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REVIEW

SUBJECT COLLECTION: EXPLORING THE NUCLEUS

# The role of nuclear $Ca^{2+}$ in maintaining neuronal homeostasis and brain health

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## ABSTRACT

Nuclear $Ca^{2+}$ has emerged as one of the most potent mediators of the dialogue between neuronal synapses and the nucleus that regulates heterochromatin states, transcription factor activity, nuclear morphology and neuronal gene expression induced by synaptic activity. Recent studies underline the importance of nuclear $Ca^{2+}$ signaling in long-lasting, activity-induced adaptation and maintenance of proper brain function. Diverse forms of neuroadaptation require transient nuclear $Ca^{2+}$ signaling and cyclic AMP-responsive element-binding protein (CREB1, referred to here as CREB) as its prime target, which works as a tunable switch to drive and modulate specific gene expression profiles associated with memory, pain, addiction and neuroprotection. Furthermore, a reduction of nuclear $Ca^{2+}$ levels has been shown to be neurotoxic and a causal factor driving the progression of neurodegenerative disorders, as well as affecting neuronal autophagy. Because of its central role in the brain, deficits in nuclear $Ca^{2+}$ signaling may underlie a continuous loss of neuroprotection in the aging brain, contributing to the pathophysiology of Alzheimer's disease. In this Review, we discuss the principles of the 'nuclear calcium hypothesis' in the context of human brain function and its role in controlling diverse forms of neuroadaptation and neuroprotection. Furthermore, we present the most relevant and promising perspectives for future studies.

**KEY WORDS: Alzheimer's disease, Autophagy, CREB signaling, Epigenetics, Lysosome, Nuclear calcium**

## Introduction

$Ca^{2+}$ ions influence numerous signaling pathways within the vast majority of cells and thus impact nearly every aspect of life (Berridge et al., 2000). In order to adapt to changing intra- and extracellular conditions, cells must induce specific signaling cascades to regulate and integrate crucial cellular processes, including proliferation, differentiation, migration and cell death (Carrión et al., 1999; Ivanova et al., 2017; Sammels et al., 2010). The spatiotemporal distribution of $Ca^{2+}$ ions is tightly controlled and contributes to the versatility of this second messenger, allowing fast and efficient genomic responses that are required for the adaptation to continuously changing conditions (Berridge et al., 2000; Carrión et al., 1999; Ivanova et al., 2017; Newton et al., 2016; Sammels et al., 2010). Due to the underlying chemistry, the importance and versatility of $Ca^{2+}$ ions influence local electrostatic fields, thus altering the structure of thousands of proteins upon forming stable complexes, as compared to monovalent ions such as $Na^{+}$ or $K^{+}$ (Clapham, 2007). Additionally, the large and complex electron shell of a $Ca^{2+}$ ion allows the formation of tight and irregular coordination bonds that are characteristic of biomolecules, unlike smaller chemical relatives such as $Mg^{2+}$ (Carafoli et al., 2001; Clapham, 2007). These $Ca^{2+}$-driven conformational modifications of proteins enable its function as a second messenger and, depending on the source of $Ca^{2+}$ release and its destination, can drive local or long distance changes in cellular processes (Hardingham et al., 1997). The role of nuclear $Ca^{2+}$ is well documented in the nervous system, where its role in the regulation of processes responsible for neuroadaptations and neuronal homeostasis is crucial (Hardingham et al., 1997, 2001). In recent years, the focus has turned to the cell nucleus as a unique location of action for $Ca^{2+}$ ions, and robust, genetically encoded tools for the measurement (using GCaMP–NLS, a $Ca^{2+}$ sensor with a nuclear localization signal) and depletion (using the $Ca^{2+}$/calmodulin-binding polypeptide CaMBP4 or parvalbumin targeted to the cell nucleus) of nuclear $Ca^{2+}$ have been developed (Bading, 2013). Activity-driven changes in nuclear $Ca^{2+}$ levels alter the neuronal gene expression program that is responsible for adaptive responses, including neuroprotection, chronic pain, memory formation and memory extinction, and allow cells to rapidly adjust to a constantly changing environment (Hemstedt et al., 2017; Limbäck-Stokin et al., 2004; Papadia et al., 2005; Simonetti et al., 2013; Weislogel et al., 2013; Zhang et al., 2009). The 'nuclear calcium hypothesis', first proposed 20 years ago, emphasizes the role of $Ca^{2+}$ flux into the nucleus and stresses its importance as a modulator of evolutionarily conserved pathways that are often dysregulated in pathological states (Bading, 2000). In this Review, we aim to provide a summary of recent findings in the field of nuclear $Ca^{2+}$ and strengthen the 'nuclear calcium hypothesis' in the context of a regulation of pivotal cellular processes in the nervous system.

## Reservoirs and sources of nuclear $Ca^{2+}$

Along with the large excess of $Ca^{2+}$ in the extracellular space, subcellular compartments constitute a second main store of $Ca^{2+}$ ions in the cellular environment (Berridge et al., 2000). Organelles, such as lysosomes, peroxisomes, mitochondria, endoplasmic reticulum (ER) and the Golgi, are well established as suppliers of $Ca^{2+}$ in response to different stimuli (Joseph et al., 2019; Lloyd-Evans and Waller-Evans, 2020; Vandecaetsbeek et al., 2011; Wacquier et al., 2019). Transient sequestration inside these structures provides a dynamic spatiotemporal distribution of $Ca^{2+}$ that facilitates efficient and specific signal transduction. In mammalian cells, $Ca^{2+}$ is released from intracellular stores via

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specialized channels, including inositol (1,4,5)-trisphosphate receptors ($IP_3Rs$), ryanodine receptors (RyRs), two-pore channels (TPCs), $Na^+/Ca^{2+}$ exchangers (NCXs) and sarcoendoplasmic reticulum $Ca^{2+}$-ATPase pumps (SERCAs) (Blaustein and Lederer, 1999; Galione, 2019; Lanner et al., 2010; Prole and Taylor, 2019; Toyoshima, 2009; Vangeel and Voets, 2019). The shared lumen of the ER, the nucleoplasmic reticulum and the nuclear envelope (NE) constitutes the most abundant $Ca^{2+}$ store and can release ions in response to different molecular triggers (Bootman and Bultynck, 2020). The NE does not represent a measurable physical barrier to shuttling of $Ca^{2+}$ between the cytoplasm and nucleoplasm, thereby allowing efficient crosstalk to maintain synapse-to-nucleus communication (Bengtson et al., 2010; Eder and Bading, 2007). The $IP_3Rs$ and RyRs, located on the outer nuclear membrane (ONM), are involved in the regulation of nuclear $Ca^{2+}$ levels (Echevarría et al., 2003; Humbert et al., 1996; Laflamme et al., 2002; Marius et al., 2006).

The NE exhibits invaginations that can reach deep into the nucleus and contribute to various cellular processes, such as genome organization, transcription and stress responses (Heessen and Fornerod, 2007; Ruault et al., 2008; Wittmann et al., 2009). These NE invaginations are a common feature of many cell types, including neurons (Jorgens et al., 2017; Malhas et al., 2011; Wittmann et al., 2009). Nuclear invaginations generally are divided into two types (I and II), which fulfill distinct functions in the crosstalk between the nucleus, the nucleoplasmic reticulum and the cytosol (Malhas et al., 2011). Type I nuclear invaginations are folds of the inner nuclear membrane (INM) that increase the surface area of the nucleoplasmic reticulum, whereas type II nuclear invaginations are lined by both membranes (INM and ONM); they increase the surface area of the cell nucleus, contain nuclear pore complexes (NPCs) and often connect to nucleoli to promote rRNA export (Bourgeois et al., 1979; Fricker et al., 1997; Schoen et al., 2017; Wittmann et al., 2009). In addition to rRNA and small molecules (such as ATP, nucleotides and ions), the prevailing functional model of passive transport (the 'rigid barrier' model) also defines macromolecules of size less than 40 kDa as able to enter or exit the nuclear space via passive diffusion (Knockenhauer and Schwartz, 2016; Timney et al., 2016). Larger macromolecules require specific transport sequences, namely a nuclear localization signal (NLS) or a nuclear export signal (NES), which are recognized by specific transport proteins responsible for shuttling the cargo macromolecules through the NPC (Cautain et al., 2015). Conversely, an interesting hypothesis has been posited based on observations of an unexpected mode of $Ca^{2+}$ flux through NPCs that, rather than being dependent on the large central NPC lumen, is instead dependent on small peripheral pores that are sensitive to ATP and $Ca^{2+}$ (Shahin et al., 2001). In the same study, blockage of passive transport through NPCs did not affect electrical conductance in isolated *Xenopus laevis* nuclei, and electron microscopy analyses revealed the formation of additional symmetrically arranged small pores around the main lumen of NPCs (Shahin et al., 2001). Although this mode of $Ca^{2+}$ diffusion needs further validation, the presence of peripheral ATP-dependent pores in NPCs has been confirmed in human fibroblasts (Maimon et al., 2012), providing an additional level of complexity to our understanding of diffusion of $Ca^{2+}$ into the nucleus (Gerasimenko and Gerasimenko, 2004; Rodrigues et al., 2009). Furthermore, synaptic activity leads to drastic nuclear morphology changes, creating a network of nuclear invaginations that penetrate deep into the nuclear interior, allowing for release of $Ca^{2+}$ deep into the nucleus (Wittmann et al., 2009).

Additionally, other pumps and channels on the NE, such as big potassium channels (BKs) (Li et al., 2014) or the NCX that couples $Ca^{2+}$ efflux and influx to the influx and efflux of $Na^+$ (Blaustein and Lederer, 1999), have been implicated in nuclear $Ca^{2+}$ signaling (Secondo et al., 2018, 2020). However, it is important to consider that NPCs span two lipid bilayers of the NE, allowing direct exchange between the cytosol and nucleoplasm, unlike transport through single-membrane gates in the NE formed by RyR or $IP_3R$ (Fig. 1B). Therefore, NPCs are considered to be the main site for $Ca^{2+}$ entry into the nucleus (Bading, 2013).

In parallel with the abovementioned mechanisms, proper $Ca^{2+}$ flux is additionally controlled by the buffering action of the ER, lysosomes and mitochondria (Berridge et al., 2000; Raffaello et al., 2016). Importantly, mitochondrial $Ca^{2+}$ overload is associated with neuronal death in a mouse model of Alzheimer's disease (AD) (Britti et al., 2020), and impaired mitochondrial $Ca^{2+}$ efflux contributes to disease progression in multiple experimental models of neurodegenerative diseases as a result of the dysregulation of the mitochondrial $Na^+/Ca^{2+}$ exchanger NCLX (also known as SLC8B1; Jadiya et al., 2019; Kostic et al., 2015; Verma et al., 2017). Our understanding of the mechanisms underlying mitochondrial $Ca^{2+}$ regulation in neurodegeneration is expanding quickly, and these mechanisms have been reviewed in detail elsewhere (Giorgi et al., 2018); however, a link to nuclear $Ca^{2+}$ signaling has not yet been made, and this remains to be assessed in future studies.

The interplay of all these abovementioned channels maintains a high capacity for $Ca^{2+}$ transport into the nucleus that can be seen as a buffering compartment providing rapid recovery from high $Ca^{2+}$ concentrations in the ER, mitochondria or cytosol in order to protect cells from harmful $Ca^{2+}$ overload (Annunziato et al., 2004; Carafoli, 1988). The term 'calcium signaling toolkit', which refers to all the $Ca^{2+}$ channels, pumps, exchangers and signaling components, was coined two decades ago (Berridge et al., 2000). Based on more recent findings, in our opinion it seems reasonable to suggest that the 'nuclear calcium signaling toolkit' is an independent set of components dedicated exclusively to proteins that are involved in the regulation of nuclear $Ca^{2+}$ (Bading, 2013). Nevertheless, this concept may appear somewhat simplified in the context of $Ca^{2+}$ signaling, as it has been shown that the 'calcium signaling toolkit' differs between brain regions, especially in pathological conditions such as AD (Grolla et al., 2013).

## Nuclear versus cytosolic $Ca^{2+}$

An increase in cytosolic $Ca^{2+}$ in response to synaptic activity can be achieved by several means and is known to be relayed to the nucleus (Fig. 1A; Box 1). Glutamate release from presynaptic terminals activates N-methyl-D-aspartate receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and kainate-type receptors on the postsynaptic site, which allow influx of $Na^+$ and smaller amounts of $Ca^{2+}$ (Fig. 1A, inset I). The influx of these ions evokes the so-called excitatory postsynaptic potential, a voltage that initiates action potentials if the depolarization at the axon hillock reaches a threshold (Bading, 2013; Bengtson et al., 2010). An action potential at the hillock propagates back to the axon and into the dendrites, causing opening of voltage-gated $Ca^{2+}$ channels (VGCCs) and, consequently, $Ca^{2+}$ influx into the cytoplasm (Fig. 1A, inset II; Bengtson et al., 2013).

$Ca^{2+}$ release into the cytoplasm can also be achieved through the activation of G-protein-coupled receptors (GPCRs) that respond to a variety of agonists, described in detail elsewhere (Huang and Thathiah, 2015). GPCR stimulation results in the activation of

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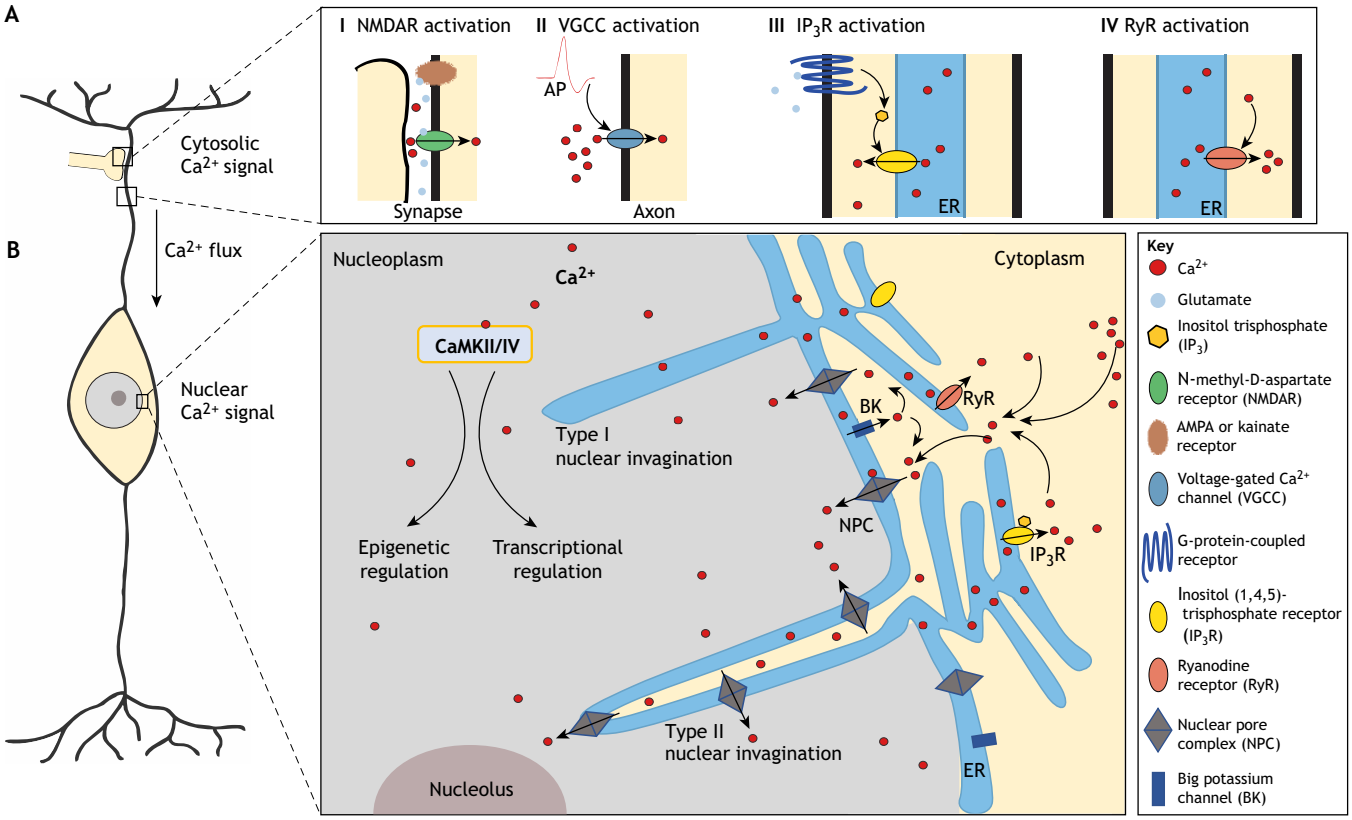


**Fig. 1. Regulation of nuclear $Ca^{2+}$-dependent gene expression in a neuronal cell.** (A) Levels of cytosolic $Ca^{2+}$ can be increased as a result of synaptic inputs such as glutamate. (I) Glutamate activates NMDARs, AMPA receptors and kainate-type glutamate receptors at the synapse, giving rise to an excitatory postsynaptic potential that may initiate an action potential (AP). (II) APs activate VGCCs in the axon, resulting in $Ca^{2+}$ entry from the extracellular space into the cytosol. (III) Stimulation of GPCRs by glutamate triggers production of $IP_3$, which in turn activates the release of $Ca^{2+}$ from the ER through $IP_3$Rs, resulting in a propagation of intercellular $Ca^{2+}$ waves. (IV) Activation of RyRs additionally amplifies $Ca^{2+}$ release from the ER or the Golgi through $Ca^{2+}$-induced $Ca^{2+}$ release. (B) $Ca^{2+}$ enters the nucleus by two main routes, either directly from the ER or from the cytoplasm. $Ca^{2+}$ ions from the ER may enter the nucleoplasm (for example via BK channels). The second route of $Ca^{2+}$ ions depends on type II nuclear invaginations, which are composed of both INM and ONM. These invaginations are enriched in NPCs, allowing for effective entry of $Ca^{2+}$ into the nucleus. While $IP_3$R, BK and RyR channels allow efflux of $Ca^{2+}$ from the ER into the cytosol, NPCs facilitate $Ca^{2+}$ transport into the nucleus. Nuclear $Ca^{2+}$ triggers activation of CaMKII and CaMKIV, which in turn modulate epigenetic and transcriptional programs, triggering defined gene expression crucial for proper neuronal function. Figure contains images adapted from Servier Medical Art (http://smart.servier.com) under the terms of a CC BY 3.0 license.

phospholipase C (PLC), which hydrolyzes phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$] located in the plasma membrane to generate two second messengers, inositol trisphosphate ($IP_3$) and diacylglycerol (DAG). $IP_3$ then activates $IP_3$Rs to induce $Ca^{2+}$ release into cytosol (Fig. 1A, inset III), which can be further amplified by $Ca^{2+}$-induced $Ca^{2+}$ release (CICR) through RyRs (Fig. 1A, inset IV). While it is widely accepted that nuclear $Ca^{2+}$ transients elicit a biological response different to that elicited by cytosolic $Ca^{2+}$ transients (Bading, 2013; Hardingham et al., 1997; Leite et al., 2003), it has been debated whether nuclear $Ca^{2+}$ is regulated independently of cytosolic $Ca^{2+}$ transients. For instance, it is known that the genomic events regulating the expression patterns of target genes in stimulated neurons are differentially controlled by nuclear versus cytosolic $Ca^{2+}$ signals (Bading, 2013; Chawla et al., 1998; Mauceri et al., 2011). Differential gene expression in response to location of $Ca^{2+}$ signal was first demonstrated by Hardingham et al. (1997), who showed that blocking nuclear $Ca^{2+}$ with the non-diffusible $Ca^{2+}$ chelator BAPTA and subsequent stimulation of L-type VGCCs results in expression of serum-response element (SRE) target genes but not those of cyclic AMP-responsive element-binding protein (CREB1, referred to here as CREB). These data suggest that SRE-mediated gene expression is controlled by an increase in cytosolic $Ca^{2+}$, whereas CREB, which binds to the cAMP-response element (CRE), requires an increase in nuclear $Ca^{2+}$ in order to stimulate its transcription-activating function (Hardingham et al., 1997). This study thus provided the first evidence for the role of nuclear $Ca^{2+}$ as a regulator of gene expression through CREB, a major transcription factor in neurons that is implicated in neuronal plasticity and long-term memory (LTM) and whose loss has a role in the pathology of AD (Mayr and Montminy, 2001; Yin et al., 1995). CREB activity is regulated by multiple kinases, including protein kinase A (PKA) and $Ca^{2+}$/calmodulin-dependent protein kinases (CaMKs), through phosphorylation on serine 133 and subsequent recruitment of the transcriptional co-activator CREB-binding protein (CBP) or its paralog p300 (also known as EP300) to CRE-containing promoters (Mayr and Montminy, 2001; Yin et al., 1994). Today, we know that nuclear $Ca^{2+}$ can relay its signals through CaMKII and CaMKIV, which work together to mediate the effects of $Ca^{2+}$ flux through L-type VGCCs and/or NMDARs in excitation–transcription coupling (Ma et al., 2014). CaMKIV is the principal regulator of gene transcription induced by synaptic activity (Bading, 2013). It is activated by a nuclear $Ca^{2+}$–calmodulin complex leading to the phosphorylation of both CREB and CBP, which is required for

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**Box 1. Nuclear $Ca^{2+}$ in synaptic plasticity**

Proper neuronal signaling requires adequate $Ca^{2+}$ flux, which is controlled by plasma membrane receptors and voltage-dependent ion channels (Bading, 2013; Brini et al., 2014; see Fig. 1). Whereas $Na^{+}$ and $K^{+}$ are used to generate short-lived action potentials (of ∼1 ms), $Ca^{2+}$-based action potentials last far longer (beyond 100 ms) and are prone to $Ca^{2+}$ buildup. Especially after prolonged and repeated stimulation, $Ca^{2+}$ accumulates in the cytosol and the nucleus, driving gene transcription and contributing to the late phase of long-term potentiation or depression of synaptic efficacy, a process that may underlie learning and that is altered in neurodegenerative diseases (Bading, 2013). Epigenetic changes and activation of specific transcriptional programs caused by flux of $Ca^{2+}$ ions into the nucleus (see Fig. 2) are two molecular processes thought to be involved in LTM, affecting long-term potentiation and long-term depression. Whereas long-term depression produces a long-lasting decrease in synaptic strength, long-term potentiation refers to a long-lasting (up to several days) increase in synaptic efficacy that involves relocalization of ion channels and transcriptional changes required for the consolidation of information storage and LTM formation (Cooke and Bliss, 2006). The development of molecular tools to specifically interfere with nuclear $Ca^{2+}$ signaling, such as CaMBP4 (Wang et al., 1995) or a nuclear-targeted version of the $Ca^{2+}$-binding protein parvalbumin, has led to key discoveries demonstrating that the late phase of long-term potentiation and formation of LTM, as well as memory extinction, require nuclear $Ca^{2+}$ signaling in mice (Hemstedt et al., 2017; Limbäck-Stokin et al., 2004) and in *Drosophila* (Weislogel et al., 2013). These findings thus identify nuclear $Ca^{2+}$ signaling as an evolutionarily conserved mechanism that controls memory consolidation and higher-order brain functions. In contrast, short-term memory (defined to last in the order of minutes) does not require gene transcription or nuclear $Ca^{2+}$ signaling (Berridge, 2014; Gibbs et al., 1979; Hemstedt et al., 2017; Limbäck-Stokin et al., 2004).

activation of CREB and CBP target gene expression (Chawla et al., 1998; Hardingham et al., 1999; Hu et al., 1999; Impey et al., 2002). In addition to the classical view that nuclear $Ca^{2+}$ influx occurs strictly by passive diffusion through NPCs (Fig. 1B), a role for $Ca^{2+}$-mobilizing machinery in nucleoplasmic reticulum with a complex branched network of invaginations has been suggested for the generation of nuclear $Ca^{2+}$ increases (Irvine, 2003; Malhas et al., 2011). Further findings indicating that the translocation of receptor tyrosine kinases (RTKs) following their activation can elicit nuclear $Ca^{2+}$ transients suggest that nuclear $Ca^{2+}$ signaling may be independent of cytosolic $Ca^{2+}$ (De Miranda et al., 2019). In one study, the activation of c-Met (also known as MET) through its ligand hepatocyte growth factor (HGF) has been found to promote its nuclear translocation, which induces $Ca^{2+}$ transients inside the nucleus (Gomes et al., 2008). Additionally, insulin receptor activation elicits a nuclear $Ca^{2+}$ response through a similar mode of action in rat hepatocytes (Rodrigues et al., 2008). However, in both cases, it is possible that an initial $Ca^{2+}$ increase is generated in the cytosol and subsequently transduced to the nucleus through NPCs. Generation of $IP_3$ to induce nuclear $Ca^{2+}$ release proceeds in the same manner as in the cytoplasm and is possibly due to availability of nuclear PLC isoforms, as well as $PI(4,5)P_2$ and $IP_3R$ (Irvine, 2003). However, to our knowledge, compelling evidence for the localization of $IP_3R$ on the INM, for example based on immunoelectron microscopy studies, does not exist. Although a few studies suggest a self-sufficiency of nuclear $Ca^{2+}$ regulation, there is thus far no convincing evidence for this claim. Conversely, a large body of work in healthy neurons has convincingly shown that influx of cytosolic $Ca^{2+}$ transients into the nucleus directly regulates nuclear $Ca^{2+}$ levels, which affect gene expression profiles through modifications of chromatin state, as discussed next.

## Epigenetic changes in response to nuclear $Ca^{2+}$ signaling

Over the past few decades, nuclear $Ca^{2+}$ has been established as one of the main regulators of epigenetic changes in the cell. As a consequence of synaptic activity, elevated nuclear $Ca^{2+}$ signaling induces chromatin remodeling, including DNA methylation and histone acetylation, which in turn regulate gene expression (Fig. 2), and has been linked to specific brain functions that are reviewed in detail elsewhere (Dulac, 2010; Fischle et al., 2003). One target of nuclear $Ca^{2+}$ signaling is methyl CpG-binding protein 2 (MECP2, also known as MBD2), a protein that binds to methylated DNA and that is thought to act as a global chromatin modifier (Guy et al., 2011). Upon stimulation of synaptic activity, MECP2 is phosphorylated on a functionally relevant residue, serine 421. This phosphorylation event requires nuclear $Ca^{2+}$ and is catalyzed by nuclear CaMKII (Buchthal et al., 2012). Although MECP2 binding to methylated DNA is traditionally associated with repression of transcription (Kinde et al., 2016; Nan et al., 1997), MECP2 has also been shown to act as a transcriptional activator, revealing a dual role as both a repressor and activator of gene expression (Chahrour et al., 2008; Horvath and Monteggia, 2018). Additionally, nuclear availability of the transcription factor forkhead box O3A (FOXO3A, also known as FOXO3), which plays a crucial role in cell death pathways, is also regulated through nuclear $Ca^{2+}$-dependent export (Dick and Bading, 2010). As CBP interacts with many transcription factors (including CREB and c-Jun, also known as JUN) and regulatory proteins, nuclear $Ca^{2+}$- and CaMKIV-driven modulation of CBP can influence a broad array of target genes in neurons, thereby regulating the proper functioning of the nervous system (Bading, 2000; Bedford et al., 2010; Cruzalegui et al., 1999). CBP contains a histone acetyltransferase (HAT) domain that is responsible for histone acetylation, which in turn initiates the induction of specific sets of target genes (Bading, 2000; Chawla et al., 1998; Vo and Goodman, 2001). Chromatin decondensation, which promotes gene expression, is additionally enhanced by the nuclear export of class IIa histone deacetylases (HDACs), which are directly regulated by a nuclear $Ca^{2+}$-dependent mechanism in response to synaptic activity (Chawla et al., 2003; Schlumm et al., 2013). By removing acetyl residues from histones, which in most cases increases chromatin condensation leading to chromatin compaction, HDACs repress the expression of numerous genes and thus antagonize the HAT-dependent activity of CBP. Recently, two class IIa histone deacetylases, HDAC4 and HDAC5, have been shown to regulate expression of early response genes (ERGs) during associative learning, and this expression pattern is associated with proper synaptic architecture and regulation of learning and memory in mice (Zhu et al., 2019). HDAC4 is highly expressed in the brain and plays a pivotal role in the maintenance of cognitive functions (Bolger and Yao, 2005; Chawla et al., 2003; Darcy et al., 2010). There is growing interest in determining whether pharmacological inhibition of HDACs indeed correlates with an enhancement of LTM. There are reports that expression of a truncated, nuclear-restricted HDAC4 mutant results in deficits in LTM and hippocampal-dependent memory formation, indicating a possible non-nuclear role of HDAC4 in normal memory formation (Sando et al., 2012). This suggests that at least some genes required for LTM are subjected to HDAC4-mediated transcriptional repression in *Drosophila* (Fitzsimons et al., 2013) and in mouse models (Fitzsimons et al., 2013; Kim et al., 2012). In parallel to affecting histone acetylation and deacetylation, nuclear $Ca^{2+}$ also contributes to epigenetic changes by inducing the expression of the *de novo* DNA methyltransferase, DNMT3A2, which triggers DNA methylation

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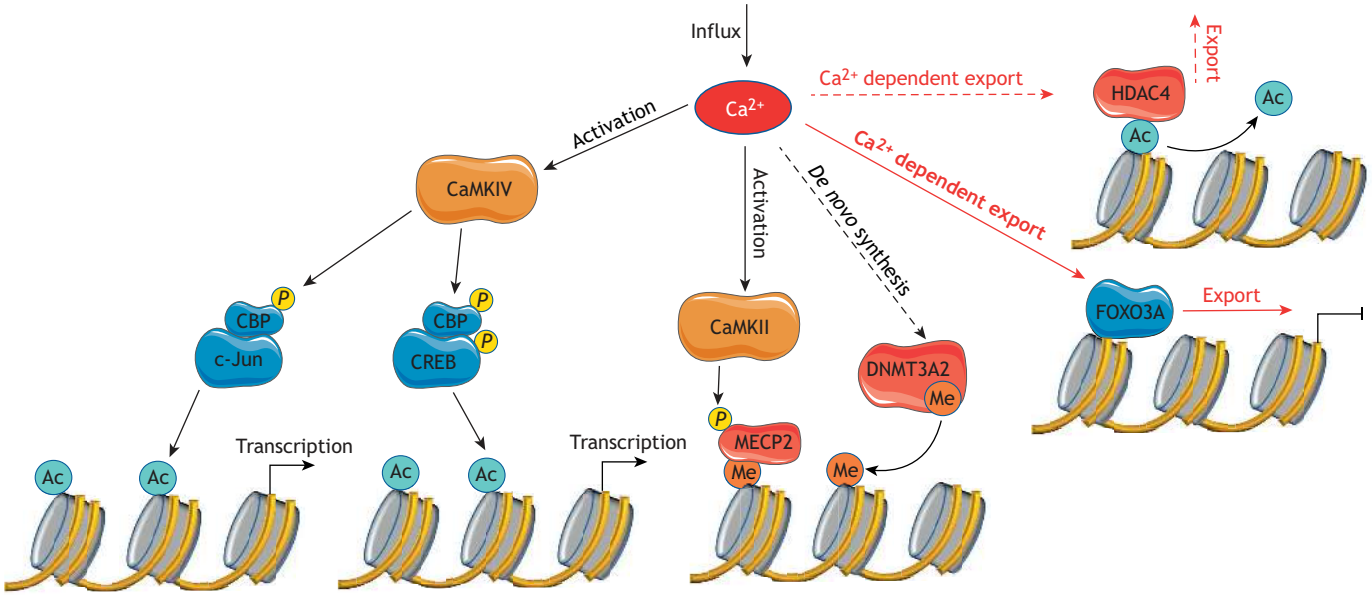


**Fig. 2. Epigenetic and transcriptional mechanisms triggered by nuclear $Ca^{2+}$.** $Ca^{2+}$ influx into the nucleus modulates the activity and localization of several proteins that can influence chromatin organization, leading to transcriptional induction via CaMK activation (black arrows) or repression of specific target genes owing to $Ca^{2+}$-dependent export of regulatory factors (red arrows). Transcriptional activity of chromatin is determined by the methylation (Me) and acetylation (Ac) of histones, which is accomplished by chromatin-modifying proteins, including CBP, DNMT3A2 and HDAC4. $Ca^{2+}$-dependent activation of CaMKIV phosphorylates (*P*) CBP, which contains a histone acetyltransferase (HAT) domain, responsible for histone acetylation and thus chromatin decondensation. Histone acetylation can be enhanced by nuclear export of HDAC4, whose enzymatic activity antagonizes the action of CBP. Activated CBP can interact with transcription factors, such as c-Jun; this provides an additional mechanism to control transcription of target genes. Additionally, availability of the transcription factor FOXO3A, which is crucial for cell-death pathways, is also regulated through its nuclear $Ca^{2+}$-dependent export. Nuclear $Ca^{2+}$ also modulates DNA methylation that is linked to transcriptionally active euchromatin. CaMKII-dependent activity of DNMT3A2 or *de novo* synthesis of this protein, as well as phosphorylation of the transcriptional regulator MECP2, are strictly regulated by the level of nuclear $Ca^{2+}$. Figure contains images adapted from Servier Medical Art (http://smart.servier.com) under the terms of a CC BY 3.0 license.

in response to neuronal activity (Oliveira et al., 2012). DNMT3A2 is linked to transcriptionally active euchromatin and has been shown to have a pivotal role in memory formation and consolidation by modulating numerous genes involved in synaptic plasticity and memory (Chen et al., 2002; Gulmez Karaca et al., 2020; Oliveira, 2016; Oliveira et al., 2016). A comprehensive transcriptome analysis has revealed that nuclear $Ca^{2+}$ triggers the expression of a large pool of ∼185 genes (Zhang et al., 2009). This pool includes transcriptional regulators that control the following neuroadaptations: (1) memory, which is regulated by CREB, downstream regulatory element antagonist modulator (DREAM, also known as KCNIP3), CBP, MECP2 and class IIa HDACs; (2) acquired neuroprotection, which is regulated by CREB and class IIa HDACs; (3) addiction, which is regulated by CREB, CBP and MECP2; and (4) pain, which is regulated by CREB, CBP, MECP2 and DREAM. The target genes of these regulators are reviewed elsewhere (Bading, 2013; Zhang et al., 2009).

Furthermore, CREB has been found to regulate the induction of a variety of autophagic genes, including those encoding SESN2, unc-51-like autophagy activating kinase 1 (ULK1), autophagy related 7 (ATG7) and transcription factor EB (TFEB) (Lee et al., 2014; Seok et al., 2014). These findings suggest a functional link between nuclear $Ca^{2+}$ and regulation of autophagy on a transcriptional level, as discussed below.

## An emerging role for CREB in the regulation of cellular clearance

Cellular clearance is required for various physiological processes and its dysregulation is observed in many human diseases (Malik et al., 2019; Mizushima and Levine, 2020). Autophagy is a complex process that facilitates the constitutive turnover of intracellular components but also eliminates potentially damaging materials in response to stress conditions (Levine and Kroemer, 2019). Thus, the maintenance of cellular clearance driven by autophagy not only regulates crucial homeostatic and pro-survival mechanisms (He and Klionsky, 2009; Klionsky, 2007), but is also involved in dendritic retraction and synaptic pruning when hyperactive in pathological conditions (Levine and Kroemer, 2019). Among the numerous triggers of autophagy, damaged organelles, infection and periods of starvation are the most common (Kroemer et al., 2010; Lum et al., 2005). As autophagy is strictly dependent on lysosomal activity, which ultimately allows the degradation of cytosolic factors, the autophagosomal (auto)-lysosomal system is a major regulator of autophagic flux (Huber and Teis, 2016; Yim and Mizushima, 2020). As the pro-survival effect of autophagy can be dysregulated in pathological states, such as cancer and neurodegenerative diseases (Yang and Klionsky, 2010), pharmacological agents that can modulate autophagy in human pathophysiological conditions have been widely investigated (Rubinsztein et al., 2012). The postmitotic nature of mature neurons renders them particularly vulnerable to consequences of autophagy deregulation. As neurons and other terminally differentiated cells are unable to dilute toxic proteins and damaged organelles by cell division, they strictly depend on basal autophagy for the proper turnover of cytoplasmic contents (Hara et al., 2006). Autophagy is also crucial for both embryonic and adult neurogenesis, and is required for correct membrane turnover in the axons (Ha et al., 2017; Komatsu et al., 2007; Vázquez et al., 2012). While nuclear $Ca^{2+}$ controls cellular clearance pathways largely at the transcriptional level, cytosolic $Ca^{2+}$ regulates autophagy in a multitude of ways, and these have been recently reviewed elsewhere (Bootman et al., 2018). In general, high cytosolic $Ca^{2+}$ stimulates autophagy, whereas $Ca^{2+}$ chelators hamper autophagic flux (Brady

et al., 2007; Gao et al., 2008; Høyer-Hansen et al., 2007; Sakaki et al., 2008).

Over the last few years, TFEB has emerged as a key regulator of autolysosomal clearance pathways. TFEB is regulated by the nutrient-sensing mechanistic target of rapamycin complex 1 (mTORC1) kinase complex that is located on lysosomal membranes (Inoki et al., 2003). When active, mTORC1 phosphorylates TFEB, allowing it to remain in the cytoplasm. During starvation, mTORC1 dissociates from lysosomal membranes and no longer phosphorylates TFEB, which now can translocate into the nucleus. Inside the nucleus, TFEB directly binds to promoter elements containing the so-called coordinated lysosomal expression and regulation (CLEAR) sequence, which regulates expression of lysosomal and autophagosomal genes (Sardiello et al., 2009; Settembre et al., 2011, 2012). Importantly, a more recently identified axis for the regulation of TFEB and autophagy activity in hepatic cells involving the farsenoid X receptor (FXR, also known as NR1H4) and CREB (FXR–CREB) has been shown to work independently of mTORC1 and to be slower and more persistent in the regulation of autophagy and activation of lysosomal gene expression than mTORC1 signaling (Lee et al., 2014; Seok et al., 2014). Notably, CREB upregulates crucial autophagy genes, such as *ATG7*, *ULK1* and *SESN2*, whereas activated FXR opposes these effects by disrupting the functional complex between CREB and CREB-regulated transcription coactivator 2 (CRTC2) required for the CREB-dependent transcription (Seok et al., 2014). It is currently unknown whether a similar axis of autophagy regulation by CREB exists in cells of neuronal origin. Among the numerous studies highlighting the importance of CREB signaling and autophagy in neuroprotection, some reports suggest that induction of autophagy and CREB are strongly linked and are interdependent in a variety of murine models of neonatal hypoxia-ischemia brain injury and β-amyloid (Aβ)-induced neurodegeneration (Carloni et al., 2010; Singh et al., 2017). Although these studies attribute the observed effects of CREB to the expression of synaptic markers, neurotransmitter receptors and ion channels, rather than directly to autophagy, we expect that functional autophagy is induced under these conditions and drives neuroprotection through clearance of neurotoxic aggregates and defective organelles. Additional epistatic analyses are required to carefully assess the interplay between CREB and autophagy in these model systems. Overall, the above studies identify CREB as novel transcriptional activator of autophagy that may underlie its neuroprotective role and could constitute a promising pharmacological target for neurodegenerative diseases. However, it is important to consider that autophagy has a destructive potential and needs to be fine-tuned to avoid its hyperactivation leading to excessive synaptic pruning and worsening of the disease condition. To decipher the complex roles of nuclear $Ca^{2+}$ and CREB in neuroprotection and conserved brain function, simpler model systems with a readily available genetic toolkit, such as *Drosophila*, offer clear advantages that are discussed below.

## Nuclear $Ca^{2+}$ signaling in long-term neuronal adaptations is evolutionarily conserved

Functional and morphological adaptations of synapses, dendrites and spines, as well as alterations in local and broader networks are essential features that underlie neuronal information processing and storage. In particular, adaptations underlying the formation of lasting memory are thought to involve functional and morphological changes within neuronal networks that result in a durable strengthening of certain communication pathways, while simultaneously depressing other pathways within the network (Bennett et al., 2018; Carasatorre and Ramirez-Amaya, 2012; Segal, 2017; Vogel-Ciernia and Wood, 2014). Neuronal adaptation is controlled by epigenetic changes and activation of specific transcriptional programs (Hsieh and Gage, 2005). The CREB family of transcription factors driven by nuclear $Ca^{2+}$ is critical in controlling memory and neuronal adaptation in animals as divergent as mice, the sea slug *Aplysia* (Kandel, 2001) and *Drosophila* (Yin et al., 1994) (see Box 1). The suite of tools developed to control nuclear $Ca^{2+}$ signaling in *Drosophila* in a temporally- and spatially-controlled manner has facilitated conceptual advances with regard to the function of nuclear $Ca^{2+}$ transients (Guo et al., 2017; Jung et al., 2020; Pfeiffer et al., 2010). By restricting the expression of the nuclear $Ca^{2+}$ blocker CaMBP4 to small subsets of distinct classes of neurons, termed Kenyon cells, within the mushroom body (MB) (Crittenden et al., 1998) – the region of the *Drosophila* brain that mediates learning and memory and contains ∼2000 Kenyon cells (Aso et al., 2014; de Belle and Heisenberg, 1994; Heisenberg et al., 1985; Modi et al., 2020) – the ∼600 γ-neurons (Aso et al., 2014) of the MB were found to be required for nuclear $Ca^{2+}$ signaling (Weislogel et al., 2013). MB γ-neurons have recently been shown to play a major role in LTM consolidation by detecting spaced learning paradigms (as opposed to massed learning without spaces), as well as orchestrating activity and LTM-related gene expression in downstream neuronal networks (Awata et al., 2019). Furthermore, a pair of modulatory neurons, the anterior paired lateral neurons, which interact directly with MB γ-neurons to facilitate odor discrimination during olfactory learning (Lin et al., 2014), undergo synchronized synaptic pruning together with MB γ-neurons during brain development in *Drosophila* (Mayseless et al., 2018). This study showed that coordinated pruning of γ-neurons and anterior paired lateral neurons in the MB depends on the activity of MB γ-neurons and nuclear $Ca^{2+}$ signaling, which controls expression of neuroprotective genes in the downstream anterior paired lateral neurons. Taken together, this work identifies nuclear $Ca^{2+}$ as a key factor involved in coordinating changes to circuit architecture (Mayseless et al., 2018).

A recent study in *Drosophila* has reported that nuclear $Ca^{2+}$ is depleted in neurons of the adult brain in the context of both aging and neurodegeneration induced by tau (also known as MAPT in mammals), and that nuclear $Ca^{2+}$ depletion is a causal factor driving tau-induced neurotoxicity (for details see below; Mahoney et al., 2020). These findings add an important dimension to our fundamental understanding of brain aging and the 'calcium hypothesis of AD' (Khachaturian, 1984; Alzheimer's Association Calcium Hypothesis Workgroup, 2017). Future studies in *Drosophila* will no doubt contribute to a more complete understanding of the involvement of nuclear $Ca^{2+}$ signaling in the neurophysiology and neuropathology.

## Nuclear $Ca^{2+}$-mediated neuroprotection and degeneration

The 'calcium hypothesis of AD', proposed in 1984 by Khachaturian, suggests a link between $Ca^{2+}$ dyshomeostasis, neurodegeneration and AD pathophysiology (Khachaturian, 1984). Since then, numerous studies have investigated the role of $Ca^{2+}$ in the pathogenesis of different neurological conditions, including AD, and these are reviewed elsewhere (Agostini and Fasolato, 2016; Galla et al., 2020; Kumar, 2020). The identification of nuclear $Ca^{2+}$ signaling as a critical regulator of higher-order brain function points toward the potential involvement of dysregulated nuclear $Ca^{2+}$ signaling in the etiology of diseases and mental disorders. While there is a vast literature focused on general $Ca^{2+}$ dyshomeostasis in AD, the involvement of nuclear $Ca^{2+}$ in the context of AD and related tauopathies has only recently been discovered (Mahoney et al., 2020;

Reddy et al., 2016). These studies utilized genetically-encoded nuclear $Ca^{2+}$ sensors (GCaMP3–NLS and GCaMP6–NLS) in induced pluripotent stem cell (iPSC)-derived neurons from patients with familial AD (FAD) (Reddy et al., 2016) and sporadic AD, as well as tau-transgenic *Drosophila* carrying human tau with an R406W mutation (Mahoney et al., 2020). iPSC-derived neurons with knockout of presenilin 1 (*PS1*) or with FAD-associated *PS1* mutation show low levels of nuclear $Ca^{2+}$, as well as reduced CaMKIV and CREB signaling (Reddy et al., 2016). Consequently, PS1-deficient cells have reduced expression of sestrin 2 (SESN2) (Reddy et al., 2016), a known target of nuclear $Ca^{2+}$ signaling (Bading, 2013) and inhibitor of mTORC1 (Wolfson et al., 2016). These results causally link nuclear $Ca^{2+}$ depletion, reduced CREB and SESN2 signaling to hyperactive mTORC1 activity in PS1-deficient cells, and also reveal that nuclear $Ca^{2+}$ depletion aggravates autophagic and autolysosomal dysfunction as a consequence of mTORC1-driven inhibition of TFEB and its CLEAR gene network (Reddy et al., 2016). Furthermore, in human iPSC-derived neurons harboring an FAD *PS1* mutation, SESN2 expression can be restored by pharmacologically elevating nuclear $Ca^{2+}$, which in turn initiates TFEB-mediated clearance (Reddy et al., 2016). Other mechanisms through which PS1 modulates nuclear $Ca^{2+}$ are possible and may involve its role as an ER-resident $Ca^{2+}$ channel (Neely et al., 2011; Száraz et al., 2013; Tu et al., 2006). Importantly, TFEB activation effectively reduces aggregation of prion proteins, such as huntingtin, Aβ and phosphorylated tau (pTau), by enhancing lysosomal function, as shown in the HD N171-82Q mouse model of Huntington's disease (Tsunemi et al., 2012), murine cortical primary astrocytes (Xiao et al., 2014) and in the rTg4510 mouse model of tauopathy (Polito et al., 2014). Additionally, in the mouse-model studies mentioned above, TFEB activity attenuates plaque pathogenesis and rescues behavioral deficits and neurodegeneration, making TFEB an attractive therapeutic target for treating AD and related tauopathies.

We have recently investigated the effects of pathogenic tau on nuclear $Ca^{2+}$ signaling and CREB using a *Drosophila* model of tauopathy, as well as iPSC-derived neurons from patients with sporadic AD (Mahoney et al., 2020). RNA-sequencing analyses reveal a significant overrepresentation of CREB-regulated genes among differentially expressed transcripts (being either down- or up-regulated genes) in tau-transgenic *Drosophila*. Consistent with deregulation of CREB signaling in tau-expressing flies, we have observed that nuclear $Ca^{2+}$ is depleted in neurons of tau-transgenic *Drosophila* and in iPSC-derived neurons from patients with sporadic AD, as determined by nuclear $Ca^{2+}$ imaging. Tau-induced nuclear $Ca^{2+}$ depletion appears to be a causal factor driving neurodegeneration, as further reduction of nuclear $Ca^{2+}$ signaling through pan-neuronal expression of CaMBP4 significantly enhances tau-induced neurodegeneration in *Drosophila* (Mahoney et al., 2020). Interestingly, BK channels are thought to play a pivotal role in nuclear $Ca^{2+}$ regulation, thus placing BK at the crossroads of nuclear $Ca^{2+}$ and neuroprotection (Contet et al., 2016; Li and Gao, 2016). Indeed, we have found that pharmacological activation of BK channels elevates nuclear $Ca^{2+}$ levels in brains of tau-transgenic *Drosophila* and significantly suppresses tau-induced neurotoxicity (Mahoney et al., 2020). These results suggest an involvement of BK channels in nuclear $Ca^{2+}$ signaling (Li et al., 2014; Mahoney et al., 2020), timing and duration of $K^+$ influx, and levels of local $Ca^{2+}$ concentrations that impact neurotransmitter release (Contet et al., 2016; Wang et al., 2015a,b). Although the mechanism underlying tau-induced reduction of nuclear $Ca^{2+}$ is unknown, we speculate that it could involve effects of pathogenic tau on nuclear architecture. Invaginations of the NE have been proposed to allow for targeted $Ca^{2+}$ release to discrete regions of the nucleus (Marius et al., 2006), and neurons from postmortem human AD brains, brains of tau-transgenic *Drosophila* (Frost et al., 2016) and iPSC-derived neurons from patients with tauopathy (Paonessa et al., 2019) all feature such invaginations. In healthy neurons, synaptic activity induces dramatic changes in nuclear morphology that could be attributed to an increase in nuclear $Ca^{2+}$ levels and associated signaling (Wittmann et al., 2009). In neurons from patients with AD, NE invaginations are lined with nuclear pores, suggesting that they could potentially deregulate nucleocytoplasmic trafficking of RNAs, proteins and other cellular factors, such as $Ca^{2+}$ (Frost et al., 2016). Indeed, studies of tau-transgenic *Drosophila* reveal that tau-induced NE invaginations contain RNA, suggesting that they actively export and/or sequester RNA (Cornelison et al., 2019). Furthermore, altered nucleocytoplasmic transport in AD has been suggested to be a consequence of the direct binding of pathogenic forms of tau to the nucleoporin subunits of NPCs, thus disrupting their structural integrity (Eftekharzadeh et al., 2018). Based on these findings, we speculate that NE invaginations, which can be induced by synaptic activity in healthy neurons (Wittmann et al., 2009) or other means in disease conditions (Frost et al., 2016), lead to a redistribution of NPCs that could affect the nuclear $Ca^{2+}$ dynamics. However, it is currently unknown whether the effects of tau on nuclear architecture are causally related to a disruption of nuclear $Ca^{2+}$ signaling and to what extent low levels of nuclear $Ca^{2+}$ drive AD pathology. To assess whether nuclear $Ca^{2+}$ signaling plays a crucial role in the pathogenesis or progression of sporadic AD, CREB activity, target gene expression and nuclear morphology will need to be correlatively analyzed in human postmortem brain tissues from patients at different stages of the disease. In summary, we argue that a dysregulation of nuclear $Ca^{2+}$ signaling is expected to trigger a cascade of events leading to the formation of known disease hallmarks and pathogenesis of neurological diseases (Fig. 3).

## Future perspectives

Recent studies exploring the roles of nuclear $Ca^{2+}$ signaling in the brain bring us closer to deciphering its importance in proper brain function and its involvement in neurodegenerative diseases. In future studies, it will be important to work towards addressing a few key aspects of nuclear $Ca^{2+}$ signaling, including the crosstalk between cytosolic and nuclear $Ca^{2+}$ in health and disease. It is still not clear whether nuclear $Ca^{2+}$ signaling can be fully autonomous and generated independently of activity-induced cytosolic $Ca^{2+}$ transients. It is also currently unknown precisely how nuclear $Ca^{2+}$ transients produce different epigenetic and transcriptional outcomes. While there are three obvious dimensions for such coding (i.e. space, time and strength), tools to monitor these parameters *in vivo* at high resolution are currently limited. Recent developments in *Drosophila* may provide more sensitive approaches for the imaging of nuclear events (Jung et al., 2020) that could potentially be combined with tools that allow quantification of $Ca^{2+}$ transients in freely moving animals (Guo et al., 2017). The use of *Drosophila* and the many available disease-associated mutants to study nuclear $Ca^{2+}$ at such high resolution will be helpful to assess the potential impact on disease onset and progression. However, as helpful as *Drosophila* and other models may be for the dissection of the mechanisms underlying (normal and altered) nuclear $Ca^{2+}$ signaling and its downstream processes, these insights always need to be considered from an evolutionary perspective: apparent conservation of mechanisms between fly and man only suggests that a common ancestor of

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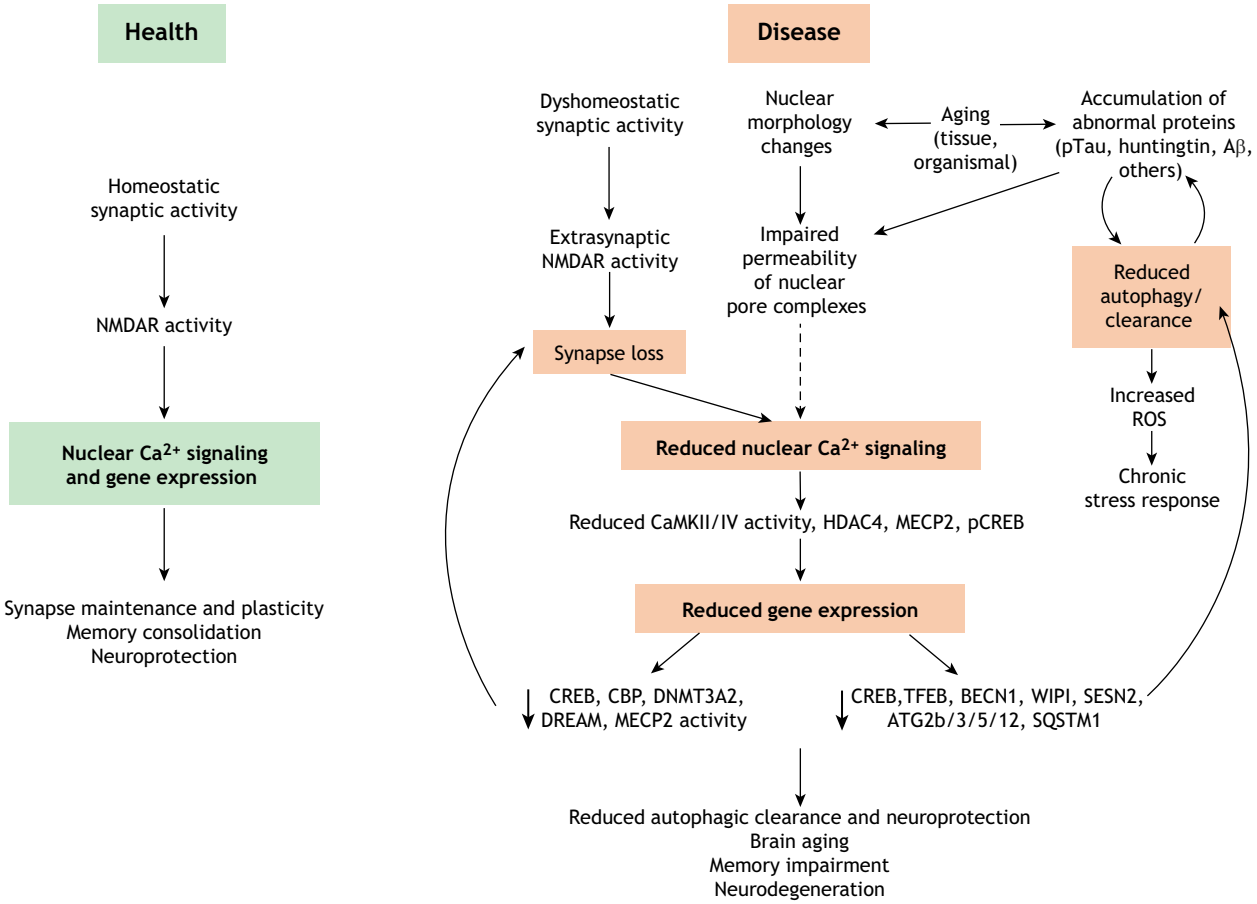


**Fig. 3. Health and disease conditions related to nuclear $Ca^{2+}$ signaling.** As a result of homeostatic synaptic and NMDAR activity, nuclear $Ca^{2+}$ signaling promotes the expression of genes required for synapse maintenance, plasticity, molecular clearance and neuroprotection. In disease conditions, synaptic loss occurs as a result of dyshomeostatic activity, leading to decreased nuclear $Ca^{2+}$ signaling. Reduced expression of nuclear $Ca^{2+}$ target genes (including *CREB*, *SESN2* and *DREAM*) leads to attenuated autophagic clearance and neuroprotection underlying memory impairment and neurodegeneration. Nuclear $Ca^{2+}$ levels are likely to be reduced by other, synapse-independent mechanisms, such as a reduced permeability of nuclear pore complexes, that might be induced by accumulation of abnormal proteins or changes of nuclear morphology during cellular aging. Reduced nuclear $Ca^{2+}$ signaling and subsequent expression of target genes further impairs autophagic lysosomal clearance and exacerbates the accumulation of abnormal proteins such as pTau, huntingtin or Aβ, and promotes further synaptic loss, leading to an aggravation of the pathological condition. ATG, autophagy-related protein; BECN1, Beclin-1; pCREB, phosphorylated CREB; ROS, reactive oxygen species; WIPI, human WD-repeat protein interacting with phosphoinositides.

mammals and insects might have applied similar functional principles to solve a problem. How these ancient functional principles are implemented in modern animals after millions of years of independent evolution therefore requires careful analysis. For example, it will be important to investigate the etiology of the disrupted nuclear morphology present in AD-patient neurons and its relationship to dysregulated nuclear $Ca^{2+}$ and CREB signaling; to uncover the mechanisms responsible for low levels of nuclear $Ca^{2+}$, despite synaptic hyperactivity in early and mid-stages of AD; and to study the role of neurodegenerative disease-causing extrasynaptic NMDA receptors that antagonize the transcription-promoting activities of nuclear $Ca^{2+}$ (Bading, 2017; Hardingham and Bading, 2010). Finally, the importance of nuclear $Ca^{2+}$ signaling in many cellular processes may potentially be translated into therapies by targeting the key players responsible for its regulation, although suitable drugs that are able to increase nuclear $Ca^{2+}$ levels are yet to be found.

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**Competing interests**

The authors declare no competing or financial interests.

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