Calcium channel blocking as a therapeutic strategy for Alzheimer’s disease: the case for isradipine

Thimmappa S. Anekonda and Joseph F. Quinn
Department of Neurology and Portland Veteran Administration Medical Center, Oregon Health & Science University, Portland, OR

Abstract

Alzheimer’s disease is the most devastating neurodegenerative disorder in the elderly, yet treatment options are severely limited. The drug development effort to modify Alzheimer’s disease pathology by intervention at beta amyloid production sites has been largely ineffective or inconclusive. The greatest challenge has been to identify and define downstream mechanisms reliably predictive of clinical symptoms. Beta amyloid accumulation leads to dysregulation of intracellular calcium by plasma membrane L-type calcium channels located on neuronal somatodendrites and axons in the hippocampus and cortex. Paradoxically, L-type calcium channel subtype Ca\textsubscript{v}1.2 also promotes synaptic plasticity and spatial memory. Increased intracellular calcium modulates amyloid precursor protein processing and affects multiple downstream pathways including increased hyperphosphorylated tau and suppression of autophagy. Isradipine is a Federal Drug Administration-approved dihydropyridine calcium channel blocker that binds selectively to Ca\textsubscript{v}1.2 in the hippocampus. Our studies have shown that isradipine in vitro attenuates beta amyloid oligomer toxicity by suppressing calcium influx into cytoplasm and by suppressing Ca\textsubscript{v}1.2 expression. We have previously shown that administration of isradipine to triple transgenic animal model for Alzheimer’s disease was well-tolerated. Our results further suggest that isradipine became bioavailable, lowered tau burden, and improved autophagy function in the brain. A better understanding of brain pharmacokinetics of calcium channel blockers will be critical for designing new experiments with appropriate drug doses in any future clinical trials for Alzheimer’s disease. This review highlights the importance of Ca\textsubscript{v}1.2 channel overexpression, the accumulation of hyperphosphorylated tau and suppression of autophagy in Alzheimer’s disease and modulation of this pathway by isradipine.

Keywords

autophagy; beta amyloid; bioavailability; tau

1. Introduction

Beta amyloid (Aβ) plaque in Alzheimer’s disease (AD) accumulates long before patients become symptomatic; therefore, many therapeutic efforts have now moved to very early intervention. Another strategy to tackle the discordance between Aβ production and AD...
symptoms is to target mechanisms of neurodegeneration which are “downstream” of Aβ production. The greatest challenge has been to identify critical pathways that directly impact clinical symptoms and then effectively modulate these pathways by pharmacological agents. We and others have observed that a specific set of downstream pathways including dysregulation of intracellular calcium (Ca²⁺), upregulation of caspase-cleaved tau (tau-C3), hyperphosphorylation of tau (ptau), and loss of cellular housekeeping or autophagy function, may contribute directly to the expression of clinical symptoms. Multiple mechanisms control these seemingly unrelated pathways. A vast amount of current literature substantiates their critical but complex role in AD pathology [1-12].

1.1 Calcium trafficking is a complex process

Ca²⁺ trafficking is a complex process. A tight functional link exists among channels located on the plasma membrane (Aβ pores; L-type calcium channels, LTCC; N-methyl D-aspartyl receptor, NMDAR), endoplasmic reticulum (ryanodine receptor, RyR; Inositol(1,4,5)P₃ receptor, InsP₃R; sarco endoplasmic reticulum calcium ATPase, SERCA), and mitochondria [13-16]. Further, presenilin proteins, involved in AD pathogenesis, are located on the ER and can leak Ca²⁺ into the cytoplasm or interact with RyR, InsP₃R, and SERCA to increase their activity [9, 12, 17]. A P86L polymorphism in a novel calcium channel called calcium homeostasis modulator 1 (CALHM1) can influence Aβ production by modulating amyloid precursor protein (APP) processing [11, 12]. Such a complexity involving a bidirectional relationship between Aβ production and calcium homeostasis pathways presents difficult experimental challenges (Figure 1; sections 1 & 2). Recent publications in the triple transgenic mouse model of AD (3xTgAD) implicate roles of RyR, InsP₃R and NMDAR in the production of Ca²⁺ and synaptic plasticity of hippocampal neurons [18-21], but the role of LTCC, especially of Caᵥ1.2, in relation to Aβ, tau, and autophagy is largely unknown. Therefore, in this review, we mainly focus on Caᵥ1.2 relationship to AD pathology.

1.2 L-type calcium channel subtype Caᵥ1.2 is a critical target for calcium channel blockers in AD brains

Aging and Aβ consistently promote Ca²⁺ influx into neurons by way of L-type calcium channels (LTCCs). Soluble intraneuronal Aβ oligomers, soluble and insoluble Aβ fibrils can increase intracellular Ca²⁺, impair neuronal function, and adversely affect synaptic functions in AD [13, 22, 23]. Ca²⁺ increase occurs through over activation of LTCCs [24]. The uncontrolled Ca²⁺ increase can trigger the overexpression of plasma membrane LTCC subtype Caᵥ1.2 in the hippocampus of AD brains and further exacerbate the pathogenic Ca²⁺ influx [1, 25, 26]. Caᵥ1.2 is located in cell bodies and dendrites, axonal terminals, and axons of neurons, and glial processes of the hippocampus [2]. Paradoxically, Caᵥ1.2 expression is essential for long-term potentiation (LTP) (independent of NMDAR-dependent LTP), synaptic plasticity, and spatial memory of the hippocampus [1, 2]. Caᵥ1.2KO in mice disrupts remote spatial memory, further confirming the importance of Caᵥ1.2 [1]. Caᵥ1.3, a closely-related LTCC subtype known to mediate the pace-making function of dopaminergic neurons in Parkinson’s disease, has no known role in hippocampal memory function [27, 28].

Our recent study has examined the role of Caᵥ1.2 in response to intracellular oligomeric Aβ because such understanding is an emerging area of relevance to AD [29]. Caᵥ1.2 channel expression is essential for long-term potentiation (LTP) independent of NMDAR-dependent LTP, synaptic plasticity, and spatial memory of the hippocampus [1-3, 5, 18, 28]. Multiple pathways involving generation of intraneuronal or soluble extracellular Aβ can induce protein kinase A (PKA), which in turn binds to LTCC and promotes increased Ca²⁺ influx [30, 31]. PKA binding to the alpha subunit of Caᵥ1.2 in the cytoplasm causes Caᵥ1.2 overexpression in the membrane [30, 31]. PKA also promotes pathological

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hyperphosphorylation of tau [32, 33] and suppression of autophagy function in AD [34] (Figure 1; sections 1 & 3).

It is important to recognize that Ca\textsubscript{v}1.2-independent pathways may also directly influence A\textsubscript{\beta} production, ptau or autophagy functions. A\textsubscript{\beta}-toxicity that is independent of Ca\textsubscript{v}1.2 may occur when intraneuronal A\textsubscript{\beta} directly enters mitochondria and disrupts cellular energy balance or promotes free radical production [35]. Alternatively, free radicals can be generated from APP in autophagosomal compartments and disrupt autophagy function without affecting Ca\textsubscript{v}1.2 [36].

1.3 Autophagy dysfunction in AD

The emerging literature suggests that autophagy, a self-cleaning cellular housekeeping mechanism, plays an important role in AD pathology [36]. Previously, it was assumed that autophagy was inducible only in response to stress but not essential for cell function. The most recent literature, however, provides unequivocal evidence for the constitutive role of autophagy in cellular homeostasis, thus making it essential for neuronal survival [37, 38]. Autophagosomal vacuoles accumulate in AD [7, 36, 39, 40], which can lead to an accelerated accumulation of ptau and tau-C3 [41-43]. Accumulated ptau, in turn, can rupture lysosomes, causing them to prematurely release proteolytic enzymes into the cytoplasm and disrupt normal autophagy function leading to neuronal death by apoptosis in AD [44-46]. A heterozygous deletion of the autophagy marker beclin-1 in Tg2576 mice increases intraneuronal A\textsubscript{\beta} accumulation, extracellular A\textsubscript{\beta} deposits, and neurodegeneration [47], suggesting that autophagy plays a key protective role against AD. Autophagy function is suppressed in several mouse models including 3xTg-AD [48-50]. Indeed one of the main functions of autophagy is to regulate mitochondrial function by enzymatic degradation of dysfunctional mitochondria and by clearing misfolded proteins in the cell [41, 51]. Our studies in Tg2576 mice provide strong evidence for mitochondrial deposition of A\textsubscript{\beta} leading to generation of free radicals and a protective role of autophagy against AD pathology [35].

1.4 Caspase-cleaved and hyperphosphorylated tau

A considerable effort has been made in the past few decades to understand tau-associated pathology in AD [52-55]. There seems to be a general consensus among experts that: (1) hyperphosphorylated tau appears early in the disease progression and is more prone to aggregation and tangle formation than the normal tau [52, 56, 57]. Increased Ca\textsuperscript{2+} can promote ptau via calpain-dependent pathway [58, 59]; (2) the presence of more 3-repeat tau conformations relative to 4-repeats can be pathogenic in AD [55, 60]; and (3) caspase-cleaved tau-C3 is fibrillogenic with much greater propensity for aggregation and formation of ptau and neurofibrillary tangles [53, 61, 62]. The most exciting and numerous roles of tau-C3 in AD pathology are still emerging in the literature. When wild type tau is cleaved mainly by caspase-3 at Asp\textsuperscript{421} site, a tau-C3 is formed [56, 62]. A recent study suggests that caspase activation may precede tangle formation in tau transgenic Tg4510 mice [63]. Some suggest that tau-C3 is present in tauopathies in the absence of A\textsubscript{\beta} pathology [43]. Lysosomal dysfunction may promote the increased formation of tau-C3 [44]. Thus, these emerging studies strongly suggest that the clearance pathway of tau-C3 is tightly linked to autophagy-lysosomal pathways in AD. Furthermore, tau-C3 is preferentially degraded by the macroautophagy pathway [41]. Ca\textsuperscript{2+} toxicity or overexpression of Ca\textsubscript{v}1.2 can also lead to mislocalization of tau into somatodendritic regions instead of normal axonal localization [64]. In somatodendritic regions, tau can damage microtubules and spines and become ptau [64].
These studies together provide a strong evidence for complex roles of $\text{A}\beta$, $\text{Ca}_{\text{v}}1.2$, $\text{Ca}^{2+}$, tau-C3, ptau, autophagy-lysosomal dysfunction in orchestrating AD pathology. We call this nexus of toxicity in short: A$\beta$-Ca$\text{v}$1.2-ptau-autophagy pathway.

2. Calcium channel blockers to break the nexus of toxicity

Usefulness of LTCC blockers (CCBs) against AD pathology is controversial. Epidemiological studies suggest that CCBs prevent [65] or slow the rate of progression of AD [66, 67]. A large clinical trial with nimodipine did not show significant benefits from the primary outcome measures but has shown moderate benefits for treatment of AD in the secondary outcome measures [68, 69]. In a recent study, however, nimodipine selectively stimulated the secretion of $\text{A}\beta_{1-42}$ in vitro and in the plasma of Tg2576 mouse model of AD, questioning the usefulness of this CCB for AD [70]. Several clinical studies have suggested that CCBs used as antihypertensive drugs may prevent cognitive decline in hypertensive subjects [71-74], but none have demonstrated a role for CCBs in AD per se. Two dihydropyridine CCBs were among the eight FDA-approved drugs selected from 485 small biomolecules screened for their ability to induce autophagy without causing toxic effects in human neuroglioma H4 cells [75]. Further, dihydropyridine-based derivatives act as potent activators of anti-aging neuroprotective protein sirtuin 1 [76], which appears to regulate autophagy function [77].

Two recent in vitro studies have shown usefulness of DHP CCBs on A$\beta$ production and A$\beta_{1-42}$ transcytosis across an in vitro blood-brain barrier (BBB) created by an apical “blood” and basolateral “brain” layers of human brain microvascular endothelial cells [78, 79]. Nivaldipine, nitrendipine, and amlodipine reduced A$\beta$ production in 7W Chinese hamster ovary (CHO) cells, which have been stably transfected with human APP751 [79]. This study further shows an improved A$\beta$ clearance by nivaldipine and nitrendipine, and an improved explorative activity for animals treated with nivaldipine in a transgenic animal model of AD (Tg PS1/APPsw) [79]. The BBB transcytosis of A$\beta_{1-42}$ also increased for several of DHP CCBs including nitrendipine, nicardipine, nimodipine, and nivaldipine [78]. In their study, isradipine had no effect on A$\beta_{1-42}$ transcytosis. Furthermore, CCBs (nitrendipine, clinidipine, nivaldipine) promoted A$\beta_{1-42}$ clearance across the BBB in wild type mice; and in animals treated with human A$\beta_{1-42}$, nivaldipine improved the cognitive functions of the animals in Morris water maze test [78]. These studies clearly suggest that DHP CCBs possess non-channeling functions that are independent of their calcium channel blocking ability, suggesting a need for thorough validation of CCBs for AD.

2.1 Why isradipine a suitable CCB for treatment of AD?

Emerging studies in models of Parkinson’s disease (PD) show neuroprotection by isradipine, an FDA-approved dihydropyridine class of CCB for hypertension [27, 80-82]. In these studies, isradipine blocks LTCC subtype cav1.3 function in dopaminergic neuron of the substantia nigra and modulates autonomous pacemaking function [27, 82, 83]. Isradipine provides protection against stroke and brain ischemia in rat models for hypertension [84, 85]. Early studies focusing on binding properties of $[^3H]$isradipine in AD and control brains suggest that the hippocampal CA1 region experiences greater cell loss in response to increased expression of LTCCs in AD brains relative to control brains [86, 87], suggesting that isradipine treatment is likely to modulate the over-expressing LTCCs in the CA1 region and preserve the hippocampal function. Isradipine can also attenuate over active LTCC function as well as oxidative stress-induced apoptotic cell death in hypobaric hypoxia model of rats and preserve their memory function [88]. Our preliminary studies have clearly shown the superior effects of isradipine over nimodipine in vitro [29]. We also predict that the brain bioavailability of therapeutic doses of isradipine is superior to that of nimodipine, as bioavailability studies in animals generally support this assertion [89, 90].

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A recent isradipine safety and tolerability study in PD provides valuable guidelines for how to evaluate the neuroprotective effects of isradipine in clinical trials [80]. In this study, subjects (average age = ~59 years) with early PD were treated with increasing doses of controlled release isradipine (5-20 mg daily doses) over a period of eight weeks. There was a dose-dependent tolerability for isradipine (94% for 5 mg; 87% for 10 mg; 68% for 15 mg; 52% for 20 mg). Isradipine did not show any significant impact on blood pressure or motor disability, but leg edema and dizziness were the two frequent adverse symptoms commonly observed in this study, leading to a conclusion that 10 mg daily dose of isradipine was a safe treatment [80]. In a Danish case-control study (average age=72 years), the effect of DHP class of CCBs was evaluated retrospectively for their neuroprotective effects on PD [27]. The commonly prescribed centrally-acting DHP CCBs (nimodipine, isradipine, nitrendipine, nifedipine), as opposed to non-DHP class of CCBs, provided up to 27% risk reduction for PD, irrespective of treatment length and duration [27]. These studies appear to suggest that careful clinical trials using isradipine in older patients are highly feasible, safe, and unlikely to cause adverse effects on the memory-related function of Ca\textsubscript{v}1.2.

\subsection*{2.1.1 In vitro studies—}
Our recent publication is the first such report to show neuroprotection of isradipine against A\textsubscript{β}\textsuperscript{-42} induced Ca\textsuperscript{2+} toxicity in human neuroblastoma/MC65 cells [29]. MC65 cells that are stably transfected with the APP-C99 gene conditionally express a fusion protein fragment of the amino-17 and carboxyl-99 residues [91, 92]. APP-C99 gene expression in these cells is controlled by a tetracycline-responsive promoter whose activity is repressed in the presence of tetracycline or induced by withdrawing tetracycline from the growth medium. Removal of tetracycline leads to expression of the C-terminal APP fragment and subsequent processing of this fragment into A\textsubscript{β} monomers followed by accumulation of intracellular A\textsubscript{β} oligomers, and precipitous cell death by about 72 hours. In this cell culture model we tested the role of cav1.2 expression on Ca\textsubscript{2+} influx and cell survival as well as protective effects of four CCBs (diltiazem, verapamil, nimodipine, isradipine) against Ca\textsubscript{2+}-induced toxicity. Isradipine was the most potent of the four CCBs tested [29]. This study suggests that intracellular A\textsubscript{β} oligomers trigger increased intracellular Ca\textsubscript{2+} influx primarily through Ca\textsubscript{v}1.2 channels. None of these CCBs prevented the formation of intracellular oligomers. Isradipine provided protection against Ca\textsubscript{2+} toxicity by both blocking calcium influx and suppressing cav1.2 expression downstream of A\textsubscript{β} formation [29]. Our study results also indicate that Ca\textsubscript{2+} levels are tightly controlled and cells respond to small variations in Ca\textsubscript{2+} and this response is sensitive to small concentrations of isradipine [29].

\subsection*{2.1.2 In vivo studies—}
We also tested isradipine for its neuroprotective functions in four evolutionarily divergent species including models for AD: human neuroblastoma/MC65 cells, transgenic \textit{Drosophila}, \textit{Manduca}, and 3Tg-AD mice [93]. In transgenic \textit{Drosophila} model, 250 \textmu M isradipine increased the survival of flies from 6.5% to 12% (p<0.5) against APP\textsubscript{L695} toxicity [93]. In moth/\textit{Manduca sexta} experiments, embryonic culture preparations were exposed to exogenous A\textsubscript{β}\textsubscript{1-42} peptide to determine the toxic effects of this peptide on neuronal development and growth in the presence or absence of 10 \textmu M isradipine [93]. Treatment with A\textsubscript{β}\textsubscript{1-42} induces concentration-dependent perturbations in the extent of migration and outgrowth of enteric nervous system. A simultaneous treatment with isradipine prevents the deleterious effects of A\textsubscript{β} [93]. Our studies further show that subcutaneous administration of isradipine (3 \textmu g/g/day; 60-day release) to 3xTgAD mice was well-tolerated and isradipine became available to the brain [29, 93]. The 3xTgAD mouse model, which harbors PS1(M146V), APPswe and tau(P301L) transgenes, develops age-dependent and region-specific A\textsubscript{β} and tau aggregations in the cortex and hippocampus that closely mimics the pathology found in human AD [94, 95]. A small cohort of 17-month-old female 3xTgAD mice (an age well after the appearance of AD pathology) were implanted.
with carrier-bound isradipine pellets (n=3, 3 mg/Kg/day, 60-day release, Innovative Research of America) or placebo control pellets (n=4). Isradipine was well-tolerated as evidenced by average weekly body weights (an indirect measurement of toxicity), which were the same for vehicle and isradipine-treated animals. Isradipine treatment also showed lowering trend for insoluble Aβ1-40 and Aβ1-42, no effect on soluble Aβ1-40, and undetectable soluble Aβ1-42 [93]. Histological Aβ burden in these animals reduced non-significantly in the hippocampus and isradipine significantly lowered IHC-detectable ptau burden in the hippocampus [93]. In a second cohort of 22-month-old female 3xTgAD (N=8) and age-matched wild type (N=8) mice, a similar isradipine or vehicle pellet implantation showed significantly upregulated LC3B protein, a marker for late-stage autophagy (unpublished results) in isradipine-treated mice. These animal studies together strongly suggest that protective functions of isradipine are similarly conserved across evolutionarily divergent species and these functions are mutually synergistic.

2.2 LTCC blocking with isradipine: implications for future research

Our novel findings show that isradipine can modulate AD pathology by influencing Aβ production upstream as well as components of the cav1.2-ptau-autophagy pathway. This will have much larger implications in developing a unique treatment strategy for AD. Isradipine appears to bind strongly to cav1.2 in the hippocampus and perhaps short-circuits the downstream pathway [3, 96, 97] (Figure 1; section 3). Mechanisms that promote the clearance of rapidly cluttering autophagosomal vacuoles in AD brains have been elusive for the past several decades, and they now appear to be an important bottleneck in moving forward with effective treatment strategies for AD. Fortunately, calcium channel blockers are emerging as modulators of autophagy function [75, 98]. We believe that an approach to use CCB to short-circuit the entire downstream pathway can overcome current hurdles in the clinical treatment of AD. We argue that isradipine is an appropriate candidate for future studies, as it appears to possess additional functions capable of modulating both upstream and downstream protective functions besides its calcium channel blocking ability.

Calcium channel blocking will have a many implications for future research and clinical trials: (1) Suppression of CaV1.2 expression through β2AR/cAMP/PKA or mitochondrial PKA-dependent pathways can defuse the upstream toxic effects of Aβ or reactive oxygen species [30, 31]. (2) PKA-dependent suppression of LC3 function in autophagy can be neutralized by blocking CaV1.2 [99, 100]. (3) Attenuated Ca2+-dependent calpain levels can downregulate ptau and caspase-cleaved tau production. It is possible that LTCC blocking may provide effective protection strategies for Parkinson’s disease, Huntington’s disease, ALS, axotomy, brain ischemia, and stroke, where autophagy or isradipine is known to play key protective roles. It is important to recognize that there may be some risk in modulating CaV1.2 expression specifically in the hippocampal CA1 pyramidal neurons, since these receptors also directly influence long-term potentiation, synaptic plasticity, and spatial memory function [3, 5, 28, 101]. However, several lines of evidence discussed at the top of this section suggest that isradipine predominantly modulates CaV1.2 rather than adversely effecting the memory function associated with normal function of CaV1.2 [27, 80, 86].

3. Bioavailability of calcium channel blockers

In the past three decades, several bioanalytical methods (radioactive labeling, gas chromatography, high pressure liquid chromatography) have been developed for assessing isradipine pharmacokinetics and pharmacodynamics in animal and human tissues [6, 86, 89, 90, 102, 103]. The most important discovery from these early methods is that isradipine undergoes extensive first-pass metabolism and nearly 90% of orally administered isradipine is absorbed in the digestive tract, limiting its bioavailability to about 17-28% in plasma. For an immediate release (IR) formulation of isradipine, a sharp peak concentration occurs in...
plasma about 1.5-2 h after administration with a terminal half-life of 8 hours [89].
Sustained-release (SR) formulations show superior bioavailability with an initial lag period
for 2-3 hrs and then a slow increase in concentration reaching a plateau between 7 to 18 hrs
after dosing. Thus, SR formulation shows a lower maximal plasma concentration (C_{max}) and
an extended maximal tissue concentration (T_{max}) as well as extended mean elimination half-
life (T_{1/2}) compared to IR formulation [89]. However, many of the early methods showed
low sensitivity, longer analytical time, and involved pre-column derivatization protocols
affected by interferences, making them prohibitively expensive for large-scale rapid
screening of clinical samples. Recently, a liquid chromatography coupled to tandem mass
spectrometry (LC-MS/MS) has been developed as sensitive, accurate, and rapid method for
assessment of isradipine bioavailability in the plasma samples from healthy volunteers
[104]. This method showed an excellent linearity between 10 to 5000 pg/ml of isradipine in
plasma, with the lower limit of quantitation (LLOQ) at 10 pg/ml plasma and a short
retention time [104]. We have recently applied this method successfully to a 3xTgAD mice
[29]. In our studies with 3xTgAD mice, we detected 33±7 ng/ml of isradipine in the plasma
and 47±1 ng/g brain tissue of the animals implanted with carrier-bound isradipine pellets (3
μg/g/day, 60-day release, Innovative Research of America, Sarasota, FL) and none in
animals implanted with placebo control pellets [29].

To be able to apply the above method to AD patients, we need to establish relationships
between plasma and brain bioavailability of isradipine first in animal models of AD. This
approach needs some practical considerations. First, there is a possibility that the plasma-to-
brain relationship for isradipine may be a non-linear function. Because isradipine can easily
cross the blood-brain barrier [105], we expect isradipine will reach the brain readily. Thus
the non-linearity argument may be somewhat muted. Second, there is a possibility that T_{max}
and T_{1/2} for isradipine may differ from mouse to human. Interestingly, cross-species
pharmacokinetics appears to be remarkably comparable between mouse and human,
including for isradipine [89, 103, 106]. So, these parameters are expected to remain similar
in mouse and human brains; thus, information obtained on mouse models can be easily
translatable to humans. Third, transgenic animal models do not fully account for the genetic
heterogeneity prevalent in the late-onset AD population. This is a serious issue and one way
to maximize heterogeneity in animal populations is by using different genotypes/animal
models and age groups. Alternatively, pharmacokinetic measures such as area under curve
(AUC) can be determined for plasma and brain to ensure a greater accuracy. Such an
approach will require multiple time points of measurements after isradipine dosing and will
increase the number of animals required for the study. In live humans, brain function or
cerebrospinal fluid levels rather that brain levels of isradipine can be modeled with plasma
levels of isradipine to develop clinically useful predictive functions.

4. Conclusions

Despite their long-standing presence and well-defined safety records, the usefulness of
CCBs for Alzheimer’s disease has been unclear. The reluctance to use CCBs to AD may be
attributed to the initial failure of nimodipine in an AD clinical trial. However, recent
experimental evidence presented in this review demonstrates that CCBs such as isradipine
possess multiple beneficial effects besides their primary L-type calcium blocking ability.
Rigorous, well-designed pre-clinical and clinical studies are expected to provide proof-of-
concept on the effectiveness of CCBs for treatment of Alzheimer’s disease.

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Figure 1.
A schematic overview of the Aβ-Ca$_{1.2}$-ptau-autophagy pathway. Three sections of the figure are separated by dashed lines for clarity. Soluble Aβ oligomers, soluble and insoluble Aβ fibrils generated from amyloid precursor protein (APP) processing cause increased expression of Ca$_{1.2}$ through beta 2 adrenergic receptor (β2AR)/cAMP (cAMP) or other unknown pathways (section 1). Aβ production can be directly modulated by mutations in the calcium homeostasis modulator 1 (CALHM1) receptor located on the endoplasmic reticulum, or in response to treatment with dihydropyridine (DHP) class of calcium channel blockers (CCBs) (section 2). Intracellular or extracellular Aβ can cause over-expression of cav1.2, increased influx of Ca$^{2+}$, disrupted autophagy, and up-regulated ptau expression (section 3). Ca$^{2+}$-calpain pathway can directly increase ptau levels or dampen autophagy function. Pathological accumulation of autophagosomal vacuoles and ptau will lead to loss of spatial memory and cognition in AD (section 3). Isradipine (ISR) appears to block this pathway.