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REVIEW

# Calcium channel blockers and dementia

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Degenerative dementia is mainly caused by Alzheimer's disease and/or cerebrovascular abnormalities. Disturbance of the intracellular calcium homeostasis is central to the pathophysiology of neurodegeneration. In Alzheimer's disease, enhanced calcium load may be brought about by extracellular accumulation of amyloid-β. Recent studies suggest that soluble forms facilitate influx through calcium-conducting ion channels in the plasma membrane, leading to excitotoxic neurodegeneration. Calcium channel blockade attenuates amyloid-β-induced neuronal decline *in vitro* and is neuroprotective in animal models. Vascular dementia, on the other hand, is caused by cerebral hypoperfusion and may benefit from calcium channel blockade due to relaxation of the cerebral vasculature. Several calcium channel blockers have been tested in clinical trials of dementia and the outcome is heterogeneous. Nimodipine as well as nilvadipine prevent cognitive decline in some trials, whereas other calcium channel blockers failed. In trials with a positive outcome, BP reduction did not seem to play a role in preventing dementia, indicating a direct protecting effect on neurons. An optimization of calcium channel blockers for the treatment of dementia may involve an increase of selectivity for presynaptic calcium channels and an improvement of the affinity to the inactivated state. Novel low molecular weight compounds suitable for proof-of-concept studies are now available.

### Abbreviations

Aβ, amyloid-β; AD, Alzheimer's disease; APP, amyloid precursor protein; LTP, long-term potentiation; VaD, vascular dementia; VGCC, voltage-gated calcium channel

## Introduction

Dementia affects 7% of the population over the age of 65, and then progressively increases with age (Hofman *et al.*, 1991; Rocca *et al.*, 1991). Alzheimer's disease (AD) is the leading cause of dementia, followed by vascular dementia (VaD). AD is characterized by three neuropathological hallmarks: extracellular aggregates of amyloid-β (Aβ) peptide (amyloid plaques), neurofibrillary tangles and synaptic loss (Bell and Cuello, 2006). According to the amyloid cascade hypothesis, overproduction of the hydrophobic peptide $A\beta_{1-42}$ is the basis for AD pathology (Hardy and Higgins, 1992).

Aggregation of $A\beta_{1-42}$ is thought to occur in several steps via fibrils, which are finally deposited as amyloid plaques. It was suggested that an alternative pathway leads to the generation of stable oligomeric aggregates, Aβ oligomers (Gellermann *et al.*, 2008; Yu *et al.*, 2009b), which are considered to mediate the toxic Aβ effects (Hardy and Selkoe, 2002). Different forms of Aβ oligomers can be generated synthetically (e.g. Stine *et al.*, 2003; Barghorn *et al.*, 2005) or are harvested from cell lines (Walsh *et al.*, 2002). These preparations were tested *in vitro* and in animal models, and the results lead to the generally accepted view that Aβ oligomers specifically disturb synaptic function (Walsh and Selkoe, 2007). Constant impairment of neurotransmission leads to a retraction of synapses, which is then evident in the autopsy of AD brains (for a review, see Nimmrich and Ebert, 2009).

Contrasting to this, VaD is caused by a variety of cerebrovascular lesions, including macroangiopathic as well as microangiopathic changes. Arteriosclerotic pathology, together with other factors like inflammation and amyloid pathology, produces small and large brain infarctions, which lead to cognitive decline (for a review, see Jellinger, 2005). VaD may be underdiagnosed and the prevalence is probably underestimated (Román, 2002).

Although the pathophysiologies of VaD and AD are distinct, vascular risk factors such as hypertension, diabetes or high cholesterol levels may predispose to both diseases (Skoog, 1998; O'Brien *et al.*, 2003; Helzner *et al.*, 2009). Brain hypoperfusion affects 60–90% of AD patients (Querfurth and LaFerla, 2010) and autopsy studies indicate that most elderly people exhibit signs of both AD and VaD, suggesting that a

clinical separation is difficult (Neuropathology Group, 2001). A coexistence of both types of dementia has also been suggested by other authors (e.g. Roman, 2005). To sufficiently treat the demented patient, pharmacological treatment may thus need to address both pathologies.

In this respect, calcium channel blockers may be an interesting class of therapeutics as they may improve cerebrovascular perfusion (Scriabine and van den Kerckhoff, 1988) and attenuate Aβ-mediated neurodegeneration (see below). A number of clinical studies examined the effect of calcium channel blockers and dementia, mainly using the brain-penetrating dihydropyridine nimodipine. Although the outcome of these trials was not satisfying, nimodipine showed some efficacy for the treatment of AD, and less for VaD.

However, nimodipine is not a 'state-of-the-art' drug. First, it lacks selectivity for a certain type of calcium channel (Diochot *et al.*, 1995). A modulation of targets other than those implicated in neuroprotection may counteract the efficacy of nimodipine. For example, lowering of systemic BP by dihydropyridine-mediated L-type channel blockade may worsen cerebral hypoperfusion and rather impair cognition. Second, ion channel blockers are now optimized to block channels preferably at pathologically overactive synapses (illustrated in Figure 1B,C). These compounds have a strong affinity to the inactivated state of the channel while sparing open or closed states ('state dependency'). The field of drug discovery has moved ahead since the development of dihydropyridines, not least by recently emerging high throughout electrophysiological methods. Automated patch clamp analysis now allows high content analysis of ion channel blockers, thereby screening compounds that favour channels at inactivated state. In light of the absence of good antidementive medication, testing calcium channel blockers with improved physicochemical properties may be worthwhile.

## Calcium hypothesis of dementia

### *Calcium signalling, excitotoxicity and AD*

Calcium is a principal intracellular messenger mediating responses to electrical and chemical stimulation. Maintenance of the precise intracellular calcium homoeostasis is fundamental to neuronal viability and functioning. During aging, the control of the intracellular calcium concentration is impaired, leading to neuronal dysfunction (Toescu and Verkhratsky, 2007). In AD, Aβ induces influx of extracellular calcium (Small *et al.*, 2009), and clinical mutations in the presenilin gene cause calcium release from the endoplasmatic reticulum (Small *et al.*, 2009; Supnet and Bezprozvany, 2010). Changes in calcium flux across different cellular membranes may lead to neuropathology and cell death.

At presynaptic terminals, voltage-gated calcium channels (VGCCs) (N and P/Q types) mediate the release of neurotrans-

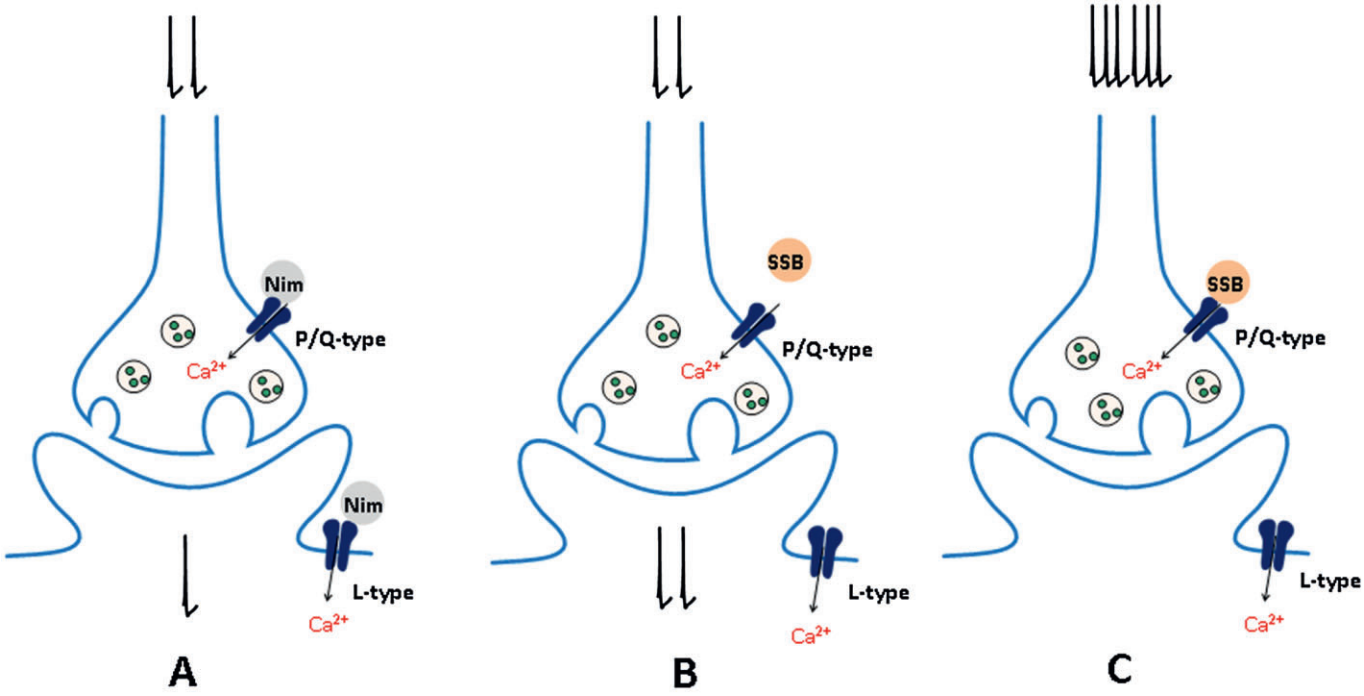


**Figure 1**

Schematic illustration of the effect of calcium channel blockers on central synaptic transmission. (A) Binding of nimodipine (Nim) to presynaptic calcium channels will diminish calcium-mediated presynaptic vesicle release. Blockade of postsynaptic L-type calcium channels will decrease the size of the excitatory postsynaptic potential and attenuate neurotransmission. As a result, synaptic signalling is impaired. (B) A state-dependent selective calcium channel blocker (SSB) is optimized for presynaptic calcium channels and does not bind at resting or open state of the channel. Normal synaptic signalling can take place. (C) During excessive neuronal activity, many presynaptic calcium channels are at inactivated state. A state-dependent blocker preferentially binds to this state and blocks further signalling.

mitter upon arrival of action potentials. A release of glutamate at central synapses facilitates calcium entry at postsynaptic sites through NMDA receptors and indirectly through L-type calcium channels. Excessive glutamate release leads to an imbalance of the postsynaptic calcium load, triggering intracellular cascades that finally cause neuronal death. This process, termed 'excitotoxicity', has been proposed to underlie the pathology of a variety of neurodegenerative disorders (Shaw and Ince, 1997; Caudle and Zhang, 2009; Grosskreutz *et al.*, 2010), including AD (Greenamyre and Young, 1989; Harkany *et al.*, 2000). Excitotoxicity can be attenuated by blocking calcium influx in both synaptic terminals as well as postsynaptic sites.

## *Aβ modulates VGCCs*

Research over the last 2 decades has revealed that administration of Aβ peptides to neurons increases the influx of calcium (Yu *et al.*, 2009). A number of proteins are modulated by Aβ, and some of them contribute to the cellular calcium regulation (e.g. VGCCs, the NMDA receptor and the calcium-activated protease calpain). Calcium cascades involve the consecutive activation of a larger set of proteins, which may explain the identification of multiple Aβ targets. Yet, a vast number of studies using different Aβ preparations found a direct modulation of different types of VGCCs:

*L-type channel.* Studies on short Aβ peptides provided an early indication of an involvement of calcium channels in the Aβ pathology. Application of $A\beta_{25-35}$ to cultured neurons caused cell degeneration, which was prevented by nimodipine (Weiss *et al.*, 1994; Ueda *et al.*, 1997). As nimodipine was originally thought to selectively modulate L-type calcium currents, it was concluded that Aβ affects L-type VGCCs (even though more recent findings also show an effect of Aβ on presynaptic calcium channels; see next subchapter). The finding that nimodipine can prevent Aβ-mediated neurotoxicity was confirmed in cortical neurons by use of a more relevant, stable oligomeric Aβ preparation (Fu *et al.*, 2006). Other calcium antagonists (verapamil, diltiazem and isradipine) all dose dependently protected Aβ-induced cellular degeneration in cultured cells (Anekonda *et al.*, 2011; Copenhaver *et al.*, 2011), strengthening the conclusion that L-type channels may mediate the toxic effect. Using calcium-sensitive dyes, several groups showed that $A\beta_{25-35}$ increases intracellular calcium levels, and different classical calcium antagonists prevent this increase *in vitro* (Silei *et al.*, 1999; Yagami *et al.*, 2002; Fu *et al.*, 2006). Ho *et al.* examined Aβ-mediated increases of the intracellular calcium load in cultured cortical neurons and showed that it was sensitive to nimopridine (Ho *et al.*, 2001). Based on the assumption that classical calcium antagonists block L-type calcium channels, the authors concluded that Aβ enhances calcium flux through these channels. These assumptions were supported by an analysis of plasma membrane currents. In cultured cells, Aβ modulates nimodipine- and nifedipine-sensitive barium currents (Davidson *et al.*, 1994; Green and Peers, 2001; Rovira *et al.*, 2002).

Direct evidence for Aβ-induced L-type channel modulation came from two studies examining the L-type channel recombinantly expressed in HEK293 cells. Whole cell recordings revealed that Aβ peptides increased the current of the L-type channel isoform Cav1.2 (Scragg *et al.*, 2004) as well as the isoform Cav1.3 (Kim and Rhim, 2011).

*N- and P/Q-type channels.* A number of publications suggest an Aβ-mediated modulation of presynaptic calcium channels. Bobich *et al.* (2004) examined the effect of Aβ oligomers on calcium channels in cortical nerve endings *in vitro*. The authors show that low concentrations (10 nM) of $A\beta_{1-42}$ oligomers facilitate the release of neurotransmitter, which was reversed by the N-type channel blocker ω-conotoxin GVIA, but not by the P/Q-type channel blocker ω-agatoxin TK or the L-type channel blocker diltiazem.

Another study analysed cultured cerebellar granule cells by voltage clamp recordings and found a strong increase of calcium currents after subchronic (24 h) exposure to 1 μM $A\beta_{1-40}$ peptide (Price *et al.*, 1998). Blocking N-type currents by conotoxin GVIA prevented current increase, indicating an Aβ-mediated facilitation of N-type currents. Nifedipine failed to reverse the facilitation, suggesting that Aβ did not affect L-type currents. Applying the same preparation of Aβ to cultured cortical neurons, MacManus and colleagues found an Aβ-induced increase of the amplitude of N- and P-type calcium currents (MacManus *et al.*, 2000). Interestingly, different aggregation states of $A\beta_{1-40}$ modulated the N-type currents bidirectionally and either increased or decreased the current (Ramsden *et al.*, 2002). A decrease of N-type currents was also found by others after chronic exposure of $A\beta_{1-42}$ peptide to NG108-15 cells (Kasparová *et al.*, 2001).

We recently showed that a stable oligomeric Aβ preparation, $A\beta_{1-42}$ globulomer, decreases the isolated P/Q-type calcium current in cultured hippocampal neurons (Nimmrich *et al.*, 2008). We then expressed the P/Q-type channel recombinantly in *Xenopus laevis* oocytes and observed a current increase after $A\beta_{1-42}$ globulomer application (Mezler *et al.*, 2012). This effect also occurred in the absence of accessory subunits, suggesting a direct effect of Aβ on the pore forming $\alpha_{1A}$ subunit.

Modulation of presynaptic function by Aβ was supported by other publications. Slutsky and colleagues performed an elegant study examining the effects of changes in endogenous extracellular Aβ concentration on neuronal activity. Inhibiting Aβ degradation in hippocampal neuronal cultures or slices facilitated accumulation of extracellular Aβ and caused an enhancement of presynaptic vesicle release (Abramov *et al.*, 2009).

It should be mentioned that some authors find an effect on all high VGCCs (N, P/Q and L types) as well as low voltage activated calcium (T-type) currents (He *et al.*, 2002). A number of studies also indicate that there are further sites of calcium entry that are modulated by Aβ. For example, Texidó *et al.* (2011) show that Aβ oligomers modulate NMDA receptors recombinantly expressed in *X. laevis* oocytes. Such down-regulation of the NMDA receptor current also reduces calcium influx into the cell, which was demonstrated in neurons by Shankar *et al.* (2007).

At this time, the spectrum of results is confusing and may be brought about by the use of different Aβ preparations. Proof-of-concept studies in animals may reveal the therapeutic relevance of each of those calcium channels.

## Animal models of dementia

A number of clinically used calcium antagonists were tested in animal models of neurodegeneration and shown to be neuroprotective (for a review, see Hunter, 1997). Blockade of P/Q-type calcium channels by the selective peptide blocker omega-agatoxin IVA was neuroprotective in a rat ischaemia model (Asakura *et al.*, 1997). Selective blockade of the N-type calcium channel by ziconotide (Berman *et al.*, 2000; Verweij *et al.*, 2000) and blockade of L-type calcium channels by verapamil (Hosaka *et al.*, 1991) also protected neurodegeneration, indicating that blockade of both pre- and postsynaptic calcium influxes could be neuroprotective. In a nucleus basalis lesion model in rats, which mimics the cholinergic degeneration in AD, verapamil prevented behavioural deficits that occur as a result of the lesion (Popović *et al.*, 1997). Blocking calcium-activated proteases further downstream prevented Aβ oligomer-induced nucleus basalis lesions, degeneration of cholinergic fibres as well as associated behavioural deficits (Granic *et al.*, 2010).

It is now well accepted that Aβ is detrimental to synaptic plasticity (Selkoe, 2008). Long-term potentiation (LTP) is a correlate for learning and memory (Bliss and Collingridge, 1993), and it is thought that LTP-like processes are disturbed in AD. Different Aβ oligomer preparations impaired LTP in rats (Walsh *et al.*, 2002), and LTP was disturbed in amyloid precursor protein (APP)-overexpressing mice in parallel to the behavioural deficits (Moechars *et al.*, 1999; Jacobsen *et al.*, 2006). Freir and colleagues used an experimental model of Aβ-induced$_{25–35}$ LTP suppression. An i.c.v. injection of Aβ peptide into rat brain diminished LTP, which was reversed by systemic application of verapamil (Freir *et al.*, 2003).

It has recently been shown that calcium channel blockers such as nilvadipine and nitrendipine may also reduce the accumulation of Aβ in the brain of APP-overexpressing mice (Paris *et al.*, 2011). In this respect, calcium channel blockers may not only function at the level of Aβ toxicity, but may even prevent production (or enhance clearance) of the toxic peptide.

## Clinical findings

The effect of calcium antagonists on dementia has mainly been studied using a number of dihydropyridine molecules that have originally been developed for the treatment of high BP. Most clinical trials focus on nimodipine, but others like nilvadipine have also been studied. Nimodipine (Suwelack *et al.*, 1985; Hogan *et al.*, 1991; Wang *et al.*, 2006) and nilvadipine (Takakura *et al.*, 1992) penetrate the blood–brain barrier effectively, and therefore are convenient calcium channel blockers for testing a direct neuroprotective effect.

### *Nimodipine*

Nimodipine is commonly used in neurology for the prevention of vasospasm in subarachnoid haemorrhage. Nimodipine was reported to improve both cognitive and behavioural symptoms in patients with so-called chronic organic brain syndrome or AD (Davidson and Stern, 1991; Eckert, 2005; Tomassoni *et al.*, 2008; Baskys and Cheng, 2012). Improvement in memory deficits and attention was observed in more than the 70% of patients with age-related dementias in post-marketing surveillance studies in Europe (Parnetti *et al.*, 1993; Bernhardt *et al.*, 1995).

The usefulness of nimodipine in patients with AD, VaD and unspecified dementia is still controversial. A Cochrane review published in 2002 has examined 14 randomized, placebo-controlled and double-blind trials from 1985 to 2000, including 3166 patients. The Cochrane report has concluded that nimodipine can be of some benefit in the treatment of patients with features of dementia of the Alzheimer's type, caused by cerebrovascular disease or mixed AD and cerebrovascular origin (López-Arrieta and Birks, 2002). Moreover, the review of the Cochrane database revealed the meta-analysis data from four trials of nimodipine in patients with VaD (López-Arrieta and Birks, 2002). These results were, unlike data with AD patients (López-Arrieta and Birks, 2002), disappointing. Thus, this meta-analysis suggests that voltage-dependent $Ca^{2+}$ channels play a limited, if any, role in pathogenesis of VaD-related symptoms, and voltage-dependent $Ca^{2+}$ channel antagonists such as nimodipine are not likely to be useful in their treatment. However, further studies focusing on particular subtypes of VaD and involving subjects at earlier stages of the disease are required.

### *Other calcium channel blockers*

A number of studies using calcium channel blockers for antihypertensive treatment examined the association of drug treatment with the risk to develop dementia. Whereas some studies did not find an overall protective effect (e.g. Yasar *et al.*, 2005), others suggest a prevention of dementia (Trompet *et al.*, 2008). While nifedipine, diltiazem and verapamil showed no efficacy, nitrendipine was preventive in hypertensive patients (Forette *et al.*, 1998; 2002). Recently, two calcium channel blockers from the class of dihydropyridines were examined side by side: nilvadipine and amlodipine (reviewed by Salomone *et al.*, 2012). Patients suffering from mild cognitive impairment were treated with nilvadipine and cognition remained stable for 20 months. At the same time, amlodipine treatment did not seem to be protective. However, both treatments lowered BP to the same extent, indicating that the protective effect was independent from the antihypertensive treatment (Hanyu *et al.*, 2007). This could be explained by the poor brain availability of amlodipine (Uchida *et al.*, 1997) and points towards a direct neuroprotective effect of nilvadipine.

## Development of novel calcium channel blockers

Taken together, the data above provide some preclinical, as well as clinical, evidence that calcium channel blockade may attenuate dementia. However, the efficacy in clinical studies is moderate and does not justify the treatment of dementia with currently available calcium antagonists. A pressing question is whether there are options to optimize these molecules for boosting clinical efficacy.

In our opinion, the most important property to be altered is target selectivity: It is feasible that increasing potency for one target (while sparing another) may improve the therapeutic efficacy and tolerability of the drug. A compound selective for presynaptic calcium channels is expected to bypass cardiovascular side effects resulting from peripheral L-type channel blockade. Calcium channel blockers were originally developed as L-type channel blockers, but they are generally unselective. Nimodipine, for example, exhibits similar potencies for L-type, P/Q-type and N-type calcium channels (Diochot *et al.*, 1995; Mannsvelder *et al.*, 1996). As the P/Q-type channel is preferably expressed in the CNS, selectivity for this channel could diminish side effects caused by block of L-, T- and N-type channels in the periphery.

The second property to be improved is state dependency: Introduction of a better preference for the inactivated state of the channel will increase the therapeutic window, and thus allow higher dosing. Binding of the non-selective calcium antagonist nimodipine versus a selective blocker is exemplified in Figure 1. Whereas nimodipine also has an impact on normal neurotransmission (Figure 1A), the state-dependent blocker only affects overactive synapses (Figure 1B,C). Efficacy of the NMDA receptor antagonist memantine in AD may indicate that diminishing excessive glutamate release is clinically relevant. It is thought that memantine also prevents neurotransmission at pathologically overactive synapse, thereby attenuating excitotoxicity. It is an attractive hypothesis that a state-dependent presynaptic calcium channel blocker may exhibit – at systems level – a memantine-like effect. Finally, calcium antagonists were developed for the treatment of cardiovascular disorders, and hence are not optimized to pass the blood–brain barrier. Although nimodipine does reach the brain after systemic application, many calcium antagonists have a low brain/plasma ratio and must be improved.

A number of tool compounds with better selectivity were recently published. Some of them were also optimized for binding to inactivated channel states. Neuromed 5, for example, potently blocks N-type channels with an $IC_{50}$ of 13–60 nM, but has little L-type activity ($IC_{50}$ = 144 μM; Yamamoto and Takahara, 2009). TROX-1 penetrates the blood–brain barrier well and potently blocks N- and P/Q-type channels with an $IC_{50}$ of 0.4 μM. It also exhibits a good level of state dependence and shows a separation from L-type channel activity (Abbadie *et al.*, 2010). A-1048400 potently blocks presynaptic calcium channels and is largely devoid of L-type activity (Scott *et al.*, 2012). It is also permeable to the blood–brain barrier and exhibits a high level of state dependency. It would be interesting to examine the effect of these compounds in animal models of dementia.

Maintenance of the precise calcium homeostasis is crucial to cells and becomes fragile in AD. Calcium channel blockers may prevent some damage by buffering excessive calcium influx through the plasma membrane. Yet, other cascades are likely to play an important role, too. For example, Aβ impairs mitochondrial function leading to degeneration of the organelle (Querfurth and LaFerla, 2010). It is unlikely that calcium channel blockers will attenuate those cascades. The ultimate treatment regimen may be a multidrug approach – perhaps combining therapeutics that prevent mitochondrial damage with those decreasing calcium entry.

## Conclusions

An overload of intracellular calcium is detrimental to neuronal function. There is evidence that Aβ increases calcium influx through the plasma membrane and that this leads to an impairment of synapse physiology or even cell death. A number of studies indicate that calcium channel blockers may prevent this pathology. They may also improve cerebrovascular perfusion by relaxing vascular smooth muscle cells in brain capillaries. Nimodipine and other calcium antagonists were tested in clinical trials for dementia, and some are effective in attenuating cognitive decline. The lack of a satisfying overall effect should not prevent further analysis. Instead, we believe that an improvement of physicochemical properties may lead to promising new drug candidates in this therapeutic indication. Calcium channel blockers were designed for diseases other than dementia and were selected for functional activity on smooth muscle cells. A better selectivity for presynaptic calcium channels may prevent systemic side effects and may allow higher dosing. It is also now state of the art to develop ion channel blockers that preferentially bind to the inactivated state of the channel, thereby targeting pathologically overactive synapses during excitotoxic processes. The design of more selective and potent calcium channel blockers with a high level of state dependency may open avenues for novel antidementive medication.

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## Conflict of interest

None.

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