyrolactones

Substituted thiobutylactones are a novel group of compounds with structural and pharmacological similarities to succinimides, and they can act as either convulsants or anticonvulsants, depending on their structure (Gross *et al.*, 1997). Both alpha-EMTBL (alpha-ethyl, alpha-methyl-gamma-thiobutyolactone) and beta-EMTBL (beta-ethyl, alpha-methyl-gamma-thiobutyolactone) reduce, but do not totally inhibit, T-type currents recorded from dorsal root ganglia (Gross *et al.*, 1997). Unfortunately, these drugs have limited experimental usage, as they regulate $GABA_A$-receptor effects (Holland *et al.*, 1990a,b). Furthermore, similar to many T-type channel antagonists, these drugs can affect HVAs, as alpha-EMTBL displays voltage-sensitive block of HVAs (Gross *et al.*, 1997). Beta-EMTBL also alters HVA currents, although at least four times as much drug is needed compared to T-type currents (Gross *et al.*, 1997).

Phenytoin (Diphenylhydantoin)

Phenytoin is used clinically to treat partial and generalized seizures, and phentoin can attenuate calcium uptake, neurotransmitter release, and calcium-dependent action potentials, in addition to blocking voltage-gated sodium channels (reviewed in Twombly *et al.*, 1988). Early studies of hippocampal development suggested that phenytoin preferentially blocked T-type currents (Yaari *et al.*, 1987). Although phenytoin reduces T-type, but not HVA, currents from ND7-23 dorsal root ganglion cell line (Kobrinsky *et al.*, 1994), NIE-115 neuroblastoma cells (Twombly *et al.*, 1988), and ventrobasal thalamic neurons (Coulter *et al.*, 1989b), 100-μM phenytoin also attenuates N- and L-type currents in CA1 hippocampal neurons (Takahashi *et al.*, 1989). Furthermore, phentoin does not inhibit all T-type currents, as T-type currents in skeletal muscle are not affected by this drug (Satoh *et al.*, 1991). It must be noted that the concentration of phenytoin needed to block T-type currents is over 10-fold more concentrated than the clinical free-serum levels (reviewed in Coulter *et al.*, 1989b), indicating that T-type channels are probably not the therapeutic cellular site of action for this anticonvulsant. However, studies of recombinant channels suggest that phenytoin may be useful in the experimental study of T-type channels. Recombinant T-type channels can be differentiated based on their sensitivity to phenytoin. Phenytoin completely blocks cur-

rents conducted by alpha1G (140 μM, IC50), but only partially reduces currents carried by alpha1H channels (8 μM, IC50) (Todorovic *et al.*, 2000). Interestingly, the sensitivity of a second population of alpha1H channels (192 μM, IC50) resembles that of alpha1G channels (Todorovic *et al.*, 2000), implying phenytoin may differentiate among subtypes of alpha1H channels. Alternatively, inhibition by phenytoin may be sensitive to the presence of modulatory molecules associated with some alpha1H channels.

Diphenylbutylpiperidine Derivatives

Diphenylbutylpiperidine derivatives (DPBPs) such as penfluridol, fluspirilene, pimozide, and flunarizine compromise one class of drugs used clinically to treat a variety of psychiatric disorders (reviewed in Pinder *et al.*, 1976; Seeman *et al.*, 1976). Although these drugs interrupt dopaminergic neurotransmission, DPBPs can inhibit nitrendipine binding in the central nervous system (Gould *et al.*, 1983) and smooth muscle contractions (Flaim *et al.*, 1985), suggesting that DPBP neuroleptics are potent calcium-channel blockers. Flunarizine was one of the first reported organic calcium antagonists to inhibit T-type currents in the central nervous system (Akaike *et al.*, 1989b; Takahashi and Akaike, 1991), and accumulating evidence suggests that DPBPs block endogenous and recombinant T-type channels (Arnoult *et al.*, 1996; Enyeart *et al.*, 1992, 1993; Santi *et al.*, 2002). Although fluspirilene, penfluridol, and pimozide block both T- and L-type calcium currents in pituitary cell lines (Enyeart *et al.*, 1990), DPBPs are more potent at inhibiting endogenous T-type currents in many cell types (Arnoult *et al.*, 1996; Enyeart *et al.*, 1992, 1993; Santi *et al.*, 2002; but see Akaike *et al.*, 1989a; Enyeart *et al.*, 1990) (Table III). For example, penfluridol (500 nM) inhibits ~80% of T-type currents and ~25% of HVA currents in thyroid carcinoma cells (Enyeart *et al.*, 1992). Although neither penfluridol nor pimozide can differentiate between recombinant channels formed by alpha1G, alpha1H, and alpha1I LVA alpha1 subunits (Santi *et al.*, 2002), flunarizine is at least four times more potent at inhibiting currents conducted by alpha1G and alpha1I compared to channels formed by alpha1H (Santi *et al.*, 2002). Interestingly, other non-DPBP neuroleptics, including clozapine (a dibenzodiazepine), haloperidol (a butyrophenone), and thioridazine (a phenothiazine) also nonselectively block endogenous and recombinant T-type currents (Enyeart *et al.*, 1992; Santi *et al.*, 2002), although with less potency than DPBP derivatives (Enyeart *et al.*, 1992; Santi *et al.*, 2002). As DPBP derivatives also inhibit dopamine receptors, L-type channels, and potassium channels (reviewed in Enyeart *et al.*, 1992; Gomora and Enyeart, 1999), these results suggest neuroleptics may affect a variety of cellular targets, including T-type channels, to alleviate symptoms of many psychiatric diseases.

Anesthetics

Although the specific cellular mechanism(s) by which general anesthetics produce their therapeutic actions are unclear at this time, anesthetics are thought to depress central nervous system excitability and/or alter synaptic transmission (Jones *et al.*, 1992). Investigations into the mechanisms of action of anesthetics suggest that T-type channels may be another site of action for these drugs (Camara *et al.*, 2001; Eskinder *et al.*, 1991; Herrington and Lingle, 1992; McDowell *et al.*, 1996, 1999; Olcese *et al.*, 1994; Viana *et al.*, 1997). Anesthetics are an unusual class of T-type channel blockers, as they can produce 100% block of T-type currents (Todorovic *et al.*, 2000). For example, many volatile anesthetics such as enflurane, halothane, and isoflurane inhibit endogenous and recombinant T-type channels in a concentration range consistent with therapeutic concentrations (Krnjevic and Puil, 1988; Terrar and Victory, 1988a,b). Although some anesthetics attenuate endogenous HVA currents as well as T-type currents (Camara *et al.*, 2001; McDowell *et al.*, 1996, 1999; Takahashi *et al.*, 1989), some anesthetics are more potent at inhibiting T-type currents (Table III). Furthermore, some anesthetics can differentiate between individual LVA alpha1 subunits. Whereas a similar concentration of propofol is required to inhibit 50% of T-type currents conducted by recombinant alpha1G and alpha1H channels (Todorovic *et al.*, 2000), octanol is over five times more potent at attenuating recombinant alpha1H channels than alpha1G channels (Todorovic *et al.*, 2000). Surprisingly, whereas nitrous oxide attenuates endogenous T-type and recombinant alpha1H currents, T-type channels formed by alpha1G appear resistant to this drug (Todorovic *et al.*, 2001). Therefore, this anesthetic may be a useful tool in defining alpha1G and alpha1H channels in situ.

Barbiturates

Barbiturates are commonly used for their anesthetic and anticonvulsant properties, and they have multiple sites of action including sodium channels (Frenkel *et al.*, 1993;Van den Berg *et al.*, 1993), $GABA_A$-activated chloride conductances, and HVAs (Gross *et al.*, 1997; Gross and Macdonald, 1988a,b; Kelly *et al.*, 1990). Barbiturates such as pentobarbital and phenobarbital can also attenuate T-type currents (Todorovic *et al.*, 2000; Todorovic and

Lingle, 1998; but see Gross and Macdonald, 1988a,b) with similar concentrations of drug necessary to inhibit either endogenous or recombinant T-type channels (Table III). Unlike many classes of drugs that attenuate T-type currents, barbiturates are able to fully block T-type currents from both recombinant and endogenous channels (Todorovic *et al.*, 2000). However, T-type channels are probably not a therapeutic site of action for barbiturates because the barbiturate concentration needed to inhibit T-type channels is significantly greater than those measured in clinical settings (reviewed in Todorovic and Lingle, 1998).

Neurosteroids

T-type channels appear to be a molecular target for some drug classes whose primary mechanism of action does not involve calcium influx through VDCCs. For example, some steroid-receptor agonists have anesthetic properties, probably through potentiation or gating of $GABA_A$ receptor-activated chloride currents (reviewed by Lambert *et al.*, 1995). However, VDCCs may also be affected by neuroactive steroid-receptor agonists (ffrench-Mullen and Spence, 1991). Both prenanolone and ACN ((3-alpha, 5-alpha, 17-beta)-3-hydroxy androstrane-17-carbonitrile) are anesthetic neurosteroids that attenuate N-, Q-, and R-type HVA currents in hippocampal and dorsal root ganglion neurons (Nakashima *et al.*, 1998). Interestingly, the related molecule (+)-ECN ((3-beta, 5-alpha, 17-beta)-17-hydroxyesterane-3-carbonitrile) reduces T-type currents, but not HVA currents in dorsal root ganglia and hippocampal neurons (Todorovic *et al.*, 1998) (Table III). Although this drug is more potent at blocking T-type channels than affecting $GABA_A$ receptors (Todorovic *et al.*, 1998), ~10-fold higher concentrations of (+)-ECN can also attenuate recombinant alpha 1E channels (Nakashima *et al.*, 1999). Taken together, these data suggest that these drugs are not selective for T-type channels. However, similar to general anesthetics, T-type channels may be a cellular site of action for at least some neurosteroids.

Phenylalkylamines

The phenylalkylamines verapamil (papaverine) and D600 (methyoxyverapamil) structurally resemble local anesthetics (see Doehring and Zamponi, 2003). They are commonly used HVA antagonists, as they preferentially attenuate L-type currents over other HVA currents (Hering *et al.*, 1989; Lee and Tsien, 1983; but see Dobrev *et al.*, 1999). Phenylalkylamines can also reduce T-type currents recorded from aortic smooth muscle cells (Akaike *et al.*, 1989a), amygdala (Kaneda and Akaike, 1989), and hypothalamus (Akaike *et al.*, 1989b), although these drugs are more potent against HVA than LVA currents (Table III). However, phenylalkylamines do not affect T-type currents in some tissues (Hoehn *et al.*, 1993; Satoh *et al.*, 1991; Sui *et al.*, 2001). It will be interesting to determine if the lack of effect on some channels is reflected in studies of recombinant channels or is dependent on the experimental protocol and/or identity of the tissue studied.

Benzodiazepines

Benzodiazepines are widely used as minor tranquilizers and anticonvulsants to treat sleep disorders, anxiety, and seizures. Binding studies suggest the central nervous system contains two benzodiazepine-binding sites differentiated by their affinity for drug binding (Bowling and DeLorenzo, 1982). The high (nM) affinity site (also known as the central type) is associated with $GABA_A$-receptor-mediated chloride conduction, and benzodiazepine increase $GABA_A$-mediated inhibition (Twyman *et al.*, 1989). In contrast, the low (μM) affinity binding site (also known as the peripheral type) is not associated with $GABA_A$ receptors. At least some benzodiazepine alter neural calcium influx (Johansen *et al.*, 1985; Nakazawa *et al.*, 1991; Taft and DeLorenzo, 1984; Thomson *et al.*, 1995; Yang *et al.*, 1987), and T-type channels may either directly or indirectly affected by benzodiazepines. For example, agonists at the central type benzodiazepine receptor (clonazepam) reduce T-type, but not HVA, currents in N1E-115 neuroblastoma cells (Watabe *et al.*, 1993). In contrast, benzodiazepines that activate either peripheral (Ro5–4864) or peripheral and central type benzodiazepine receptors (diazepam, nitrezepam) attenuate LVA and HVA currents equally (Watabe *et al.*, 1993). Benzodiazepines also attenuate sodium and potassium current (Yang *et al.*, 1987; reviewed in Reuveny *et al.*, 1993; Watabe *et al.*, 1993), suggesting the presence of multiple cellular targets for some benzodiazepines.

Amiloride

Low concentrations of the pyrazine diuretic amiloride were first reported to preferentially interact with endogenous T-type channels in mouse neuroblastoma and dorsal root ganglion cells as HVA currents were attenuated by less than 20% (Formenti *et al.*, 1993; Tang *et al.*, 1988) (Table III). Like most T-type channels blockers, the pharmacological profile of amiloride is not ideal, as higher amiloride concentrations (300 μM) attenuate LVA and HVA currents in central nervous system neurons

(Takahashi *et al.*, 1989). Furthermore, all T-type channels do not appear sensitive to amiloride. Endogenous T-type channels in vascular smooth muscle cells (Akaike *et al.*, 1989a), cardiac myocytes (Tytgat *et al.*, 1996), and GH3 pituitary cells (Herrington and Lingle, 1992) are more resistant to the actions of amiloride compared to peripheral neurons (Table III). Interestingly, recombinant alpha 1G channels are among the most resistant T-type channels (Lacinová *et al.*, 2000) (Table III), perhaps indicating that amiloride-sensitive endogenous T-type channels are more likely to be composed of alpha 1H or alpha 1I than alpha 1G. Unfortunately, amiloride can also block tetrodotoxin-insensitive sodium channels (Palmer, 1984), and a variety of ion exchange proteins (Aronson, 1985; Schellenberg *et al.*, 1983), limiting its experimental use.

Mibefradil

Mibefradil (Ro 40–5967; Posicor) is a novel tetralol derivative similar in structure to verapamil that had promising antihypertensive and antianginal properties when tested in humans (Osterrieder and Holck, 1989; reviewed in Massie, 1998; Oparil, 1998). Mibefradil preferentially relaxes coronary vasculature over peripheral vasculature (reviewed in Clozel *et al.*, 1997), and blocks neural T-type currents recorded in neuroblastoma cells (Randall and Tsien, 1997), sensory neurons (Todorovic and Lingle, 1998), spinal motoneurons (Viana *et al.*, 1997), and cerebellar Purkinje cells (McDonough and Bean, 1998). Although mibefradil can attenuate endogenous and recombinant HVA currents (Bernatchez *et al.*, 2001; Bezprozvanny and Tsien, 1995; Leuranguer *et al.*, 2001; Mehrke *et al.*, 1994), mibefradil is more potent at blocking both endogenous and recombinant T-type currents than HVA currents (McDonough and Bean, 1998; Mishra and Hermsmeyer, 1994; but see Viana *et al.*, 1997) (Table III). Unfortunately, mibefradil also attenuates voltage-gated potassium currents in a similar concentration range (<1 μM IC50) necessary to attenuate some endogenous T-type channels (Liu *et al.*, 1999) (see Table III). Furthermore, mibefradil inhibits the action of cytochromes P450 3A4 and 2D6, enzymes used to metabolize a number of therapeutic agents (reviewed in Po and Zhang, 1998), resulting in the removal of mibefradil from the clinical market.

Zonisamide

Zonisamide (AD-810, CI-912) is a sulfonamide derivative used clinically in Japan to treat a number of seizure disorders (reviewed in Oommen and Mathews, 1999). Although zonisamide can reduce T-type currents without affecting L-type currents in cortical neurons (Suzuki *et al.*, 1992), 100-μM zonisamide attenuates both T- and L-type currents in adrenal glomerulosa cells (Rossier *et al.*, 1996). Zonisamide also blocks voltage-dependent sodium channels, alters GABAergic and dopamine signaling, and can act as a free radical scavenger (reviewed in Oommen and Mathews, 1999), thus limiting its experimental usage and suggesting multiple therapeutic sites of action.

Peptides

Invertebrate toxins have been very useful in the study of ion channels and HVAs (see Doering and Zamponi, 2003). Although peptide blockers are very effective antagonists of individual HVA channel isoforms, most peptide toxins do not affect T-type channels. For example, neither ω-conotoxin GVIA (Akaike *et al.*, 1989a; Perchenet *et al.*, 2000; Randall and Tsien, 1997; Satoh *et al.*, 1991; Takahashi *et al.*, 1989; but see Ye and Akaike, 1993), nor ω-agatoxin (Mintz *et al.*, 1991; Perchenet *et al.*, 2000) block T-type channels. In contrast, kurtoxin, a newly purified scorpion (*Parabuthus transvaalicus*) toxin, antagonizes T-type currents conducted by recombinant alpha 1G or alpha1H channels (Chuang *et al.*, 1998), and endogenous T-type currents recorded from thalamic neurons (Sidach and Mintz, 2002). Although kurtoxin (350 nM) does not inhibit currents conducted by recombinant channels formed by alpha1A, alpha1B, alpha1C, or alpha1E (Chuang *et al.*, 1998), similar concentrations of kurtoxin attenuate endogenous N- and L-type currents and facilitate P-type currents (Sidach and Mintz, 2002). Kurtoxin also appears to interact with voltage-gated sodium channels (Chuang *et al.*, 1998), thus limiting its experimental use.

Invertebrate toxins may also contain biologically active polyamines that can specifically block HVAs (Llinás *et al.*, 1989). Arginine polyamine has a similar structure to a component of a funnel web spider toxin (Cherksey *et al.*, 1989), and differentiates between T-type and HVA channels, with IC50 values of 10 nM and 3 μM, respectively (Scott *et al.*, 1992). Unfortunately, arginine polyamine can also attenuate endogenous potassium and chloride currents, although at concentrations greater than those needed to reduce T-type currents (Scott *et al.*, 1992), suggesting some use in experimental studies.

Conclusions

Despite the lack of highly selective T-type channel antagonists, the use of pharmacological agents has

revealed that T-type currents contribute to a wide range of physiological processes in normal neural and nonneural tissues (reviewed in Yunker and McEnery, 2003). Although there is not a single identifying pharmacological criterion for T-type currents, over 15 classes of drugs are suspected to affect T-type channels. T-type channels may be important therapeutic targets in the treatment of epilepsy (reviewed in Yunker and McEnery, 2003), pain (Bilici *et al.*, 2001; Dogrul *et al.*, 2001, 2002; Matthews and Dickenson, 2001; Todorovic *et al.*, 2001), resting tremors (Gomez-Mancilla *et al.*, 1992), asthma (Janssen, 1997; Muramatsu *et al.*, 1997), cardiac hypertrophy (Ito *et al.*, 1991, 1994; Martinez *et al.*, 1999; Nuss and Houser, 1993; Sen and Smith, 1994; Xu and Best, 1990), cardiac ischemia (Sandmann *et al.*, 1998, 1999, 2000), hypertension (Angus *et al.*, 2000; Lam *et al.*, 1998; Mishra and Hermsmeyer, 1994; Sarsero *et al.*, 1998; Schmitt *et al.*, 1995; Vacher *et al.*, 1996), cancer, and diabetes (reviewed in Yunker and McEnery, 2003). It is anticipated that the discovery of more selective T-type channel blockers will further our basic understanding of the molecular composition and physiological functions of T-type channels, and aid in the treatment of a variety of neural and nonneural diseases.

ACKNOWLEDGMENTS

I thank Dr Maureen W. McEnery for her critical comments and continuous support of this review, and Dr Stephen W. Jones for his critical comments on this manuscript. This review was made possible by NIH MH55747 (MWM), AHA 96001250 (MWM), a NSF SGER award (MWM), and a Presidential Research Initiative Grant from CWRU.

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