Calcium ion entry through voltage-gated calcium channels is essential for cellular signalling in a wide variety of cells and multiple physiological processes. Perturbations of voltage-gated calcium channel function can lead to pathophysiological consequences. Calcium binding proteins serve as calcium sensors and regulate the calcium channel properties via feedback mechanisms. This review highlights the current evidences of calcium binding protein-mediated channel regulation in human diseases.

Keywords: calcium binding proteins; voltage-gated calcium channels; EF-hand motif; calmodulin; calcium binding protein; calcineurin; calpain; visinin-like protein

Calcium binding protein-mediated regulation of voltage-gated calcium channels linked to human diseases

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Calcium (Ca\(^{2+}\)) entry via voltage-gated calcium channels (VGCCs), conveys the electric signals to intracellular transduction cascades in a wide variety of cells including neurons, muscle cells and endocrine cells\(^{[1]}\). Ca\(^{2+}\) dependent-signalling cascades are largely mediated by Ca\(^{2+}\) binding proteins\(^{[2, 3]}\), and are essential for multiple cellular and subcellular processes in physiological conditions. Perturbations of VGCCs functions can cause abnormality of cellular events, leading to pathological consequences. Ca\(^{2+}\) binding proteins mediate Ca\(^{2+}\)–dependent signal transduction pathways and regulate Ca\(^{2+}\) influx via the VGCCs in Ca\(^{2+}\)-dependent feedback mechanisms.

VGCCs are classified into L-, N-, P/Q-, R-, and T-types, based on their distinct electrophysiological and pharmacological properties\(^{[4, 5]}\). VGCCs are heteromultimeric protein complexes composed of a pore forming α\(_1\) and four distinct auxiliary subunits: α\(_2\), δ, β, and γ subunits\(^{[6–7]}\). Mammalian α\(_1\) subunits are encoded by at least 10 distinct genes\(^{[6, 7]}\). The high voltage-activated VGCCs include Ca\(_{1.1}\) and Ca\(_{1.2}\) subfamilies. The Ca\(_{1.1}\) subfamily (Ca\(_{1.1.1}\) to Ca\(_{1.1.4}\)) conducts L-type Ca\(^{2+}\) current and includes the channels containing α\(_{1\alpha}\), α\(_{1\gamma}\), α\(_{1\delta}\), and α\(_{1\beta}\) subunits. The Ca\(_{1.2}\) subfamily (Ca\(_{1.2.1}\) to Ca\(_{1.2.3}\)) conducts P/Q-type, N-type, and R-type Ca\(^{2+}\) currents, through the channels containing α\(_{1\alpha'}\), α\(_{1\beta'}\), and α\(_{1\gamma}\) subunits, respectively. The Ca\(_{1.3}\) subfamily (Ca\(_{1.3.1}\) to Ca\(_{1.3.3}\)) conducts low voltage-activated T-type Ca\(^{2+}\) current mediated by the channels containing α\(_{1\alpha'^{o}}\), α\(_{1\beta'}\), and α\(_{1\gamma}\) subunits, respectively. The cell- and tissue-specific expression of these subunits allows for a vast variety of the channel subtypes exhibiting distinct functions.

Ca\(^{2+}\)-binding proteins containing EF-hand Ca\(^{2+}\) binding motifs regulate mostly high voltage-activated VGCCs\(^{[8–12]}\). The EF-hand motif is a conserved Ca\(^{2+}\)-binding structure, spanning a region of 30–35 amino acids containing a 12-residue Ca\(^{2+}\) binding loop flanked by the N- and C-terminal α-helix regions which are differentially exposed in the presence of Ca\(^{2+}\)\(^{[3, 13, 14]}\). Each EF-hand protein has distinct Ca\(^{2+}\) binding affinity and cellular localization. The EF-hand Ca\(^{2+}\)-binding protein superfamilies\(^{[2, 3, 15]}\), such as calmodulin (CaM), calcineurin, calcium binding proteins (CaBP), and neuronal Ca\(^{2+}\) sensors (NCSs), contains 2 to 4 functioning EF-hand Ca\(^{2+}\) binding domains. The EF-hand Ca\(^{2+}\)-binding proteins may achieve their cellular effects through Ca\(^{2+}\)-dependent or Ca\(^{2+}\)-independent signalling mechanisms\(^{[16, 17]}\) (Figure 1). Many EF-hand Ca\(^{2+}\)-binding proteins alter Ca\(^{2+}\) kinetics directly through regulation of VGCC properties\(^{[8–12]}\). With the availability of human genetic databases and advanced molecular technologies, growing evidences suggest that dysfunctions in Ca\(^{2+}\)-binding protein mediated VGCC regulation may be one of the mechanisms leading to human diseases.
Calmodulin mediated P/Q-type regulation in familial hemiplegic migraine type 1

The best studied Ca\(^{2+}\) binding protein that regulates VGCCs is CaM\(^{[18–20]}\). CaM contains 4 functional EF-hand motifs\(^{[21, 22]}\), and regulates VGCCs properties in an enzyme-inhibitor like fashion\(^{[23]}\). CaM binds to various high-voltage activated VGCCs and causes the Ca\(^{2+}\)-dependent inactivation (CDI)\(^{[8, 9, 24, 25]}\) or Ca\(^{2+}\)-dependent facilitation (CDF)\(^{[10, 12, 26]}\) (Figure 1). In brief, CaM has a higher binding affinity to Ca\(^{2+}\) in the N-lobe than the C-lobe EF-hand motifs. This allows for antagonistic regulation of the Ca\(^{2+}\) channel through differential Ca\(^{2+}\) binding to CaM\(^{[27]}\). Specifically, CDI of Ca\(^{2+}\) channels\(^{[8, 9, 24]}\) and CDF of CaV2.1 channels depend on Ca\(^{2+}\) binding to the C-lobe of CaM\(^{[18, 27]}\). Conversely, Ca\(^{2+}\) binding to the N-lobe of CaM induces CDI of CaV2.1 channels\(^{[10, 12, 26]}\), CaV2.2\(^{[10, 12]}\), and CaV2.3\(^{[10]}\) type channels. The differential regulatory effects of CaM on VGCCs are likely due to different conformational changes in the structure of CaM following Ca\(^{2+}\) binding at alternate sites. CaM-mediated regulation of the presynaptic VGCCs results in a dual feedback regulation. The cellular and molecular mechanisms underlying CaM mediated VGCC regulation have been extensively reviewed previously\(^{[18–20]}\).

FHM is characterized by recurrent migraines and includes visual disturbance, sensory loss, hemiparesis and ataxia. FHM type 1 is an autosomal dominant type of migraine with aura and hemiparesis, which is linked to the VGCC \(\alpha_1\)-subunit gene, CACNL1A4 encoding CaV2.1\(^{[29–31]}\). All five FHM1 mutations change the biophysical properties of CaV2.1 channels, leading to both gain and loss of P/Q-type channel function\(^{[32, 33]}\). Specifically, single channel recording showed that the mutations enhanced the open probability of the CaV2.1 channels and shifted the activation gating of the channel to more negative voltages, allowing increased Ca\(^{2+}\) influx at more negative membrane potentials in cerebellar neurons\(^{[33, 34]}\).

Common treatments with Ca\(^{2+}\) channel blockers, such as verapamil, is effective in some FHM1 patients, carrying the CACNA1A mutations due to decreased open probability of P/Q-type CaV2.1 channels and reduced Ca\(^{2+}\) influx\(^{[35]}\). Consistent with reports of increased open-channel probability\(^{[32, 33]}\), a recent study showed that FHM-1 missense mutants of the C-terminus in CaV2.1 subunit, R192Q and S218L, permitted a larger Ca\(^{2+}\) influx during action potentials than the wildtype channels in the cerebellar neurons\(^{[36]}\). Interestingly, these FHM-1 gain-of-function missense mutations characteristically occlude CDF of human CaV2.1 channels in both recombinant preparations and the cerebellar Purkinje cells. The altered CDF of CaV2.1 channels coincided with a decrease in short-term synaptic facilitation at the parallel fiber-to-purkinje cell synapse in the cerebellum in FHM-1 mutant mice\(^{[36]}\). The compelling evidence suggests that FHM-1 gain-of-function missense mutations of CaV2.1 channels favour a constitutively facilitated state that prevents further Ca\(^{2+}\)-dependent CaM-mediated channel facilitation. It is hypothesized that disruption of CaV2.1 CDF may cause the cerebellar ataxia-associated FHM-1 due to an imbalance between excitatory and inhibitory inputs to the cerebellar Purkinje cells. This disruption suppresses the intrinsic pacemaker activity of these cells, thus leading to motor deficits\(^{[36]}\). The knock-in

Figure 1. Ca\(^{2+}\) binding proteins regulate voltage-gated Ca\(^{2+}\) channels (VGCCs) via Ca\(^{2+}\)-dependent inactivation (CDI), Ca\(^{2+}\)-dependent facilitation (CDF) and Ca\(^{2+}\)-independent regulation (CIR) of the channels, hence contributing to Ca\(^{2+}\) homeostasis. Disrupting Ca\(^{2+}\)-binding protein-mediated VGCC regulation results in pathophysiological processes leading to human diseases. CDI: Ca\(^{2+}\) ions entering the cell through VGCCs bind to Ca\(^{2+}\) binding proteins to (a) inactivate the channel via negative feedback mechanism, reducing further Ca\(^{2+}\) entry through the channel and (b) lead to downstream mechanisms and pathways implicated in human diseases. CDF: Ca\(^{2+}\) ions entering the cell through VGCCs bind to Ca\(^{2+}\) binding proteins to (c) facilitate the channel via a positive feedback mechanism, thus enhancing further Ca\(^{2+}\) entry through the channel and (d) lead to downstream mechanisms and pathways implicated in human diseases. CIR: Ca\(^{2+}\) binding proteins, in absence of Ca\(^{2+}\) binding (e) regulate VGCCs and (f) lead to downstream mechanisms and pathways implicated in human diseases.
mouse model carrying FHM-1 R192Q mutation exhibited an enhanced velocity of cortical spreading depression in vivo[34], and it is thus important to demonstrate whether the cortical hyper-excitability is also associated with perturbation of CDF of the mutant CaV2.1 in future studies.

**CaBPs mediated L-type channel inactivation**

CaBPs consist of 8 members (CaBP 1–8) and are considered similar to CaM in that they bear four recognizable, but not necessarily functional EF-hands[37]. CaBP1, also known as caldendrin (a splice variant of CaBP1)[38], has ~50% sequence homology to CaM and is widely expressed in the brain, including the cerebral cortex, hippocampus, in the cone bipolar and amacrine cells of the retina[39], and in the inner hair cells. CaBP1 interacts with CaV2.1 P/Q-type channels[40, 41], and L-type channels[42]. CaBP1 accelerates inactivation kinetics, prevents CaM-induced CaV2.1 channel facilitation, and shifts the voltage-dependent activation of CaV2.1 channels[43]. These effects of CaBP1 are mediated by binding to the CaM-binding IQ-domain in the α1A subunit of CaV1.2 channels. CaBP1 binding to the CaM binding domain (CBD) of α1C causes a significantly faster inactivation of CaV2.1 channel than CaM.

CaBPs regulate L-type channels in a Ca2+-independent manner[40, 42–44] (Figure 1), in contrast to CaM. CaBP1 and CaBP4 act as negative regulators to compete with CaM binding to the C-terminal IQ motif in the α1A and CaV1.3 subunit[42, 44–46]. CaBP1 also interacts with the N-terminal domain of α1A to prolong the channel activation, independent of CaM effect[42, 44]. Some CaBPs, such as CaBP1 and CaBP4, have the capacity to negatively regulate influx of Ca2+ through a direct inhibitory interaction with plasma membrane P/Q-type channels in cochlear cells[45–47]. In the inner ear, at least 4 CaBPs have been found in hair cells, including CaBP1, CaBP2, CaBP4 and CaBP5. Sustained activation of presynaptic CaV1.3 channels triggers graded changes in neurotransmitter release which is required for sound detection[46]. CaBP1 binding to CaV1.3 channels on CaM interaction sites, induced a stronger, than CaBP4, inhibition of Ca2+-dependent channel inactivation[48]. Closely co-localization between CaBP1 and CaV1.3 at the presynaptic ribbon synapse of adult inner hair cells further suggests CaBP1-mediated inhibitory effect on Ca2+-dependent inactivation of CaV1.3 channel is critical for auditory transmission[49].

CaBP4[48] and CaBP5[49] regulates L-type channels in photoreceptors. CaBP4 is located at the photoreceptor synaptic terminals in the retina, and is important for developing and sustaining synaptic transmission to bipolar cells[45]. CaBP4 regulates CaV1.4 channel and shifts the activation of CaV1.4 to more hyperpolarized potentials through a direct interaction with the C-terminal domain of the CaV1.4 channel protein. CaBP4/- mice exhibited visual deficits similar to that caused by dysfunction of CaV1.4 channels[45, 50, 51]. CaBP4, like CaBP1, is found to interact with CaM-binding IQ domain in CaV1.3 to dampen the inactivation of the channel[45, 46]. CaBP4 has the capacity to eliminate even the baseline Ca2+ dependent inactivation of CaV1.3[45]. Phosphorylation of S37 of CaBP4 by protein kinase Cζ in retina regulates CaV1.3, likely by facilitating the low-affinity interaction which exerts inhibitory regulation of CaV1.3 channel inactivation[49]. Phosphorylation of CaBP4 is critical for tuning presynaptic Ca2+ signals required for light-induced neurotransmitter release. Incomplete congenital stationary night blindness (CSNB2) is linked to mutations in both CaBP4[52, 53] and CaV1.4[54–56]. Interrelation between CaBP4 and CaV1.4 in CSNB2 remains to be determined.

**Bestrophin-1 mediated CaV1.3 modulation in macular degeneration**

Bestrophins are a family of calcium-activated chloride channels[57] encoded with VMD2 (Best vitelliform maculopathy-dystrophy-2) gene on chromosome 11q13[58]. Human bestrophin-1 (hBest1) is a founding member of the family and contains one EF-hand (EF1, 350–390) at the C-terminal and a regulatory domain adjacent to EF1 that is required for Ca2+ activation of the channel[59]. EF1 has a slightly higher Ca2+-binding affinity than the third EF hand of CaM and lower affinity than the second EF hand of troponin C. Mutations in hBest1 are involved in ~100 human diseases[59].

Retinal cell death, induced by glaucoma, diabetic retnopathy and age-related macular degeneration are primarily caused by a form of metabolic stress which results from a lack of nutrient supply. This process is initiated primarily through the activation of NMDA receptors with a subsequent influx of Ca2+ and Na+ ions into the cells[60]. The close relationship between ataxia and macular degeneration suggests that these disorders may share a common molecular network[61]. Oxidative stress, an important cause of retinal pigment epithelium death and subsequent age-related macular degeneration, induces calcium overload and leads to cell injury[62]. Oxidative stress induced elevation of Ca2+ level is sensitive to VGCC blocker[63], suggesting the role of VGCCs in retinal cell death.

The hBest1 is localized at the basolateral plasma membrane of the retinal pigment epithelium cells[63]. Mutations of the hBest1 gene are associated with macular degeneration[58]. Bestrophin-1 is co-localized with CaV1.3 channels and the auxiliary β4 subunit in the cell membrane in the retinal pigment epithelium, and inhibits CaV1.3 channels via a direct interaction with the CaV4β4 subunit[64, 65]. Mutations of hBest1 on P330 and P334 prevented Best1-mediated inhibition of CaV1.3[64, 65]. These findings provide new insights into the mechanisms of the retinal degeneration involved in hBest1-mediated CaV1.3 channel regulation.

**Calcineurin regulation of Ca2+ channels in human diseases**

Calcineurin is a calcium-dependent phosphatase activated by Ca2+/CaM[66]. It is a heterodimer and consists of a 59 kDa catalytic subunit and a 19 kDa Ca2+-binding regulatory subunit. Calcineurin regulatory subunit is encoded with four putative EF-hand Ca2+-binding motifs[53]. The high-affinity Ca2+ binding site has a Kd of ~24 nmol/L to Ca2+ whereas three low-affinity binding sites have a Kd of 15 µmol/L to Ca2+[63]. Calcineurin regulates L-type channels in both myocytes[67] and actinucleopeptides. In vivo[34], calcineurin regulates CaV1.3 channels by facilitating the low-affinity interaction which exerts inhibitory regulation of CaV1.3 channel inactivation[49]. Phosphorylation of CaBP4 is critical for tuning presynaptic Ca2+ signals required for light-induced neurotransmitter release. Incomplete congenital stationary night blindness (CSNB2) is linked to mutations in both CaBP4[52, 53] and CaV1.4[54–56]. Interrelation between CaBP4 and CaV1.4 in CSNB2 remains to be determined.
Calcineurin regulation of CaV_1.2 L-type channel in cardiac hypertrophy

Ca^{2+} signalling pathways play a critical role in the development of cardiac hypertrophy, one of the predisposing factors related to hypertension and development of heart failure. The downstream effector of calcineurin, NFAT signalling transduction pathway, plays a critical role in pathological cardiac hypertrophy response\cite{70, 71}. L-type CaV_1.2 channels play an important role in blood pressure and development of myogenic tone. In cardiac muscles, L-type currents through CaV_1.2 channels stimulate the excitation-contraction coupling. The C-terminus of this channel serves an autoinhibitory role to mediate the fight-or-flight response. Inactivation of CaV_1.2 was found to reduce mean arterial blood pressure in mice and there was a severe dampening of response to penylephrine and angiotensin II, due to a significant portion of penylephrine-induced resistance being dependent on calcium influx through the CaV_1.2 channel\cite{72}. The truncation in the distal C-terminus of the α_1 subunit of CaV_1.2 leads to 10-15 fold increase in channel activity in mammalian cell lines\cite{73}. The increased force of contraction during the fight-or-flight response is thought to be mediated by regulation of CaV_1.2 channels via activation of secondary systems which act to phosphorylate the channel\cite{74}. Deletion of this C-terminus causes a reduction in Ca^{2+} currents, as a result of lower surface expression of the channel, and leads to development of cardiac hypertrophy and premature death after E15 during embryonic development in mice\cite{25}.

Recently, an EF-hand containing Ca^{2+} and integrin-binding protein-1 (CIB1) was found to specifically enhance cardiac pathological hypertrophy, without a role in altering physiological hypertrophy, through a regulation of calcineurin interaction with the sarcolemma\cite{79}. One mechanism of calcineurin function is thought to be via L-type channels, which mediates Ca^{2+} influx into cardiomyocytes. Transgenic mice expressing an activated form of calcineurin were found to exhibit an enhanced I_{Ca} density compared with the non-transgenic littermates and to have a faster kinetics of I_{Ca} inactivation\cite{62}. Calcineurin can directly bind to both N- and C-termini (a.a. 1943-1971) of CaV_1.2 channels, and dephosphorylate the channels, which in turn increase the channel conductance\cite{76}. Magnesium ions (Mg^{2+}) bind to the C-terminal EF-hand to inhibit CaV_1.2 channels, thereby reducing Ca^{2+} influx to maintain the intracellular Ca^{2+} at low levels\cite{77}. Supplement of Mg^{2+} during global ischemia resulted in myocardial protection and improved functional recovery\cite{78}. These evidences suggest that calcineurin serves as a key modulator of Ca^{2+}-dependent pathways via regulation of CaV_1.2 activities and in turn mediates the pathological electrical remodelling in cardiac hypertrophy.

Calcineurin regulation of L-type channels in neurodegenerative diseases

Calcineurin selectively enhances L-type channel activity in hippocampal neurons\cite{68, 69}. Application of FK506, an inhibitor of calcineurin, reduces high-voltage-activated Ca^{2+} current via L-type, but not P/Q- or N-type channels\cite{68}. PKA and calcineurin bind to A-kinase anchoring protein 79/150 (AKAP79/150), which interact with endogenous and recombinant CaV_1.2 channels in hippocampal neurons and HEK293 cells, respectively\cite{86}. Disruption of AKAP79/150-calcineurin anchoring increases Ca^{2+} current amplitude\cite{69}. In contrast to CaM, calcineurin does not affect Ca^{2+}-dependent inactivation of the neuronal L- or N-type channels; this conclusion is based on the findings that FK506 has no effect on the time-course of Ca^{2+} current inactivation of L-type channel in rat pituitary tumor cell line (GH3) and N-type channels in chicken dorsal root ganglion neurons, while Ca^{2+}-dependent inactivation of the channels is prevented by Ca^{2+} chelator EGTA\cite{79}. Calcineurin promotes dephosphorylation of 3', 5'-cyclic AMP response element binding protein (CREB)\cite{29}. Overexpression of calcineurin prevents\cite{30} and inhibition of calcineurin enhances long-term memory formation\cite{80, 81}. The activity of calcineurin increases in the hippocampus during aging, and L-type channel block reduces calcineurin activity\cite{83}. Cleavage of calcineurin by Ca^{2+}-sensitive protease calpain\cite{82} enhances its phosphatase activity, which coincides with an increase in the number of neurofibrillary tangles in human brains of patients with Alzheimer’s disease\cite{83}. Interestingly, amyloid-β protein also increases the activity of calcineurin, leading to dephosphorylation of the proapoptotic protein BAD (Bcl-2/Bcl-XL-antagonist) causing cell death\cite{84} and subsequent activation of apoptotic pathways in Alzheimer’s disease\cite{85}. Calcineurin activity is implicated in age-related Ca^{2+} dysregulation in neurodegenerative disorders\cite{69}. However, the role of EF-hand motifs in calcineurin-enhanced L-type channel activation, and the causal relation between calcineurin and VGCC regulation in degenerative disorders remain to be further investigated.

Perspectives and future directions

Functional diversity within related Ca^{2+}-binding proteins may enhance the specificity of Ca^{2+} signalling by VGCCs in different cellular contexts. These channels undergo feedback mechanisms by Ca^{2+}-dependent facilitation or inactivation. Such feedback is largely mediated by Ca^{2+} binding proteins. Increasing evidences demonstrate that the diverse and integrative roles of the abundant calcium binding proteins in VGCC regulation and Ca^{2+} signalling may be attributed to human diseases. However, our understanding of the role of such regulation in human diseases is rather limited, due to the complexity of the intracellular protein networks in which integrative functions of Ca^{2+} binding proteins must alter continuously to fit to the dynamic changes of Ca^{2+} signalling.

Many Ca^{2+} binding proteins have been found to regulate VGCCs, however, little is known about how such regulations are related to the pathophysiological processes. For instance, neuronal Ca^{2+} sensor-1/frequenin-1 (NCS-1/frag1) containing three functional EF-hand Ca^{2+} binding motifs\cite{92, 93, 94} exhibits a 10 fold higher affinity for Ca^{2+} than CaM\cite{95}. NCS-1 is highly localized at the presynaptic terminal of the vertebrates\cite{96, 97} and...
invertebrates[88, 96-98], and facilitates synaptic transmission. It increases the P/Q-type Ca\(^{2+}\) current in the Calyx of Held of the giant presynaptic terminal[99] and regulates the presynaptic N-type channels in motoneurons[99] and growth cone VGCCs in Lymnaea neurons[100, 101]. Another example is visinin-like protein-2 (VILIP-2), a highly homologous subfamily of NCS proteins and capable of undergoing Ca\(^{2+}\)-myristoyl switch[102, 103]. VILIP-2 slows inactivation[104] and enhances facilitation[105] of the presynaptic P/Q-type Ca\(^{2+}\) channels, by a direct interaction with the CBD of the C-terminus of Ca,2.1. However, whether and how NCS-1 or VILIP-2-mediated VGCC regulation contributes to human diseases remain unclear. Conversely, down-regulation of VILIP-1 has been reported in several types of human cancers[106, 107] and in heart failure/cardiac hypertrophy[108]. However, whether VILIP-1 effect is associated with VGCC regulation is unknown. Thus, it is necessary to further investigate if there is interrelation between VGCC regulation by Ca\(^{2+}\) binding proteins and human diseases.

Dysregulation of Ca\(^{2+}\) homeostasis leads to pathophysiological processes related to human diseases. For instance, a disruption of basal and stimulus-dependent Ca\(^{2+}\) levels has been reported in brains of patients suffering from Alzheimer’s disease[109]. The level of Ca\(^{2+}\)-sensitive protease calpain-1 in the prefrontal cortex is 3-fold higher in the postmortem brains of individuals with Alzheimer’s disease, than those with other neurodegenerative disorders, such as Huntington’s or Parkinson’s disease. Calpain-1 activates Ca\(^{2+}\)-sensitive phosphatase calcineurin by cleaving lysine501 at the C-terminal[83]. The abnormally enhanced calpain and truncated calcineurin activities correlate with the level of secreted amyloid precursor protein and progression of Alzheimer’s disease[110, 111]. Thus, disruption of Ca\(^{2+}\) homeostasis in neuropathology of Alzheimer’s disease may be mediated by hyperactivity of calpain-1 and calcineurin. Similarly, α-synuclein, a key protein in the pathophysiology of Parkinson’s disease[112, 113], binds to calmodulin in a Ca\(^{2+}\)-dependent manner[114]. α-Synuclein-calmodulin interaction accelerates fibrillation of synuclein, crucial for forming the core of Lewy bodies. α-Synuclein also colocalizes with other Ca\(^{2+}\)-binding proteins, including calbindin and parvalbumin[115], implicating the significance of Ca\(^{2+}\)-dependent signalling in the development of Parkinson’s disease. One implication of these findings is that a tight regulation of Ca\(^{2+}\) homeostasis by Ca\(^{2+}\)/Ca\(^{2+}\)-sensitive proteins serves as a compelling mechanism for pathophysiological processes in neurodegenerative and/or cardiovascular disorders. Understanding such mechanisms allows us to identify potential drug targets for delaying or prevention of the onset of the related human diseases. However, this line of research is still at its infancy, and deserves further attention. With current advancement in genetic and epigenetic sequencing techniques and increased availability of the gene and protein databases of human diseases, exploring the role of Ca\(^{2+}\) binding proteins in VGCC regulation and their involvement in human diseases are becoming feasible in future studies.

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