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The Role of L-Type Calcium Channels in Neuronal Excitability and Aging

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Abstract

Over the last two decades there has been significant progress towards understanding the neural substrates that underlie age-related cognitive decline. Although many of the exact molecular and cellular mechanisms have yet to be fully understood, there is consensus that alterations in neuronal calcium homeostasis contribute to age-related deficits in learning and memory. Furthermore, it is thought that the age-related changes in calcium homeostasis are driven, at least in part, by changes in calcium channel expression. In this review, we focus on the role of a specific class of calcium channels: L-type voltage-gated calcium channels (LVGCCs). We provide the reader with a general introduction to voltage-gated calcium channels, followed by a more detailed description of LVGCCs and how they serve to regulate neuronal excitability via the post burst afterhyperpolarization (AHP). We conclude by reviewing studies that link the slow component of the AHP to learning and memory, and discuss how age-related increases in LVGCC expression may underlie cognitive decline by mediating a decrease in neuronal excitability.

Keywords

age-related cognitive decline; neuronal excitability; L-type voltage-gated calcium channels; $Ca_V1.2$; $Ca_V1.3$; slow afterhyperpolarization; sAHP

Introduction to Voltage-Gated Calcium Channels

Voltage-gated calcium channels (VGCCs) are multi-subunit membrane complexes that permit calcium to cross the plasma membrane in response to depolarizing shifts in membrane potential. In mammals, VGCCs are widely distributed across multiple organ systems and cell types. As with other ionic species, the direction of flow across the membrane is driven in a concentration-dependent manner, and in the case of calcium, the

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extracellular concentration far exceeds that measured inside the cell. In neurons, the intracellular Ca^{2+} concentration is in the tens of nanomolar range while the extracellular concentration is in the *millimolar* range, a difference of a thousand-fold or greater (Clapham, 2007)! This steep concentration gradient ensures a rapid and robust signaling mechanism for a multiplicity of neuronal functions.

Voltage-gated calcium channels in neurons are typically comprised of a pore forming subunit and several "auxiliary" subunits. The pore forming (α_1) subunit proteins are relatively large (~200 kD) and the entire ion channel pore is formed from a single α1 subunit, consisting of four repeated domains each containing six transmembrane domains (for review, see Catterall, 2011). The auxiliary subunits (α2δ and β) are important for α1 subunit trafficking to the plasma membrane with subcellular domain specificity and can modulate α1 subunit voltage dependency and kinetics (Dolphin, 2016). In addition, there exists a γ subunit which appears to be part of the calcium channel complex found in skeletal muscle but is not found in neurons (Dolphin, 2016).

For the uninitiated, the nomenclature surrounding VGCCs can be somewhat confusing. This is in part because calcium channels are still often referred to in terms of the underlying currents, many of which were characterized prior to the identification of the actual channel proteins (and the genes that encode them). Calcium currents were originally classified based upon their voltage of activation (high voltage activated [HVA] vs low voltage activated [LVA]), inactivation kinetics and sensitivity to specific blockers (which were determined empirically). For example, the "L-type" current is classically described as being large and long-lasting while the "T-type" current is tiny and transient, and "N-type" are somewhere in between, being neither L- nor T-type (reviewed by Tsien, Lipscombe, Madison, Bley, and Fox, 1988). In addition, L-type currents are blocked by dihydropyridines such as nimodipine and N-type currents are blocked by the cone snail toxin ω-conotoxin, but T-type currents are not sensitive to either (Tsien et al., 1988). Further classification of calcium currents was greatly facilitated by the use of venom extracted from the funnel web spider (*Agelenopsis aperta*). Initial experiments used crude fractions (Llinas, Sugimori, and Cherksey, 1989) but before long the active peptide (ω-agatoxin-IVA) was isolated, which effectively blocked high-threshold calcium currents in the rat cerebellum (Mintz, Venema, Swiderek, Lee, Bean, and Adams, 1992). Because these calcium currents were first described in Purkinje neurons (Llinas et al., 1989), they were named P-type currents. While specific channels are today often referred to using nomenclature derived from the underlying currents (e.g. L-type voltage-gated calcium channel), the channels that gate the P current are referred to as P/Q-type. The Q-current was first described in cultures of cerebellar granule cells and could be separated from the P current on the basis of inactivation kinetics and ω-agatoxin-IVA sensitivity (Randall and Tsien, 1995). However, cloning and expression studies have led to the conclusion that both currents are gated by splice variants of the same α-pore forming subunit (Bourinet, Soong, Sutton, Slaymaker, Mathews, Monteil, Zamponi, Nargeot, and Snutch, 1999), giving rise to the P/Q-type moniker. In the same report first describing the Q-current, the authors also described a high threshold current in cerebellar granule cells which was insensitive to antagonism by nimodipine, ω-agatoxin-IVA, or ω-conotoxin, distinguishing it from the other high voltage activated currents (L, P/Q and N). This current was named R-type as it appeared to be resistant to L, P/Q, and N current antagonists

(Randall and Tsien, 1995). While there now exists a standard naming system that is similar to that used for voltage-gated K+ channels (see below), the use of L, N, R, P/Q, and T when discussing calcium channels is still common practice, in no small part because using the current-derived nomenclature adds a functional connotation.

With the advent and rapid adoption of molecular cloning methods, researchers in the voltage-gated calcium channel field quickly began to identify genes responsible for encoding the pore-forming subunit and auxiliary subunits. In 1994, the field adopted a unified nomenclature which named the genes that encoded the pore forming subunits as α_{1A} though α_{1Z}. At the time, six distinct pore-forming subunits genes had already been cloned. Starting with α_{1A}, these genes were named in the order in which they were discovered. The exception to this rule was α_{1S} to acknowledge the recently deceased Shosaku Numa who cloned the very first LVGCC gene from skeletal muscle (hence the “S” designation). Therefore, the five remaining genes were designated α_{1A} though α_{1E} (Birnbaumer, Campbell, Catterall, Harpold, Hofmann, Horne, Mori, Schwartz, Snutch, Tanabe, and et al., 1994). However, as more α_1 subunits were subsequently cloned, there arose the possibility that the pore-forming subunit α_{1L} would be cloned and it may or may not mediate an L-type current, which might create confusion. Thus, the field adopted a new nomenclature similar to that previously established for voltage-gated K^+ channels (Chandy and Gutman, 1993). In this scheme, the charge carrying ion (Ca) is denoted with the biophysical mechanism by which it is regulated (voltage; V) in subscript (Ca_V). Further, the pore-forming subunits were grouped into three families (Ca_V1, Ca_V2 & Ca_V3) based on protein sequence homology; then family members were numbered in order of discovery (Ertel, Campbell, Harpold, Hofmann, Mori, Perez-Reyes, Schwartz, Snutch, Tanabe, Birnbaumer, Tsien, and Catterall, 2000). Table 1 summaries these different nomenclatures and includes the Human Genome Organization (HUGO) Gene Nomenclature Committee (HGNC) approved symbol for the human gene (which interestingly still retains the “alpha” to denote the alpha subunit [eg. CACN**A1C**] in the gene symbol).

Postsynaptic VGCCs: The L-Type Calcium Channel

If neuroscientists are familiar with voltage-gated calcium channels at all, they are most likely familiar with the P/Q- and N-type channels as these are involved in neurotransmitter release and are often referred to as “presynaptic” channels. On the other hand, L-type VGCCs (referred to hereafter as LVGCCs) are thought of as being “postsynaptic” as they are not involved in neurotransmitter release; instead, in most neurons, LVGCCs gate calcium influx in response to large depolarizing shifts in membrane potential. There are four known LVGCCs but only two, $Ca_V1.2$ and $Ca_V1.3$, are highly expressed in brain. While $Ca_V1.2$ and $Ca_V1.3$ share a fair amount of homology both in terms of DNA and protein sequence (Snutch, Leonard, Gilbert, Lester, and Davidson, 1990), they differ significantly in terms of their biophysical properties as well as their distribution throughout the brain and within neuronal compartments. Within the hippocampus, LVGCCs exhibit a differential expression pattern with $Ca_V1.2$ being heavily expressed in the pyramidal neuron cell body layer in CA1, in both the cell bodies and dendritic fields of CA2 and CA3, and in the dendrites of dentate gyrus; on the other hand, $Ca_V1.3$ is localized to the cell bodies and proximal dendrites throughout the hippocampus (Hell, Westenbroek, Warner, Ahlijanian, Prystay,

Gilbert, Snutch, and Catterall, 1993). In addition to having different distributions within the hippocampus, experiments using heterologous expression systems suggest that $Ca_V1.2$ and $Ca_V1.3$ LVGCCs have different activation thresholds, with $Ca_V1.3$ channels opening approximately 20mV more hyperpolarized than $Ca_V1.2$ (Helton, Xu, and Lipscombe, 2005; Lipscombe, Helton, and Xu, 2004; Xu and Lipscombe, 2001).

One of the most fascinating aspects of LVGCCs is the diverse roles that they play and the timescales over which they initiate changes in neuronal function. While the bulk of this review will focus primarily on the millisecond to second time range, it should be noted that LVGCCs have been implicated in a wide range of subcellular processes associated with learning and memory that span much longer time frames (hours to weeks). For example, it has been known for some time that the calcium influx gated by LVGCCs plays a key role in adult neurogenesis in the hippocampus. Early work using LVGCC antagonists (such as nifedipine) significantly reduced neurogenesis in rats when administered systemically (Deisseroth, Singla, Toda, Monje, Palmer, and Malenka, 2004). More recent studies using knockout mice have confirmed a role for $Ca_V1.2$ and $Ca_V1.3$ in adult neurogenesis (Kim, Park, Lee, Choi, Kim, and Kim, 2017; Lee, De Jesus-Cortes, Kabir, Knobbe, Orr, Burgdorf, Huntington, McDaniel, Britt, Hoffmann, Brat, Rajadhyaksha, and Pieper, 2016; Marschallinger, Sah, Schmuckermair, Unger, Rotheneichner, Kharitonova, Waclawiczek, Gerner, Jaksch-Bogensperger, Berger, Striessnig, Singewald, Couillard-Despres, and Aigner, 2015; Temme, Bell, Fisher, and Murphy, 2016; Volkening, Schonig, Kronenberg, Bartsch, and Weber, 2017). Adult neurogenesis has long been implicated in learning and memory, most notably in forms of learning that require “pattern separation/completion” (Tuncdemir, Lacefield, and Hen, 2019). Consistent with this idea, deletion of $Ca_V1.2$ disrupts both spatial learning in the water maze and context discrimination during Pavlovian fear conditioning with experimental conditions that are thought to require pattern completion/separation, but spares performance in versions of these tasks that are less reliant upon the dentate gyrus (Temme et al., 2016).

The Post Burst AHP

The post burst AHP (afterhyperpolarization) is, as the name implies, a hyperpolarizing potential that follows a train of action potentials. The post burst AHP is thought to regulate neuronal excitability by holding the cell below the firing threshold for an extended period of time following a burst of action potentials. The post burst AHP is often subdivided by time domains: the fast AHP (fAHP) which immediately follows the burst; the medium AHP (mAHP) which is usually ~200 ms after the burst and often includes the maximum hyperpolarization; and the slow AHP (sAHP) which is often measured at ~1000 ms after the burst and persists for thousands of milliseconds (Faber and Sah, 2002; 2003; Gustafsson and Wigstrom, 1981; Sah, 1996; Sah and Faber, 2002). The ultimate source of each of these three phases of the hyperpolarizing potential is undoubtedly efflux of K^+, but the exact identity of the responsible K^+ channel(s) and how they regulate neuronal excitability is still somewhat debated. For example, in CA1 pyramidal neurons, a number of reports have suggested that the mAHP (and thus excitability) is regulated by members of the small conductance Ca^{2+}-activated K^+ channel (SK, [$K_{Ca}2.x$]) family (Stackman, Hammond, Linardatos, Gerlach, Maylie, Adelman, and Tzounopoulos, 2002; Stocker, 2004; Stocker,

Krause, and Pedarzani, 1999) while other reports suggest it is predominated by a combination of voltage-gated K^+ channels (KCNQ/M, [K_V7.x]) and hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels (Gu, Hu, Vervaeke, and Storm, 2008; Gu, Vervaeke, Hu, and Storm, 2005). More recently, it has been suggested that SK channels play a role in regulating excitability, but only when KCNQ/M channel function has been compromised (Chen, Benninger, and Yaari, 2014). Similarly, there exists some controversy regarding the potassium channels that underlie the sAHP with evidence supporting both a role for (King, Rizwan, Asmara, Heath, Engbers, Dykstra, Bartoletti, Hameed, Zamponi, and Turner, 2015; Turner, Asmara, Engbers, Miclat, Rizwan, Sahu, and Zamponi, 2016) and against (Wang, Mateos-Aparicio, Honigsperger, Raghuram, Wu, Ridder, Sah, Maylie, Storm, and Adelman, 2016) IK channels (intermediate conductance Ca^{2+}-activated K^+, [K_{Ca}3.1]). Several factors have likely contributed to the field's inability to settle on a single ground truth regarding the subcellular mechanism(s) that regulate the different phases of the post burst AHP. These include the method of recording (current- vs voltage-clamp; sharp vs whole-cell patch), the organism (mouse, rat, rabbit, cat), the age of the animal, and which cell type is being examined. Even when a number of these factors are made equivalent, details such as the internal recording solution (e.g. Kaczorowski, Disterhoft, and Spruston, 2007; Zhang, Weiner, Valiante, Velumian, Watson, Jahromi, Schertzer, Pennefather, and Carlen, 1994), the genetic background (Moore, Throesch, and Murphy, 2011; Murphy, Fedorov, Giese, Ohno, Friedman, Chen, and Silva, 2004), and recording temperature (Gulledge, Dasari, Onoue, Stephens, Hasse, and Avesar, 2013; Tiwari, Mohan, Biala, and Yaari, 2018) can influence the appearance and plasticity of the AHP. Setting aside the controversies regarding the identity of the K+ channel(s) which underlie the post burst AHP, there is general agreement that the sAHP is dependent upon calcium influx that is gated by LVGCCs (although see Gulledge et al., 2013), which will be the focus of the discussion below.

The sAHP in Learning and Memory

The sAHP was originally described in 1980 (Alger and Nicoll, 1980; Hotson and Prince, 1980) in the CA1 region of the hippocampus, but it is observed in a variety of brain regions, including the amygdala (Power, Bocklisch, Curby, and Sah, 2011) and the sensorimotor cortex (Schwindt, Spain, and Crill, 1988; Schwindt, Spain, Foehring, Chubb, and Crill, 1988; Schwindt, Spain, Foehring, Stafstrom, Chubb, and Crill, 1988), as well as in interneurons in the striatum (Goldberg and Wilson, 2005). It is well appreciated that the sAHP is modulated by and functions to support several forms of learning (Coulter, Lo Turco, Kubota, Disterhoft, Moore, and Alkon, 1989; Disterhoft, Coulter, and Alkon, 1986; Disterhoft, Golden, Read, Coulter, and Alkon, 1988; Saar, Grossman, and Barkai, 1998; Sehgal, Ehlers, and Moyer, 2014). Many of the early insights into the relationship between the sAHP and learning came from trace eyeblink experiments, initially in rabbits and then in rats (and more recently in mice). In this task, a brief tone (the conditioned stimulus, CS) predicts an air puff delivered to the eye (the unconditioned stimulus, US) after an intervening (trace) interval of several hundred milliseconds. Animals that successfully acquire the task learn this association and close the nictitating membrane covering the eye (conditioned response, CR) to avoid the air puff. Unlike other forms of eyeblink conditioning, trace eyeblink conditioning is dependent upon an intact hippocampus.

Therefore, following training in trace eyeblink conditioning, when intracellular recordings are obtained from CA1 pyramidal neurons in *ex vivo* hippocampal slices, learning performance can be directly correlated with changes in the sAHP. Groundbreaking work from the Disterhoft lab showed that young adult animals that successfully learned the CS-US association exhibited a reduced sAHP (and increased neuronal excitability) when compared to neurons in slices from naïve animals (that had received no training experience), pseudoconditioned animals (that had received unpaired presentations of the CS and US), and, importantly, from "slow-learner" animals that were trained under identical conditions, but did not demonstrate a criterion level of correct CRs and thus were not considered to have learned the task (Disterhoft, Thompson, Moyer, and Mogul, 1996). The reduced sAHP amplitude in the trace eyeblink task appears to be transient in nature: recordings made 7 days after successful learning revealed a sAHP which was indistinguishable from the sAHP recorded in slices from control animals (Moyer, Thompson, and Disterhoft, 1996). This suggests that the reduction in the post-burst AHP may be necessary to permit an animal to learn a task, but likely does not represent the encoded memory itself. While the sAHP has been studied most intensively in the hippocampus, changes in sAHP amplitude have been observed in other brain regions in the context of other learning paradigms, including in the piriform cortex after odor discrimination learning (Saar et al., 1998) and in the amygdala after Pavlovian fear conditioning (Sehgal et al., 2014).

At present it remains somewhat unclear how learning-related changes in the sAHP manifest. Evidence from *ex vivo* slice preparations suggests that modulation of the sAHP can occur in a cell autonomous fashion because long-lasting reductions in the sAHP have been induced by high frequency stimulation that drives intercellular depolarization (Cohen-Matsliah, Motanis, Rosenblum, and Barkai, 2010; Kaczorowski et al., 2007). Interestingly, both a significantly larger sAHP as well as a significantly smaller sAHP can adversely impact learning and memory. For example, aging has consistently been shown to affect the sAHP. Recordings made in *ex vivo* slices from aged animals reveal a larger sAHP compared to that recorded in slices from young adult animals (e.g. Landfield and Pitler, 1984; Moyer, Thompson, Black, and Disterhoft, 1992). Further, this increase in magnitude has been associated with poorer performance in behavioral learning and memory tasks (e.g. Kaczorowski and Disterhoft, 2009; Murphy et al., 2004). Perhaps the most convincing evidence linking age-related increases in sAHP amplitude to learning/memory impairments exploits the observation that aged rabbits and rats (and inbred mice under some conditions; see Murphy, Rahnama, and Silva, 2006) often comprise two distinct populations. While not always a 50/50 split, when compared to young animals, approximately one half of the aged animals will exhibit comparable performance ("learners") while the other half will either take longer to learn the task or fail to learn the task altogether ("slow-learners" or "non-learners"). Following behavioral characterization, animals are sacrificed and *ex vivo* recordings of the sAHP amplitude are made in acute slices, which can be correlated with the individual animal's behavioral performance. Using this approach an inverse relationship between sAHP amplitude and memory has been demonstrated in a number of learning paradigms including trace eyeblink conditioning (Matthews, Linardakis, and Disterhoft, 2009; Moyer, Power, Thompson, and Disterhoft, 2000) and the Morris water maze (Tombaugh, Rowe, and Rose, 2005).

Conversely, *reduction* of the sAHP amplitude has also been shown to lead to learning and memory deficits. For example, genetic deletion of *Kcnab2*, the gene that encodes $K_V\beta2$, which is an auxiliary potassium channel subunit that modulates rates of endogenously inactivating $K_V1.4$ currents (McCormack, McCormack, Tanouye, Rudy, and Stuhmer, 1995), significantly reduces the sAHP in the lateral amygdala. Consistent with the central role that the amygdala plays in Pavlovian fear conditioning, the decreased sAHP observed in the *Kcnab2* null mice was associated with disruptions in both contextual and cued (tone CS) fear conditioning (Perkowski and Murphy, 2011). Similarly, deletion of $K_V\beta1.1$ significantly reduces the sAHP amplitude and disrupts reversal learning in mice (Giese, Storm, Reuter, Fedorov, Shao, Leicher, Pongs, and Silva, 1998).

Taken together, these data suggest that there may be an effective range for the sAHP (and possibly for the other components as well; see Matthews et al., 2009) in which it is capable of influencing learning and memory. In cases where a genetic or pharmacological intervention has moved the sAHP outside this range (either smaller or larger), training may be unable to sufficiently modulate the sAHP to induce learning and memory. Alternatively, the intracellular mechanisms that are involved in producing a larger or smaller sAHP may occlude the activity-dependent plasticity of the sAHP that is required for learning and memory.

Age-related Changes in LVGCC and the sAHP

From the early 1990s, evidence has accumulated suggesting that there is an age-related alteration in calcium homeostasis. One of the first experiments to support this hypothesis found an age-related increase in calcium spike duration, which is a measure of calcium influx via voltage-gated calcium channels (Pitler and Landfield, 1990). Later, in an elegant study using on-cell voltage clamp recordings, Philip Landfield's group (Thibault and Landfield, 1996) demonstrated that CA1 pyramidal neurons from aged animals had enhanced LVGCC density when compared to young and middle-aged rats. Notably, this increase in current density was correlated with a decrease in performance in the Morris water maze, suggesting that the increase in channel density contributed significantly to the age-related decline in hippocampal-dependent learning (Thibault and Landfield, 1996). These studies demonstrating an age-related dysregulation of intracellular calcium have been corroborated by calcium imaging (e.g. Hemond and Jaffe, 2005; Thibault, Hadley, and Landfield, 2001), which showed an increase in $[Ca^{2+}]_I$ in response to repetitive spiking (Hemond and Jaffe, 2005; Thibault et al., 2001) in neurons from aged animals. Importantly, the intracellular calcium concentration $[Ca^{2+}]_i$ at rest in these neurons was similar to that observed in young animals. These results suggest that the high voltageactivated, postsynaptically localized LVGCCs represent the source of increased $[Ca^{2+}]_I$ in aged animals. This idea is supported by experiments in which LVGCCs were targeted pharmacologically in aged animals. For example, nimodipine (a LVGCC blocker) has been demonstrated to modulate the AHP preferentially in *ex vivo* slices prepared from aged rabbits (Moyer et al., 1992). Similarly, nimodipine reduced the I_{sAHP} (the current that underlies the sAHP) by a greater magnitude in aged neurons as compared to young neurons from rats and rabbits (Lima and Marrion, 2007; Power, Wu, Sametsky, Oh, and Disterhoft, 2002). Taken together, the data show that expression of LVGCCs is upregulated during aging

and that this increase is correlated with cognitive impairments; further, the sAHP, which is Ca^{2+}-dependent, is also increased with age and correlated with cognitive impairments, Therefore, a model has emerged whereby age-related upregulation of LVGCCs leads to an increase in the magnitude of the sAHP, which in turn results in learning and memory deficits in aged animals. However, determining the exact identity of the LVGCC subunit(s) that is upregulated during aging has been somewhat challenging. Early work correlating LVGCC current density with mRNA levels (using RT-PCR) at the level of individual neurons suggested that $Ca_V1.3$ expression was upregulated during aging (Chen, Blalock, Thibault, Kaminker, and Landfield, 2000). Similarly, studies using LVGCC antibodies and immunoblotting suggested that $Ca_V1.3$ protein levels in CA1 hippocampus were increased in aged rats (Veng and Browning, 2002) which correlated with age-related impairments in working memory (Veng, Mesches, and Browning, 2003). However, it also appears that phosphorylation of $Ca_V1.2$ by cAMP-dependent protein kinase A (PKA) is significantly increased in the hippocampus of aged rats (Davare and Hell, 2003), although not in aged mice (Murphy, Shah, Hell, and Silva, 2005). While none of these reports directly conflict with one another, a complete picture has yet to emerge regarding age-related changes in LVGCC protein levels. This is likely due in part to the lack of specificity of the antibodies and the technical and methodological challenges associated with their use in quantitative studies. Voltage-gated ion channels, in general, are known to be difficult to target immunohistochemically (Rhodes and Trimmer, 2006) and LVGCCs appear to be especially sensitive to a variety of experimental conditions including acrylamide concentration (e.g. Buonarati, Henderson, Murphy, Horne, and Hell, 2017). In addition, when LVGCC protein levels are quantified using bulk homogenates, there appears to be an age-related decrease in both $Ca_V1.2$ and $Ca_V1.3$, but when examination is restricted to protein in/on the cell surface, a region-specific, age-related increase in LVGCC expression is revealed (Nunez-Santana, Oh, Antion, Lee, Hell, and Disterhoft, 2014). While there has yet to be a definitive study which ascribes the relative contributions of $Ca_V1.2$ or $Ca_V1.3$ to the age-related increase in activity dependent $[Ca^{2+}]_i$, there are several lines of evidence to suggest that calcium influx via $Ca_V1.3$ is a major source of calcium associated with the sAHP under normal conditions. For example, in mice genetic ablation of *Cacna1d* but not *Cacna1c* resulted in a significant reduction in the sAHP in CA1 hippocampus (Gamelli, McKinney, White, and Murphy, 2011). More recent studies utilizing direct stochastic optical reconstruction microscopy (dSTORM) suggest that $Ca_V1.3$ clusters into a complex with KCa3.1 on the plasma membrane and that this complex is anchored to ryanodine receptors localized on the endoplasmic reticulum (Sahu, Wazen, Colarusso, Chen, Zamponi, and Turner, 2019). Importantly, disruption of this complex reduces the I_{sAHP}. Finally, we have recently generated a transgenic mouse line which over-expresses an epitope tagged form of $Ca_V1.3$ (Krueger, Moore, Parent, McKinney, Lee, and Murphy, 2017). The expression levels of $Ca_V1.3$ in CA1 hippocampus of these mice are similar to what we have previously observed in aged mice and the sAHP is similarly increased (Figure 1).

Interestingly, young mice over-expressing Cav1.3 also show impairments in learning and memory tasks, similar to those observed in aged wild-type mice (Moore, S. personal observation; see also Moore, Slater, and Murphy, 2012). Taken collectively, these data suggest that an age-related increase in $Ca_V1.3$ results in enhanced activity-dependent

$[Ca^{2+}]_I$, mediates the enhanced sAHP, and contributes to learning and memory deficits in aged animals.

Additional Mechanisms Contributing to Age-Related Changes in Ca^{2+} Homeostasis

The focus of this review is to highlight the role that LVGCCs play in age-related changes in neuronal excitability and cognition. However, it should be noted that the alterations in LVGCC expression/function occur concurrently with other age-related changes in calcium homeostasis. For example, several studies have suggested that intracellular stores provide the source of calcium for activating the Ca^{2+}-activated K^+ channel(s) that mediate the sAHP. Both depletion of intracellular stores or blockage of ryanodine receptors, which mediate release of calcium from intracellular stores, reduced the sAHP in aged animals (Bodhinathan, Kumar, and Foster, 2010; Gant, Sama, Landfield, and Thibault, 2006; Kumar and Foster, 2004). Interestingly, LVGCCs are known to be one source of calcium that can trigger Ca^{2+}-induced Ca^{2+} release from intracellular stores and the effect of depletion of intracellular stores on the sAHP can be reversed using a LVGCC agonist (Kumar and Foster, 2004). It is likely that this and other processes could contribute to the age-related dysregulation of Ca^{2+} homeostasis, and may be differentially recruited in certain cell types or regions, and/or may act in synergistically in concert to disrupt calcium signaling in aged animals.

Concluding Thoughts

Although the evidence supporting the idea that aging is accompanied by an increase in LVGCC expression and a subsequent increase in the sAHP is substantial, many questions remain unanswered. One obvious question is: why? Is the age-related upregulation of LVGCCs a consequence of some other, unknown neurosenescence? Or perhaps the upregulation of LVGCC expression is a compensatory response. Given that even modest prolonged elevations of $[Ca^{2+}]_i$ can be neurotoxic and the fact that neurons expend a significant amount of energy (in the form of ATP) to maintain minimal levels of $[Ca^{2+}]_{i,}$, this seems unlikely. An equally important and related question is: how? If one accepts the premise that the end result of the age-related upregulation of LVGCCs is impaired cognitive function, this proves to be a critical question. At present, there are no subunit specific LVGCC blockers. Because $Ca_V1.2$ is abundantly expressed in cardiac myocytes and vascular tissue, off target effects of the existing non-specific antagonists somewhat limits their use. In this regard the results from the recent phase III NILVAD trial are informative (Lawlor, Segurado, Kennelly, Olde Rikkert, Howard, Pasquier, Borjesson-Hanson, Tsolaki, Lucca, Molloy, Coen, Riepe, Kalman, Kenny, Cregg, O'Dwyer, Walsh, Adams, Banzi, Breuilh, Daly, Hendrix, Aisen, Gaynor, Sheikhi, Taekema, Verhey, Nemni, Nobili, Franceschi, Frisoni, Zanetti, Konsta, Anastasios, Nenopoulou, Tsolaki-Tagaraki, Pakaski, Dereeper, de la Sayette, Senechal, Lavenu, Devendeville, Calais, Crawford, Mullan, and Group, 2018). In this randomized, placebo-controlled, double-blind trial, patients with mild- and moderate-stage Alzheimer's disease where treated with nilvadipine (a LVGCC blocker similar to nimodipine) or a placebo. Unfortunately, nilvadipine did not alter the trajectory of cognitive decline in this study at the selected dose (8 mg/day). This dose was selected in part because it was thought that a higher dosing regimen might reduce blood pressure to an unsafe level.

Although treated patients on average did have a small reduction in blood pressure at the end of the trial, the authors concluded that “the effect on blood pressure quite modest, so it would probably have been safe to give a higher dose.” (Lawlor et al., 2018). These results highlight the difficulty in even designing a trial in the absence of subunit specific pharmacology and emphasize the need for a renewed effort toward drug discovery in this area. Finally, it is worth noting that, in addition to cognitive aging, dysregulation of voltage-gated calcium channels has been implicated in a number of other conditions. For example, LVGCCs have been implicated in Parkinson’s disease (Liss and Striessnig, 2019) and substance abuse (Burgdorf, Schierberl, Lee, Fischer, Van Kempen, Mudragel, Huganir, Milner, Glass, and Rajadhyaksha, 2017) and variants in CACNA1C have been implicated in a wide array of psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics, 2013). In this regard, future advances made in better understanding the role of LVGCCs in aging and cognition will likely have considerable impacts on a broad range of neurological and psychiatric disease states.

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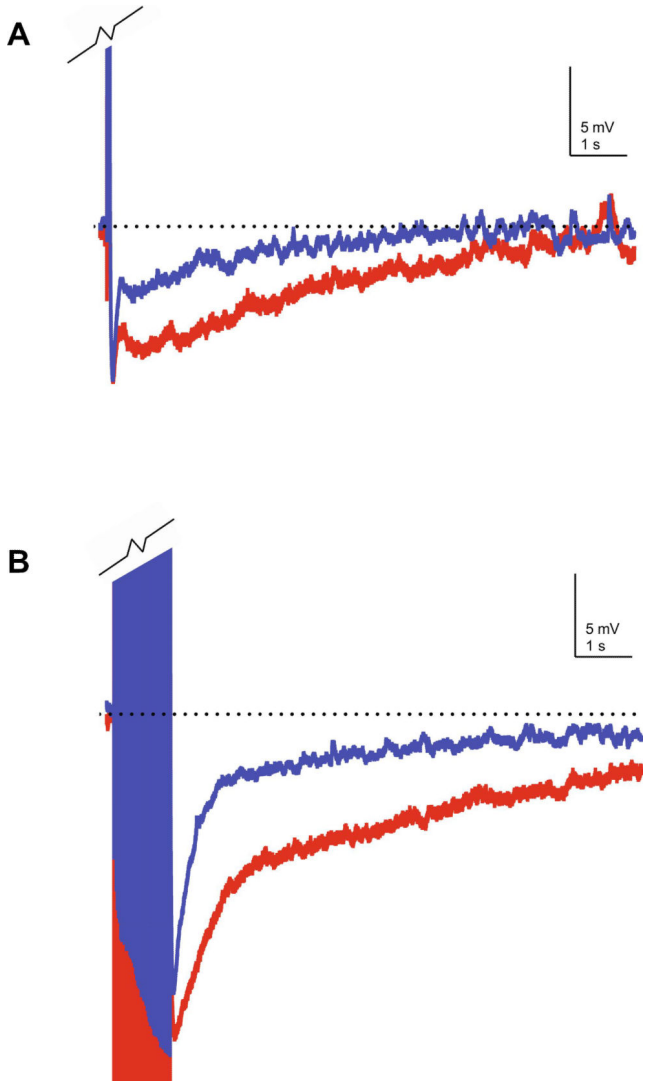

Figure 1.

Representative sAHP recordings from CaV1.3 over-expressing mice. Whole-cell current-clamp recordings were made in CA1 hippocampus pyramidal neurons in ex vivo slices prepared from young (4 mo) wild-type (blue) and CaV1.3 over-expressing (red) mice. A) The sAHP elicited by a 50 ms depolarizing step that is sufficient to elicit five action potentials. B) The sAHP recorded in response to a 1 s train of action potentials at 50 Hz. In both cases, the sAHP was increased in the CaV1.3 over-expressing mice compared to that observed in wild-type mice. Action potentials have been truncated to emphasize the sAHP. Dotted line approximates the resting membrane potential.

Table 1.

Current voltage-gated calcium channel nomenclature (after Catterall, Lenaeus, and Gamal El-Din, 2020).

Current	Protein Name	Alpha Subunit	Gene Name (human)	Activation Voltage
L-type	$Ca_V1.1$	α1S	*CACNA1S*	High
L-type	$Ca_V1.2$	α1C	*CACNA1C*	High
L-type	$Ca_V1.3$	α1D	*CACNA1D*	High
L-type	$Ca_V1.4$	α1F	*CACNA1F*	High
P/Q-type	$Ca_V2.1$	α1A	*CACNA1A*	High
N-type	$Ca_V2.2$	α1B	*CACNA1B*	High
R-type	$Ca_V2.3$	α1E	*CACNA1E*	High
T-type	$Ca_V3.1$	α1G	*CACNA1G*	Low
T-type	$Ca_V3.2$	α1H	*CACNA1H*	Low
T-type	$Ca_V1.3$	α1I	*CACNA1I*	Low