

REVIEW

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# Calcium/calmodulin-dependent kinase II and Alzheimer's disease

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## Abstract

CaMKII is a remarkably complex protein kinase, known to have a fundamental role in synaptic plasticity and memory formation. Further, CaMKII has also been suggested to be a tau kinase. CaMKII dysregulation may therefore be a modulator of toxicity in Alzheimer's disease, a dementia characterised by aberrant calcium signalling, synapse and neuronal loss, and impaired memory. Here, we first examine the evidence for CaMKII dysregulation in Alzheimer's patients and draw parallels to findings in disease models which recapitulate key aspects of the disease. We then put forward the hypothesis that these changes critically contribute to neurodegeneration and memory impairment in Alzheimer's disease.

**Keywords:** CaMKII, Alzheimer's disease, Post-mortem brain, Autophosphorylation, Memory, Tau

## Background

The most common form of adult dementia, Alzheimer's disease (AD) is characterised by progressive loss of selective cognitive functions, particularly those related to memory. It was in the early 20<sup>th</sup> century that Alois Alzheimer first described the presence of 'positive' lesions such as senile plaques (SPs) and neurofibrillary tangles (NFTs) in the brain of a patient suffering from dementia (for a translation see [1]). However, it was not until the mid- to late 1980s that these were found to comprise aggregated amyloid- $\beta$  (A $\beta$ ) peptides [2–4] and hyperphosphorylated tau protein [5–8], respectively. Although AD pathogenesis is yet to be fully elucidated, it has been posited that the A $\beta$  peptide is central to disease onset. The "amyloid cascade" hypothesis suggests that A $\beta$ , resulting from aberrant cleavage of the amyloid precursor protein (APP) by  $\beta$ - and  $\gamma$ -secretases, can aggregate into a toxic species, leading to a series of events that culminate in AD pathology [9, 10]. New evidence suggests alternative proteolytic pathways of APP by  $\eta$ -secretases can lead to production of a toxic amyloid- $\eta$  (A $\eta$ ) species that can also contribute to AD pathology [11].

While SPs and NFTs are useful diagnostic markers during post-mortem examination, it is actually the occurrence of 'negative' lesions such as synaptic loss, which

precedes neuronal loss, that best correlates with the advancement of cognitive decline. Several reports have noted the progressive loss of synaptic boutons and other synaptic elements in brains of patients with symptoms ranging from mild cognitive impairment (MCI) to early-mild AD [12–17]. Hippocampal and cortical regions show the most marked loss of these features, reflecting their importance in processes of memory formation and storage. The precise mechanism by which synaptic dysfunction occurs in the AD brain is unknown; *in vitro* studies have shown that A $\beta$  oligomers can directly bind to synaptic sites [18] and reduce long-term potentiation (LTP) [19–21], while facilitating long-term depression (LTD) [22]. A $\beta$  oligomers can compromise synaptic function at both pre- and post-synaptic sites, but their early targets may in fact be excitatory post-synapses [23], where they can alter several signalling pathways.

There is significant evidence that intracellular calcium (Ca<sup>2+</sup>) homeostasis is disrupted in both sporadic and familial forms of AD, and can exacerbate A $\beta$  formation and promote tau hyperphosphorylation (for reviews see [24, 25]). Additionally A $\beta$  can influence cellular pathways involved in Ca<sup>2+</sup> buffering, compromising the ability of neurons to respond to excitotoxic challenge [26], suggestive of a pathogenic feed-forward cycle where A $\beta$  and Ca<sup>2+</sup> can concomitantly impair synaptic morphology, trigger neuronal apoptosis, and eventually lead to deterioration of cognition [27]. The key players in such a

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pathological cascade are most likely molecules that lie downstream of  $\text{Ca}^{2+}$ -signalling and are also present in excitatory synapses where A $\beta$  oligomers likely initially bind. One candidate is the  $\text{Ca}^{2+}$ /calmodulin (CaM)-dependent protein kinase II (CaMKII), the major post-synaptic protein at excitatory synapses. This kinase is fundamentally important for synaptic plasticity and memory formation. Here we discuss evidence for the involvement of CaMKII in AD pathogenesis.

### CaMKII: regulation and function

CaMKII is a holoenzyme of 12 subunits, each derived from one of four genes ( $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$ ) [28]. In rat forebrain,  $\alpha$ CaMKII and  $\beta$ CaMKII are the most abundant subunits, with the former expressed 3–4 times more than the latter [29], and can assemble into homo- or heteromeric holoenzymes [30]. The expression and function of  $\alpha$  and  $\beta$ CaMKII differ; while  $\alpha$  is expressed exclusively in glutamatergic neurons [31], the  $\beta$  subunit is also expressed in inhibitory interneurons [32]. Further,  $\beta$ CaMKII, but not  $\alpha$ , binds to F-actin, which is relieved upon activation by  $\text{Ca}^{2+}$ /CaM [33]. This dissociation is thought to regulate morphological changes at the synapse [34]. Functionally,  $\alpha$ CaMKII activity is essential for synaptic plasticity and memory formation, as elegantly demonstrated in knock-in mutant mice [35]. It may also have a structural role as it can bind to various proteins at the synapse [36] and its expression is extremely abundant (about 1.4% of hippocampal protein) [29]. In contrast,  $\beta$ CaMKII activity is not required for synaptic plasticity and memory formation [37], indicating that the primary function of this subunit is structural.

CaMKII holoenzymes are activated by the binding of  $\text{Ca}^{2+}$ /CaM, and also by NMDA receptors (NMDARs) and L-type voltage-gated  $\text{Ca}^{2+}$  channels (VGCCs) at the synapse [38]. An important aspect of  $\alpha$ CaMKII activity is its autophosphorylation at threonine-286 (T286) (for review see [39]). This autophosphorylation results from an interaction between subunits within the holoenzyme and switches the subunit activity from a  $\text{Ca}^{2+}$ /CaM-dependent to – independent state. This ‘autonomous’ activity persists at the synapse for about one minute after stimulation [38]. However, T286 autophosphorylation can last longer and the dissociation between prolonged autophosphorylation and autonomous activity is not understood [39, 40]. Studies with T286 autophosphorylation-deficient knock-in mutants have shown that this event is fundamentally important for NMDAR-dependent LTP at hippocampal CA1 synapses [41–43] but not at perforant path-granule cell synapses [44]. Furthermore, T286 autophosphorylation is essential for spatial memory formation [41, 45]. Besides T286 autophosphorylation,  $\alpha$ CaMKII is also regulated by other autophosphorylation events, phosphatase activity and endogenous inhibitor proteins (for reviews see [36, 46]).

### CaMKII abnormalities in AD

Expression analyses of post-mortem disease brain can be very informative, in that prominent disease-related dysfunction is detectable. In contrast, studies with AD models, in rodents or in vitro, suffer from inadequate modelling of disease cause. The limitation of post-mortem studies is that they may be confounded by post-mortem delay, which can range from several hours to one day, during which protein expression may decrease and, in particular, post-translational protein modifications such as phosphorylation may be compromised. Another limitation is that they offer only one time point for analysis; however the severity of disease at the time of death can be estimated [47].

Semi-quantitative western blot studies with post-mortem tissue have suggested that  $\alpha$ CaMKII protein expression level is not altered in hippocampus, frontal cortex or other cortical areas in the severe stages of AD [48, 49]. However, immunohistochemical analyses have indicated that  $\alpha$ CaMKII-expressing neurons, which are excitatory, are selectively lost in hippocampal area CA1 in severe AD [50, 51] (but see [52, 53]). The remaining excitatory neurons in CA1 appear to express increased levels of  $\alpha$ CaMKII [50, 51]. Interestingly, increased  $\alpha$ CaMKII expression is not found in hippocampal area CA3 in severe AD [51], a region which has almost no neuronal loss in the end stages of AD, in stark contrast to substantial neuronal loss in CA1 [54].

Changes in distribution of CaMKII mRNA in AD brain are more difficult to determine. One study finds reduced hybridisation of  $\alpha$ CaMKII mRNA in CA1, but only when neuronal loss associated with severe NFT formation is observed [55], echoing the findings of Simonian et al. However another study finds an increase in hybridisation throughout the AD hippocampus, especially in the dentate gyrus (DG) and CA3 regions [56]. A more recent microarray analysis of several brain regions from AD patients discloses that alterations in the expression of CaMKII mRNA may be far more composite than previously thought, with genes encoding different subunits showing different directions in expression changes across brain regions [57].

Early western blot studies suggest that autophosphorylation of  $\alpha$ CaMKII at T286 is reduced in hippocampus and frontal cortex of the severe AD brain [48]. This is also reflected by the fact that cortical regions show a total loss of immunoreactivity for active conformations of CaM and reduced immunoreactivity for other forms [58]. However, this result has not been replicated [59]. Instead, it has emerged that in CA3 and the DG of AD brain, the subcellular localisation of  $\alpha$ CaMKII autophosphorylation is altered [59]. p(T286)- $\alpha$ CaMKII is specifically decreased in dendrites and synapses, and increased

in perikarya of CA3 neurons and granule cells of the DG. This altered distribution correlates with cognitive impairment both in patients with AD and its prodrome MCI [59]. Studies using cultured fibroblasts and lymphocytes from patients also suggest dysregulated CaMKII activity in AD [60, 61].

### CaMKII dysregulation in AD models

The study of molecular dysfunction in AD has been greatly advanced by the development of transgenic mouse models that recapitulate some AD hallmarks. However, such models usually overexpress mutated forms of the human APP gene, and therefore are not fully representative of the causes underlying AD [62]. Additionally, they are confounded by artefacts due to increased transgene expression, and ageing, the main risk factor of AD, is not sufficiently addressed. Nonetheless, if a molecular dysregulation is similar in post-mortem AD brain and in AD models, it is very likely that it occurs in the disease.

Studies on AD models, like post-mortem analyses, suggest abnormalities in regulation of CaMKII. One of the most widely used AD models is the Tg2576 mouse, which carries the APP<sub>Swe</sub> mutation (K670N/M671L). While the total levels of  $\alpha/\beta$ CaMKII are not altered in the frontal cortex of these mice, there is a significant alteration in their subcellular distribution, from synapse to cytosol. This change is not due to synaptic loss and is also seen in levels of active  $\alpha$ CaMKII, suggesting a selective loss of synaptic CaMKII [63]. Another commonly used mouse model contains mutations in both APP and presenilin-1 (PS1), a component of the  $\gamma$ -secretase complex. Two studies find altered hippocampal expression of p(T286)- $\alpha$ CaMKII in these mice, and one additionally finds reduced levels of the CaMKII-binding VGCC Ca<sub>v</sub>1.2 and elevated CaM [64, 65]. Altered  $\alpha$ CaMKII distribution is also found in a mouse model of sporadic AD in which amyloid oligomers are injected into the ventricles. This acute treatment results in a shift of p(T286)- $\alpha$ CaMKII from apical dendrites/spines to the somata of CA3 pyramidal neurons and is blocked by inhibition of the phosphatase calcineurin, which augments phosphatase-1 activity [59].

A calcineurin-dependent redistribution of autophosphorylated  $\alpha$ CaMKII also occurs in A $\beta$  oligomer-treated primary neuronal cultures [59, 63]. Moreover, treating hippocampal neurons with A $\beta$  oligomers impairs  $\alpha$ CaMKII activation [64, 66]. In contrast to rodent models, there is no change in CaM levels and greater expression of Ca<sub>v</sub>1.2 channels [64], a finding which is confirmed by an independent study [67]. This may be the result of cell cultures modelling earlier stages of the disease where there is no neuronal loss [64], or due to a lack of fully functional synapses.

### Impact of dysregulated CaMKII in AD

Post-mortem analyses and studies with AD models indicate that T286-autophosphorylation of  $\alpha$ CaMKII is impaired at synapses in the disease. Considering this autophosphorylation is essential for NMDAR-dependent LTP at CA1 synapses and spatial memory formation [41, 42, 45, 68, 69], the redistribution of p(T286)- $\alpha$ CaMKII could contribute to cognitive impairment in AD. Consistent with this, the reduction of T286-autophosphorylation in apical dendrites of granule cells of the DG in subjects with MCI and AD correlates with cognitive dysfunction as measured by MMSE scores [59]. Moreover, spatial training of Tg2576 mice increases T286-autophosphorylation of  $\alpha$ CaMKII in the hippocampus and rescues deficits in contextual memory formation [70], suggesting deficits in T286 autophosphorylation are key to causing impairments in synaptic plasticity and memory formation in AD. This idea is confirmed in studies with A $\beta$ -treated cultured primary neurons, which have reduced surface expression of AMPA receptor (AMPA) subunit GluA1 and impaired AMPAR-mediated synaptic transmission. Knockdown of CaMKII mimics these effects and CaMKII overexpression rescues these [63]. An analogous observation is seen when treating rat hippocampal slices with A $\beta$ <sub>1-42</sub>, where A $\beta$  inhibits CaMKII activation and blocks the stimulation-dependent phosphorylation of a CaMKII-specific site on GluA1 [71]. Furthermore, it has been suggested that neurotrophin-induced enhancement of p(T286)- $\alpha$ CaMKII leads to rescue of A $\beta$ -induced deficits in LTP at hippocampal synapses [72].

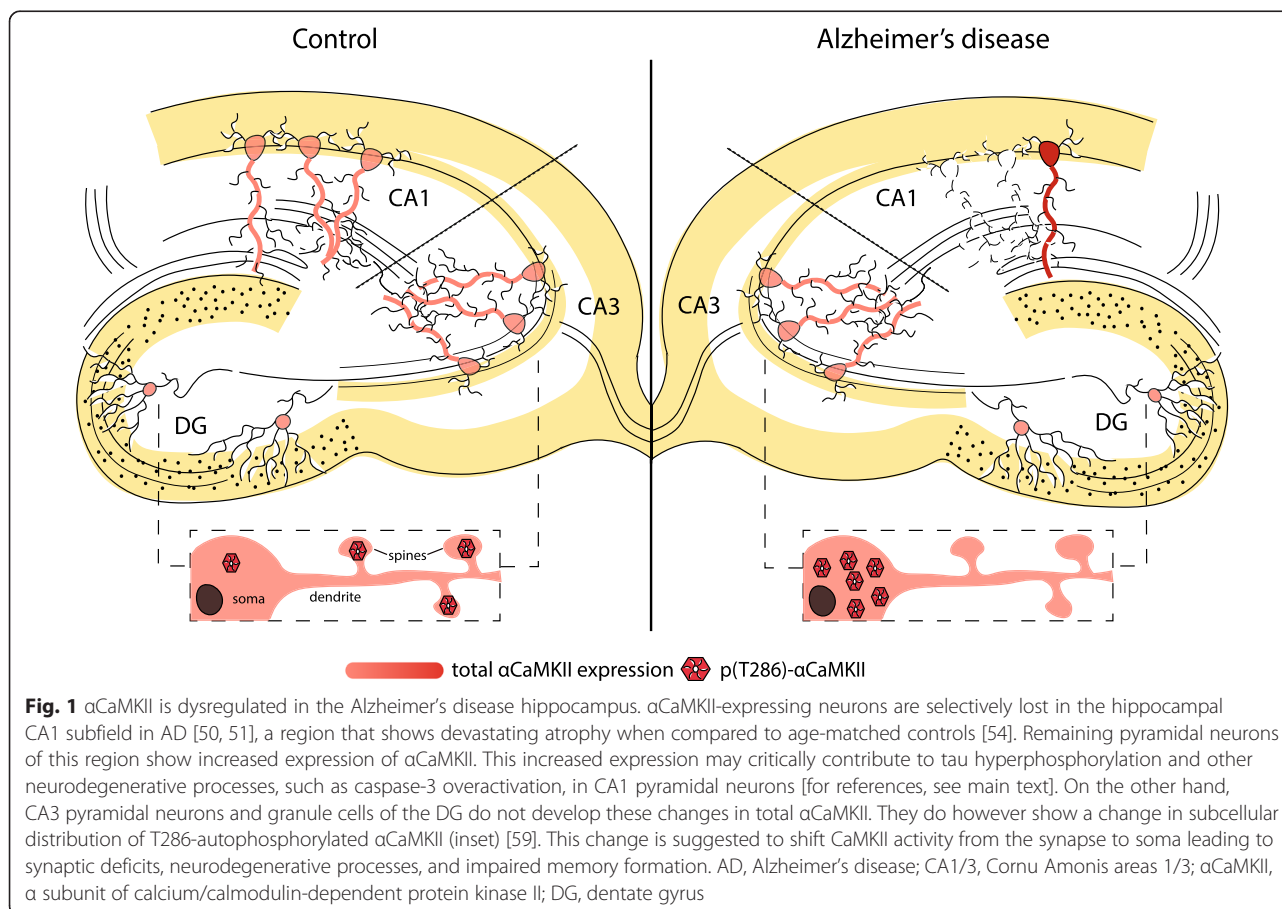
At the neuropathological level, the finding that APP can be phosphorylated *in vitro* by several kinases including CaMKII [73], puts forward the hypothesis that there could be a possible link between CaMKII and A $\beta$  production. Both McKee and Wang remark on some colocalisation of  $\alpha$ CaMKII with SPs, with differences in the deposition pattern around diffuse and neuritic plaques [50, 51]. It has been found that phosphorylation on T668 of APP is elevated in AD brain and can regulate its cleavage by  $\beta$ -secretases [74], but this is not known to be a CaMKII site of phosphorylation. It has also been suggested that phosphorylation of CaMKII sites (T654/S655) can alter the conformation of APP [75] and regulate its trafficking [76], but direct evidence that CaMKII is involved is lacking.

The correlation between CaMKII and tau phosphorylation is much stronger. Increased  $\alpha$ CaMKII expression in CA1 neurons [50, 51] and increased  $\alpha$ CaMKII autophosphorylation in cell bodies of CA3 neurons and granule cells in the DG [59, 63] suggest that outside of synapses,  $\alpha$ CaMKII is hyperactive. Being a tau kinase, this hyperactivity could contribute to NFT formation. NFTs are made of paired helical filaments (PHFs) which contain tau protein hyperphosphorylated at many sites

[77]. Several analyses of AD brain find that  $\alpha$ CaMKII expression in cell bodies frequently co-localises with NFTs or tau mRNA [50, 51, 53, 55, 78, 79]. Mass spectrometry has also revealed that AD brain tau is phosphorylated by CaMKII at several different sites [80]. CaMKII phosphorylation of tau alters its electrophoretic mobility and structure, in a manner specific to PHF-tau [81–83]. Additionally, isolation of PHFs from AD brains results in co-purification with  $\alpha$ CaMKII, 4–7 times more than is observed in controls [78]. The difficulty in analysing the importance of CaMKII in tau hyperphosphorylation arises from the fact that tau can be phosphorylated by several other kinases at CaMKII sites. It has been found that phosphorylation by CaMKII alone only partially inhibits binding of tau to microtubules [84]. Additionally several post-mortem studies note that not all  $\alpha$ CaMKII-expressing neurons develop NFTs [51, 53, 55], suggesting that other tau kinases/phosphatases are involved. A likely scenario is one where  $\alpha$ CaMKII phosphorylation of tau can prime its phosphorylation by other kinases such as cdk5 and GSK3- $\beta$  [85, 86]. Collectively, it is conceivable that CaMKII can contribute to NFT formation in AD.

The loss of synaptic proteins in AD, combined with dysregulated CaMKII, may also lead to neuronal death. It

has been suggested that  $\alpha$ CaMKII and the post-synaptic protein PSD-95 can compete for binding to the C-terminus of the NMDAR subunit NR2A upon physiological stimulus [87]. Treating hippocampal neurons with antisense oligonucleotides to PSD-95 leads to increased association of both total and p(T286)- $\alpha$ CaMKII with NR2A/B subunits, although the total levels of  $\alpha$ CaMKII are unaltered [88]. This is paralleled by an increase in cell death which can be rescued by pharmacological inhibition of CaMKII. Interestingly, hippocampal neurons are more susceptible to this type of injury than cortical neurons, and in organotypic hippocampal slices, CA1 neurons show greater susceptibility than CA3 or DG neurons. This reflects the hierarchical decline of brain areas during disease progression [54], further suggesting that  $\alpha$ CaMKII/NR2A co-expression may be a causal factor for cell death in AD. Additionally, selectively inhibiting CaMKII in  $A\beta$ -treated primary cortical cultures reduces amyloid-induced activity of caspases-2 and -3 as well as tau phosphorylation [89]. It is conceivable that the upregulation of  $\alpha$ CaMKII in CA1 may be directly responsible for the severe atrophy seen in this region. CaMKII may also be involved in other signalling cascades related to neuronal decline [90–93].



## Conclusions

It has been established that CaMKII is dysregulated in AD hippocampus (Fig. 1). We suggest that this dysregulation is a key contributor to synaptic degeneration, NFT formation and memory deficits. However, the nature of CaMKII dysregulation is undoubtedly complex and several questions remain unanswered. One key question is 'how' this dysregulation can occur. So far, the focus has been on levels of total or T286 autophosphorylated  $\alpha$ CaMKII. Other aspects of CaMKII regulation and activity need to be addressed, such as distribution of unphosphorylated CaMKII in AD brain, and other important sites of autophosphorylation such as T305/6. Other subunits such as  $\beta$  and  $\gamma$  may also be integral to CaMKII dysregulation. For example,  $\beta$ CaMKII autophosphorylation can regulate its dissociation from F-actin, thereby allowing cytoskeletal remodelling in glutamatergic excitatory synapses, a necessary occurrence for LTP induction [94]. Impaired  $\text{Ca}^{2+}$  signalling could therefore impact upon both this dissociation and the reassociation between  $\beta$ CaMKII and F-actin, an event crucial for stabilisation of newly remodelled actin and LTP maintenance. Additionally,  $\gamma$ CaMKII can act as a  $\text{Ca}^{2+}$ /CaM shuttle to the nucleus to alter gene expression (for review see [95]). Another fundamental issue is how CaMKII is dysregulated specifically in the CA1 region, an area showing devastating neuronal loss in AD compared to normal ageing. Is increased  $\alpha$ CaMKII expression in remaining CA1 neurons a compensatory effect or a precursor to neurotoxicity? How does this relate to the subcellular distribution of total and p(T286)  $\alpha$ CaMKII in CA1, and are these changes also calcineurin-dependent? Finally, it remains to be determined whether CaMKII is essential for synaptic dysfunction, cognitive impairment and NFT formation in AD. Can restoring synaptic activity of CaMKII in models of AD prevent cognitive dysfunction? Can reducing somatic CaMKII in an in vivo model of tau pathology prevent or abolish tangle formation? Elucidating these questions will investigate the hypothesis that dysregulated CaMKII is a key contributor to synaptic dysfunction, neurodegeneration and memory impairment in AD, and may point to novel treatment routes.

## Abbreviations

A $\beta$ : Amyloid- $\beta$ ; AD: Alzheimer's disease; A $\eta$ : Amyloid- $\eta$ ; AMPAR:  $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor; APP: Amyloid precursor protein; CA1/3: Cornu Ammonis areas 1/3; CaMKII: Calcium/calmodulin binding protein kinase II; cdk5: cyclin-dependent kinase 5; DG: Dentate gyrus; GluA1: AMPAR subunit; GSK3- $\beta$ : Glycogen synthase kinase 3- $\beta$ ; LTD/LTP: Long-term depression/potential; MCI: Mild cognitive impairment; MMSE: Mini-mental state examination; NFT: Neurofibrillary tangle; NMDAR: N-methyl-D-aspartic acid receptor; NR2A/B: NMDAR subunits; PHF: Paired helical filament; PS1: Presenilin-1; PSD-95: Post-synaptic density protein 95; SP: Senile plaque; VGCC: Voltage-gated calcium channel.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

Both AG and KPG wrote, read and approved the final manuscript.

## Acknowledgements

This work was supported by the Medical Research Council. We would like to thank Dr. Wendy Noble for comments on the final manuscript. This article is a contribution to a series of invited reviews on Molecules of Neural Disorders.

Received: 28 September 2015 Accepted: 13 November 2015

Published online: 24 November 2015

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