Danger: High Voltage—The Role of Voltage-Gated Calcium Channels in Central Nervous System Pathology

Andrea Schampel 1 and Stefanie Kuerten 2,*

1 Institute of Anatomy and Cell Biology, University of Würzburg, 97070 Würzburg, Germany; andrea.schampel@uni-wuerzburg.de
2 Institute of Anatomy and Cell Biology, Friedrich-Alexander University Erlangen-Nürnberg, 91054 Erlangen, Germany
* Correspondence: stefanie.kuerten@fau.de; Tel.: +49-9131-85-22264

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Abstract: Voltage-gated calcium channels (VGCCs) are widely distributed within the central nervous system (CNS) and presumed to play an important role in the pathophysiology of a broad spectrum of CNS disorders including Alzheimer’s and Parkinson’s disease as well as multiple sclerosis. Several calcium channel blockers have been in clinical practice for many years so that their toxicity and side effects are well studied. However, these drugs are primarily used for the treatment of cardiovascular diseases and most if not all effects on brain functions are secondary to peripheral effects on blood pressure and circulation. While the use of calcium channel antagonists for the treatment of CNS diseases therefore still heavily depends on the development of novel strategies to specifically target different channels and channel subunits, this review is meant to provide an impulse to further emphasize the importance of future research towards this goal.

Keywords: calcium; calcium channel antagonists; CNS; EAE; neurodegeneration; MS; regeneration; remyelination

1. Calcium and Voltage-Gated Calcium Channels (VGCCs)

Calcium is one of the most important intracellular second messengers in the central nervous system (CNS). It regulates numerous cellular processes due to its electrogenic properties. These processes include neurotransmitter release, excitation, cell growth, proliferation, gene expression, long-term potentiation, plasticity and apoptosis [1–3]. In order to trigger and maintain Ca\(^{2+}\)-dependent processes, an influx of cytosolic calcium from the extracytoplasmic space is required. This is achieved by calcium release from internal calcium stores or by entry of calcium ions via the cell membrane. In electrically excitable cells, voltage-gated calcium channels (VGCCs) are the main route for calcium entry into the cell after depolarization of the membrane. Despite mediating calcium influx, VGCCs also regulate intracellular processes depending on their localization. In cardiomyocytes, VGCCs regulate contraction processes; in endocrine cells, they control the secretion of hormones and in the CNS, they modulate the release of neurotransmitters [4]. Structurally, VGCCs are heteromultimeric complexes consisting of a central pore-forming Ca\(_\alpha\)\(_\alpha_1\) subunit, which is conductive for ions. The central pore-forming subunit is convoyed by several auxiliary subunits (\(\alpha_{2}\delta_{1-4}, \beta_{1-4}\) and \(\gamma_{1-8}\)) [5,6]. So far, ten different Ca\(_\alpha\)\(_\alpha_1\) subunits have been described and classified according to their pharmacological and electrophysiological properties into high-voltage activated (HVA) and low-voltage activated (LVA) Ca\(^{2+}\) channels [4,5]. HVA Ca\(^{2+}\) channels include dihydropyridine-sensitive L (“long-lasting”) type Ca\(_\alpha_1.1–1.4\) and non-L-type Ca\(_\alpha_2.1–2.3\) channels, which are less sensitive for DHP. Compared to LVA channels, which consist of the T (“transient”) type Ca\(^{2+}\) channels Ca\(_\alpha_{3.1–3.3}\), HVA channels require...
much stronger depolarization to reach the activation threshold. Additionally, they show prolonged channel opening [4–6] (Table 1).

Table 1. Classification of voltage-gated calcium channels (VGCCs) according to their voltage-dependent activation.

| High-Voltage Activated    | Family       | Low-Voltage Activated    | Family          |
|---------------------------|--------------|--------------------------|-----------------|
| L-type (“long-lasting”) VGCC | Ca\textsubscript{v}1.1–Ca\textsubscript{v}1.4 | T-type (“transient”) VGCC | Ca\textsubscript{v}3.1–Ca\textsubscript{v}3.3 |
| P-type (“Purkinje cell”) / Q-type VGCC | Ca\textsubscript{v}2.1 |                    |                 |
| N-type (“neural”) VGCC | Ca\textsubscript{v}2.2 |                    |                 |
| R-type (“residual” / “resistant”) VGCC | Ca\textsubscript{v}2.3 |                    |                 |

Within the nervous system, several types of VGCCs are expressed. They are detectable in many brain areas such as the cortex, thalamus and the hippocampus. P/Q-, T- and N-type VGCCs are the most common ones in the CNS [7]. Presynaptic P/Q- and N-type VGCCs induce neurotransmitter release and T-type VGCCs facilitate rhythmic burst firing of neurons. L-type VGCCs are localized on neuronal cell bodies as well as on dendrites and spines. Postsynaptic L-type VGCCs regulate gene expression and neuronal excitability (Figure 1) [4]. Some types of glial cells such as astrocytes, oligodendrocytes and glial precursor cells have also been shown to express VGCCs [2,8–11]. Outside the nervous system the heart, skeletal muscle cells, cells of the retina, endocrine cells, cochlear hair cells and cells of the immune system have been reported to express VGCCs or VGCC-like channels (Figure 1) [12–15].

2. Signs of Calcium-Mediated Cellular Damage

Intracytoplasmic calcium levels have to be strictly regulated in order to prevent cellular damage. In the CNS, neuronal organelles such as neurofilaments—and in particular mitochondria—are vulnerable to cytotoxicity [3,16–19]. Mitochondria play different roles in organisms, which comprise...
cellular respiration, temporary calcium storage, calcium buffering, maintenance of structural integrity and mediation of apoptosis [19–21]. Mitochondrial function can be directly influenced by extracellular signalling molecules. Increased nitric oxide (NO) levels, for instance, can alter gene expression and induce dysfunction of mitochondria. This in turn causes dysregulation of calcium homeostasis, resulting in enhanced cellular degeneration [19] and finally apoptosis of neurons and oligodendrocytes. Mitochondrial dysfunction can be detected ultrastructurally by an increased size (swelling) of mitochondria, reflecting an enhanced local energy demand [20,22,23]. Increased intracytoplasmic calcium levels also weaken neuronal integrity as they promote breakdown of the cytoskeleton, including actin, tubulin and intermediate filaments. This becomes evident both histologically and ultrastructurally as cytoplasmic blebbing and accumulation or dissolution of filaments [24,25]. Other detectable signs of calcium-mediated damage are dilatation of the endoplasmic reticulum and cytosolic shrinkage [24,25].

3. VGCCs in the Pathophysiology and Treatment of CNS Diseases

Studies of human diseases, mouse, rat and cell culture models indicate an important contribution of VGCCs to several neurological and psychiatric disorders, blindness and pain (Table 2) [26]. Of these conditions in particular Parkinson’s and Alzheimer’s disease have been in the focus of research mainly due to their tremendous socioeconomic relevance. In Parkinson’s disease, it has been demonstrated that dihydropyridines—potent VGCC antagonists—reduce the overall population risk in humans [27,28]. Evaluation of the pathogenesis of Alzheimer’s disease has revealed that pathogenic amyloid β (Aβ) peptides elevate L-type VGCC activity in cell cultures [29–36]. In addition, there was increased radiolabel binding to L-type VGCCs in the brains of Alzheimer’s disease patients post mortem [37]. Along these lines, L-type VGCC activity has been reported to be elevated during aging [38,39] and it is assumed to be involved in age-related alterations of synaptic function [38,40], membrane excitability [41] and cognition [42,43]. Yet, there is some controversy because studies of a mouse model of Alzheimer’s disease rather observed a decrease in L-type VGCC currents, suggesting a complex interplay between several factors including aging, the amount of circulating Aβ, Ca²⁺ dysregulation and Ca²⁺ release from the endoplasmic reticulum [44].

The continuous interest in using VGCCs as therapeutic targets to treat CNS disorders is also reflected by currently ongoing clinical trials, of which the majority uses L-type calcium channel antagonists. On the one hand, the L-type calcium channel blocker amlodipine is tested in a trial to reduce the risk for Alzheimer’s disease (NCT02913664) and a phase III trial on the use of the L-type calcium channel antagonist nilvadipine to treat Alzheimer’s disease was recently completed (NCT02017340) with results that are still expected. On the other hand, there are ongoing studies on the efficacy of isradipine in early Parkinson’s disease (NCT02168842). Yet, studies in a mouse model of Parkinson’s disease ask for caution since the plasma concentrations of isradipine approved for therapy were not neuroprotective, most likely due to the fact that the drug fails to reduce somatic calcium oscillations of dopaminergic neurons of the substantia nigra [45]. Isradipine is also currently investigated for cognitive enhancement in schizophrenia and schizoaffective disorder (NCT01658150). In addition, the drug is tested for the treatment of nicotine dependence (NCT03083353). There is one trial using the novel drug CX-8998, a T-type VGCC antagonist for the treatment of essential tremor (NCT03101241). Most recently, nimodipine—a Caᵥ1.2 antagonist—was shown to be neuroprotective in the setting of experimental autoimmune encephalomyelitis—the most common animal model for multiple sclerosis—by limiting microglia-mediated damage of the CNS and promoting remyelination [46]. Interestingly, microglia are devoid of the Caᵥ1.2 channel [46] so that the exact mechanism by which nimodipine acts on microglia still has to be elucidated in future studies. Table 2 summarizes hallmark diseases/syndromes and symptoms that are thought to be associated with VGCC involvement.
Table 2. Involvement of VGCCs in neurologic and psychiatric disorders.

| Channel  | Disease/Symptom                          | Species                          |
|----------|------------------------------------------|----------------------------------|
| Ca\(_{v}\)1.2 | Autism/Timothy syndrome                  | Human [47]                       |
|          | Conditioned fear                         | Mouse [48]                       |
|          | Depression/Mood disorders                | Human, mouse [49,50]             |
|          | Febrile seizures                         | Rat [51]                         |
|          | Multiple sclerosis                       | Mouse [46]                       |
|          | Pain                                     | Mouse, rat [52–54]               |
|          | Parkinson’s disease                      | Human, mouse (reviewed in [28])  |
| Ca\(_{v}\)1.3 | Deafness                                | Mouse [56,57]                    |
|          | Depression                               | Human, mouse [50,58]             |
|          | Pain                                     | Rat [52,53]                      |
|          | Parkinson’s disease                      | Human, mouse (reviewed in [28])  |
| Ca\(_{v}\)1.4 | (Incomplete X-linked congenital stationary) night blindness | Human [59,60] |
| Ca\(_{v}\)2.1 | Episodic ataxia type 2 and familiar hemiplegic migraine type 1 | Human [61–63] |
|          | Spinocerebellar ataxia 6                 | Human [64,65]                    |
| Ca\(_{v}\)2.2 | Pain                                     | Mouse [54]                       |
| Ca\(_{v}\)2.3 | Anxiety                                  | Mouse [66]                       |
|          | Absence epilepsy                         | Mouse [66]                       |
|          | Pain                                     | Mouse [67]                       |
| Ca\(_{v}\)3.1 | Thalamocortical network activity/ absence epilepsy | Mouse [68] |
| Ca\(_{v}\)3.1–3.3 | Autism/Autism spectrum disorders           | Human [69]                       |
|          | Pain                                     | Human, mouse, rat (reviewed in [70]) |
|          | Parkinson’s disease/locomotor deficits   | Rat [71]                         |
| Various VGCCs | Alzheimer’s disease/dementia               | Mouse, rat, human (reviewed in [72]) |

Overall, several studies regarding the role of VGCCs in CNS pathology exist and several attempts have been made to use VGCC antagonists as therapeutic targets in this context. While historically, VGCCs were targets of the first synthesized drugs [6], the establishment of ion channel-specific therapies for CNS disorders has so far proven to be difficult. Yet, the availability of a broad range of modern technologies such as RNAi, function-blocking antibodies and gene-editing present promising therapeutic avenues, which may be of particular importance for several still incurable and devastating CNS disorders including Alzheimer’s and Parkinson’s disease as well as multiple sclerosis.

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Abbreviations

- A\(_{\beta}\) Amyloid \(\beta\)
- CNS Central nervous system
- HVA High-voltage activated
- LVA Low-voltage activated
- VGCC Voltage-gated calcium channel

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