T-type calcium channel blockers – new and notable

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Abstract. Since cloning of the T-type or CaV3.1 calcium channel family in 1998–1999 much progress was made in investigation of their regulation. Most effective metal CaV3 channel blockers are trivalent cations from lanthanide group together with transition metals La3+ and Y3+. Divalent cations Zn2+, Cu2+ and Ni2+ inhibit CaV3.2 channels more efficiently than CaV3.1 and CaV3.3 channels via second high-affinity binding site including histidine H191 specific for the CaV3.2 channel. Dihydropyridines and phenylalkylamines in addition to block of L-type calcium channel can inhibit CaV3 channels in clinically relevant concentration.

Key words: T-type calcium channels — Dihydropyridines — Phenylalkylamines — Zn2+, Cu2+, Ni2+, Co2+, Cd2+, La3+, Er3+, Y3+

T-type or low-voltage-activated or according to the most recent classification CaV3 channels (Ertel et al. 2000) are distinguished by their negative voltage threshold for activation, which is between −70 mV and −60 mV. Such a low activation threshold allows them to participate together with sodium channels in initiation of action potential generation or even generate so-called low threshold action potentials in the absence of sodium channels. CaV3 channels play a role in pathologies including hypertension, heart failure, sleep disorders, epilepsy, drug addiction and neuropathic pain. Currently, three representatives of this channel class are known: CaV3.1, CaV3.2 and CaV3.3. CaV3.1 and CaV3.2 channels are ubiquitously expressed. The CaV3.2 was found in brain, peripheral nervous tissue (dorsal root ganglion, autonomic ganglia), heart (myocytes, pacemaker cells), smooth muscle, skeletal muscle, bone (osteoblasts), endocrine cells (adrenal, pituitary, pancreas, thyroid) and in sperm. The CaV3.1 was found in all mentioned tissues except for skeletal muscle. Expression of the CaV3.3 channels is restricted to the brain and peripheral nervous tissue (for references see Iftinca and Zamponi 2009).

Detail understanding of mechanisms underlying their regulation may greatly facilitate development of new therapies. Metal ions represent a preferred tool for the mapping of a permeation pathway and for the description of voltage sensor activation. L-type calcium channel blockers dihydropyridines (DHP) and phenylalkylamines (PAA) are widely used for treatment of cardiovascular diseases therefore their potential ability to regulate T-type calcium channels is of major interest. This review concentrates predominantly on facts reported since the last review (Lacinova 2004).

Metal ions

Divalent metal cations (M2+)

Divalent metal cations are commonly known blockers of both high- and low-voltage-activated calcium channels (VACC) lacking high degree of selectivity for a specific VACC class. Cd2+ fully blocks high-VACC in concentrations 5–50 µM (Fox et al. 1987; Lacampagne et al. 1994; Bleakman et al. 1995). Millimolar concentration of Co2+ is necessary for complete block of high-VACC (Wakamori et al. 1998; Fan and Palade 1999). Compare to high-VACC Co2+ is more effective and Cd2+ less effective in blocking CaV3 channels with IC50s in hundreds of µM (Diaz et al. 2005). CaV3.2 channels are approximately 3-fold more sensitive than the CaV3.1 and CaV3.3 channels (see Table 1). Consistent with an occlusion of the channel’s conductive pore the inward currents were strongly blocked while outward current were only moderately affected by Co2+ and Cd2+ (Diaz et al. 2005). Interestingly, Co2+ accelerated tail currents, while Cd2+ slowed those (Diaz et al. 2005). As Co2+ ions have relatively small ionic radius (0.74 Å) it is possible that Co2+ re-enters the channel pore during repolarization and blocks it.
Table 1. Half-maximal inhibition concentrations (IC50s) for inhibition of CaV3.3 channels in mammalian cells by selected agents evaluated at a holding potential HP = –100 mV, unless noted otherwise

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<th>Agent</th>
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<tbody>
<tr>
<td>Zn2+</td>
<td>80 μM</td>
<td>0.8 μM</td>
<td>160 μM</td>
<td>15 μM (plasma)</td>
</tr>
<tr>
<td></td>
<td>197 μMb</td>
<td>24 μMb</td>
<td>152 μMb</td>
<td>100–150 μM (brain)</td>
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<tr>
<td>Cu2+</td>
<td>–</td>
<td>0.9 μMd</td>
<td>–</td>
<td>0.1–0.8 μM (plasma)</td>
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<td></td>
<td>12 μM (mixture of subtypes)</td>
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<td></td>
<td>up to 400 μM (brain)</td>
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<tr>
<td>Ni2+</td>
<td>250 μM</td>
<td>12 μM</td>
<td>216 μM</td>
<td>–</td>
</tr>
<tr>
<td>Co2+</td>
<td>335 μM</td>
<td>122 μM</td>
<td>345 μM</td>
<td>–</td>
</tr>
<tr>
<td>Cd2+</td>
<td>128 μM</td>
<td>65 μM</td>
<td>157 μM</td>
<td>–</td>
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<td></td>
<td>&lt;10 μM</td>
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cantly bigger Cd2+ (ionic radius 0.97 Å) gets trapped inside conductive pore and prevents channel closing.

Zn2+, Cu2+ and Ni2+ block CaV3.1 and CaV3.3 channels with potency similar to Co2+ and Cd2+ (see Table 1). These three ions are distinguished by 10–20-fold higher efficiency of CaV3.2 channel inhibition (Table 1). Zn2+ and Cu2+ are nutritional elements with physiological significance. They are present in moderate concentration in human plasma but may occur in high concentration in brain (Mathie et al. 2006; Richelle et al. 2006). Both Zn2+ and Cu2+ are essential divalent cations involved in regulation of several cellular processes including neuronal excitability, synaptic plasticity, gene expression and enzymatic reactions. Zinc blocks VACC in order of efficiency CaV1.2 > CaV3.2 > CaV2.3 > CaV2.2 = CaV2.1 ≥ CaV3.3 = CaV3.1 (Sun et al. 2007). Study published along with Sun's report confirmed relative selectivity of Zn2+ ions for CaV3.2 channels compared to CaV3.1 and CaV3.3 channels (Traboulsie et al. 2007). It was explained by Nelson and coauthors (Nelson et al. 2007b) who have shown that Zn2+ constitutively inhibits the CaV3.2 channel via an interaction site involving histidine H191 in extracellular loop connecting IS3-IS4 segments, i.e., within the putative voltage sensor of the channel. CaV3.1 and CaV3.3 channels have a glutamine at corresponding position. Binding pocket for Zn2+ on CaV3.2 channel was further refined by Kang and coauthors that identified D189-G190-H191 in IS3-IS4 loop and D122 in IS2 helix as its main constituents (Kang et al. 2010). As zinc is a common contaminant of experimental solutions this finding has an important implication for experiments on CaV3.3 channels in general. Inhibition of the CaV3.2 channel can be relieved by zinc-chelating agents including L-cysteine, dithiothreitol, bovine serum albumin, diethylthreitol, and N,N,N′,N′-tetra-2-picolylethlenediamine. Relief of the inhibition lowers the threshold for nociceptor excitability both in vitro and in vivo and represents novel mechanism of nociceptor sensitization (Nelson et al. 2007b). Finding that modulation of the CaV3.3 channels increased the frequency and the duration of thalamocortical firing (Cataldi et al. 2007; Noh et al. 2010a) implies that endogenous Zn2+ may have a role in controlling thalamocortical oscillations as well.

Binding pocket defined by histidine H191 underlies also relative selectivity of Cu2+ (Nelson et al. 2007a) and Ni2+ (Kang et al. 2010) for CaV3.2 over CaV3.1 and CaV3.3 channels. This high-affinity site specific to the CaV3.2 channel is located within voltage sensor of the channel domain I. Zn2+, Cu2+ and Ni2+ inhibit the current via high-affinity site by stabilizing closed state of the channel. This interaction does not alter kinetics or voltage dependence of current activation, inactivation and deactivation.

Interaction with the second low-affinity site located inside the conductive pore modulates the current through CaV3.1 and CaV3.3 channels in a complex manner. Nickel positively shifts voltage dependence of activation and accelerates deactivation of the CaV3.1 channel (Lacinova et al. 2000). Zinc negatively shifts voltage dependencies of activation and inactivation and slows inactivation kinetics of CaV3.1 and CaV3.3 channels (Traboulsie et al. 2007). Further, it slows

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dramatically deactivation of the CaV3.3 channel (Traboulsie et al. 2007) and moderately slows deactivation of the CaV3.1 channel (Noh et al. 2010b). None of these effects was observed on CaV3.2 channels (Traboulsie et al. 2007) most probably because at zinc concentration necessary for their occurrence the channel is already fully blocked via high affinity site located on the voltage sensor.

**Trivalent metal cations (M3+)**

Analysis of gating current reflecting activation of voltage sensor of a channel supplies information on basic regulatory mechanisms. Necessary pre-requisition is complete inhibition of ion current by a blocker which blocks the channel conducting pore without affecting movement of voltage sensor of the channel itself. Divalent cations modify kinetics and/or voltage dependencies of activation, inactivation and deactivation of CaV3.1 and CaV3.3 channel (Lacinova et al. 2000; Diaz et al. 2005; Cataldi et al. 2007; Traboulsie et al. 2007; Objejero-Paz et al. 2008; Noh et al. 2010b). Further, Zn2+, Cu2+ and Ni2+ interact directly with the voltage sensor of the CaV3.2 channel (Kang et al. 2006; Nelson et al. 2007a,b; Kang et al. 2010). Therefore trivalent cations La3+ (Lacinoa et al. 2002; Talavera and Nilius 2006) and more recently Er3+ (Karmazinova and Lacinoa 2010; Karmazinova et al. 2011) were used as CaV3 channel blockers for measurements of gating currents. Trivalent cations from lanthanide group and transition metals La3+ and Y3+ are the most effective cationic blockers of CaV3 channels (in order of potency Y3+ > Er3+ > Gd3+ > Ce3+ > Ho3+ > Yb3+ > Nd3+ > La3+ > Sc3+) with IC50s in nanomolar region (Mlinar and Enyeart 1993; Beedle et al. 2002). They act solely by entering and occluding the conductive pore of the channel. All currently known features of CaV3 channels inhibition by M3+ can be interpreted in accord with this mechanism:

1) consistent with an open channel block inhibition of inward current amplitude by M3+ was largely voltage-independent within physiological range of membrane depolarizations (Mlinar and Enyeart 1993; Beedle et al. 2002; Objejero-Paz et al. 2004);

2) M3+ did not alter kinetic of inward current trace (Mlinar and Enyeart 1993; Beedle et al. 2002; Lacinoa et al. 2007) and such alteration is considered a signature of an inactivated channel's inhibition;

3) inhibitory potency of M3+ decreases when concentration of charge carrier increases (Beedle et al. 2002) suggesting competition for the same binding site inside the conducting pore;

4) inhibitory potency of M3+ decreases when Ca2+ instead of Ba2+ is used as a charge carrier (Beedle et al. 2002) consistent with more effective competition of Ca2+ with M3+ for the same binding site inside the conducting pore;

5) inhibition can be relieved by depolarization to extremely positive voltages (Objejero-Paz et al. 2004) consistent with repulsion of M3+ out of conducting pore;

6) acceleration of tail currents by several M3+ can be explained by rapid re-block of open channels cleared from blocking ion by preceding depolarization (Objejero-Paz et al. 2004);

7) blocking potency of M3+ varied inversely with their ionic radii (Mlinar and Enyeart 1993; Beedle et al. 2002) consistent with more difficult entry of bigger ions into conducting pore.

**Dihydropyridines and phenylalkylamines**

DHP were thought to selectively interact with L-type calcium channels (Tsien et al. 1988; Hess 1990; Triggle 2007), however, more recently their interaction with voltage-dependent potassium channels was reported (Lin et al. 2001; Gao et al. 2005; Caro et al. 2011). They were developed and are still widely used for a treatment of cardiovascular disorders. PAA are clinically used as L-type calcium channels, nevertheless, they interact with potassium ion channels, too (Lefvre et al. 1991; Robe and Grissmer 2000; Rybalchenko et al. 2001).

Initially, T-type calcium channels were described as DHP-insensitive. Nevertheless, during recent years several authors reported block of CaV3 channels by DHPs in micromolar or even nanomolar concentrations (Table 1). Nimodipine and isradipine blocked the CaV3.1 channel with an IC50 below 10 µM (Drigelova et al. 2009). This value is more than two decimal orders higher than the IC50 = 16 nM reported for the CaV1.2 channel at a HP = –80 mV (Schuster et al. 1996). Furukawa and collaborators (Furukawa et al. 2005) demonstrated that amlodipine, barnidipine, manidipine and nicardipine inhibit with similar efficiency T-type (CaV3.1) and L-type (CaV1.2) calcium channels expressed in *Xenopus* oocytes. In the same model, benidipine and efonidipine were even slightly more effective in blocking T-type than L-type calcium channels with IC50s close to 10 µM (Furukawa et al. 2005).

More detailed analysis demonstrated strong voltage- and isomer-dependency of the inhibition of the CaV3.1 channel by efonidipine (Furukawa et al. 2004). In mammalian BHK cells R(−) efonidipine blocked CaV3.1 channels at a holding potential (HP) –100 mV with an IC50 about 10 µM and at a HP –60 mV with an IC50 about 0.1 µM. S(+) enantiomer had similar effect on both channels at both HPs (Furukawa et al. 2004). More effective was efonidipine in inhibition of the CaV3.2 channel in HEK 293 cells with an IC50 of 240 nM at a HP –90 mV (Inayoshi et al. 2011). Benidipine blocked the CaV3.2 channel expressed in HEK 293 cells with an IC50 140 nM (Inayoshi et al. 2011). (S, S) benidipine was slightly
better blocker (IC\textsubscript{50} = 40 nM) than (R, R) benidipine (IC\textsubscript{50} = 146 nM) (Inayoshi et al. 2011).

Perez-Reyes and coauthors (Perez-Reyes et al. 2009) analyzed inhibition of the calcium transport through the \(\text{Cav}3.2\) channels expressed in HEK 293 cells by variety of DHPs. Efonidipine, felodipine, isradipine and nifedipine appeared to be potent T-type channel blockers with IC\textsubscript{50} < 3 \(\mu\)M while amloidipine and nifedipine were less efficient with IC\textsubscript{50} 31 \(\mu\)M and 21 \(\mu\)M, respectively (Perez-Reyes et al. 2009).

The most efficient \(\text{Cav}3\) channel blockers efonidipine and benidipine do block also L-type calcium channels. Furukawa and coauthors (Furukawa et al. 2004) called efonidipine selective T-type calcium channel blocker as they found an IC\textsubscript{50} for the \(\text{Cav}3.1\) channel in millimolar region. However, more recently Tanaka and coauthors (Tanaka et al. 2010) reported the half-maximal inhibitory concentration for the \(\text{Cav}3.1\) channels around 1 \(\mu\)M, i.e., comparable with the IC\textsubscript{50} for the \(\text{Cav}3.2\) channel (Perez-Reyes et al. 2009) and the \(\text{Cav}3.1\) channel (Furukawa et al. 2004). Further, in mouse ventricular cardiomyocytes efonidipine half-maximal block of both L-type and T-type calcium currents required the same concentration of efonidipine 10 \(\mu\)M (Horiba et al. 2008). Even considering that in such preparation identity of individual VACC cannot be equivocally distinguished this finding questions suggested selectivity of efonidipine for T-type calcium channels.

Benidipine seems to be more selective T-type calcium channel blocker as the half-maximal blocking concentration for the \(\text{Cav}1.2\) channel was 14 \(\mu\)M (Furukawa et al. 1999), i.e., 100-fold higher than the half-maximal inhibitory concentration for the \(\text{Cav}3.2\) channel (Inayoshi et al. 2011). Still such claim should be taken with certain caution as the formers were measured in \textit{Xenopus} oocytes while the latter was measured in mammalian (HEK 293) cell line.

Most commonly used PAA verapamil was previously shown to block T-type calcium channels in smooth muscle cells with an IC\textsubscript{50} = 30 \(\mu\)M (Kuga et al. 1990) and in spermatogenic cells with an IC\textsubscript{50} = 70 \(\mu\)M (Arnoult et al. 1998). In mammalian expression system verapamil inhibited the \(\text{Cav}3.1\) channel with an IC\textsubscript{50} = 21 \(\mu\)M at a HP of –130 mV and with an IC\textsubscript{50} = 5 \(\mu\)M at a HP of –70 mV (Freeze et al. 2006). The later is close to values 3–8 \(\mu\)M reported for recombinantly expressed \(\text{Cav}1.2\) channel (Lacovita et al. 1995; Johnson et al. 1996) and for \(\text{Cav}1.2\) channel in cardiac myocytes (Wegener and Nawrath 1995). Charged 4-desmethoxyverapamil (D888) blocked the recombinant \(\text{Cav}3.1\) with virtually the same efficiency as neutral verapamil with an IC\textsubscript{50} less than 20 \(\mu\)M (Bergson et al. 2011). D888 is almost thousand-fold more effective L-type calcium channels blocker. An IC\textsubscript{50} reported for recombinant \(\text{Cav}1.2\) channels is 50 nM (Hockerman et al. 1995; Johnson et al. 1996).

Conclusion

Block of VACC by metal cations was traditionally viewed as simple physical occlusion of the channel’s conducting pore. High affinity interaction with the binding pocket located at extracellular part of the voltage sensor is a novel mechanism. It is notable, that the later does not influence voltage dependence or kinetics of the current while the former may modulate the current kinetics and/or voltage dependence in a complex manner. DHPs and PAAs were widely used in clinical practice as L-type calcium channel blockers. Now it is becoming clear that several of them can block T-type calcium channels at clinically relevant concentrations.

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