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SYMPOSIUM REVIEW

Calcium regulation of neural rhythms, memory and Alzheimer's disease

Michael J. Berridge

Babraham Institute, Babrahm, Cambridge CB22 3AT, UK

Abstract Alzheimer's disease (AD) begins with a decline in cognition followed by neuronal cell death and dementia. These changes have been linked to a deregulation of Ca^{2+} signalling caused by a progressive increase in the resting level of Ca^{2+}, which may influence cognition by interfering with the rhythm rheostat that controls the sleep/wake cycle. The rise in resting levels of Ca^{2+} may not alter the processes of memory acquisition during consciousness (gamma and theta rhythms), but may duplicate some of the events that occur during the slow oscillations responsible for the twin processes of memory consolidation and memory erasure that occur during sleep. The persistent elevation in the resting level of Ca^{2+} induced by an accumulation of amyloid β (Aβ) oligomers duplicates a similar small global elevation normally restricted to the period of slow oscillations when memories are erased during sleep. In AD, such a rapid erasure of memories soon after they are acquired during the wake period means that they are not retained for consolidation during sleep. The Aβ deregulates Ca^{2+} signalling through direct effects on the neurons and indirectly by inducing inflammatory responses in the microglia and astrocytes. Some of these deleterious effects of Aβ may be alleviated by vitamin D.

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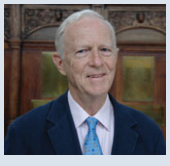
Corresponding author M. J. Berridge: The Babraham Institute, Babraham, Cambridge, CB22 3AT, UK. Email: michael.berridge@babraham.ac.uk

Abbreviations AD, Alzheimer's disease; Aβ, amyloid β; CAN, Ca^{2+}-activated non-selective cation channel; CaSR, Ca^{2+}-sensitive receptor; GSH, glutathione; HCN1, hyperpolarizing-activated cyclic nucleotide-gated 1; $InsP_3$, inositol 1,4,5-trisphosphate; LTD, long-term depression; LTP, long-term potentiation; mTOR, mammalian target of rapamycin; NCX, Na^+/Ca^{2+} exchanger; NREM, non-rapid eye movement; NLRP, NACHT, LRR and PYD domains-containing protein; PMCA, plasma membrane Ca^{2+}-ATPases; $PtdIns4,5P_2$, phosphatidylinositol 4,5-bisphosphate; RGS4, regulator of G protein signalling 4; ROS, reactive oxygen species; RYR, ryanodine receptor; TREM-2, triggering receptor expressed in myeloid cells 2; TNFα, tumour necrosis factor α; VDR, vitamin D receptor.

Introduction

Neurons have highly developed Ca^{2+} signalling systems (Berridge, 1998) responsible for regulating neural functions such as brain rhythms, information processing, learning and memory. Remodelling of these Ca^{2+} signalling pathways that create inappropriate Ca^{2+} responses have been linked to many major neural diseases (Khachaturian 1989; LaFerla 2002; Stutzmann 2007; Thibault *et al.* 2007; Bezprozvanny & Mattson, 2008;



Michael Berridge is an Emeritus Babraham Fellow at the Babraham Institute in Cambridge. He received his B.Sc. in 1960 from the University of Rhodesia and Nyasaland in Salisbury, Rhodesia and was awarded his Ph.D. from the University of Cambridge in 1964. His current research interest is focused on the role of inositol trisphosphate ($InsP_3$) in controlling the spatiotemporal aspects of Ca^{2+} signalling with particular emphasis on neural signalling and neural diseases such as Alzheimer's disease, bipolar disorder and schizophrenia.

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Berridge 2011, 2012*a*,*b*). In the case of Alzheimer's disease (AD), Ca^{2+} levels are set too high and this has an impact on many neural functions and particularly memory formation and consolidation. Why subtle deregulation of Ca^{2+} signalling can have such a marked effect on memory remains somewhat mysterious. Memory formation is a complex process that depends on memory acquisition during consciousness followed by memory consolidation and erasure during sleep. To obtain a better understanding of AD, therefore, the first part of this review explores the way Ca^{2+} signalling participates, in not only controlling brain rhythms, but also how it generates memories that occur during the markedly different brain rhythms that characterize the sleep–wake cycle. The remodelling of Ca^{2+} signalling in AD may explain the observation that this sleep–wake cycle is markedly disrupted in AD with an increase in wakefulness (Roh *et al.* 2012). The second part of the review explores the possibility that the deregulation of Ca^{2+} signalling that occurs in AD results in the continuous activation of a Ca^{2+}-dependent memory erasure mechanism, which is normally restricted to the early phase of sleep. Such a mechanism could explain why memories are rapidly lost soon after they are acquired during periods of wakefulness.

Neural rhythms and neural functions

The brain is highly rhythmical and the different neural rhythms that occur during the sleep–wake cycle regulate its multiple functions. These rhythms can be divided into the fast gamma (20–80 Hz), alpha (8–12 Hz) and theta (6–10 Hz) oscillations, which occur during the awake state, and the slower delta (1–4 Hz) and slow oscillations (<1 Hz) that occur during sleep (Fig. 1). These different oscillatory modes are regulated by the ascending arousal system that consists of a heterogeneous population of neurons that project their axons throughout the brain where transmitters such as orexin, acetylcholine, noradrenaline, 5-hydroxytryptamine, histamine and dopamine are released on to the excitatory and inhibitory neurons that constitute functional neural circuits (Pace-Schott & Hobson 2002; Datta 2010). These transmitters then act on receptors coupled to signalling pathways to adjust the level of the tonic excitatory drive that regulates these different oscillatory states (Fig. 1).

Variations in the activity of this tonic excitatory drive functions much like a rhythm rheostat in that it controls a hierarchy of rhythms with the lowest frequencies occurring during sleep that are then switched to the higher frequency rhythms of the wake state (Fig. 1). The Ca^{2+} signalling mechanisms control the rhythm rheostat and have to operate within the parameters of the ongoing rhythms to regulate memory formation, consolidation and erasure. Memory acquisition occurs during fast gamma rhythms during consciousness, while the slow oscillations mediate memory consolidation and erasure during sleep. The sleep–wake cycle is markedly disrupted in AD with an increase in wakefulness associated with a decrease in the slow oscillation responsible for non-rapid eye movement (NREM) sleep rhythms (Roh *et al.* 2012).

Gamma and theta rhythms and calcium signalling mechanisms

The fast theta and gamma oscillations, which are highly synchronous throughout the brain, are generated by a typical network oscillator consisting of fast spiking inhibitory interneurons and excitatory neurons that interact with each other through a positive/negative feedback loop (Fig. 2). Each inhibitory interneuron controls the activity of a large array of excitatory neurons all of which send axon collaterals back to the inhibitory interneuron. Most information is available for the gamma rhythms where the interneurons fire an action potential on each cycle and this induces a brief hyperpolarization in all the excitatory neurons that occurs synchronously over extensive areas of the brain (Hájos & Paulsen 2009). In contrast to this continuous firing of the inhibitory neurons, the excitatory neurons fire much less frequently with each action potential occurring within a narrow time window towards the end of each pacemaker depolarization (Fig. 2). This gamma oscillation synchronization provides a precise timing mechanism that enables excitatory neurons located in different parts of the brain to communicate with each other by firing together as part of a circuit as they process sensory information. This action potential coincidence is also crucial for triggering the input-specific Ca^{2+} transients responsible for memory formation.

Important Ca^{2+} signalling events occur when excitatory neurons, which are connected together as part of a neuronal circuit, fire action potentials that are synchronized by the gamma oscillation rhythm. Such action potential coincidence (Fig. 2) is important for memory formation through a process of spike time-dependent plasticity, which favours the induction of long-term potentiation (LTP) (Caporale & Dan 2008). Depolarization of a neuron while it receives a pulse of glutamate from another neuron serves to open the NMDA receptors (NMDARs) on the activated spines to allow rapid entry of Ca^{2+} to trigger LTP (Fig. 3*A*). A form of NMDAR-independent synaptic plasticity is induced by Ca^{2+} entering through $Ca_V1.2$ channels (Moosmang *et al.* 2005). The brief high concentration spike of Ca^{2+}, which is highly localized within the activated spine, induces at least three immediate biochemical events: phosphorylation of

the AMPA receptors (AMPARs), exocytosis of vesicles containing new AMPARs and activation of actin polymerization resulting in a change in the shape of the spine. These biochemical events are the basis of new memories (Citri & Malenka 2008) that are then retained until either consolidated or erased during the slow oscillations that occur during NREM sleep. The mechanisms responsible for memory formation seem to operate normally in AD, but are not retained long enough to be consolidated during sleep. A clue as to why these memories are rapidly erased in AD has emerged from analysing the mechanisms responsible for memory erasure that are normally restricted to the period of slow oscillations that occur during NREM sleep.

Slow oscillation and calcium signalling mechanisms

The slow (<1 Hz) oscillations, which occur during NREM sleep, have been linked to both memory consolidation and erasure (Diekelmann & Born 2010). The onset of these endogenous slow oscillations, which occurs when the tonic excitatory drive is reduced at the onset of sleep (Fig. 1), has typical UP states when the membrane potential (V_m) is depolarized to approximately –65 mV that alternates with DOWN states where the membrane is hyperpolarized by 10–15 mV. These slow oscillations occur in near synchrony throughout the brain and this enables neurons to communicate with each other as they fire rapid bursts of action potentials on the crest of each UP state (Massimini *et al.* 2004). This synchrony is achieved

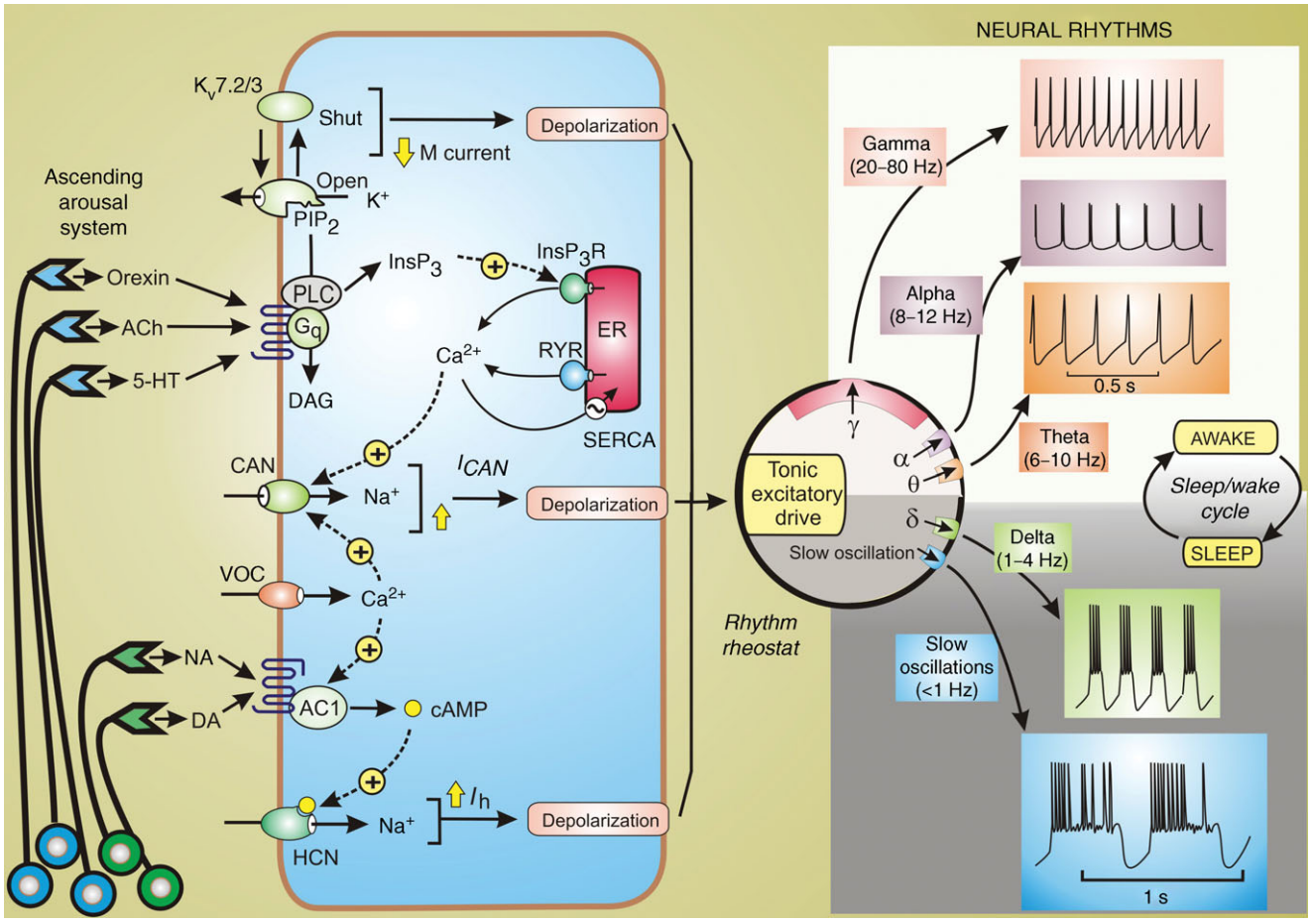

Figure 1. Tonic excitatory drive and the control of neuronal rhythms.
Neurons of the ascending arousal systems release transmitters such as orexin, acetylcholine (ACh), 5-hydroxytryptamine (5-HT), dopamine (DA) and noradrenaline (NA), which induce signalling systems to control neural rhythms that occur during the sleep/wake cycle. The tonic excitatory drive mechanism depends on membrane depolarization driven by different signalling mechanisms. Hydrolysis of the phospholipid PtdIns4,5P_2 has two effects. First, it closes the K_V 7.2/7.3 channels responsible for the M current. Switching off this M current depolarizes the membrane to increase neuronal activity. Secondly, the formation of inositol 1,4,5-trisphosphate ($InsP_3$) releases Ca^{2+} that stimulates the Ca^{2+}-activated non-selective cation (CAN) channel. The CAN channel can also be activated by Ca^{2+} entering through the voltage-operated Ca^{2+} (VOC) channel. The NA and DA act through the cyclic AMP signalling pathway to enhance the activity of the hyperpolarizing-activated cyclic nucleotide-gated (HCN) channel responsible for the depolarizing I_h current.

through a slow wave propagation mechanism whereby the action potentials that occur at the start of the UP state in one neuron entrains neighbouring neurons to initiate their slow oscillation thereby a wave of excitation propagates through the brain travelling at approximately 3 m s^{-1} in an anterior–posterior direction. The signalling mechanisms that occur during these slow oscillations are responsible for both memory consolidation and erasure.

A decline in the tonic excitatory drive that occurs during NREM sleep turns down the rhythm rheostat to set the stage for oscillations to occur (Fig. 1). A decrease in the activity of the metabotropic transmitters that stimulate the hydrolysis of PtdIns4,5P_2 enables this lipid to accumulate such that it can open the KV7.2/KV7.3 channels resulting in an increase in the M current that provides the membrane hyperpolarization that drives the DOWN state. The endogenous oscillator that drives the alternating UP and DOWN states depends on an interaction between different channels (Fig. 4) (Crunelli *et al.* 2005, 2006). During the DOWN state, there is steady pacemaker depolarization that depends on both a hyperpolarizing-activated cyclic nucleotide-gated 1 (HCN1) channel and a Ca^{2+}-dependent non-selective cation channel (CAN). The latter is activated directly by Ca^{2+} whereas the HCN1 is modulated indirectly by Ca^{2+} acting on adenylyl cyclase (AC) to provide cyclic AMP. This cyclic AMP does not activate HCN1 directly, but it alters the open probability by shifting the activation curve towards more depolarizing potentials.

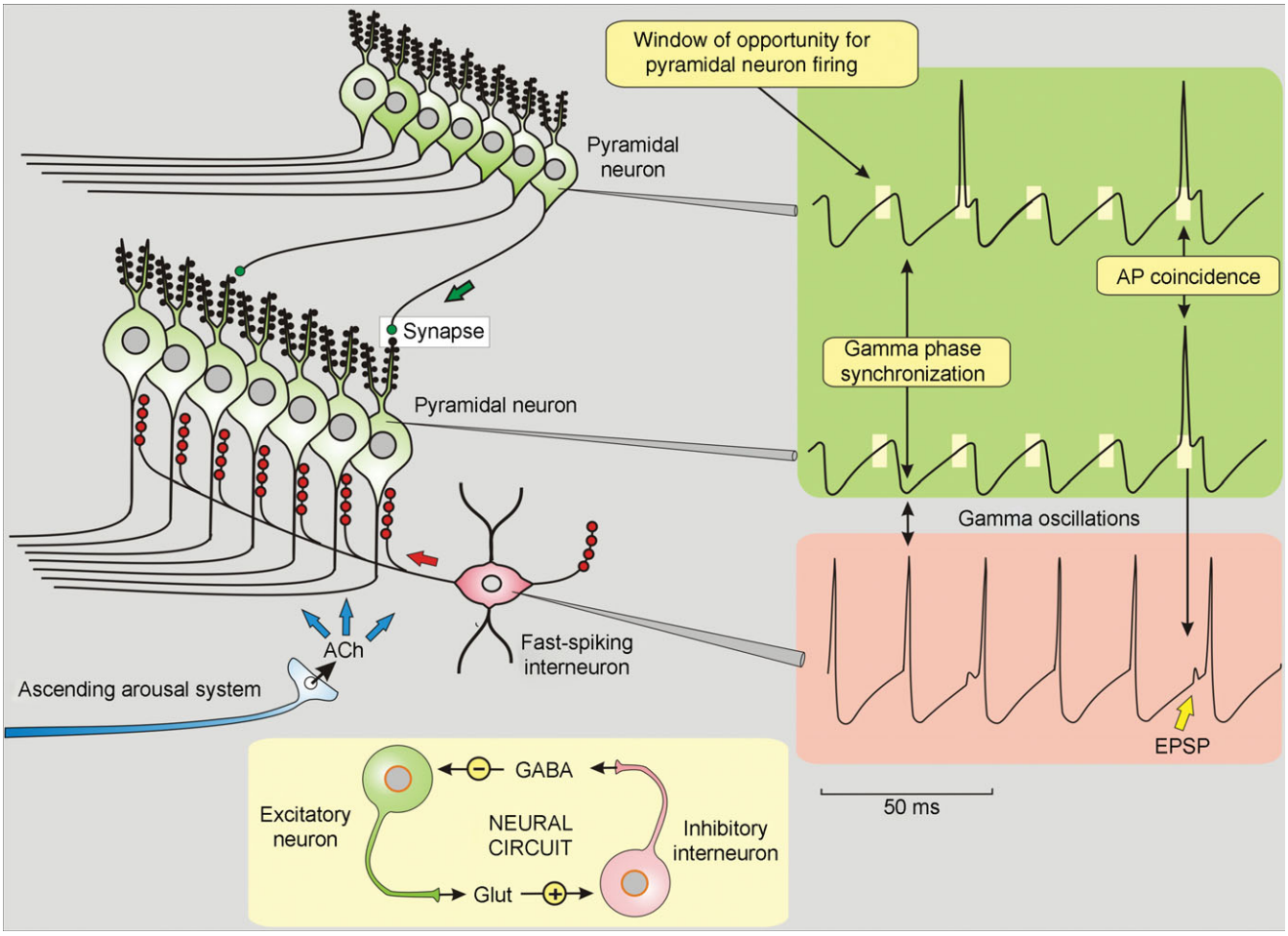

Figure 2. Neuronal network gamma oscillations.
Most neural circuits consist of fast spiking inhibitory interneurons (red) and excitatory neurons (green) interacting with each other through a positive/negative feedback loop (see inset at the bottom). Each interneuron controls the activity of many excitatory neurons (red arrows) all of which send axon collaterals back to the inhibitory interneuron (green arrow). The interneuron fires an AP on each gamma cycle and this serves to induce synchronous hyperpolarizations in all the excitatory neurons. The excitatory neurons fire much less frequently towards the end of the pacemaker depolarization. The inhibitory interneuron registers each of these APs as a small EPSP that sum to activate the interneuron to fire an AP to initiate another gamma oscillatory cycle. ACh, acetylcholine; AP, action potential; EPSP, excitatory postsynaptic potential.

The beginning of the UP state is characterized by the opening of Ca_V3 T-type channels that produce a low-threshold Ca^{2+} spike(s), but these channels then inactivate to become a persistent inward current, also known as the T window current, to provide a tonic depolarization that helps to maintain the UP state (Crunelli *et al.* 2005, 2006). The opening of these T type channels, which are located on the soma and

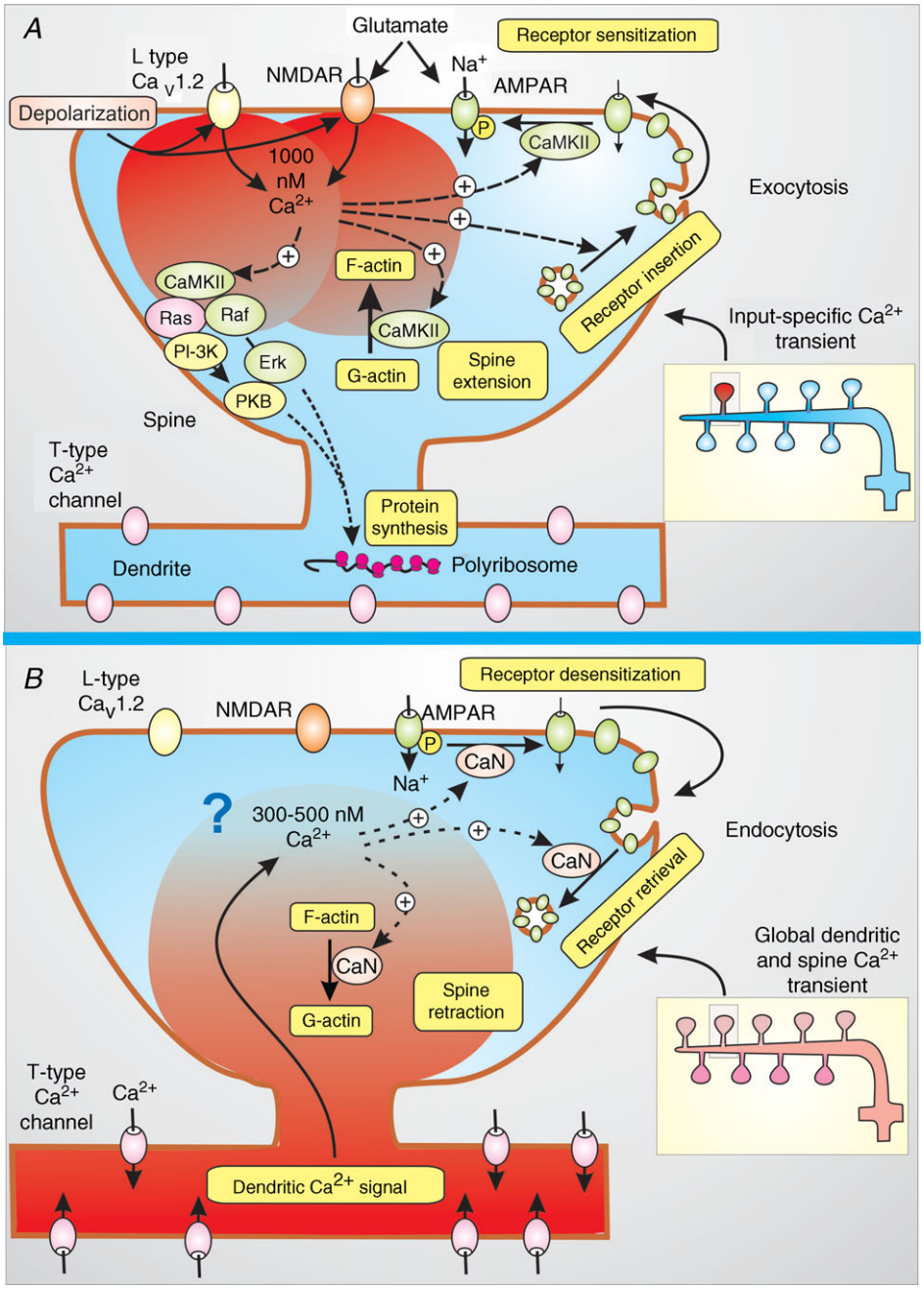

Figure 3. Ca^{2+}-induced synaptic plasticity during memory formation (*A*) and memory erasure (*B*). *A*, the opening of NMDA receptors (NMDARs) or $Ca_v1.2$ L-type Ca^{2+} channels generate large local increases in Ca^{2+} within specific spines (see inset). This localized Ca^{2+} signal induces long-term potentiation (LTP) that depends on AMPA receptor (AMPAR) phosphorylation by CaMKII, AMPAR insertion that increases the number of receptors in the postsynaptic membrane, actin remodelling that changes spine morphology and protein synthesis at polyribosomes located at the base of each spine. *B*, lower levels of Ca^{2+} in the spines, which may depend on Ca^{2+} diffusing in from the global dendritic Ca^{2+} waves of the slow oscillations that occur during sleep, activates long-term depression (LTD) that depends on calcineurin (CaN) acting to reverse many of the processes that occur during LTP.

dendrites, results in a global elevation of Ca^{2+} that not only spreads through the dendrites, but it also diffuses into the spines (Errington *et al.* 2012). During the course of a slow oscillation, therefore, there are two important Ca^{2+} signalling events taking place that may have a major impact on memory formation. First, the global elevation that spreads into all of the spines may function to activate long-term depression (LTD) to erase temporary memories (Fig. 3*B*). Secondly, it is likely that there are localized pulses of Ca^{2+} within specific spines during rapid action potentials that occur on the crest of each slow oscillation as memories that are reactivated in the hippocampus are redistributed to the cortex where they are consolidated into longer-term memories during sleep.

It has been proposed that memories acquired during the wake period are stored temporarily in the synaptic connections of relevant brain circuits located mainly in the hippocampus. Some of these temporary memories represent novel information that will be retained, but many other memory traces are erased during sleep to avoid cluttering up the brain with irrelevant information. This synaptic homeostasis hypothesis proposes that the redundant information stored in those potentiated synaptic connections are returned to baseline levels during sleep (Tononi & Cirelli, 2006; Vyazovskiy *et al.* 2008). The way in which some memories are consolidated and retained while others are erased is not known. The following speculation suggests that these two processes may run concurrently, even within individual neurons,

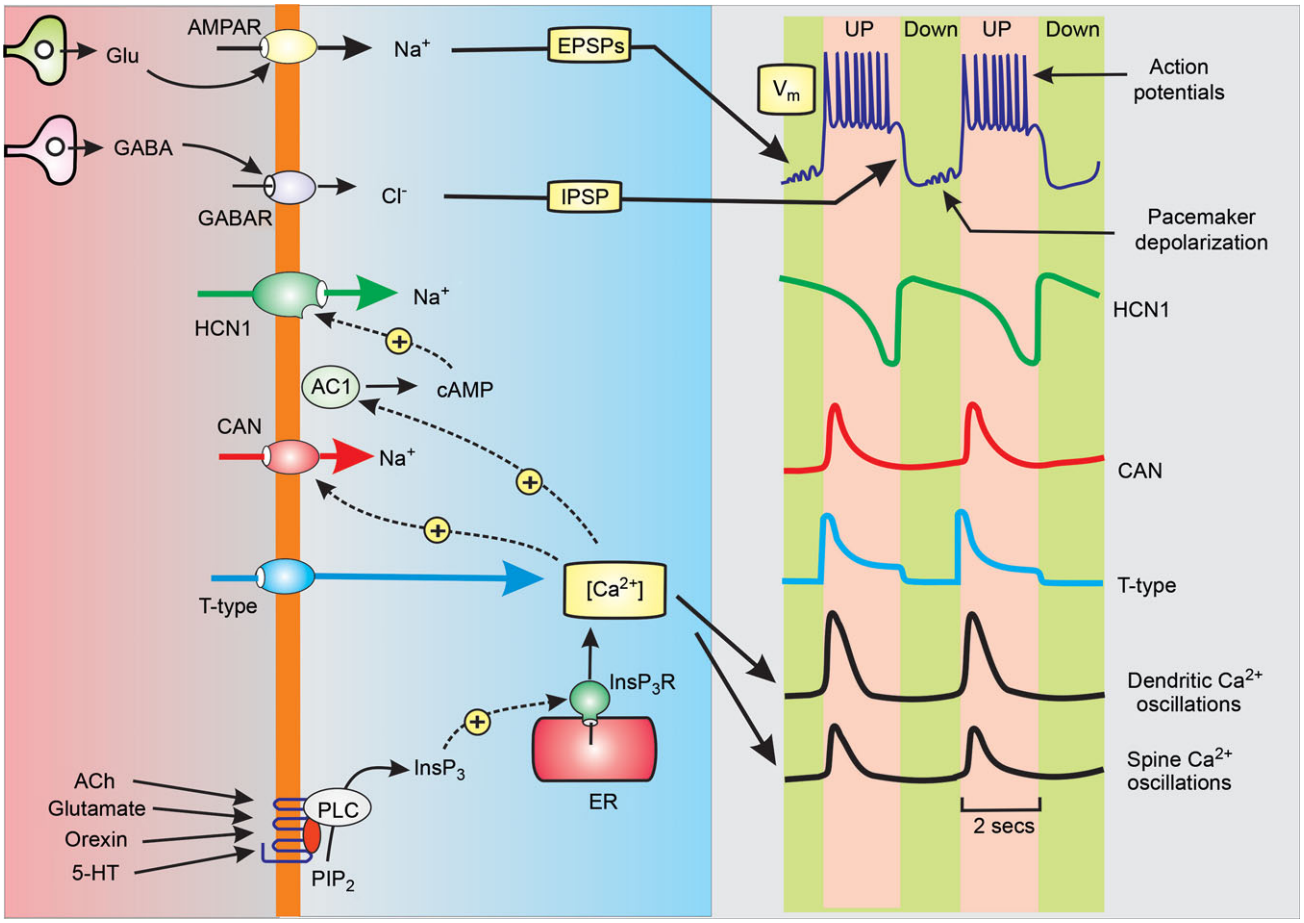

Figure 4. This hypothetical scheme describes the main ionic channels and signalling mechanisms that have been implicated in generating the slow oscillations characterized by periodic UP (red panels) and DOWN (green panels) states.
The CaV3 T-type channels, which are located on the dendrites, are switched on at the beginning of an UP state to provide a low-threshold Ca^{2+} spike(s), but then inactivate to become a persistent inward current, also known as the T window current, to provide a tonic depolarization that helps to maintain the UP state. Opening of these T channels at the beginning of each UP state results in a global elevation of Ca^{2+} that spreads rapidly down the dendrites and into the spines where it may act to induce long-term depression (see Fig. 3*B*). ACh, acetylcholine; CaN, calcineurin; ER, endoplasmic reticulum; 5-HT, 5-hydroxytryptamine; InsP3, inositol 1,4,5-trisphosphate; HCN, hyperpolarizing-activated cyclic nucleotide-gated (channel).

due to a spatial separation of the Ca^{2+} signalling events during slow oscillations.

The fast action potentials that occur during the UP state of the slow oscillation (Fig. 4) probably reflects the neural activity responsible for memory consolidation. The spindles and ripples that appear in EEG recordings during sleep are thought to reflect the hippocampal–cortical dialogue as labile information stored in the hippocampus is transferred for more permanent storage in the cortex (Ji & Wilson 2007). The ripples represent high-frequency bursts of action potentials as memories are reactivated in the hippocampus, whereas the spindles result from the oscillatory firing of thalamocortical neuronal loops as this information is received and consolidated in the cortex (Diekelmann & Born 2010). Activation and transfer of these memories may depend on the same spike time-dependent plasticity mechanisms described earlier (Fig. 3*A*). The large and persistent pulsing of Ca^{2+}, restricted to activated spines, will contribute to consolidation by stimulating protein synthesis by polysomes located at the base of each spine.

At the same time that novel memories are being consolidated, other memories are being deleted and it is conceivable that these processes may run concurrently in individual neurons. The erasure mechanism is not fully understood, but Errington *et al.* (2012) have suggested that the global elevation in Ca^{2+} that occurs during the slow oscillation might play a role in the mechanism of 'homeostatic synaptic plasticity'. The most probable explanation for this is that the global elevation of Ca^{2+}, which is known to invade the spines, will activate LTD. The specific proposal is that Ca^{2+} in the dendrites diffuses into the spine where it may reach levels in the 300–500 nM range that will activate LTD resulting in memory erasure (Fig. 3*B*). This Ca^{2+}-dependent erasure depends on activation of calcineurin that reverses the three processes that occurred during LTP, i.e. AMPARs are dephosphorylated, AMPARs are retrieved from the spine surface through endocytosis and the actin filaments are depolymerized. In this way, the conundrum as to how memory consolidation and erasure can run concurrently can be resolved if high levels of Ca^{2+} necessary for LTP are localized to those spines undergoing consolidation, whereas all redundant memories can be erased *en masse* through the global elevation of lower levels of Ca^{2+} that pervade the spines to activate LTD. The loss of memory in AD may result from a similar erasure being activated continuously during the wake period when memories are acquired.

Dysregulation of Ca^{2+} signalling and Alzheimer's disease

The development of AD is driven by the accumulation of amyloid β (Aβ) oligomers, which are a neuron-derived pathogenic factor that brings about the loss of memory and neuronal cell death that characterizes the progression of AD. The Ca^{2+} hypothesis of AD suggests that these deleterious effects of Aβ depend on a dysregulation of Ca^{2+} signalling (Khachaturian 1989; LaFerla 2002; Stutzmann 2007; Thibault *et al.* 2007; Bezprozvanny & Mattson 2008; Stutzmann & Mattson 2011; Berridge 2010, 2011, 2012*b*). The basic idea is that abnormal amyloid metabolism induces an upregulation of neuronal Ca^{2+} signalling that is responsible for the initial decline in memory and subsequent apoptosis. When Ca^{2+} is measured in the spines and dendrites of cortical pyramidal neurons of transgenic mice, there was a higher than normal resting level in those neurons located close to amyloid deposits (Kuchibhotla *et al.* 2008). Similarly, the resting level of Ca^{2+} in the cortical neurons of triple transgenic AD animals was 247 nmol l^{-1}, which was twice that found in the non-transgenic controls (110 nmol l^{-1}) (Lopez *et al.* 2008). In addition, there is increasing evidence that Aβ also acts on neighbouring microglial cells and astrocytes (Abramov *et al.* 2004; Saijo & Glass, 2011) to induce local inflammatory responses that contributes to Ca^{2+} signalling deregulation. The following sequence of events attempts to explain these multiple actions of Aβ on neurons, microglia and astrocytes to induce the upregulation of Ca^{2+} signalling that may be responsible for AD (the numbers on Fig. 5 correspond to those outlined below):

(1) Neuronal Ca^{2+} signalling deregulation may depend on changes in both the entry of external Ca^{2+} and its release from internal stores. The Aβ oligomers that accumulate outside diseased neurons can bring about an elevation in Ca^{2+} through different mechanisms. They can be inserted into the membrane to form channels (Demuro *et al.* 2011) or they can activate the Ca^{2+}-sensitive receptor (CaSR) to increase the level of $InsP_3$ (Ye *et al.* 1997; Chiarini *et al.* 2009; Armato *et al.* 2012). The CaSR is coupled to phospholipase C through the G protein G_q, which is inhibited by the regulator of G protein signalling 4 (RGS4). The level of RGS4 is reduced in the human AD brain and this may further enhance the generation of $InsP_3$ (Emilsson *et al.* 2006). Injection of Aβ into *Xenopus* oocytes stimulated the production of $InsP_3$ through a G protein-dependent activation of phospholipase C (Demuro & Parker 2013) providing further evidence that some of the actions of Aβ might be mediated by an increase in the $InsP_3/Ca^{2+}$ signalling pathway.

(2) An increase in the formation of $InsP_3$ will enhance the amount of Ca^{2+} being released from the endoplasmic reticulum by the $InsP_3$ receptors ($InsP_3Rs$). Indeed, a feature of AD is an increase in the activity of $InsP_3Rs$ (Cheung *et al.* 2008; Müller *et al.* 2011).

This elevation in $InsP_3$-dependent Ca^{2+} signalling, which needs to be turned down for slow oscillations to occur during sleep, may explain the observation that the sleep–wake cycle is markedly disrupted in AD with an increase in wakefulness (Roh *et al.* 2012). In transgenic mice, an increase in amyloids may induce global elevations of Ca^{2+} through a burst firing-mediated mechanism that depends on glutamate activating an $InsP_3/Ca^{2+}$ signalling pathway (Czarnecki *et al.* 2007). Expression of the $Ca_v1.2$ L-type Ca^{2+} channel, which has been implicated in LTP induction (Moosmang *et al.* 2005) (Fig. 3*A*), is induced by Aβ (Webster *et al.* 2006; Dursun *et al.* 2011) and this will enhance the release of Ca^{2+} from ryanodine receptors (RYRs). Such an action would be enhanced further by the increased expression of the RYR, particularly the RYR3 isoform (Supnet *et al.* 2006). Neuronal levels of the Ca^{2+} buffer calbindin-28 k are known to be reduced in AD (Sutherland *et al.* 1992). In addition, Aβ may also reduce Ca^{2+} extrusion from the cell by inhibiting both the plasma membrane Ca^{2+}-ATPase (PMCA) and the Na^+/K^+-ATPase that maintains the Na^+/Ca^{2+} exchanger (NCX) (Mark *et al.* 1995). Thus, there are a number of mechanisms that could contribute to the upregulation of Ca^{2+} signalling to account for persistent elevation in the resting level of Ca^{2+} (Kuchibhotla *et al.* 2008; Lopez *et al.* 2008).

(3) This dysregulation of neuronal Ca^{2+} signalling seems to be exacerbated by Aβ-induced

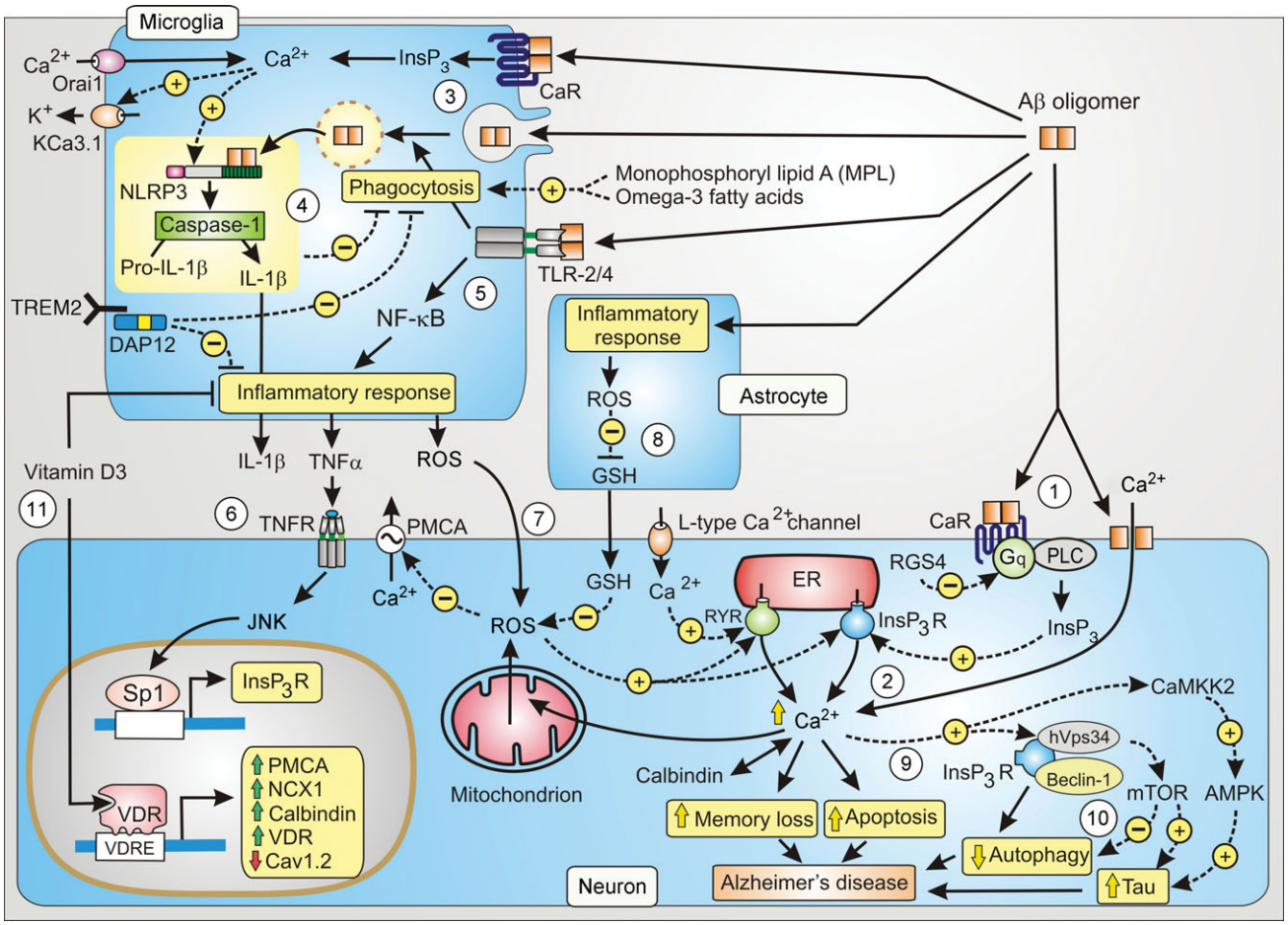

Figure 5. Ca^{2+} hypothesis of AD.
The development of AD is induced by the accumulation of Aβ oligomers that have a number of actions. The Aβ can act directly on the neurons to bring about elevations in Ca^{2+} that have been linked to the initial phase of memory loss and the subsequent increase in apoptosis that characterizes the development of AD. The Aβ can also induce inflammatory responses in neighbouring microglia and astrocytes that activate processes that enhance this dysregulation of Ca^{2+} signalling. Vitamin D3 may alleviate the development of AD by inhibiting the inflammatory responses and by increasing the expression of processes that reduce the elevation of Ca^{2+}. Aβ, amyloid β; AD, Alzheimer's disease; GSH, glutathione; IL, interleukin; $InsP_3$, inositol 1,4,5-trisphosphate; mTOR, mammalian target of rapamycin; PLC, phospholipase C; PMCA, plasma membrane Ca^{2+}-ATPases; ROS, reactive oxygen species; RYR, ryanodine receptor; TNF, tumor necrosis factor; VDR, vitamin D receptor; VDRE, vitamin D response element.

neuroinflammation that occurs during AD (Saijo & Glass 2011). Aβ-induced Ca^{2+} signals can enhance microglial inflammatory responses by increasing the release of cytokines and reactive oxygen species (ROS) (Farber & Kettenmann 2006). The Aβ also acts through CaSRs to produce $InsP_3$ that then releases Ca^{2+} from internal stores (Lee *et al.* 2012). Depletion of these stores then triggers store-operated Ca^{2+} entry through the Orai1 channel (Ohana *et al.* 2009) that is maintained by the hyperpolarization induced by the calcium-activated potassium channel KCa3.1. Microglial-dependent neurotoxicity could be reduced *in vivo* by inhibiting these KCa3.1 channels with triarylmethane-34 (Kaushal *et al.* 2007; Maezawa *et al.* 2011) thus emphasizing the significance of Ca^{2+} in regulating neuroinflammation. Drugs thought to reduce inflammation such as Ro5-4864, which is a ligand for the translocator protein, reduce both the accumulation of Aβ and the decline in cognition in transgenic AD mice (Barron *et al.* 2013).

(4) One of the consequences of the Aβ-dependent elevation of microglial Ca^{2+} is activation of the inflammasome. The oligomers that are taken up in the phagosome vesicles enter the cytosol to increase NLRP3 activity resulting in stimulation of caspase-1 that cleaves pro-interleukin-1β (IL-1β) to form IL-1β (Fig. 5). The inflammasome inhibits phagocytic clearance of Aβ and has been strongly implicated in AD (Heneka *et al.* 2013). The triggering receptor expressed in myeloid cells 2 (TREM-2), which functions as a negative regulator of innate immunity, suppresses the ability of the microglia to release inflammatory mediators such as tumour necrosis factor (TNF)α. TREM2 is a transmembrane glycoprotein that associates with DNAX-activating protein 12. A variant of TREM2, which reduces the anti-inflammatory role of TREM2, is associated with a markedly increased risk of developing AD (Guerreiro *et al.* 2013; Jonsson *et al.* 2013).

(5) Aβ can also induce microglial inflammation by stimulating toll-like receptors (TLR-2 and TLR-4). Polymorphisms in these receptors have been associated with an increased susceptibility and progression of AD (Minoretti *et al.* 2006; Yu *et al.* 2011, 2012). Activation of the TLR-2/4 receptors can have both beneficial and deleterious actions. With regard to the former, TLR-2/4 receptors stimulate phagocytosis that removes and destroys Aβ. The deleterious effects depend upon activation of the NF-κB signalling pathway that increase release of proinflammatory mediators such as TNFα and ROS, all of which can enhance neuronal Ca^{2+} signalling. Increased susceptibility and progression of AD have been linked to polymorphisms in TNFα (Di Bona *et al.* 2009; Yang *et al.* 2009). The monophosphoryl lipid A has an interesting property of being able to promote the beneficial phagocytic mechanism while not inducing the deleterious inflammatory response and thus may be an effective treatment for AD (Michaud *et al.* 2013). Omega-3 fatty acids can also enhance phagocytosis of Aβ to reduce the formation of proinflammatory cytokines (Hjorth *et al.* 2013).

(6) The TNFα and IL-1β released from the microglia can have a number of actions. The TNFα binds to the TNF receptor to contribute to neuronal cell death by activating apoptosis. The TNFα can also enhance Ca^{2+} signalling by acting through the JNK signalling pathway to increase the expression of $InsP_3R1$ by phosphorylating the transcription factor specificity protein 1 (Sp1) (Park *et al.* 2009). Both TNFα and IL-1β can also influence memory by altering the electrophysiological correlates of LTP and LTD (Cunningham *et al.* 1996; Albensi & Mattson 2000).

(7) The exogenous ROS, which diffuses into the neuron, will add to that being produced by the mitochondria and can enhance Ca^{2+} signalling in several ways. It can increase the sensitivity of both the $InsP_3Rs$ and RYRs to increase the release of Ca^{2+} while inhibiting the PMCA Ca^{2+} pump (Lock *et al.* 2011). These two effects of ROS, which will increase the resting level of Ca^{2+}, will potentially set up a positive feedback system in that the excess Ca^{2+} will increase mitochondrial ROS formation (Müller *et al.* 2011). Inhibition of ROS formation by a mitochondrial-targeted antioxidant MitoQ prevents the cognitive decline in a transgenic mouse model of AD (McManus *et al.* 2011).

(8) Aβ acts on the astrocytes to induce an inflammatory response and the resulting increase in ROS decreases the level of the antioxidant glutathione (GSH), which has serious repercussions for the neuron as it receives its GSH from the astrocytes (Abramov *et al.* 2004). A decrease in neuronal GSH levels will enable ROS to have a greater impact on Ca^{2+} levels as outlined above.

(9) A number of mechanisms have been proposed to describe how the elevation in the resting level of Ca^{2+} accounts for symptoms of AD. The characteristic loss of memory that occurs in the early stages of AD may be driven by the abnormal resting levels of Ca^{2+}, which is manifest either as a persistent elevation in the level of Ca^{2+} in the dendrites and spines (Kuchibhotla *et al.* 2008) or as an increase in spontaneous Ca^{2+} transients (Busche *et al.* 2008, 2012). This increase in Ca^{2+} signalling, may disrupt cognition by activating LTD through the mechanism

described earlier (Fig. 3*B*) (Berridge, 2010, 2011). As the disease progresses, elevation of Ca^{2+} will begin to rise further to a point where it will activate apoptosis resulting in the neuronal cell loss responsible for the final stages of dementia.

(10) A marked feature of AD is a decline in autophagy (Son *et al.* 2012), which seems to be associated with an increase in the activity of the mammalian target of rapamycin (mTOR) (Caccamo *et al.* 2010, 2013). The $InsP_3R$ is known to play a role in autophagy by assembling a complex containing regulators such as Beclin-1, Bcl-2 and hVps34 (Criollo *et al.* 2007; Vicencio *et al.* 2009). The level of Beclin-1, which is a key component of the autophagy complex, is known to be reduced in AD (Pickford *et al.* 2008). The decline in autophagy in AD may be related to an increase in $InsP_3$ that disrupts the autophagic complex by binding to the $InsP_3R$. The drug Li^+, which is known to reduce the risk of developing AD (Nunes *et al.* 2007), can reduce this inhibitory effect by lowering the level of $InsP_3$ (Sarkar *et al.* 2005). Autophagy may also be reduced in AD by the elevated levels of Ca^{2+} that can disrupt the complex by activating hVps34 (Gulati *et al.* 2008). The activation of hVps34 may also account for the increase in mTOR (Gulati *et al.* 2008) that could explain the decline of autophagy in AD. The cognitive decline in mouse models of AD is reduced by rapamycin, which inhibits the activity of mTOR (Caccamo *et al.* 2010, 2013). Another role for mTOR is to phosphorylate Tau to increase its pathological role in AD. The elevation of Ca^{2+} can also stimulate CaMKK2 to increase the activity of AMPK that then enhances the phosphorylation of Tau thus contributing to the symptoms of AD (Mairet-Coello *et al.* 2013).

(11) There is considerable evidence for a link between vitamin D deficiency and the onset of AD and other neurodegenerative diseases such as multiple sclerosis and Parkinson's disease (Garcion *et al.* 2002; Tuohimaa *et al.* 2009; Berridge 2012*b*; Wang *et al.* 2012; Lu'o'ng & Nguyên 2013). Expression of the vitamin D receptor (VDR) is reduced in the hippocampus of patients with AD (Sutherland *et al.* 1992) and VDR polymorphisms have been identified as risk factors for AD (Lehmann *et al.* 2011; Wang *et al.* 2012).There is evidence that Aβ acts to both reduce the expression of VDR while increasing the expression of the $Ca_v2.1$ Ca^{2+} channel.

Administration of vitamin D can reverse many of the changes induced by Aβ. In cultured primary neurons, vitamin D acts to increase the expression of the VDR and it reduces the expression of the $Ca_v1.2$ L-type Ca^{2+} channel (Brewer *et al.* 2006; Taniura *et al.* 2006; Dursun *et al.* 2011; Gezen-Ak *et al.* 2011). In the intestine, vitamin D is known to increase the expression of proteins such as PMCA, NCX1 and Ca^{2+} buffers such as calbindin-28 k and parvalbumin (Wasserman 2004; Pérez *et al.* 2008). It seems reasonable to propose that vitamin D may reduce the risk of AD by promoting the expression of those proteins, such as PMCA and NCX1, that act to lower the level of intracellular Ca^{2+} (Berridge 2012*b*). Vitamin D can also have a beneficial effect by dampening down the microglial inflammatory responses to reduce the formation of TNFα.

In summary, the build-up of Aβ oligomers during the onset of AD has a profound effect on the activity of the local community of cells in the brain. The inflammatory response in both the microglia and astrocytes contribute to dysregulation of neural Ca^{2+} signalling that seems to be one of the major factors in the development of AD. It is argued that in the early stages of AD, this alteration in signalling is manifest as a persistent elevation of the resting level of Ca^{2+} that results in memories acquired during the wake period being rapidly erased before they can be consolidated during sleep. Vitamin D may play a critical role in memory retention by regulating the expression of the Ca^{2+} components necessary to maintain low resting levels of Ca^{2+}.

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Additional information

Competing interests

None declared.

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