Review: Ca\textsubscript{v}2.3 R-type Voltage-Gated Ca\textsuperscript{2+} Channels - Functional Implications in Convulsive and Non-convulsive Seizure Activity

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Abstract:

Background:

Researchers have gained substantial insight into mechanisms of synaptic transmission, hyperexcitability, excitotoxicity and neurodegeneration within the last decades. Voltage-gated Ca\textsuperscript{2+} channels are of central relevance in these processes. In particular, they are key elements in the etiopathogenesis of numerous seizure types and epilepsies. Earlier studies predominantly targeted on Ca\textsubscript{v}2.1 P/Q-type and Ca\textsubscript{v}3.2 T-type Ca\textsuperscript{2+} channels relevant for absence epileptogenesis. Recent findings bring other channels entities more into focus such as the Ca\textsubscript{v}2.3 R-type Ca\textsuperscript{2+} channel which exhibits an intriguing role in ictogenesis and seizure propagation. Ca\textsubscript{v}2.3 R-type voltage gated Ca\textsuperscript{2+} channels (VGCC) emerged to be important factors in the pathogenesis of absence epilepsy, human juvenile myoclonic epilepsy (JME), and cellular epileptiform activity, e.g. in CA1 neurons. They also serve as potential target for various antiepileptic drugs, such as lamotrigine and topiramate.

Objective:

This review provides a summary of structure, function and pharmacology of VGCCs and their fundamental role in cellular Ca\textsuperscript{2+} homeostasis. We elaborate the unique modulatory properties of Ca\textsubscript{v}2.3 R-type Ca\textsuperscript{2+} channels and point to recent findings in the proictogenic and proneuroapoptotic role of Ca\textsubscript{v}2.3 R-type VGCCs in generalized convulsive tonic–clonic and complex-partial hippocampal seizures and its role in non-convulsive absence like seizure activity.

Conclusion:

Development of novel Ca\textsubscript{v}2.3 specific modulators can be effective in the pharmacological treatment of epilepsies and other neurological disorders.

Keywords: Absence epilepsy, Afterdepolarisation, Ictal discharges, Low-threshold Ca\textsuperscript{2+} spike, Plateau potentials, R-type, Seizure.

STRUCTURE, FUNCTION AND PHARMACOLOGY OF VOLTAGE-GATED Ca\textsuperscript{2+} CHANNELS

Voltage-gated Ca\textsuperscript{2+} channels (VGCCs) are of central relevance in mediating Ca\textsuperscript{2+} influx into living cells. They can trigger numerous physiological processes such as excitation-contraction coupling [1, 2], excitation-secretion coupling [3], hormone and transmitter release [4 - 6] and regulation of gene expression [7, 8]. From a structural point of view, VGCCs are heteromultimeric complexes built up of a central pore-forming, ion-conducting Ca\textsubscript{v}2.x subunit and various

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auxiliary subunits ($\alpha_2\delta$, $\beta_{1-4}$ and $\gamma_{1-8}$) (Fig. 1). Ten different $\text{Ca}_v$-$\alpha_1$ subunits have been characterized which can be classified based on their electrophysiological and pharmacological properties into high-voltage activated (HVA) and low-voltage activated (LVA) $\text{Ca}^{2+}$ channels. HVA $\text{Ca}^{2+}$ channels are further grouped into dihydropyridine (DHP)-sensitive L (“long-lasting”) type $\text{Ca}_v$,1.1–1.4 and non-L-type $\text{Ca}_v$,2.1–2.3 channels which are less DHP-sensitive. The LVA T- (“transient/tinny”) type $\text{Ca}^{2+}$ channels include $\text{Ca}_v$,3.1-3.3 [4, 9, 10]. The latter channels are characterized by rather negative membrane potential activation threshold, a fast inactivation, and small single-channel conductance [10]. By contrast, HVA L- and non-L-type channels require much stronger depolarization to reach activation threshold [11], exhibit higher single-channel conductances, and show prolonged-channel opening in comparison to T-type channels [4, 12]. However, $\text{Ca}_v$,1.3 L-type $\text{Ca}^{2+}$ channels were reported to exhibit mid-voltage activating characteristics under special physiological and electrophysiological conditions [12 - 15]. Pharmacodynamically, HVA L-type $\text{Ca}^{2+}$-channels are highly sensitive towards DHPS (e.g. nifedipine), phenylalkylamines (e.g. verapamil, gallopamil, devapamil) and benzothiazepines (e.g. diltiazem) [14, 16 - 18]. Recently, $\omega$-TRTX-Cc1a, derived from the venom of the tarantula Citharischius crawshayi (now Pelinobius muticus), turned out to be a potent and selective blocker of $\text{Ca}_v$,1.2 and $\text{Ca}_v$,1.3 $\text{Ca}^{2+}$ channels [19]. Experimental activators of L-type channels include BayK8644, FPL64176, PCA50941 and SZ(+)-(S)-202-791, none of which is however used in clinical application settings [20].

Fig. (1). Structural buildup of voltage-gated $\text{Ca}^{2+}$ channel complexes. Voltage-gated $\text{Ca}^{2+}$ channels are composed of a central pore-forming and ion-conducting $\alpha_1$ subunit as well a variable subset of auxiliary subunits, including $\alpha_2\delta$, $\beta$ and $\gamma$-subunits. The $\beta$-subunit is located intracellularly whereas the $\gamma$ and $\delta$ subunits are placed within the plasma membrane. The $\alpha_1$ subunit is covalently bound to the $\delta$ subunit via a disulfide bond and localized extracellularly. Both the $\text{Ca}_v$-$\alpha_1$ subunits as well as the auxiliary subunits are important drug targets (reprinted from [68]).

Synaptic transmission throughout the CNS is strongly dependent on presynaptic $\text{Ca}^{2+}$ influx through the $\text{Ca}_v$,2.1-$\text{Ca}_v$,2.3 VGCCs. In addition to triggering exocytosis, $\text{Ca}^{2+}$ influx also mediates complex patterns of short-term synaptic plasticity. The different $\text{Ca}_v$,2 VGCCs vary in their functional coupling to synaptic transmission over different frequency ranges. This has tremendous impact on the frequency tuning of presynaptic neuromodulation and synaptic dynamics [21]. HVA $\text{Ca}_v$,2 non-L-type $\text{Ca}^{2+}$ channels which are predominately engaged in synaptic transmission in the brain are effectively inhibited by various peptide snail and spider toxins. Omega ($\omega$)-agatoxin IVA, derived from the funnel web
spider *Agelenopsis aperta* preferentially targets Ca\(_{\text{2.1}}\) Ca\(^{2+}\) channels. Other Ca\(_{\text{2.1}}\) blockers include \(\omega\)-agatoxin IIIA, \(\omega\)-agatoxin IVB, peptide toxins from the venom of the marine snail *Conus geographus*, *i.e.* \(\omega\)-conotoxin MVIIID, \(\omega\)-conotoxin CVIB, \(\omega\)-conotoxin CVIC, the spider toxin \(\omega\)-phonotoxin IIA derived from *Phoneutria nigriventer*, DW13.3 extracted from the venom of the spider *Filistata hibernalis* and the scorpion venom toxin Kurtoxin [20, 22 - 24]. Though widely used in basic science, none of these blockers has reached clinical application so far. Omega (\(\omega\))-conotoxin GVIA derived from *Conus geographus* preferentially blocks Ca\(_{\text{2.2}}\) Ca\(^{2+}\) channels. Further Ca\(_{\text{2.2}}\) Ca\(^{2+}\) channels blockers are \(\omega\)-conotoxin MVIIA, \(\omega\)-conotoxin CVIA, \(\omega\)-conotoxin CVIB; \(\omega\)-conotoxin CVIC, \(\omega\)-conotoxin CVID, \(\omega\)-conotoxin SO-3, DW 13.3 and Huwentoxin HWTX I [23 - 25]. Omega (\(\omega\))-conotoxin MVIIIC, a toxin from the venom gland of the marine snail *Conus magnus*, targets both Ca\(_{\text{2.1}}\) and Ca\(_{\text{2.2}}\) Ca\(^{2+}\) channels [4, 26 - 30]. In contrary, glycerotoxin from the venom of *Glycera convoluta* was shown to act as an activator of Ca\(_{\text{2.2}}\) Ca\(^{2+}\) channels [31]. Although most naturally derived peptide toxins are predominantly of experimental interest and not yet applicable in humans, Ca\(_{\text{2.1}}\)-2.3 VGCCs turned out to serve more and more as potential targets in epilepsy, pain treatment and other neurological diseases. Gabapentin, for example, inhibits Ca\(_{\text{2.1}}\) Ca\(^{2+}\) channels via interaction with the \(\alpha\),\(\delta\) auxiliary subunits (albeit non-selectively), and it can influence pain and epilepsy in humans [32]. Ziconotide (\(\omega\)-conotoxin MVIIA, *i.e.* SNX-111), a toxin derived from the marine piscivorous snail *Conus geographus*, is likely to inhibit Ca\(_{\text{2.2}}\) Ca\(^{2+}\) channels and is a potent drug in humans who turned out to be refractory or non-tolerant to opioids [29, 30]. The GABA\(_{\text{b}}\) receptor agonist baclofen can strongly inhibit Ca\(_{\text{2.1}}\) and Ca\(_{\text{2.3}}\) whereas \(\epsilon\)-Vc1.1, a cyclized version of the analgesic \(\alpha\)-conotoxin Vc1.1 acting through GABA\(_{\text{b}}\) receptors, did not affect Ca\(_{\text{2.1}}\) but severely inhibited Ca\(_{\text{2.3}}\) Ca\(^{2+}\) channels. These findings support the view that Vc1.1 inhibition of Ca\(_{\text{2.3}}\) VGCCs defines Ca\(_{\text{2.3}}\) Ca\(^{2+}\) channels as a potential target in analgesic treatment [33]. For the LVA Ca\(_{\text{3}}\) Ca\(^{2+}\) channels, a number of potential inhibitors have been evaluated, such as the tetraline derivative mibefradil and the scorpion toxin kurtoxin [34]. Other potential T-type Ca\(^{2+}\) channel blockers include Protoxin-I or \(\beta\)-theraphotoxin-Tp1a (ProTx-I), NNC55-0396, ML-218 and pimozide. Recently, azetidinones and spiro-azetidines have been described as novel potential blockers of the T-type Ca\(^{2+}\) channel Ca\(_{\text{3.2}}\) being of potential relevance for the treatment of neuropathic and inflammatory pain [35]. However, these potential T-type blockers have not reached clinical application so far. Diphenylalkylamine derivatives such as flunarizin or cinnarizin exhibit a non-specific blockade on VGCCs. Recently, new generation state-dependent T-type Ca\(^{2+}\) channel antagonists such as TTA-P2 and TTA-A2 have been described which seem to interfere preferentially with inactivated T-type Ca\(^{2+}\) channels [36]. Both state-dependent blockers exhibit analgesic effects in rodent models of pain. Z123212, a bi-targeting inhibitor of voltage-dependent Na\(^{+}\) channels and T-type Ca\(^{2+}\) channels exerts its analgesic effect by selectively targeting the slow inactivated state of the channels [37]. Notably, phase I clinical trials for the treatment of pain are currently performed for Z944, a state-dependent T-type channel inhibitor. Several pharmaceutical companies have focused their preclinical research on T-type Ca\(^{2+}\) channels inhibitors and activators and the future will reveal if clinical drugs finally emerge from these efforts. Importantly, LVA T-type Ca\(^{2+}\) channels are also sensitive to divalent heavy metal ions, such as Ni\(^{2+}\), Zn\(^{2+}\) or Cu\(^{2+}\) ions [4, 10]. Using a heterologous expression system, Ca\(_{\text{1.2}},\) Ca\(_{\text{2.3}}\) and Ca\(_{\text{3.2}}\) VGCCs were originally reported to be the most Zn\(^{2+}\) sensitive Ca\(^{2+}\) channels with IC\(_{50}\) values of 10.9 ± 3.4 μM, 31.8 ± 12.3 μM and 24.1 ± 1.9 μM, respectively [38]. Recently, it was also shown that Ca\(_{\text{1.2}}\) and Ca\(_{\text{1.3}}\) isoforms can serve as Zn\(^{2+}\) permeation routes mediating Zn\(^{2+}\) flux across the plasma membrane [39]. The functional relevance of this VGCC mediated Zn\(^{2+}\) flux related to Zn\(^{2+}\) transporter protein activity remains unclear.

Importantly, Zn\(^{2+}\) can exert distinct and partially opposite effects on Ca\(_{\text{3.1}}\)-3.3 T-type Ca\(^{2+}\) channels [40]. Whereas Ca\(_{\text{3.2}}\) Ca\(^{2+}\) channels were blocked by submicromolar Zn\(^{2+}\) concentrations (IC\(_{50}\) = 0.78 ± 0.07 μM), Ca\(_{\text{3.1}}\) and Ca\(_{\text{3.3}}\) Ca\(^{2+}\) channels turned out to be less sensitive to Zn\(^{2+}\) (IC\(_{50}\) = 81.7 ± 9.1 μM and IC\(_{50}\) = 158.6 ± 13.2 μM, respectively). Hence, Zn\(^{2+}\) can be used for the pharmacological distinction of different T-type Ca\(^{2+}\) channels. On the electrophysiological level, different Zn\(^{2+}\) effects can be explained by subtype-specific modulation of Zn\(^{2+}\) acting on multiple binding sites of Ca\(_{\text{3.1}}\) and Ca\(_{\text{3.3}}\) channels and altering their gating mechanisms. As a possible allosteric modulator of Ca\(^{2+}\) channels, Zn\(^{2+}\) is responsible for a shift to more negative potentials of the steady-state inactivation curves of Ca\(_{\text{3.1}}\)-3.3 T-type Ca\(^{2+}\) channels and the steady-state activation curve of Ca\(_{\text{3.1}}\) and Ca\(_{\text{3.3}}\) Ca\(^{2+}\) channels [40]. Furthermore, inhibitory effects of Zn\(^{2+}\) are use-dependent and strongly suggest preferential Zn\(^{2+}\) binding to the resting state of T-type Ca\(^{2+}\) channels. Inactivation kinetics for Ca\(_{\text{3.1}}\) and Ca\(_{\text{3.3}}\) were significantly slowed, but not for Ca\(_{\text{3.2}}\) VGCCs. Deactivation kinetics of Ca\(_{\text{3.3}}\) Ca\(^{2+}\) channels were also significantly slowed upon Zn\(^{2+}\) exposure. However, Ca\(_{\text{3.1}}\) and Ca\(_{\text{3.2}}\) tail currents remained affected. An increased Ca\(_{\text{3.3}}\) mediated Ca\(^{2+}\) current was observed after Zn\(^{2+}\) application
and resulted in increased duration of Ca,3.3 mediated action potentials. Consequently, Zn\(^{2+}\) can apparently serve as an opener of Ca,3.3 Ca\(^{2+}\) channel [40].

Within the last decade, Zn\(^{2+}\) emerged to be one of the most important heavy metal ions within the CNS, to the extent that it is was sometimes referred to as “the calcium of the twenty-first century” [41]. Both divalent trace metals, Zn\(^{2+}\) and Cu\(^{2+}\), are implicated in a range of neurological disease states in humans that are characterized by alterations in neuronal excitability and/or neurodegeneration. Importantly, Zn\(^{2+}\) is known to exert significant effects on epileptic activity and excitotoxicity. However, the role of Zn\(^{2+}\) and Cu\(^{2+}\) in epilepsy and excitotoxicity is complex, and partially ambivalent. Whereas a number of studies illustrate that Zn\(^{2+}\) is a potential ionic mediator of selective neuronal injury [42 - 45], others provide strong evidence that Zn\(^{2+}\) is a powerful neuroprotector [41, 46 - 53]. Similarly, Zn\(^{2+}\) was reported to serve as both a proconvulsant [54] and anticonvulsant [55, 56] in humans and various animal models. These findings further support the apparent „Janus“-like behavior of Zn\(^{2+}\) ions in modulating neurodegeneration and seizure susceptibility. However, most of these prima facie contradictory observations described in the literature are based on differences in voltage- and ligand-gated ion channel expression within various neuronal cell types investigated, e.g. hippocampal interneurons versus pyramidal cells. Following KA-induced limbic seizures, hippocampal interneurons exhibit a dramatic increase in cytosolic Zn\(^{2+}\)-concentration and cell death which is supposed to be due to mitochondrial dysfunction [44] and activation of specific Zn\(^{2+}\)-signaling pathways [57]. Hippocampal interneurons were further reported to express Ca\(^{2+}\)-permeable AMPA-receptors [58], and to release Zn\(^{2+}\) from mitochondria and other intracellular stores or metallothioneins [44]. Zn\(^{2+}\)-levels turned out to be higher in interneurons compared to hippocampal pyramidal cells [59] due to differences in Ca\(^{2+}\)-AMPA-receptor expression. Ca\(^{2+}\)-buffering systems and differences in mitochondrial metabolism [60]. Compared to interneurons, CA3 pyramidal cells display only a moderate increase in internal Ca\(^{2+}\)-levels after KA treatment [59]. Findings of Zn\(^{2+}\)-release, intracellular Zn\(^{2+}\)-accumulation and its effects on KA-seizure susceptibility and excitotoxicity are rather divergent as well. Whereas extracellular chelation of Zn\(^{2+}\) in one study neither affected hippocampal excitability nor seizure-induced cell death [61], studies by Takeda et al. illustrated that Zn\(^{2+}\) can clearly attenuate KA-induced limbic seizure activity and concomitant neurodegeneration in the CA3 region, or induce inverse effects, when being chelated extracellularly [46 - 53, 62]. Thus, by complex modulation of the inhibition - excitation balance involving VGCCs, Zn\(^{2+}\)-homeostasis is crucial for both the induction of and the prevention of hyperexcitability-related seizure development and neurodegeneration. Most importantly, Zn\(^{2+}\) ions can exhibit not only different modulatory effects on numerous voltage- and ligand-gated ion channels such as VGCCs, but also enter cells via different channels including VGCCs, AMPA-, NMDA- and KA-receptors, particularly when neurons exhibit repetitive activation or hyperexcitability [41, 45, 63]. Thus, both Ca\(^{2+}\) and Zn\(^{2+}\) can serve as synaptic or transynaptic second messengers with extracellular diffusion, e.g. spillover effects at mossy fibre terminals enabling complex heterosynaptic modulation. In line with these findings, synaptically released Zn\(^{2+}\) can effectively inhibit long-term potentiation (LTP) presynaptically at the mossy fiber synapse [64]. These findings directly corroborate the crucial role of HVA Ca,2.3 R-type Ca\(^{2+}\) channels, serving as a Zn\(^{2+}\) target in presynaptic LTP [38, 65, 66] as will be outlined below (Fig. 2).

In drug research and development there is a strong need for new medical entities, i.e. first-in-class medicines that preferentially target individual Ca\(^{2+}\) channel entities. Arranz-Tagarro et al. [20] provided a summary of 23 patents in the period 2011-2013 claiming selectivity of newly synthesized compounds for HVA L- and N-type and LVA T-type Ca\(^{2+}\) channels. It’s noteworthy that indications of L-type blocker patents are mostly related to treatment of Parkinson’s disease but also cardiovascular and neurodegenerative diseases. However, those blocking N- and T-type Ca\(^{2+}\) channels predominantly address neuropathic pain at the spinal cord, but also intractable pain of peripheral diabetic neuropathy, herpes, cancer, trigeminal neuralgia, migraine, post-surgery and inflammatory pain. Within the Ca,3 T-type subfamily, a specific pharmaceutical focus has been on Ca,3.2 Ca\(^{2+}\) channels. The most often claimed indication, particularly for T-type Ca\(^{2+}\) channels, is epilepsy. Pathophysiologically, some seizures and epilepsy entities share common neuronal circuits with similar pathophysiological dysrhythmics. As outlined below this holds true for the thalamocortical (TC)-corticothalamic circuitry which is essential for the generation of slow-wave-sleep (SWS). Aberrant network activity i.e. hyperoscillation within this circuitry can result in absence epilepsy. Thus, Ca\(^{2+}\) channel modulators targeting absence epilepsy might also be effective in the treatment of sleep disorders for example. A major drawback in the development of Ca\(^{2+}\) channel blockers is the wide distribution of various Ca\(^{2+}\) channel subtypes with similar molecular structure in the brain and peripheral tissues. This may give rise to intolerable side effects. Given the tremendous physiological implications of VGCCs, it is not surprising that numerous voltage-gated Ca\(^{2+}\)-channelopathies have been
identified so far [67, 68] (Table 1).

Table 1. Pharmacology and tissue distribution of VGCCs as well as related channelopathies (reprinted from [68]).

| Ca,-αi | Pharmacology                  | Tissue affected | Syndromes associated                                      |
|--------|-------------------------------|-----------------|------------------------------------------------------------|
| Ca,1.1 | Dihydropyridine, Benzoiazepine, Phenyalkylamine, TaCatoxin, Calciseptine Calcinudine, FS-2 | skeletal musclesubiquitary | Hypokalemic periodic paralysis type 1 (HypoPP1), malignant hyperthermia type 5 (MHSS) Timothy syndrome (LQT8, epilepsy) Not known |
| Ca,1.2 |                               | ubiquitary       | x-linked congenital stationary night blindness 2 (xCSNB2), X-linked cone-rod dystrophy type 3 (CORDX3) |
| Ca,1.3 |                               | retina           |                                             |
| Ca,1.4 |                               | CNS/heart        |                                             |
| Ca,2.1 | αα-Agatoxin IVA                | CNS              | Absence-epilepsy, episodic ataxia type 2, spinocerebellar ataxia type 6, familial hemiplegic migraine, Lambert-Eaton myastenia-syndrome |
| Ca,2.2 | αα-Conotoxin GVIA              | CNS/PNS          | Lambert-Eaton myastenia-syndrome |
| Ca,2.3 | SNX-482, Ni2^+                 | CNS/PNS          | Not known |
| Ca,3.1 |                               | CNS/PNS          | Absence-epilepsy (CAE), Autism spectrum disorders (ASD) |
| Ca,3.2 |                               | CNS/heart        | Not known |
| Ca,3.3 | Mibebradil, Kurtoxin, Ni2^+    | CNS              |                                          |

Besides the pore-forming αi subunits, it is noteworthy that the auxiliary subunits αδ1,4, β1,4 and γ1,8 can substantially...
influence the basic electrophysiological and pharmacological characteristics as well as the plasma membrane translocation of the Ca\(_{\text{\beta}}\)-\(\alpha\) subunits [6, 69] and might also serve as targets in future drug research and development.

The Ca\(_{\text{\beta}}\) subunit for example determines the plasma membrane density of the pore-forming Ca\(_{\text{\beta}}\)_2.3 \(\alpha\) subunit. Four leucine residues in Ca\(_{\text{\beta}}\) form a hydrophilic pocket surrounding key residues in the Ca\(_{\text{\beta}}\)_2.3 \(\alpha\)-domain. This interaction seems to play an important role in conferring Ca\(_{\text{\beta}}\)-induced modulation of the protein density of Ca\(_{\text{\beta}}\)_2.3 subunits in Ca\(_{\text{2+}}\) channels [70]. In this context, interaction partners of VGCCs turned out to be most relevant in drug discovery and development, particularly in the field of epilepsy. Recently, an exceptional study on quantitative proteomics of Ca\(_{\text{2+}}\) channel nano-environments, using knockout-controlled multiple epitope affinity purifications together with high-resolution quantitative mass spectroscopy was carried out to unravel the molecular players in local subcellular signalling [71]. About 200 proteins have been identified that clearly differ in abundance, stability of assembly and preference for the individual Ca\(_{\text{2+}}\) subunits. These potential interaction partners included kinases and phosphatases, cytoskeleton proteins, enzymes, SNAREs, modulators and small G-protein coupled receptors, ion channels and transporters, adaptors, extracellular matrix proteins, cytomatrix components, protein trafficking components and additional proteins of yet unknown function.

**Ca\(_{\text{2+}}\) CHANNELS IN ICTOGENESIS AND EPILEPTOGENESIS**

Under physiological conditions, Ca\(_{\text{2+}}\) influx into functional neurons is organized in a complex fashion including amplitude, frequency and space as the spatiotemporally integrated free cytosolic Ca\(_{\text{2+}}\) concentration encodes specific information [72]. In general, cytosolic Ca\(_{\text{2+}}\) increase is mediated via release from intracellular Ca\(_{\text{2+}}\) stores, such as the endoplasmatic and sarcoplasmatic reticulum, via Na\(^+/\)Ca\(_{\text{2+}}\) exchanger, VGCCs and an armamentarium of other, often less-specific voltage- and ligand gated cation channels. VGCCs effectively couple complex neural activation patterns to cytosolic Ca\(_{\text{2+}}\) influx. Until internal Ca\(_{\text{2+}}\) buffering procedures restore the resting intracellular Ca\(_{\text{2+}}\) levels [73, 74], the cytosolic Ca\(_{\text{2+}}\) concentration triggers crucial cellular functions, e.g. channel modulation, release of neurotransmitters and gene transcription. The Ca\(_{\text{2+}}\) influx via VGCCs is supposed to be of central relevance in hyperexcitability and excitotoxicity mediated neurodegeneration. For example, the so called Ca\(_{\text{2+}}\) hypothesis of epileptogenesis proposes that altered cytosolic Ca\(_{\text{2+}}\) levels may play a critical role in icotonogenesis and epileptogenesis [75 - 78]. Both HVA and LVA Ca\(_{\text{2+}}\) channels are predominant mediators of internal Ca\(_{\text{2+}}\) elevation during most epileptiform activity [75, 79]. In hippocampal neurons it has been reported that the density of Ca\(_{\text{2+}}\) current was up-regulated during icotonogenesis / epileptogenesis [80] and inhibition of VGCCs substantially depressed epileptiform activity [81, 82]. On the cellular electrophysiological level, Ca\(_{\text{2+}}\) channels were proven to be of central importance in mediating potential ictiform / epileptiform activity, such as afterdepolarization (ADP), plateau potentials (PP) and exacerbation of low-threshold Ca\(_{\text{2+}}\) spikes (LTCS) / rebound burst firing thus mediating seizure initiation, propagation and kindling [34, 83 - 86]. In addition, VGCCs exert major effects in excitotoxicity and neurodegeneration contributing to the devastating pathophysiology of human neuronal diseases associated with neurodegeneration [87 - 89]. Therefore, pharmacological modulation of VGCCs is a promising approach in functional interference with seizure activity, excitotoxicity and neurodegeneration [90 - 96]. As outlined below, many studies regarding the involvement of VGCCs in icotonogenesis and epileptogenesis were carried out on HVA Ca\(_{\text{2.1}}\) and LVA Ca\(_{\text{3}}\) type Ca\(_{\text{2+}}\) channels. However, within the last years, a specific focus has been on the unexpected role of Ca\(_{\text{2.3}}\) R-type VGCCs in the field of epilepsy.

**WHAT MAKES Ca\(_{\text{2.3}}\) R-TYPE Ca\(_{\text{2+}}\) CHANNELS SPECIAL?**

The Ca\(_{\text{2.3}}\) R-type Ca\(_{\text{2+}}\) channel exhibits a complex histological and cellular distribution pattern with Ca\(_{\text{2.3}}\) being expressed in the peripheral and central nervous system (CNS), the endocrine [97, 98], cardiovascular [99 - 101], reproductive [102 - 105], and gastrointestinal system [106]. Additionally, Ca\(_{\text{2.3}}\) is of central relevance in the developing lung [107] and sensing organs such as the inner ear and organ of Corti [108]. In the last 15 years researchers have gained tremendous insight into the functional role of Ca\(_{\text{2.3}}\) Ca\(_{\text{2+}}\) channels based on the generation of Ca\(_{\text{2.3}}\) deficient mice. Within the CNS, Ca\(_{\text{2.3}}\) VGCCs are involved in presynaptic / postsynaptic plasticity and neurotransmitter release [65, 66]. Additionally, Ca\(_{\text{2.3}}\) Ca\(_{\text{2+}}\) channels were shown to be engaged in the control of pain behavior [109], the physiology of fear [110] and myelogenesis [111]. Interestingly, Ca\(_{\text{2.3}}\) VGCCs are also involved in the semaphorin 3A mediated conversion of axons to dendrites and the control of neuronal identity during nervous system development [112]. Furthermore, Ca\(_{\text{2.3}}\) Ca\(_{\text{2+}}\) channels seem to exhibit a protective function in ischemic neuronal injury [113] and contribute to vasospasms following subarachnoid hemorrhage in humans [114]. Ca\(_{\text{2.3}}\) R-type
VGCCs were also thought to play a crucial role in mediating analgesic opioid effects and underlying pain pathways. Although it remains unknown to a large extent whether single-nucleotide polymorphisms of the human CACNA1E gene encoding Ca,2.3 VGCCs affect the analgesic effects of opioids, there is increasing evidence of a link between CACNA1E gene polymorphisms and fentanyl sensitivity [115]. Besides Ca,1.2, the Ca,2.3 VGCC is also expressed in colonic primary sensory neurons and was reported to be of major importance in visceral inflammatory hyperalgesia [116]. Inhibition of Ca,2.3 VGCCs by eugenol was also shown to contribute to its analgesic effect [117]. The expression of Ca,2.3e as the main R-type VGCC isoform in nociceptive DRG neurons also points to a potential target for pain treatment, e.g. in the trigeminal and spinal cord system [118, 119]. Furthermore, Ca,2.3 Ca\(^{2+}\) channels were detected in small to medium muscle afferent neurons revealing the following expression pattern: Ca,2.2 > Ca,2.1 ≥ Ca,2.3 > Ca,1.2 channels [120]. Notably, Ca,2.3 VGCC are dominantly expressed presynaptically, e.g. in mossy fibers of the hippocampus [121] and the pallidal globe [122], besides Ca,2.1 [123] and Ca,2.2 [124] and it is also expressed at the neuromuscular junction [125]. At the presynaptic site, a minor fraction of Ca,2.3 VGCCs are localized to the active zone of the vesicle fusion machinery and thus functionally contributes to neurotransmission [123]. A dominant fraction however, is localized more peripheral in the synapse responsible for synaptic plasticity, e.g. long-term potentiation (LTP) [66]. In addition, it should be noted that Ca,2.3 R-type VGCCs are homogenously expressed on the cell soma and the dendritic arbor. The dendritic expression pattern is highly complex and only present in certain CNS nuclei and specific cell types, such as CA1 neurons. The highly organized spatial distribution pattern of Ca,2.3 Ca\(^{2+}\) channels with predominant expression in the proximal or distal dendrites clearly differs from other HVA VGCCs [126]. Functionally, Ca,2.3 was reported to underlie the generation of Ca\(^{2+}\)-dependent APs. The latter are conducted along the ramified dendritic arbor which serves an important entry site of Ca\(^{2+}\) and crucial factor in neural electrogensis [127]. This characteristic somatodendritic function of Ca,2.3 VGCCs is likely to be involved in a number of characteristicictiform / epileptiform electrical phenomena. Ca,2.3 R-type Ca\(^{2+}\) channels were considered to be unique as they turned out to be resistant to most Ca\(^{2+}\) channel blockers. In 1998 however, the spider peptide toxin SNX-482, derived from the venom of the tarantula Hysterocrates gigas (homologous to the spider peptides grammatoxin S1A and hanatoxin), was demonstrated to be a selective Ca,2.3 Ca\(^{2+}\) channel antagonist at low nanomolar concentrations (IC\(_{50}\) = 15-30 nM) [128]. Recently however it turned out that SNX-482 also dramatically reduces A-type K\(^{+}\) currents in mouse dopaminergic neurons from the substantia nigra pars compacta. Patch-clamp studies on K,4.3 stably transfected HEK293 cells revealed an IC\(_{50}\) < 3nM which indicates a substantially higher potency than for SNX-482 inhibition of Ca,2.3 Ca\(^{2+}\) channels [129]. Thus, caution has to be exercised when interpreting SNX-482 antagonistic effects on cells and neural circuits where these channels are actually expressed. Ca,2.3 blocking effects were also reported for DW 13.3, the Phoneutria (Ctenus) nigriventer (Brazil armed spider) toxin ω-CTenitoxin-Pn2a including ω-PnTx3-3, ω-PnTx3-6 and ω-phonetoxin IIA [20]. In addition, Ca,2.3 Ca\(^{2+}\) channels exhibit high sensitivity to divalent heavy metal ion such as Ni\(^{2+}\) (IC\(_{50}\) = 27 μM), a property that they share with Ca,3.2 Ca\(^{2+}\) T-type channels (IC\(_{50}\) = 5-10 μM [130]). Furthermore, in vitro dose-concentration studies using the HEK 293 heterologous expression system and calibrated heavy metal ion concentrations revealed that Ca,2.3 is a most sensitive target of Zn\(^{2+}\) and Cu\(^{2+}\) ions with IC\(_{50}\) values of 1.3 ± 0.2 μM and IC\(_{50}\) = 18.2 ± 3.7 nM, respectively, using voltage steps to -20 mV representative for effects on activation gating. In the same setting IC\(_{50}\) values of 8.1 ± 1.4 μM for Zn\(^{2+}\) and 269 ± 101 nM for Cu\(^{2+}\) representative for action on conductance with voltage steps to +20 mV were obtained [131]. This clearly differs from other ion channels and receptors, e.g. NMDAR (IC\(_{50}\) = 270 nM) and Ca,3.2 (IC\(_{50}\) = 900 nM) [132, 133]. Abolishing the effects on potential binding sites of divalent heavy metal ions by chelation or by substitution of key amino acid residues in the IS1–IS2 (H111) and IS3–IS4 (H179 and H183) loops substantially enhanced Ca,2.3 mediated Ca\(^{2+}\) influx. This is mediated by a shift in the voltage-dependence of activation towards more negative membrane potentials [131]. The authors further demonstrated that Cu\(^{2+}\) modulates the voltage dependence of Ca,2.3 Ca\(^{2+}\) channels by affecting gating charge movements. The presence of Cu\(^{2+}\) ions resulted in a delay in activation gating and a reduction of voltage sensitivity of the channel. It was further shown that neurotransmitters, such as glutamate and glycine can serve as trace metal chelators per se and thus substantially regulate activity of Ca,2.3 VGCCs by modulating their voltage-dependent gating. Interestingly, glutamate substantially potentiated the activity of Ca,2.3 Ca\(^{2+}\) channels at hyperpolarized potentials by shifting their voltage-dependent activation curve towards more negative voltages. Most importantly, the glutamate effect on Ca,2.3 Ca\(^{2+}\) channels was clearly based on the chelating effect and mechanistically distinct from the activation of intracellular signal transduction cascades [134]. Glutamate effects on Ca,2.3 are exerted from the extracellular space and although the trace metal binding character has been documented before [135] it was not considered to be physiologically relevant until now.
Importantly, it has never been mentioned before that trace amounts of divalent heavy metals that often contaminate external solutions [130, 136] can exert tonic antagonistic effects on Ca,2.3 voltage-dependent gating. Due to the observed shifts in IV-curves and changes in current kinetics in the presence of various Zn\textsuperscript{2+} and Cu\textsuperscript{2+} concentrations, Ca,2.3 VGCC turned out to be mid-voltage activated in a Zn\textsuperscript{2+} and Cu\textsuperscript{2+} low/free environment. It has been estimated that an average HEPES–TEA solution contains about 50 nM Cu\textsuperscript{2+}, which can result in a 17 mV negative shift in the Ca,2.3 Ca\textsuperscript{2+} activation curve. In addition, trace metal chelation also enhanced Ca,2.3 Ca\textsuperscript{2+} current inactivation kinetics [131]. These findings are likely to have a severe impact on our view on Ca,2.3 VGCCs and require a thorough re-assessment of previously reported electrophysiological studies on Ca,2.3 VGCCs. Additionally, they demonstrate that basic electrophysiological properties of VGCCs can be modulated by local changes in environmental cell conditions and that a plethora of new (patho) for the Ca,2.3 VGCC entity (Fig. 2). It should further be noted that extracellular acidification can decrease Ca\textsuperscript{2+} current amplitude and results in a depolarizing shift in the activation potential (V\textsubscript{1/2}) of VGCCs. These effects hold true for all VGCC including Ca,2.3, but differences occur between individual VGCC entities and the underlying molecular mechanisms remain unknown. Alterations of Ca\textsuperscript{2+} current amplitude effectuated by extracellular acidification or alkalisation were shown to be of higher importance for Ca,2.3 R type VGCCs than for Ca,2.1 P/Q-type channels for example [137].

MODULATION OF Ca,2.3 VGCCS VIA DIFFERENT RECEPTORS AND SIGNALING CASCADES

A number of Ca,2.3 splice variants have been described [138] and this diversity is likely to be potentiated by co-assembly with different auxiliary subunits such as α,δ, β, and γ. The Ca,2.3 VGCC is modulated biochemically by interconversion, i.e., phosphorylation and dephosphorylation. These two processes are of central relevance as they can alter fundamental electrophysiological properties of the channel and are related to the induction and perseveration of epileptiform burst activity in neurons [139] as outlined below. Interestingly, Ca,2.3 VGCCs are automodulated in a bidirectional manner depending on the Ca\textsuperscript{2+} influx via Ca,2.3 R-type Ca\textsuperscript{2+} channels. If cytosolic Ca\textsuperscript{2+} concentrations are low, Ca,2.3 activation via protein kinase C (PKC) slows down the inactivation kinetics and enhances recovery from short-term inactivation [140, 141]. This mechanism represents a positive feedback based on the presence of exon 19 that represents an arginine rich insert 1 in the cytosolic II–III loop [138]. In consequence, Ca,2.3e R-type Ca\textsuperscript{2+} channels lacking exon 19 encoded insert 1, exhibit only residual phorbol ester mediated stimulation which is however still significant. This view is supported by the observation that coexpression of PKC\textalpha with Ca,2.3e results in similar kinetics of inactivation and recovery as obtained for the full length II–III loop splice variant Ca,2.3d. These findings suggest that the expression pattern of Ca,2.3 splice variants in different brain regions is of significant relevance for neuronal mechanisms underlying neuroprotection, icto-/epileptogenesis and seizure propagation [94]. Importantly, a positive feedback mechanism by Ca\textsuperscript{2+} influx was also reported for L-type Ca\textsuperscript{2+} channels and is mediated through Ca\textsuperscript{2+}/calmodulin kinase II [142]. At elevated cytosolic Ca\textsuperscript{2+} concentrations however, a prominent Ca\textsuperscript{2+}-dependent inactivation renders the channel activity to further increase [143]. PKC-mediated protein phosphorylation is of major physiological relevance, mediating intracellular messengers and hormonal effects. VGCCs serve as effectors in numerous regulatory neurotransmitter and hormonal pathways initiated by G-proteins. This G-protein mediated regulation of VGCCs can either be indirect via second messengers and/or protein kinases or direct via physical interaction between G-protein subunits and the Ca, α\textsubscript{1}-subunit. Functional studies elicited that G-protein interaction reversibly inhibits neuronal non-L type Ca\textsuperscript{2+}-channels. Peak current amplitude is reduced and activation kinetics is slowed. The effects of the heterotrimeric G-proteins on VGCC are well described for the G\textsubscript{i/o} dimer [144, 145], whereas the role of G\textsubscript{i} is yet not well understood. There is strong evidence that G\textsubscript{i/o} directly interacts with the I–II linker of the Ca, α\textsubscript{1}-subunit [146, 147]. Furthermore, the N-terminus of Ca,2 α\textsubscript{1} subunits also seems to be involved in G-protein coupled modulation [148] including Ca,2.3. The G\textsubscript{i/o} interaction site within the I–II linker partially overlaps the AID (α\textsubscript{i}-interacting domain) where β subunits bind. This observation suggests a physical competition between the agonistic β-subunits [148, 149] and the antagonistic effects of G\textsubscript{i/o} [150]. Interestingly, it turned out that G\textsubscript{i/o} exhibits inhibitory effects on LVA Ca,3 T-type Ca\textsuperscript{2+}-channels via interaction with the II–III-loop [151]. There are further hints of a sophisticated interdependence between G-protein pathways and PKC as activation of PKC antagonizes adjacent receptor-mediated G-protein inhibition of VGCC [147, 152]. Accumulation of internal Ca\textsuperscript{2+} at low concentrations leads to tonic activation of Ca,2.3d resulting in enhanced responses, i.e., slowed inactivation and accelerated recovery from inactivation [140]. It has been reported by Dietrich et al. [66] that Ca,2.3 Ca\textsuperscript{2+} channels contribute selectively to the so-called residual internal Ca\textsuperscript{2+} concentration which is essential for various forms of synaptic plasticity, but contributes less to the release of
neurotransmitters. However, this residual internal Ca$^{2+}$ can reach concentration of up to 0.5 mM [153, 154] and is capable of facilitating Ca$^{2+}$ currents through Ca$_{2,3}$d channels [140]. A positive feedback mechanism based on PKC activation might later be attenuated by negative feedback involving the N-lobe calmodulin-dependent modulation [143] and therefore help to maintain physiological internal Ca$^{2+}$ concentrations. The PKC mediated modulation is one final step in the muscarinergic signal transduction cascade. It had been described earlier that Ca$_{2,3}$ Ca$^{2+}$ channels when expressed in HEK cells with M$_t$ muscarinic receptors, exhibit a biphasic modulation [155 - 157]. Muscarinic inhibition of Ca$_{2,3}$ VGCCs is mediated by G$_{b/2y}$ subunits, whereas stimulation is mediated by pertussis toxin-insensitive G$_s$ subunits [158]. These authors compared the modulation of Ca$_{2,3}$ Ca$^{2+}$ channels by the three G$_{a11}$-coupled muscarinic receptors M$_t$, M$_i$ and M$_o$, revealing that these receptors trigger comparable stimulation of Ca$_{2,3}$ channels. The signaling pathway that mediates stimulation was analyzed for M$_t$ receptors in detail indicating that muscarinic stimulation of Ca$_{2,3}$ involves signaling by G$_{a11}$, diacylglycerol (DAC), and a Ca$^{2+}$-independent PKC. In contrast to stimulation, the G$_{b/2y}$ mediated magnitude of Ca$_{2,3}$ inhibition depended on the receptor subtype, with M$_t$ and M$_i$ receptors producing larger Ca$_{2,3}$ inhibition than M$_o$ receptors. Interestingly, muscarinic inhibition of Ca$_{2,3}$ Ca$^{2+}$ channels was notably enhanced during pharmacological suppression of PKC, suggesting the presence of cross-talk between G$_{b/2y}$-mediated inhibition and PKC-mediated stimulation of Ca$_{2,3}$ R-type Ca$^{2+}$ channels similar to what has been described previously for N-type channels. The role of muscarinic modulation of Ca$_{2,3}$ VGCCs in ictogenesis and seizure activity will be discussed below. It should be noted that Ca$_{2,3}$ is also substantially regulated by small GTPase RhoA [159] and it was speculated that this might influence synaptic transmission during brain development and contribute to pathophysiological processes when axon regeneration and growth cone kinetics are impaired [159].

Ca$_{2,3}$ TYPE VGCCS IN CONVULSIVE SEIZURE ACTIVITY

Aberrant burst activity is a typical feature of neuronal epileptiform activity. Each cellular burst is based on a slow, persistent depolarization, the so-called PP [160] which can last up to seconds [161, 162]. A PP is regenerative, spike dependent and is mediated by the summation of depolarizing APs [163, 164]. In addition, internal Ca$^{2+}$ levels attain a plateau that is typically 4200 nM above rest and reached after several seconds of activity. However, the PP generally collapses soon, once the electrical activity has ceased and the membrane repolarizes again [163, 164]. As regards PP termination, it has been suggested that an increase of internal Ca$^{2+}$ and the subsequent activation of a Ca$^{2+}$-dependent K$^+$-mediated afterhyperpolarisation (AHP) might account for this phenomenon [165, 166]. Besides, a shift from Ca$^{2+}$-dependent facilitation to Ca$^{2+}$-dependent inactivation of VGCCs with increased internal Ca$^{2+}$ levels might also be involved. Generally, PPs and ADP are common electrophysiological phenomena in different neuronal cell entities in different brain regions such as spinal and brainstem motor neurons, spinal interneurons, dorsal horn neurons, subicular and entorhinal cortical cells, subthalamic nucleus neurons, suprachiasmatic neurons, striatal cholinergic neurons and hippocampal pyramidal cells [167]. Nevertheless, the entire voltage- and ligand-gated ion channel armamentarium underlying PP and ADP generation is still not fully understood. Recent studies more and more suggest that Ca$_{2,3}$ VGCCs are potent players in PP and ADP generation thus serving an important role in ictogenesis [168 - 175].

Importantly, one has to consider that these data were recorded from various tissue preparations from different species and that dihydropyridines involved in these studies exert complex action on VGCCs. Experimental conditions, such as neuronal membrane potential or penetration depth of various VGCC blockers in CNS slices can severely modulate electrophysiological results [176 - 178].

Various neurological and cardiovascular studies have suggested that Ca$_{1,3}$ could mediate both a low-threshold and low-dihydropyridine sensitive L-type Ca$^{2+}$ current [12, 15]. In consequence, Ca$_{1,3}$ was speculated to be involved in PP generation in different neuronal cell types. Whereas the electrophysiological behavior of LVA Ca$_{1,3}$ Ca$^{2+}$ channels has been described recently [12, 14], Ca$_{2,3}$ had already been known to exhibit low- to mid-voltage activated activity based on both activation and steady-state inactivation kinetics prominent at relatively negative membrane potentials [99, 167, 179 - 183]. In addition, Ca$_{2,3}$ R-type Ca$^{2+}$ channels were shown to contribute to sustained PPs and ADPs in hippocampal CA1 neurons with the latter known to enhance neural excitability and epileptogenicity [85, 184]. Studies by Fraser and MacVicar [185] and Fraser et al. [186] demonstrated that carbachol mediated cholinergic stimulation of CA1 neurons causes slow ADP and long lasting PP both of which resemble epileptiform activity. In general, activation of the cholinergic system is a well-known approach to induce limbic seizures both in vitro and in vivo [187 - 190]. Importantly, PPs are important electrophysiological phenomena in ictogenesis mediated by Ca$^{2+}$ influx through VGCCs. They are modulated upon muscarinic receptor activation and mediate activation of guanylate cyclase activity and
subsequent increase in cGMP [191] (Fig. 3). Ca,2.3 R-type VGCCs were proven to be responsible for Ca\(^{2+}\) influx in dendritic spines, e.g. of CA1 neurons [192] and it was further depicted that a reduction of R-type Ca\(^{2+}\) current reduces the accumulation of postsynaptic [Ca\(^{2+}\)], particularly following recurrent synaptic activation [193, 194]. Notably, stimulation of metabotropic muscarinic receptors via carbachol for example results in inhibition of L-, N-, and P/Q-type VGCCs [195 - 197]. In contrast, R-type Ca\(^{2+}\) current is significantly enhanced [198 - 200]. Topiramate, an AED drug that was shown to block carbachol-induced PPs in subicular bursting cells [201] was used by Kuzmiski et al. [85] to directly prove that topiramate can dampen the generation of PPs by inhibiting R-type VGCCs. Pharmacodynamically, topiramate has a multi-target character interacting with, e.g. voltage-gated sodium channels, VGCCs and AMPA/kainate receptors or GABA(A) receptors [85, 202]. Kuzmiski et al. [85] utilized Ca,2,3 expressing tsA-201 cells that were co-transfected with β\(_{2,3}\) and α\(_{2,3}\) auxiliary subunits to demonstrate that topiramate can block Ca,2,3 mediated Ca\(^{2+}\) currents at therapeutically relevant concentrations. Their studies revealed an IC\(_{50}\) of 50.9 μM and complex alterations in electrophysiological characteristics including a shift of the steady-state inactivation curve to more negative potentials. The Ca\(^{2+}\) spikes that were provoked in this study were transient and high-threshold activated. Following application of TTX and a cocktail of VGCC blockers (i.a. nifedipine 10 μM) to eliminate other current components, the remaining Ca\(^{2+}\) spike was based on R-type mediated Ca\(^{2+}\) current. The latter was increased upon carbachol administration concomitant to an enhanced spike frequency and decreased threshold of Ca,2,3-mediated spiking. As expected, topiramate significantly reduced the R-type Ca\(^{2+}\) spike amplitude. Kuzmiski et al. [85] did not report on experiments to block R-type Ca\(^{2+}\) currents using SNX-482 [128] which serves as a rather selective blocker of Ca,2,3 R-type channels. However, as outlined above the Ca,2,3 Ca\(^{2+}\) channel selectivity of SNX-482 has recently been substantially challenged [129]. Ca,2,3 Ca\(^{2+}\) channels were reported to contribute at around 80% to R-type Ca\(^{2+}\) current in CA1 neurons. Furthermore, the R-type component turned out to be sensitive to low Ni\(^{2+}\) concentrations (50 μM). Taking into account that 10 μM nifedipine can effectively block Ca,2,3 VGCCs [99, 180] one might speculate that a realistic Ca,2,3-mediated topiramate effect on carbachol-enhanced Ca\(^{2+}\) spiking is even more prominent. In the past, detailed studies were carried out to define the signal transduction cascade between muscarinic receptors and Ca,2,3 VGCCs. Melliti et al. [155] and Bannister et al. [158] provided detailed insight how Ca,2,3 VGCCs are modulated upon M\(_1\), M\(_3\) and M\(_4\) muscarinergic receptor stimulation. Importantly, all three muscarinic receptors can exert complex effects on Ca,2,3 VGCCs. Whereas a pertussis toxin-insensitive Ga\(_{o/1}\) subunit, PLCβ, DAG and a Ca\(^{2+}\)-independent PKC signal transduction mechanism mediates stimulation of Ca,2,3, the G\(_{i/o}\) subunits exert inhibitory action on Ca,2,3 VGCCs [203]. Moreover, M\(_1\)/M\(_3\) muscarinic receptor activation was demonstrated to augment R-type, but not LVA T-type Ca\(^{2+}\) currents in rat CA1 pyramidal neurons following selective blockade of N-, P/Q-, and L-type Ca\(^{2+}\) currents [84]. Hippocampal pyramidal neurons are known to highly express postsynaptic M\(_1\) and M\(_3\) receptors [204, 205] which are Ga\(_{o/1}\)-coupled. Activation of M\(_3\)/M\(_3\) and attached G-proteins results in synthesis of DAG and IP3 following PLC activation. DAG can activate Ca\(^{2+}\)-independent group II PKCs, most likely PKC\(\delta\) [84]. This findings goes together with the observation that R-type Ca\(^{2+}\) currents are inhibited upon muscarinic receptor stimulation in CA1 neurons once PKC is inhibited. This phenomenon is due to the activation of pertussis toxin-sensitive G-protein-coupled M\(_1\)/M\(_3\) receptors as well as G\(_{lo}\) subunits [157, 158]. The hippocampal icotigenic potency of Ca,2,3 VGCCs is also confirmed by the observation that mice lacking the M\(_1\) receptor display reduced seizure susceptibility following pilocarpine administration [206]. One should consider that etiopathogenetic mechanisms of icotogenesis and/or epileptogenesis can also include other voltage-dependent Ca\(^{2+}\) conductance as well [207]. During early stages of epileptogenesis, Hendriksen et al. [208] observed a significant increase in Ca,2,1, Ca,1,3- and particularly Ca,2,3 α\(_1\) mRNA levels in the hippocampal compared to control animals in an electrical stimulation model [208].

Within the last decade there has been an increasing number of reports that directly link VGCCs to specific epilepsy entities in humans as well. Indeed, a number of mutations within the ion-conducting Ca\(_{o/1}\) subunits and the auxiliary subunits (β, α\(_{2,3}\), and γ) of VGCCs were shown to be involved in convulsive and non-convulsive seizure activities in humans. These include i.a. childhood absence epilepsy (CAE) or juvenile myoclonus epilepsy (JME). Mutations in the HVA Ca,2,1 VGCC for example were detected in patients suffering from absence epilepsy, episodic ataxia type 2 (EA2), and spinocerebellar ataxia type 6 (SCA6). LVA T-type Ca\(^{2+}\) channels such as Ca,3,2, were proven to be important in the etiology of CAE. In addition, they are important targets for a number of AEDs, e.g., suxinimides, lamotrigine (LTG) and zonisamide (ZNS). Although Ca,2,3 R-type VGCCs are highly expressed in the central nervous system, Ca,2,3 related epilepsy entities have rarely been reported. In one study, mutations in EFHC1, a C terminal interaction partner of Ca,2,3 VGCCs, were shown to cause JME in humans. EFHC1 is known to induce neuronal
Ca\textsubscript{2.3} Ca\textsuperscript{2+} Channels and Seizures

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apoptosis by functional interdependence with Ca\textsubscript{2.3} and related mutations in EFHC1 were shown to disrupt C-terminal binding. Interestingly, the lack of apoptosis causes increased cell density and hyperexcitable neural circuits in affected patients. More in vivo data on Ca\textsubscript{2.3} VGCCs in epileptogenesis are available on the preclinical level. Electroencephalographic characterization of Ca\textsubscript{2.3} deficient mice exhibited no indications of spontaneous epileptiform graphoelements. However, seizure susceptibility testing proved that Ca\textsubscript{2.3} VGCCs can contribute to seizure initiation, propagation, termination, and kindling [92, 139, 209]. Pentyleneetrazol (PTZ)-seizure susceptibility was reduced and seizure architecture exhibited severe alterations in Ca\textsubscript{2.3} mice compared with control mice, supporting the proconvulsive action of Ca\textsubscript{2.3} VGCC [94, 96]. Similar findings were also obtained in Ca\textsubscript{2.3} deficient mice following kainic acid (KA) and N-methyl-D-aspartate (NMDA) administration [95]. It turned out that Ca\textsubscript{2.3} mice are also less susceptible to hippocampal seizures compared to control animals and that Ca\textsubscript{2.3} Ca\textsuperscript{2+} channels are not only involved in hippocampal ictogenesis but also complex rhythm generation in the septohippocampal network [210]. It was shown that Ca\textsubscript{2.3} VGCCs contribute to the genesis of atropine-sensitive type II. Urethane-induced atropine-sensitive type II theta oscillations are induced by muscarinic signaling via G\alpha_q, PLC\beta_1, InsP_3, DAG and PKC (Fig. 3) [210]. Unlike PLC \beta_1 deletion, ablation of Ca\textsubscript{2.3} does not result in a total abolishment of type II theta oscillations. However, the temporal characteristics of theta distribution, i.e. theta architecture was significantly altered upon Ca\textsubscript{2.3} deletion [210]. Thus, Ca\textsubscript{2.3} VGCC are also of tremendous in relevance septohippocampal synchronization associated with theta oscillation [210].

![Functional implications of Ca\textsubscript{2.3} R-type VGCC in cellular epileptiform activity, excitotoxicity and thetagenesis.](image)

Ca\textsubscript{2.3} mediated Ca\textsuperscript{2+} influx triggers varies intracellular cascades. One cascade mediates the activation of cyclic-nucleotide gated channels leading to plateau potentials and superimposed bursting. Associated hyperexcitability and Ca\textsuperscript{2+} overload can result in excitotoxicity and neuronal apoptosis. Note that Ca\textsubscript{2.3} Ca\textsuperscript{2+} channels are modulated by muscarinic signaling. The G\alpha_q, DAG and PKC pathway was reported to be associated with thetagenesis as well (reprinted from [260]).

Ca\textsubscript{2.3} VGCCs IN NON-CONVULSIVE SEIZURE ACTIVITY

Behaviorally, typical absence epilepsy is the prototype of non-convulsive seizure activity. It is characterized by a sudden onset and termination of paroxysmal loss of consciousness that is accompanied by bilateral synchronous spike-wave discharges (SWD). The frequency of these SWD turned out to be species-specific [211]. It has been shown several years ago that the TC circuitry, particularly the contribution of the ventrobasal thalamus and the reticular thalamic nucleus (RTN) are functionally involved in the initiation and propagation of absence seizures [212]. In addition, also extrathalamocortical structures, e.g. the reticular formation, the pedunculopontine tegmental nucleus, the laterodorsal tegmental nucleus, the basal nucleus of Meynert, the raphe nuclei, the locus coeruleus and cerebellar structures are functionally connected to the TC circuitry. Interestingly, brain structures like hippocampus or cerebellum that are classically not known to be involved in the generation of absence SWDs in fact also participate in the
development of the absence epilepsy phenotype [213]. On the pathophysiological level, TC dysrhythmia is assumed to be the substrate of SWDs. Electrophysiologically, thalamic relay neurons but also others have the unique capability to shift between different functional states, i.e. the tonic mode, the intermediate mode and the burst firing mode. These different modes strongly regulate transmission of external information to the cortex [214]. The tonic firing mode is typical of stages of high vigilance. When ascending activity originating from deeper brain structures decreases, thalamic relay neurons re- and hyperpolarize. They first exhibit the intermediate mode and finally display rebound burst firing. A number of voltage- and ligand-gated channels involved have been characterized including hyperpolarization and cyclic-nucleotide gated, non-specific cation channels (e.g. HCN2, HCN4) and LVA Ca\(_{\text{2.1-3.3}}\) T-type Ca\(^{2+}\) channels that can trigger LTCSs with superimposed bursts of conventional Na\(^+\)/K\(^+\) APs. Rebound burst firing can be terminated by both voltage- and Ca\(^{2+}\) - activated current entities, e.g., \(I_{\text{A}}\) and \(I_{\text{K(Ca2+)}}\). Rebound burst firing in the TC circuitry is characteristic of low vigilance as holds true for slow wave sleep (SWS). Furthermore, reinforced oscillatory activity accompanied with intensive rebound burst firing of RTN and thalamic relay neurons is of central importance in the etiopathogenesis of absence epilepsy. Within the TC network, oscillatory activity is substantially triggered and sustained by the RTN which helps to control information gating and transfer from the periphery over the thalamus to the cortex. The shell-shaped RTN is strategically placed lateral to the ventrobasal thalamic relay nucleus and exerts inhibitory GABAergic activity on RTN cells themselves as well as on thalamic relay neurons [212]. Interestingly, a number of single-mutation mouse models of absence epilepsy have been described most of which related to genetic ablation of VGCCs. This underlines the critical role of VGCCs in absence epileptogenesis. In particular, HVA Ca\(_{\text{2.1}}\) and Ca\(_{\text{3.2}}\) LVA T-type Ca\(^{2+}\) channels were proven to be of central relevance in this field. For example, the Ca\(_{\text{3.1}}\) VGCC knock-out mouse model was reported to display resistance to absence seizures and a lack of burst firing in TC relay neurons [215]. In addition, Ca\(_{\text{3.1}}\)\(^{-/-}\) mice exhibited altered sleep architecture and a clear lack of delta waves [216]. The Ca\(_{\text{3.1}}\) Ca\(^{2+}\) channel is strongly expressed within thalamic relay neurons. Results obtained from Ca\(_{\text{3.1}}\)\(^{-/-}\) mice strongly indicate that other VGCCs including Ca\(_{\text{2.3}}\) are also of functional relevance within the TC circuitry. In contrast to Ca\(_{\text{3.1}}\)\(^{-/-}\) mice, Ca\(_{\text{2.1}}\) deficient animals are susceptible to absence epilepsy characterized by typical SWDs and motoric arrest [217]. The ablation of the Ca\(_{\text{2.1}}\) P/Q-type VGCCs causes progressive ataxia and altered synaptic transmission in Ca\(_{\text{2.1}}\)\(^{-/-}\) transgenic mice. Amazingly, Ca\(_{\text{3}}\) T-type Ca\(^{2+}\) currents were increased in TC relay neurons obtained from these mice [218]. When Ca\(_{\text{2.1}}\)\(^{-/-}\);Ca\(_{\text{3.1}}\)\(^{-/-}\) double knock-out mice were generated, mice did not exhibit spontaneous SWDs anymore and no T-type Ca\(^{2+}\) current in TC relay neurons could be detected [219]. Besides, Ca\(_{\text{3.1}}\) VGCCs might be involved in movement disorders such as paroxysmal dyskinesia and ataxia [220, 221]. Summing up, enhanced T-type Ca\(^{2+}\) currents in various cellular components of the TC network were shown to be a critical phenomenon in absence epileptogenesis although it does not seem to be a must [219]. Clearly, Ca\(_{\text{3}}\) T- and Ca\(_{\text{2.1}}\) P/Q-type VGCCs are not the only electrophysiological players within the TC circuitry. Gabaergic interneurons of the cortex and the RTN as well as extrathalamocortical structures were proven to express Ca\(_{\text{3.2}}\) VGCCs [96, 179, 222 - 225]. A lot of studies as regards the role of Ca\(_{\text{2.3}}\) VGCCs in absence epileptogenesis were carried out in Wistar Albino Glaxo rats (WAG/Rij) and Genetic Absence Epilepsy Rats from Strasbourg (GAERS). In the latter, increased T-type Ca\(^{2+}\) currents in reticular thalamic neurons have been reported [226] and subsequently also changes in Ca\(_{\text{3.1}}\) and Ca\(_{\text{3.2}}\) Ca\(^{2+}\) channel expression in related thalamic nuclei, i.e. the adult ventroposterior thalamic nuclei and the RTN, respectively [223]. Importantly, de Borman et al. [222] and Lakaye et al. [213] described a prominent decrease of Ca\(_{\text{2.3}}\) VGCC in two extrathalamocortical brain structures in GAERS, the brainstem and the cerebellum both of which project to the TC circuitry, capable of modulating its oscillatory activity [227 - 229]. In addition, the WAG/Rij rat model of absence epilepsy displays altered VGCC expression as well. Development of SWDs in WAG/Rij rats goes together with an enhanced expression of Ca\(_{\text{2.1}}\) VGCC in the RTN. Interestingly, van de de Bovenkamp-Janssen et al. [224, 225] elicited that control rats showed elevated Ca\(_{\text{2.3}}\) VGCC expression in the RTN from 3 to 6 months of age. In contrast, WAG/Rij rats of the same age clearly lacked this increase in Ca\(_{\text{2.3}}\) expression concomitant with the first occurrence of SWDs. These observations are further supported pharmacologically. Lamotrigine is known to inhibit Ca\(_{\text{2.3}}\) VGCCs [230] and effectively suppressed not only SWDs in both GAERS and WAG/Rij rats [211, 231] but also TC burst activity in rat brain slices [232]. Still, the unique electrophysiological features and neuronal implications of Ca\(_{\text{2.3}}\) VGCC expression within RTN cells, GABAergic interneurons and various extrathalamocortical structures on TC oscillatory action are not yet fully understood. Initial investigation of absence seizure susceptibility in Ca\(_{\text{2.3}}\)\(^{-/-}\) mice elicited that Ca\(_{\text{2.3}}\) affects TC hyperoscillation and absence seizure architecture. In accordance to reports on the absence-preventive effect of Bay K8644-enhanced HVA Ca\(^{2+}\) currents, one might expected that HVA Non-L-type Ca\(_{\text{2.3}}\) Ca\(^{2+}\) channels might support the
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In the last decade, the functional involvement of Ca,2.3 T-type VGCCs in mouse sleep architecture has been investigated in detail, finally resulting in the Ca,2.3 channel model of TC rhythmicity. As outlined above, T-type VGCCs are differentially distributed throughout the thalamus. Ca,3.1 T-type VGCCs are dominantly expressed in thalamic relay cells whereas Ca,3.2 and Ca,3.3 VGCCs are localized in RTN neurons. Gene ablation studies on Ca,3.1\(^{-/-}\) mice showed that lack of Ca,3.1 mediated Ca\(^{2+}\) influx in thalamic relay cells results in lack of burst firing activity due to impaired LTCS activity. However, region specific, i.e., cortical, not thalamic Ca,3.1 deletion did not result in altered sleep. These findings resulted in a complex model of Ca,3.1 Ca\(^{2+}\) channels in regulating TC rhythmicity and sleep. Based on this model, ablation of Ca,3.2 and/or Ca,3.3 might result in a phenotype comparable to that of Ca,3.1\(^{-/-}\) mice. However, although effects of Ca,3.3 ablation on sleep spindles have been described, we are still lacking detailed sleep analysis in Ca,3.2 and Ca,3.3 knock-out mice. The model might predict that ablation of Ca,3.2 and Ca,3.3 results in impaired SWS. However, it was recently reported from a patent application that pharmacological blockade of Ca,3.2 VGCCs can result in enhanced rather than impaired sleep, the reason of which remains to be determined. Moreover, transition rates and sleep architecture were altered. The latter findings strongly suggest that interpretation of sleep architecture in transgenic mice cannot be limited to the TC network itself, or thalamic nuclei in specific but also has to include extrathalamocortical structures as well (see below).
Like Ca,3.2 and Ca,3.3, the Ca,2.3 R-type Ca\(^{2+}\) channels are expressed in the RTN, but not thalamic relay neurons. In addition, Ca,2.3 transcripts are present in cortical interneurons. Moreover, Ca,2.3 VGCCs are expressed in a number of extra-thalamic cortical structures, such as the mesopontine REM-NREM modulators (the locus coeruleus, the dorsal raphe nuclei, the pedunculopontine, and the laterodorsal tegmental nuclei), the diencephalic sleep onset controllers (hypothalamic nuclei including the ventrolateral/lateral preoptic region and the tuberomammillary basal forebrain), the cerebellum, the basal ganglia and the hippocampus [94, 96]. These structures are known to project to the TC circuitry and substantially modify its activity via different neuromodulators, e.g., noradrenaline, histamine, serotonin (5-HT), and acetylcholine [92, 211, 241]. Other important Ca,2.3 expressing structures include the suprachiasmatic nucleus involved in the regulation of the circadian rhythm and also sleep architecture [242, 243] and the amygdala which is also involved in sleep regulation. It’s noteworthy that Ca,2.3 Ca\(^{2+}\) channels are of major relevance in the amygdala physiology. Lee et al. [110] intensively studied the molecular and electrophysiological characteristics of R-type Ca\(^{2+}\) channels in central amygdala neurons proving that Ca,2.3 underlies R-type Ca\(^{2+}\) currents in these cells. However, the functional consequences of Ca,2.3 based R-type Ca\(^{2+}\) currents in specialized amygdala neurons, i.e., Wake-ON, REM-ON, and NREM-ON Ace neurons remain largely unknown. However, findings from sleep analysis in Ca,2.3-/- mice clearly point to the fact that a valid model of TC rhythmicity needs to include input also from extrathalamicocortical structures. In conclusion, there is strong evidence that Ca,2.3 VGCCs play a primary role in SWS, the etiology and pathogenesis of absence epilepsy and SWD generation.

**Ca,2.3 R-TYPE VGCC CHANNEL MODULATION AND ITS CLINICAL CONSEQUENCES**

VGCCs are important targets for numerous AEDs [139, 244, 245]. Most AEDs were shown to inhibit HVA or LVA Ca\(^{2+}\) channels others than Ca,2.3 VGCCs. Based on the findings described above, there is striking evidence that Ca,2.3 VGCCs can serve as targets in convulsive and non-convulsive seizure pharmacotherapy. Lamotrigine (LTG) for example is a multi-target AED for the treatment of typical absence seizures and the Lennox-Gastaut syndrome [246, 247]. Pharmacodynamically, it acts via inhibition of both voltage-gated Na\(^{+}\) and Ca\(^{2+}\) channels [248]. LTG targets Ca,2.1 and Ca,2.2 VGCCs [249, 250], but also Ca,2.3 R-type and Ca,3 T-type channels [230]. Interestingly, LTG inhibits R-type Ca\(^{2+}\) currents stronger than T-type currents. Thus, Ca,2.3 Ca\(^{2+}\) channels seem to be involved in the anti-absence activity of LTG suggesting an important role of Ca,2.3 VGCCs in the etiopathogenesis of absence epilepsy. LTG at a concentration of 10 μM is capable of inhibiting Ca,2.3-α, coexpressed with β, by 30% when applying therapeutically relevant brain concentrations of 4–40 μM [230]. Contrarily, Ca,3.1 and Ca,3.3 T-type Ca\(^{2+}\) channels exhibited only minor sensitivity to LTG.

In addition, Lamotrigine (LTG) was shown to dampen transient cytosolic [Ca\(^{2+}\)] \(\text{in rat pyramidal neurons. This is of relevance as alterations in intracellular Ca}\(^{2+}\) homeostasis are known to play an important role in the genesis of epileptiform discharges. Inhibiting transient elevations in neuronal [Ca\(^{2+}\)], by Lamotrigine (LTG) correlates with its anticonvulsant efficacy and could thus prevent neurons from hypereexcitability and excitotoxicity [79]. Notably, sipatrigine or 202W92 can also inhibit Ca,2.3 VGCCs with IC\(_{50}\) values of 10 μM which is within therapeutically relevant brain concentrations of 20–100 μM for sipatrigine and 56 μM for 202W92. Furthermore, both sipatrigine and 202W92 exhibited neuroprotective effects in various animal models of ischemia [251, 252] and displayed anticonvulsant efficacy in both genetically epilepsy-prone rats and DBA/2 audiogenic mice [230, 253]. Importantly, McNaughton et al. [254] have characterized other potential Ca,2.3 blockers that might be relevant in antiepileptic treatment, i.e. carbonic anhydrase inhibitors. The latter include for example ethoxyzolamide, acetazolamide and dichlorphenamidine. Carbonic anhydrase inhibitors have numerous clinical applications, e.g. induction of diuresis, ocular hypertension relief and treatment of altitude sickness [255, 256]. However, epidemiological approaches also suggest their efficacy in patients suffering from absence epilepsy [255]. Ethoxyzolamide inhibited Ca,2.3 mediated R-type Ca\(^{2+}\) current by 66-74% at 10 μM. On the other hand, dichlorphenamidine (10 μM) which is used for treatment of generalized epilepsies resulted in a 24-76% reduction of R-type current [254]. Importantly, topiramate, a standard AED nowadays shares structural similarities with carbonic anhydrase inhibitors and indeed also exerts remaining inhibitory action on carbonic anhydrases. Topiramate had already been reported to inhibit L-type Ca\(^{2+}\) currents [257]. Recently however, it was also proven [85, 254] that topiramate severely inhibits Ca,2.3 Ca\(^{2+}\) channels by 68-77% when applied at therapeutically relevant concentrations of 10 μM. Furthermore, Kuzmiski et al. [85] showed that topiramate can block PPs in hippocampal CA1 neurons due its inhibitory action on Ca,2.3 Ca\(^{2+}\) channels. As outlined above, PPs are of significant relevance in promoting epileptiform burst activity. Thus, inhibition of Ca,2.3 Ca\(^{2+}\) channels by topiramate is
responsible for a reduction in repetitive neural firing, spontaneous epileptiform burst activity and recurrent seizures [258]. It’s noteworthy that many AEDs, e.g. topiramate or Lamotrigine (LTG) that were proven to block Ca\textsubscript{2.3} Ca\textsuperscript{2+} channels are multi-target drugs acting on an armamentarium of voltage- and ligand- gated ion channels.

Given the functional involvement of Ca\textsubscript{2.3} VGCCs in the etiopathogenesis of both convulsive and non-convulsive seizures but also sleep (patho)physiology, future development of highly specific Ca\textsubscript{2.3} Ca\textsuperscript{2+} channels blockers will be of tremendous pharmacotherapeutic relevance and a benefit for patients.

ABBREVIATIONS

| Abbreviation | Definition |
|--------------|------------|
| AED          | Anti-epileptic drugs |
| ADP          | Afterdepolarisation |
| AHP          | Afterhyperpolarisation |
| AP           | Action potential |
| CNS          | Central nervous system |
| DHP          | Dihydropyridine |
| EEG          | Electroencephalogram |
| ECoG         | Electrocorticogram |
| EMG          | Electromyogram |
| GAERS        | Genetic Absence Epilepsy Rats from Strasbourg |
| HEK          | Human embryonic kidney |
| HVA          | High-voltage activated |
| LVA          | Low-voltage activated |
| LTG          | Lamotrigine |
| KA           | Kainic acid |
| LTCS         | Low-threshold Ca\textsuperscript{2+} spike |
| NMDA         | N-methyl-D-aspartat |
| PKC          | Protein kinase C |
| PP           | Plateau potential |
| RTN          | Reticular thalamic nucleus |
| SK           | Small conductance potassium channel |
| SWD          | Spike-wave discharge |
| SWS          | Slow-wave sleep |
| TC           | Thalamocortical |
| VGCC         | Voltage-gated calcium channel |

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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