BioFactors

Critical Review

Voltage-gated calcium channels and disease

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Abstract.

Voltage-gated calcium channels are a family of integral membrane calcium-selective proteins found in all excitable and many nonexcitable cells. Calcium influx affects membrane electrical properties by depolarizing cells and generally increasing excitability. Calcium entry further regulates multiple intracellular signaling pathways as well as the biochemical factors that mediate physiological functions such as neurotransmitter release and muscle contraction. Small changes in the biophysical properties or expression of calcium channels can result in pathophysiological changes leading to serious chronic disorders. In humans, mutations in calcium channel genes have been linked to a number of serious neurological, retinal, cardiac, and muscular disorders.

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1. Calcium channel subtypes

Native calcium channel subtypes are classified according to their voltage-dependent and kinetic biophysical properties combined with their sensitivities to pharmacological agents. At the molecular genetic level, calcium channels are defined according to their main α_1 subunit type (Ca_V), a large integral membrane class of protein (~200–260 kDa) which contains the structural and functional machinery required to conduct calcium ions; a calcium-selective pore, voltage sensor, and gating mechanisms [1]. High voltage-activated (HVA) calcium channels have a positive membrane potential threshold for opening (e.g. −40 mV) and are further classified as L-type ($Ca_V1.1$, $Ca_V1.2$, $Ca_V1.3$, $Ca_V1.4$), P/Q-type ($Ca_V2.1$), N-type ($Ca_V2.2$), and R-type ($Ca_V2.3$) based upon distinct pharmacological sensitivities [2]. Low voltage-activated (LVA) channels (also known as "T-type") open transiently, exhibit a relatively negative membrane potential threshold for activation (e.g. −60 mV) and are molecularly classified into three types; $Ca_V3.1$, $Ca_V3.2$, and $Ca_V3.3$ [3]. The distinction between HVA and LVA channels concerning initial activation is not absolute as the $Ca_V1.3$ L-type channel displays a more negative opening threshold than typical HVA channels and $Ca_V2.3$ R-type channel exhibits some characteristics more often associated with LVA channels. In addition to the 10 Ca_V α_1 subunit genes in mammals, numerous structural and functional Ca_V variants for each subtype are known to result from alternative splicing mechanisms.

Calcium channels generally activate, inactivate, and deactivate slower than voltage-activated sodium channels and can therefore be distinguished on a temporal basis. When comparing the different calcium channel subtypes, HVA channels generally display slower inactivation kinetics than LVA channels and HVA channels generally deactivate much more rapidly [4]. Therefore, HVA channels typically generate long lasting calcium influxes upon long depolarizations and short calcium influxes upon brief depolarizations, whereas T-type channels conduct short calcium influxes under both brief and long depolarizations [4]. T-type channels also generate what is known as a "window current" as a result of an overlap in the membrane potentials at which they activate and inactivate, generating a small tonic inward current around resting membrane potentials [5].

In addition to the main calcium conducting α_1 subunit, several ancillary proteins (β, $\alpha_2\delta$, and γ subunits) have been shown biochemically to be associated with the HVA Ca_V subunits to form multimeric complexes (Fig. 1). Exogenous expression studies indicate that the ancillary subunits modify HVA Ca_V subunit biophysical properties, intracellular transport/processing, and second-messenger-dependent modulation [2,3]. In vertebrates, four β subunit genes ($\beta1$–$\beta4$), four $\alpha_2\delta$ subunit genes ($\alpha_2\delta_1$–$\alpha_2\delta_4$), and eight γ subunit genes have been identified ($\gamma_{1\text{-}8}$).

2. Calcium channels and epilepsy

Epileptic seizures often display different properties and involve distinct regions of the brain, reflecting the fact that

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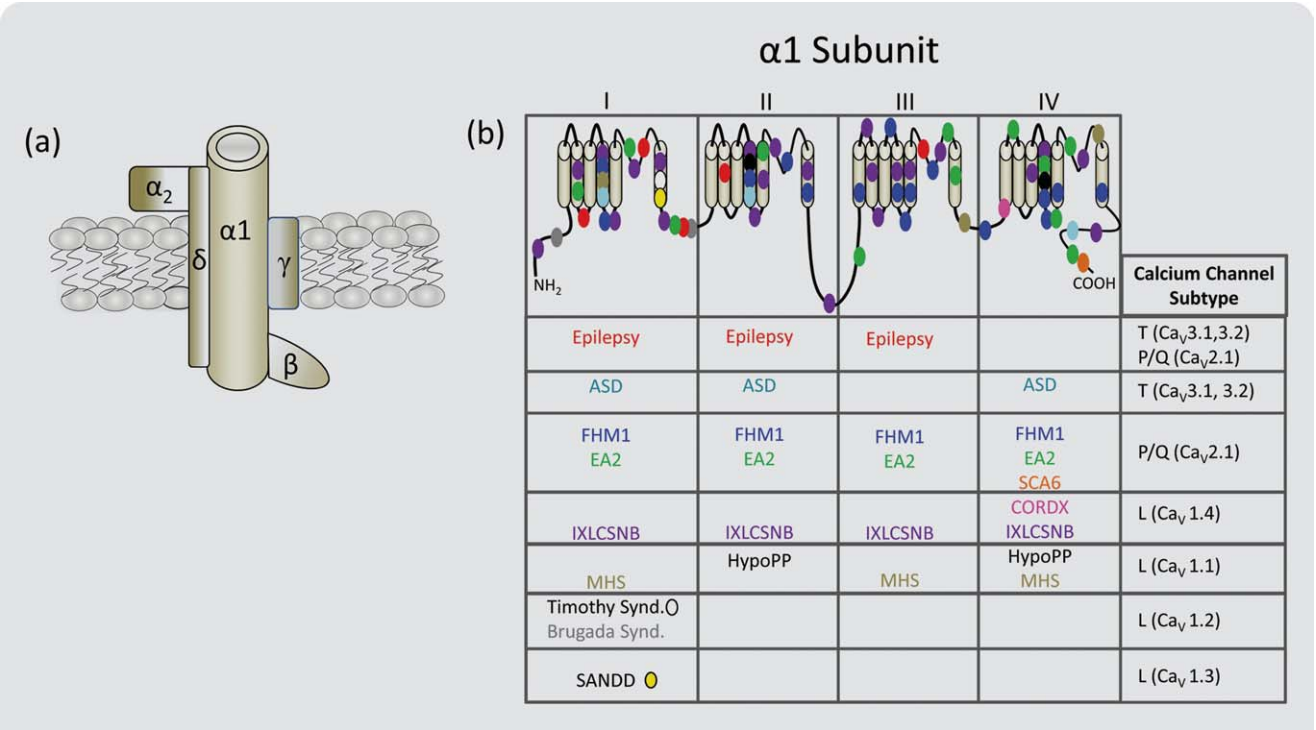

Fig. 1. Calcium channel structure and human mutations. (a) Schematic of the HVA calcium channel complex indicating the pore forming α_1 (Cav) subunit along with ancillary β, γ, and $\alpha_2\delta$ subunits. (b) Predicted topology of the α_1 subunit with its four domain (I-IV) and six transmembrane segment (S1-S6) structure. *Inset (colored dots)* **Locations of known human calcium channel mutations according to domain and segment (multiple mutations in same segment or linker are represented with a single dot); Childhood Absence Epilepsy and Idiopathic Generalized Epilepsy Mutations (Epilepsy), Autism Spectrum Disorders (ASDs), Familial Hemiplegic Migraine type-1 (FHM1), Episodic Ataxia type-2 (EA2), Spinocerebellar Ataxia type-6 (SCA6), Incomplete X-linked Congenital Stationary Night Blindness (IXLCSNB), X-linked Cone-Rod Dystrophy (CORDX), Hypokalemic Periodic Paralysis (HypoPP), Malignant Hyperthermia Susceptibility (MHS), Timothy Syndrome, Brugada syndrome, Sino-Atrial Node Dysfunction and Deafness (SANDD). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]**

the underlying pathophysiological mechanisms can vary widely between seizure type and between patients with phenotypically similar seizures. Patients with similar genetic mutations or sensitivities to particular pharmacological agents have led to a number of calcium channel subtypes being associated with potential roles in the genesis and/or propagation of epileptic seizures. The mechanisms by which altered calcium channel activity modifies neuronal firing properties to promote the epileptic phenotype is a topic of intense research at present.

2.1. T-type calcium channels and epilepsy

Within subpopulations of idiopathic generalized and childhood absence epilepsy patients, the *CACNA1G* (encoding $Ca_V3.1$) and *CACNA1H* (encoding $Ca_V3.2$) genes have been found to contain a variety of missense mutations (Fig. 1) [6–9]. In exogenous expression analyses, some mutations have been shown to increase expression and/or confer altered biophysical properties to the channels, although others have no distinguishable effects [10]. In general, consistent with the notion that epilepsy is a disorder of hyperexcitability, the majority of the mutations display gain-of-function characteristics such as hyperpolarizing shifts in activation thresholds and increased current density. Many of the mutations are clustered around the intracellular linker connecting transmembrane segments S2 and S3 in domain I and thought to affect surface expression of the channel (Fig. 1). While these mutations alone may not be sufficient to induce an epileptic phenotype, they could increase excitability in a manner that contributes towards the generation or propagation of seizures.

In support of the involvement of T-type calcium channels in epilepsies, animal studies demonstrate that enhanced $Ca_V3.1$ and $Ca_V3.2$ channel activity is pro-epileptogenic. The elevated expression of $Ca_V3.1$ and $Ca_V3.2$ channels has been observed in thalamic neurons from the WAG/Rij and GAERS rat models of absence epilepsy, respectively [11–13]. In addition, in GAERS the $Ca_V3.2$ channel gene contains a single missense mutation that correlates with seizure expression and induces a gain-of-function in channel biophysical properties [14]. Further, the genetic enhancement of $Ca_V3.1$ expression has been shown to induce absence epilepsy in otherwise normal mice and the genetic of ablation $Ca_V3.1$ results in resistance to pharmacological induction of absence seizures [15,16].

Systemic administration of the muscarinic receptor agonist pilocarpine to rodents induces short-term temporal lobe epilepsy (TLE) and long-term complex-partial epilepsy [17]. Significant damage is observed in hippocampal, thalamic, cortical, and striatal structures following the short-term phase, and correlates with increased burst firing in hippocampal neurons [18,19]. The increased burst firing appears to result from elevated $Ca_V3.2$ expression and altered channel biophysical properties leading to increased T-type currents in the apical dendrites of hippocampal CA1 neurons. Contrastingly, in pilocarpine treated $Ca_V3.2$ knock-out mice the number of seizures is attenuated, burst firing is abolished and neuronal damage in the CA1 region is reduced [19]. Similar increases in T-type currents have been observed in the Schaffer collateral stimulation kindling model of limbic epilepsy [20]. Overall, $Ca_V3.2$ seems to have a strong pro-epileptogenic influence and may also be linked to seizure-related neuronal damage.

The mechanism whereby T-type calcium channels promote epileptic seizures is thought to in part lie with their ability to generate a cascade depolarization lasting ~100-200 ms and known as a low threshold spike (LTS) [4,21]. It is upon the crest of this LTS that sodium and potassium channels activate, initiating a high frequency series of action potentials, known as a "burst," which have been seen to correlate with seizure-related spike-wave discharges (SWDs) on electroencephalography recordings [4,22]. Burst firing likely promotes the high level of synchronicity that leads to the recruitment of both adjacent and remotely interconnected neurons into firing oscillating volleys of neural activity as epileptic seizures propagate. T-type calcium channels are also thought capable of inducing intracellular oscillations that might contribute to the initiation of some seizures in the epileptic focus (e.g., the cortex in absence seizures [23–28]). Clinically, several therapeutic antiepileptics, including ethosuximide, phenytoin, valproate, and zonisamide are thought to exert at least some of their effects by attenuation of T-type calcium channel activity and thereby preventing oscillations and burst firing [29–35].

2.2. HVA calcium channels and epilepsy

P/Q-type channels are highly expressed presynaptically, where they are critically involved in synaptic neurotransmission and exert a powerful influence on neuronal excitability [36]. Mutations in the *CACNA1A* gene encoding the $Ca_V2.1$ subunit of both P-type and Q-type channels [37] have been identified in some human cases of epileptic seizure, although such cases are relatively rare. For example, some patients suffering from Familial Hemiplegic Migraine type 1 (FHM-1; see below) display generalized tonic-clonic seizures and/or complex-partial limbic seizures [38–40].

Patients suffering from Episodic Ataxia type 2 (EA2) exhibit spontaneous ataxia (poor muscle coordination) and a portion also suffer from migraine and epileptic seizures. One patient identified with primary generalized epilepsy in conjunction with episodic, and progressive ataxia possessed a *CACNA1A* mutation predicted to result in truncation of the P/Q channel [41]. In another instance, five members of a family were found to suffer from a combination of absence seizures and episodic ataxia and all contained a missense mutation in their *CACNA1* gene [42]. In these instances, the EA2 mutations were found to result in a loss-of-function P/Q phenotype when assessed exogenously. A further *CACNA1A* mutation was found in an EA2 patient suffering from seizure episodes, as well as ataxia amongst other neural dysfunction; however, no functional effects on P/Q-type channel properties have been reported [43].

In a number of mouse models of EA2, animals exhibit both absence seizures and ataxia (*Tottering, Leaner, Rolling Nagoya*) and have been shown to possess mutations that result in reduced P/Q-type channel function or expression [44,45]. Accordingly, knockdown of the P/Q-type channel alone is sufficient to mimic many of the characteristics of the EA2 mutated mice [46]. However, another mouse strain (*Rocker*) containing an EA2 P/Q-type channel mutation displays absence seizures and ataxia but without any known effects on the channel [47]. Interestingly, in the WAG/Rij model of absence epilepsy, an increase in the expression of P/Q-type channels is observed in the reticular thalamic nucleus, concomitant with the increase observed in $Ca_V3.1$ in thalamocortical neurons. Conversely, in the *Tottering* mouse an upregulation of $Ca_V3.1$ is observed with reduced P/Q function and also genetic ablation of $Ca_V3.1$ reduces seizures in a number of P/Q channel-mutated mice strains [48–50]. At this point, it is difficult to discern exactly which aspects of the pathological phenotypes directly result from specific channel mutations and which might result from secondary alterations induced by compensatory adaption of the nervous system.

Following kindling in the rodent model of temporal lobe epilepsy, expression of the $Ca_V1.3$ L-type, P/Q-type, and R-type channels are upregulated, and HVA currents are increased in CA1 and dentate gyrus cells [20,51]. Interestingly, these same channels are upregulated in the inferior colliculus in the Genetic Epilepsy Prone Rats (GEPR-3), following a single audiogenic seizure [52,53] and the expression of $Ca_V1.3$ L-type and R-type channels is increased even before they display seizures. The brain circuitry involved in these seizures is quite distinct, yet the same channels display upregulation in both models, perhaps indicating a general role for these channels in priming the hyperexcitable activity observed in epileptic foci. The R-type channel is of further interest since R-type knockout mice display resistance to pharmacologically-induced generalized seizures as well as to pharmacologically-induced and kindling-induced limbic seizures, but increased susceptibility to pharmacologically-induced absence seizures [54–57]. The therapeutic antiepileptic drugs lamotrigine, carbamazepine, topiramate, and leviteracetam have all been shown to have an inhibitory effect on HVA calcium channels [35,58–62].

2.3. Calcium channel ancillary subunits and models of epilepsy

The β, $\alpha_2\delta$, and γ ancillary calcium channel subunits have also been implicated in epilepsy [10]. *Lethargic* mice, which

contain a mutation that genetically deletes the β_4 subunit exhibit SWDs and ataxia and neuronally display attenuated presynaptic function [63]. In the GEPR-3 model of generalized epilepsy, increased β_3 subunit expression is observed in seizure-naïve rats and increases further following a single audiogenic seizure [53].

Strains of mice have been developed with mutations in the $\alpha_2\delta_2$ subunit (known as *ducky* and *ducky^{2J}*) which display SWDs and ataxia [64,65]. In addition, the *entla* mouse displays a mutation that renders the $\alpha_2\delta_2$ subunit non-functional and these animals also display SWDs [66]. Cerebellar Purkinje neurons from *Ducky, ducky^{2J}*, and *entla* mice all display a corresponding reduction in P/Q-type current density via reduced membrane expression of the channel [64–66]. Expression of the $\alpha_2\delta$ subunit is also decreased in seizure-naïve GEPR-3 rats and decreases further following induction of a single audiogenic seizure [53].

The *stargazer* and *waggler* mouse epilepsy models display mutations in their γ_2 subunit protein, also known as "stargazin." These mutations increase the inactivation of P/Q-type channels and both mice display SWDs, which are exacerbated in *waggler* mice due to an additional knockout of the γ_4 subunit [67]. In addition to the calcium channel ancillary role for this subunit, stargazin is known to be involved in the synaptic trafficking and biophysical modulation of AMPA receptors. Thus, it is possible that a percentage of the phenotype associated with the mutations could involve this AMPA receptor trafficking. This may also be the case in GAERS, where stargazin is upregulated in both the somatosensory cortex and thalamus [68].

It is evident that these mutations have the potential to induce pathophysiological changes that may lead to seizures; however, the specific effects of the many ancillary subunit alterations on cellular excitability remain difficult to establish since they often occur in tandem with alterations in Ca_V subunit expression and activity. The therapeutic antiepileptic drug, gabapentin, is predicted to mediate it effects through direct inhibition of calcium influx via action on $\alpha_2\delta_1$ and $\alpha_2\delta_2$ but not the $\alpha_2\delta_3$ and $\alpha_2\delta_4$ subunits [69–71], although this notion is controversial [62,72].

3. T-type channels and autism spectrum disorders

Autism spectrum disorders (ASDs) are a diverse group of neurological conditions characterized by impaired social interaction and communication with restricted and repetitive behavior. In a study examining the genetic components 461 patients with ASDs, mutations were identified in the *CACNA1H* gene encoding $Ca_V3.2$ in six patients from different families (Fig. 1) [73]. While loss-of-function effects have been observed as a result of the mutations introduced into exogenously expressed $Ca_V3.2$ channels, the low incidence of occurrence and lack of segregation with the disease phenotype suggest that any role in ASD is likely part of a much wider neural impairment. Of note, a recent study has identified the *CACNA1G* gene as a potential novel candidate for ASD [74].

4. P/Q-type channels and congenital migraine

4.1. Familial hemiplegic migraine type 1

Migraine headaches are a debilitating neurological/vascular condition in which sufferers experience painful headache alone or in association with an aura (usually visual or auditory) [75,76]. FHM-1 is an autosomal dominant hereditary disorder in which patients experience typical characteristics of migraine, although additionally with unilateral paralysis (hemiplegia). The neuronal phenotype includes a wave of hyperexcitability followed by long lasting depression of activity that spreads across the cortex over a few to tens of minutes (known as cortical spreading depression; CSD). Involvement of the trigeminal vascular system is thought to play a key role in the painful headache aspects of migraine [76]. Approximately 50% of FHM-1 patients possess missense mutations in the *CACNA1A* gene encoding the $Ca_V2.1$ subunit of the P/Q-type calcium channel (Fig. 1) [77].

The effects of FHM-1 mutations in heterologous systems have yielded varying results with regards to changes in P/Q-type channel expression and altered biophysical properties (for a more detailed review see [44,45]). However, it generally appears that a gain-of-function is more often observed than a loss-of-function with regard to the FHM1 mutations [45]. Mice genetically modified to express the human R192Q and S218L FHM-1 mutations have allowed comprehensive studies *in vivo* and *in vitro* [78]. Behaviorally, the R192Q and S218L mutations result in phenotypes that closely mimic the human conditions; a modest effect of R192Q and prominent ataxia induced by S218L. Both strains also display a lower threshold for CSD as well as increased rates of CSD, again similar to that for humans with the S218L allele being the more severe. At the biophysical level, the mutations induce modest (R192Q) and prominent (S218L) gain-of-function by increasing channel availability (increasing neurotransmitter release at presynaptic terminals) and also both affect P/Q-type channel regulation by camodulin and alter synaptic efficacy [79,80].

5. P/Q-type channels and ataxias

5.1. Episodic ataxia type-2

Another autosomal disorder involving mutations in *CACNA1A* is EA2 in which patients suffer random attacks of poor muscle coordination that can last from a few hours to days, although successful treatment can often be achieved with the carbonic anhydrase inhibitor, acetazolamide [81]. Several dozen *CACNA1A* gene mutations have been identified in patients with EA2 and also in some strains of mice exhibiting many of the typical traits of the disorder. The various mutations are localized throughout putative transmembrane and intracellular regions of the $Ca_V2.1$ subunit and are either missense or introduce premature stop codons (Fig. 1; for detailed review see [44,45]). The functional effects of the mutations involve total or partial loss-of-function, via either decreased channel expression predicted to result from protein misfolding and attenuated transport to the plasma

membrane and/or shifts in the voltage threshold for activation [45,82–84]. Interestingly, EA2 mutated channels induce a dominant negative effect on wild type P/Q-type channels and it is has been hypothesized that channel degradation may be enhanced in cells expressing mutation-containing channels [85]. Mice suffering from ataxia (*Tottering, Leaner, Rolling-Nagoya, and Rocker*) express P/Q-type channel mutations with similar loss-of-function effects to those found in EA2 patients. Analyses largely reveal similar phenotypes to those observed for the human EA2 mutations, including decreased current density or depolarizing shifts in the threshold for activation, resulting in attenuated neurotransmitter release from presynaptic terminals [86,87]. As yet, no biophysical effects of the *Rocker* $Ca_V2.1$ mutation (T13010K) have been reported [47].

5.2. Spinocerebellar ataxia-type 6

A second ataxic condition attributed to genetic alteration of $Ca_V2.1$ is spinocerebellar ataxia type-6 (SCA6), in which patients suffer from cerebellar atrophy, leading to movement disorders such as incoordination, loss of proprioception and involuntary eye movement (nystagmus) [88]. Genetic investigations reveal increased numbers of CAG repeats (⋯›21) in exon 47 of the *CACNA1A* gene (Fig. 1). Of the P/Q-type channelopathies, the mechanism of disease etiology is least well understood for SCA6. While, some biophysical alterations to channel properties have been associated with elevated CAG repeats [89], it is also proposed that neuronal cell death is induced by nuclear or perinuclear aggregation of the expanded $Ca_V2.1$ carboxyl-terminal fragments, proteolytically cleaved from the parent channel [90].

6. $Ca_V1.4$ L-type calcium channel and retinal disorders

The $Ca_V1.4$ L-type channel is of critical importance in retina where photoreceptor relay cells depend on $Ca_V1.4$ for neurotransmitter release from presynaptic terminals [91]. X-linked Cone-Rod Dystrophy (CORDX) is a disorder in which patients suffer from a number of visual impairments including altered or reduced field of vision, photophobia and abnormal color definition [92]. To date, one mutation has been identified in the *CACNA1F* gene encoding $Ca_V1.4$ in a single family of CORDX sufferers (Fig. 1). This mutation appears to affect alternative splicing, and although the exact effect on the channel biophysical properties is unknown it is thought to induce truncation or deletions of the $Ca_V1.4$ channel [93].

A second retinal disorder linked to mutations in $Ca_V1.4$ is Incomplete X-linked Congenital Stationary Night Blindness (IXLCSNB), which exhibits clinically as varying degrees of night blindness but can also cause short or long sightedness, involuntary eye movement and in rare cases it is linked to intellectual disability [45,94]. A large number of mutations (⋯›60) in *CACNA1F* have been identified in IXLCSNB patients (Fig. 1) [95]. In general, both rod and cone cells display functional deficiencies in generating nerve impulses in agreement with attenuated neurotransmission; however, when studied exogenously in heterologous systems, the functional consequences of the mutations have varied between gain-of-function, loss-of-function, and no discernable effects [96,97].

7. $Ca_V1.1$ L-type calcium channel and muscular disorders

7.1. Hypokalemic Periodic Paralysis

In the transverse tubules of skeletal muscle, $Ca_V1.1$ L-type channels are involved in the excitation-contraction coupling by inducing sarcoplasmic calcium release via interaction with ryanodine receptors (although not requiring calcium influx through $Ca_V1.1$) [98]. A form of autosomal dominantly inherited muscle weakness, known as Hypokalemic Periodic Paralysis (HypoPP), has been associated with mutations in the *CACNA1S* gene, encoding $Ca_V1.1$ (Fig. 1) [99]. Patients suffering from HypoPP develop variable degrees of muscle weakness, typically from adolescence, and experiments on skeletal muscle excised from patients have revealed a reduced level of excitability in combination with an increase in sodium conductance [100]. The majority of HypoPP-related mutations identified occur in $Ca_V1.1$ voltage-sensing S_4 domains and generally appear to cause a loss-of-function phenotype, often attenuating current density or shifting activation thresholds to more depolarized membrane potentials (for detailed review see [45,99]). Whether the pathophysiology associated with HypoPP results from reduced calcium influx, a reduced interaction of $Ca_V1.1$ with the ryanodine receptor or by another calcium-dependent pathway is not currently known.

7.2. Malignant Hyperthermia Susceptibility

Patients suffering from malignant hyperthermia susceptibility (MHS) display a predisposition to muscle hypermetabolism following administration of muscle relaxants and volatile anesthetics [101]. In affected individuals, these agents cause skeletal muscle cells to undergo calcium release from intracellular stores, inducing muscle contraction and followed by lactic acidosis and increased temperature as a result of increased metabolism. These pathophysiological alterations can in turn lead to cardiac arrhythmias and renal failure, potentially resulting in death. Indeed, there is a high incidence of mortality in untreated cases, although successful treatment can be mediated by administration of dantrolene, preventing calcium release from intracellular stores. In two families with this autosomal dominantly inherited disorder, the same mutation was identified in the *CACNA1S* gene (Fig. 1) [45,95,102]. The mutation was found to lower the half-maximal voltage required to induce intracellular calcium release and to also increase sensitivity to caffeine-mediated calcium release from intracellular stores [95,103]. Another *CACNA1S* mutation has been identified in a subgroup of MHS patients, although no biophysical effects on $Ca_V1.1$ properties have been reported [104]. Finally, a third *CACNA1S* mutation has recently been identified in an Italian family suffering from MHS and which was shown to increase $Ca_V1.1$ channel activation kinetics and to increase sensitivity to caffeine-mediated calcium release [105].

8. $Ca_V1.2$ L-type calcium channel and cardiac disorders

8.1. Timothy Syndrome

Timothy Syndrome (TS) is phenotypically manifest across a number of different physiological systems, likely as a result of the widespread distribution of $Ca_V1.2$ L-type channels [106]. The most common identifiers of TS are cardiac arrhythmias associated with prolonged QT syndrome and the fusion of one or more fingers (syndactyly). Facial abnormalities, such as a flattened nasal bridge and small teeth and physical malformations in heart are also often observed. Neurologically, developmental delays and ASDs are also reported; however, as the average age of survival for TS patients is only $\sim$2.5 years, many patients do not survive long enough to adequately assess neurological fitness. A number of mutations have been identified in the *CACNA1C* gene of TS patients, encoding the $Ca_V1.2$ channel [45,95]. In experiments investigating the functional consequence of the TS mutations, all have been found to prolong calcium entry by severely impairing channel inactivation and by altering gating via calcium-sensitive modulatory proteins [107,108]. These combined biophysical effects can likely account for the prolonged QT time and cardiac arrhythmias, although the underlying causes of the physical deformities are less well understood.

8.2. Brugada syndrome

Patients suffering from Brugada syndrome display abnormal electrocardiograms and have an increased susceptibility to Sudden Cardiac Death via ventricular fibrillation [109]. In a study examining genetic causes of Brugada syndrome, 3 out of 82 individuals displaying elevated ST-segment elevation and short Q-T intervals were found to possess mutations in two different domains of the *CACNA1C* gene encoding the $Ca_V1.2$ $\alpha 1$ subunit as well as in *CACNA1B2* encoding the ancillary β_2 subunit [110]. When examined exogenously, all three mutations decreased macroscopic L-type currents and with one of these appearing to act through attenuating $Ca_V1.2$ membrane trafficking to the plasma membrane.

9. $Ca_V1.3$ L-type calcium channels in sino-atrial node dysfunction and deafness

$Ca_V1.3$ L-type calcium channels, are known to activate at more hyperpolarized potentials than "typical" HVA channels. In addition to mediating sino-atrial node depolarization and cardiac pacemaking, they are also critical for hearing as they are involved in sound transmission in cochlear inner hair cells [95,111]. In two consanguineous families where members suffered from sino-atrial node dysfunction and deafness, a common mutation was found in the *CACNA1D* gene encoding $Ca_V1.3$ [112]. When examined exogenously, the glycine insertion mutation in the channel pore-forming region of a specific $Ca_V1.3$ splice variant resulted in a complete loss of function through interruption of the channel gating mechanism. Furthermore, mice lacking $Ca_V1.3$ display a phenotype, which closely resembles the human condition [111].

10. Summary

There is clear evidence from human calcium channelopathies and animal models that voltage-gated calcium channels crucially contribute to a plethora of physiological systems. Over the last 30 years, combined advances in genetic screening and structure-function analyses with cloned channels have further defined that both gain-of-function and loss-of-function alterations to calcium channel properties can lead to deleterious effects. While alterations associated with loss-of-function changes in channel properties are predicted to be more difficult to treat clinically, the long use of L-type calcium channel blockers for cardiovascular disease suggests that the development of subtype specific antagonists is a validated approach for the treatment of calcium channelopathies associated with gain-of-function (e.g. epilepsy, congenital migraine).

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