Neuronal and glial calcium signaling in Alzheimer’s disease

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Abstract

Cognitive impairment and emotional disturbances in Alzheimer’s disease (AD) result from the degeneration of synapses and death of neurons in the limbic system and associated regions of the cerebral cortex. An alteration in the proteolytic processing of the amyloid precursor protein (APP) results in increased production and accumulation of amyloid β-peptide (Aβ) in the brain. Aβ has been shown to cause synaptic dysfunction and can render neurons vulnerable to excitotoxicity and apoptosis by a mechanism involving disruption of cellular calcium homeostasis. By inducing membrane lipid peroxidation and generation of the aldehyde 4-hydroxynonenal, Aβ impairs the function of membrane ion-motive ATPases and glucose and glutamate transporters, and can enhance calcium influx through voltage-dependent and ligand-gated calcium channels. Reduced levels of a secreted form of APP which normally regulates synaptic plasticity and cell survival may also promote disruption of synaptic calcium homeostasis in AD. Some cases of inherited AD are caused by mutations in presenilins 1 and 2 which perturb endoplasmic reticulum (ER) calcium homeostasis such that greater amounts of calcium are released upon stimulation, possibly as the result of alterations in IP3 and ryanodine receptor channels, Ca2+-ATPases and the ER stress protein Herp. Abnormalities in calcium regulation in astrocytes, oligodendrocytes, and microglia have also been documented in studies of experimental models of AD, suggesting contributions of these alterations to neuronal dysfunction and cell death in AD. Collectively, the available data show that perturbed cellular calcium homeostasis plays a prominent role in the pathogenesis of AD, suggesting potential benefits of preventative and therapeutic strategies that stabilize cellular calcium homeostasis.

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1. Introduction

There are currently more than 4 million Americans living with Alzheimer’s disease (AD), a devastating and always fatal neurodegenerative disorder characterized by progressive impairment of cognitive function and emotional disturbances. The disease process involves the degeneration of synapses and neurons in brain regions that play fundamental roles in learning and memory including the hippocampus, entorhinal cortex, basal forebrain, amygdala, frontal cortex, and inferior parietal cortex [1]. Two histological hallmarks of these brain regions of AD patients are the presence of aggregates of the amyloid β-peptide (Aβ) in the form of plaques, and the presence of filamentous intracellular aggregates of the microtubule-associated protein tau—the so-called neurofibrillary tangles.

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Analyses of brain tissue from AD patients have provided evidence suggesting that alterations in cellular calcium homeostasis are associated with the neurodegenerative process. Levels of free and protein-bound calcium are increased in neurons containing neurofibrillary tangles as compared with tangle-free neurons [2]. Nixon and coworkers [3,4] have shown that levels of activated calcium-dependent proteases are also increased in neurofibrillary tangle-bearing neurons. The increased levels of calcium may precede tangle formation because levels of calcium/calmodulin-dependent protein kinase II are increased in neurons that are vulnerable to degeneration [5] and is associated with paired helical filaments [6]. In addition, levels of tissue transglutaminase (a calcium-activated enzyme) are increased in AD brain tissue [7], and can induce cross-linking of tau protein in vitro [8]. Studies of cultured neurons have provided evidence that elevated intracellular calcium levels, resulting from overactivation of glutamate receptors, can induce changes in the cytoskeleton similar to those seen in neurofibrillary tangles.
Fig. 1. Central role of altered cellular calcium homeostasis in the pathogenesis of different age-related neurodegenerative disorders. Different genetic and environmental factors may cause or increase the risk of specific neurodegenerative disorders. However, each factor cooperates with age-related increases in oxidative stress and metabolic compromise to disrupt neuronal calcium homeostasis resulting in synaptic dysfunction and cell death. Alteration in glial cell calcium homeostasis may occur and contribute to inflammatory processes and white matter damage in neurodegenerative disorders.

[9] Similar alterations in the cytoskeleton can be induced in hippocampal neurons in vivo in response to severe epileptic seizures; the alterations were exacerbated by physiological stressors that elevate glucocorticoid levels [10].

In the present article, we review data, primarily from this laboratory, that provide insight into the cellular and molecular mechanisms that result in perturbed neuronal calcium homeostasis in AD, and how altered calcium signaling plays a pivotal role in synaptic dysfunction and neuronal death. Due to space constraints we have not attempted a comprehensive review of this topic, but do acknowledge the many important contributions not cited here by way of reference to recent relevant review articles [11–13]. We also note at the outset that alterations in cellular calcium homeostasis occur in other neurodegenerative disorders including Parkinson’s and Huntington’s diseases, ischemic stroke, and amyotrophic lateral sclerosis [14–17]. While the factor(s) that initiate the neurodegenerative cascade may differ among these disorders, oxidative stress and metabolic compromise are important contributors to perturbed neuronal calcium homeostasis in each disorder (Fig. 1). Dysregulation of calcium signaling, in turn, likely contributes to synaptic dysfunction and excitotoxic and/or apoptotic death of the vulnerable neuronal populations. Therefore, at least some of the cellular and molecular mechanisms described below in relation to AD, are also relevant to other neurodegenerative disorders, a fact easily appreciated by reading other articles in this special issue of Cell Calcium.

2. APP metabolites and neuronal calcium homeostasis

A major alteration in AD patients, and in some experimental models of AD, is altered proteolytic processing of the β-amyloid precursor protein (APP). The alteration involves increased cleavage at either end of Aβ by β- and γ-secretases resulting in increased production of Aβ, particularly the longer 42 amino acid Aβ which has a greater propensity to self-aggregate and is more toxic to neurons than the shorter 40 amino acid peptide [18]. In addition, cleavage of APP in the middle of the Aβ sequence by an enzyme called α-secretase is reduced resulting in decreased production of a secreted form of APP (sAPP) that is believed to play important roles in regulating synaptic plasticity and promoting the survival of neurons. In rare inherited cases of AD the alteration in APP processing results from mutations in APP itself or in presenilins 1 or 2. The cause(s) of the altered APP processing in the more common sporadic forms of AD is not clear, but increased levels of intracellular calcium might play a role. As evidence, exposure of cultured cells to agents that induce calcium influx results in increased production of Aβ [19], and mutations in presenilin 1 (PS1) that cause AD perturb calcium homeostasis and also increase Aβ production [20–22]. The increased production and aggregation of neurotoxic forms of Aβ is believed to cause neuronal degeneration and death by promoting apoptosis and excitotoxicity [18,23]. Apoptosis induced by Aβ may be mediated by proteins such as Par-4, Bax, and p53 [24,25].
One line of evidence that strongly supports a role for perturbed cellular calcium homeostasis in the pathogenesis of AD comes from studies of the effects of Aβ and sAPP on neurons (Fig. 2). During the process of self-aggregation, Aβ generates hydrogen peroxide and hydroxyl radical via chemical reactions requiring Cu²⁺ or Fe²⁺ [26–29]. The production of these reactive oxygen species induces membrane lipid peroxidation which can impair the function of membrane ion-motive ATPases (Na⁺/K⁺- and Ca²⁺-ATPases), and glucose and glutamate transporters, resulting in membrane depolarization and a decrease in cellular ATP levels [30–32]. These effects of Aβ can raise an elevation of basal intracellular calcium levels and greatly enhance calcium overload upon activation of glutamate receptors [30,33]. The ability of antioxidants such as vitamin E, estrogen, and uric acid to prevent impairment of the membrane transporters and to stabilize cellular calcium homeostasis supports a key role for membrane lipid peroxidation in disruption of calcium homeostasis by Aβ [28,34,35]. Studies of APP mutant transgenic mice with Aβ deposits in their brains provide evidence that Aβ disrupts neuronal calcium homeostasis in vivo [36].

Lipid peroxidation, such as that induced by Aβ, disrupts Ca²⁺ homeostasis by a mechanism involving the production of an aldehyde called 4-hydroxy-2,3-nonenal (HNE) which is generated from peroxidized membrane fatty acids [37]. HNE covalently modifies proteins on cysteine, lysine and histidine residues by a process called Michael addition. Such modification of ion-motive ATPases, the neuronal glucose transporter GLUT3 and the astrocyte glutamate transporter GLT-1 impairs their functions [31,32,38]. When cultured neurons are exposed to HNE, a delayed elevation of intracellular calcium levels occurs that precedes, and is required for the delayed apoptotic death of the neurons [37]. Cell may normally detoxify HNE by its binding to glutathione, a cysteine-containing tripeptide which can protect neurons from being killed by Aβ and exposure to iron [37]. Analyses of AD patient tissues suggest that lipid peroxidation is prominent in neurons associated with Aβ deposits, and that levels of HNE are increased in neurons and cerebrospinal fluid of AD patients [39,40]. Interestingly, one of the proteins modified by HNE in AD is tau, and experimental data suggest that covalent modification of tau may promote its cross-linking and hyperphosphorylation [41]. Subtoxic levels of Aβ may impair synaptic functions of neurons. For example, Aβ can impair coupling of muscarinic acetylcholine receptors to the GTP-binding protein Gq11 in cortical neurons, resulting in an attenuated Ca²⁺ response to cholinergic agonists [42]; this effect of Aβ is likely mediated by HNE [43]. The latter effect of Aβ might contribute to cognitive impairment in AD because infusion of HNE or Fe²⁺ into the basal forebrain of adult rats disrupts cholinergic signaling and impairs spatial learning [44].

In addition to oxidative stress-mediated effects of Aβ on neuronal calcium homeostasis, the peptide may exert more direct effects on calcium-regulating systems. For example, whole-cell patch clamp analyses of cultured neurons provided evidence that Aβ can potentiate the activation of voltage-dependent calcium channels [45]. It was also reported that Aβ can block potassium channels [46] which would be expected to promote excitotoxicity. Finally, it has been reported that Aβ can itself form calcium-conducting
Subcellular sites of regulation of calcium homeostasis involved in neuronal plasticity and survival. Cytoplasmic calcium concentrations are regulated by a complex array of calcium channel and transporter proteins in the plasma membrane, ER, and mitochondria. Calcium regulates the expression of a variety of genes and modulates the function of various proteins by regulating protein phosphorylation. Calcium is an important regulator of synaptic plasticity, neurite outgrowth, and cell survival. Alterations in calcium regulation in one or more organelles can impair synaptic function and, if severe and sustained, can kill neurons.

The decreased levels of sAPP that result from altered APP processing may contribute to perturbed neuronal calcium homeostasis in AD. Studies of the mechanisms that regulate sAPP production, and of the biological actions of sAPP, suggest important roles for this secreted protein in regulating synaptic plasticity and cell survival. APP is present at high levels in presynaptic terminals where it is released in response to electrical activity. Whole-cell patch clamp analyses of ion currents in cultured hippocampal neurons have shown that sAPP suppresses neuronal excitability by activating a cGMP-mediated signaling pathway that results in the activation of potassium channels and membrane hyperpolarization [50]. The latter action of sAPP stabilizes cellular Ca\textsuperscript{2+} homeostasis and likely plays a role in the ability of sAPP to protect neurons against excitotoxic injury and Aβ toxicity [28,51]. Neuroprotective effects of sAPP have also been documented in vivo [51]. Analyses of the effects of sAPP on synaptic transmission in hippocampal slices from adult rats have provided evidence that sAPP plays important roles in regulating learning and memory processes [52], a possibility supported by in vivo studies [53]. Collectively, the data suggest that decreased levels of sAPP contribute to the disruption of calcium homeostasis and neuronal degeneration in AD.

3. Presenilins and neuronal calcium homeostasis

PS1 and presenilin 2 (PS2) are integral membrane proteins that are evolutionarily conserved and widely expressed in many different cells types, in the brain, neurons contain particularly high levels of PS1 and PS2. A role for PS1 and PS2 in the pathogenesis of AD was established when it was shown that mutations in PS1 or PS2 are responsible for some cases of early-onset autosomal dominant familial AD (FAD; [54]). PS1 mutations account for many more cases of FAD than do PS2 mutations, with more than 80 different missense mutations in PS1 being documented so far. Studies of the pathogenic mechanism of PS1 mutations have revealed a role for perturbed cellular calcium homeostasis. PS1 is present at particularly high levels in the ER. When FAD mutant forms of PS1 are overexpressed in cultured neural cells, the cells exhibit increased elevations of cytoplasmic calcium levels when stimulated with agonists, such as carbachol and bradykinin, that induce calcium release from the ER [20,21,55,56]. Cells expressing mutant PS1 also exhibit increased calcium responses to thapsigargin, an inhibitor of the ER calcium-ATPase, suggesting that the mutations increase the pool of ER calcium available for release. A consequence of the enhanced calcium release is that cells expressing mutant PS1 are more vulnerable to death induced by a variety of stimuli including trophic factor withdrawal and exposure to oxidative, ischemic, and metabolic insults.
PS1 mutations promote mitochondrial dysfunction, which may be secondary to alterations in calcium homeostasis [57,59]. Studies of hippocampal neurons from PS1 mutant knockin mice have confirmed that PS1 mutations result in an abnormality of ER calcium regulation, and further showed that the abnormality increases the vulnerability of neurons to excitotoxicity and apoptosis [59]. How do PS1 mutations alter the regulation of ER calcium stores? One possibility is that they modify the function of ER calcium-regulating proteins (Fig. 4). Calcium release from ryanodine-sensitive calcium stores is greatly increased in cells expressing mutant PS1 [60]. Levels of ryanodine receptors are increased in cultured cells and in the brains of mice expressing mutant PS1 [60]. In addition to enhancing calcium release from IP3- and ryanodine-sensitive stores, presenilins can alter capacitative calcium entry [61,62]. Immunoprecipitation analyses have provided evidence that PS1 can directly bind to the ryanodine receptor protein [60]. In addition, PS2 interacts with sorcin, a protein that modulates ryanodine receptors [63]. A number of other calcium-related proteins have been reported to interact with presenilins including calsenilin [64,65], ubiquilin [66] and calpains [67] suggesting roles for these proteins in the pathogenesis of AD. A different mechanism by which PS1 mutations may increase the amount of calcium released from the ER is by inducing an increase in the volume of the ER. It has been reported that PS1 mutations can induce or enhance so-called ER stress responses [68], and this could stimulate an increase in the amount of the ER the cell contains, and hence an increase in the size of the ER calcium pool. The alteration in ER calcium release may result in an impairment of capacitative calcium entry through plasma membrane channels [61].

In response to ER stress, cells activate homeostatic and protective responses mediated by, and affecting, calcium homeostasis. For example, when calcium is released from the ER in high amounts a cytoprotective cascade is activated that involves NF-kB [69], a transcription factor known to protect neurons against insults relevant to the pathogenesis of AD including Aβ [70]. We have found that a novel 54 kDa ER membrane protein called homocysteine inducible ER protein (Herp) is present in neurons and is induced by ER stress [71]. Herp stabilizes ER calcium homeostasis and thereby protects neurons against Aβ toxicity and other insults relevant to AD. Interestingly, Herp is cleaved in AD patients suggesting it may participate in the pathogenesis of AD.
by caspase-3 in cells undergoing apoptosis and prevention of this cleavage by mutagenesis of the caspase cleavage site in Herp protects cells against apoptosis [71]. Levels of the caspase cleavage fragment of Herp are increased in the brains of Alzheimer’s patients and mice with amyloid deposits, suggesting a role for Herp in disease pathogenesis. Thus, Herp serves a neuroprotective function under conditions of ER stress by its ability to promote maintenance of cellular calcium homeostasis.

4. Synapses are the primary sites of calcium dysregulation in AD

The following proteins involved in calcium regulation are highly concentrated in pre- and or post-synaptic terminals: voltage-dependent calcium channels (L, N, and T channels), ionotropic glutamate receptors (NMDA, AMPA, and kainate receptors), metabotropic glutamate receptors, ion-motive ATPases (Na+/K+-ATPase and Ca2+-ATPase), ER ryanodine and IP3 receptors, mitochondrial calcium-handling systems (calcium uniporter, ATP-sensitive potassium channels, permeability transition pore). Evidence described above and elsewhere suggests that several of these synaptic calcium-regulating proteins is adversely affected in AD [3,7,9,39,60,72–76]. Degeneration of synapses is believed to occur early in the disease process and to correlate strongly with cognitive deficits [77]. More direct evidence for specific alterations in synaptic calcium regulation in AD comes from studies of synapses in AD patients and animal models relevant to AD.

Studies of synaptosome preparations and of transgenic mice expressing AD-linked APP and/or PS1 mutations have provided considerable evidence that synaptic calcium homeostasis is perturbed in AD, and that synaptic calcium dysregulation is an early and pivotal event in the degeneration of neurons in AD. Exposure of synaptosomes from the adult human hippocampus to Aβ resulted in impairment of the plasma membrane calcium-ATPase, as well as the sodium pump [30]. Exposure of rat cortical synaptosomes to Aβ results in impairment of ion-motive ATPases, and glucose and glutamate transport, as a consequence of membrane lipid peroxidation [78]. Synaptosomes from PS1 mutant transgenic mice exhibit abnormal calcium homeostasis characterized by enhanced depolarization and excitatory amino acid-induced elevations of intracellular calcium [79]. Evidence that altered APP processing can impair synaptic function in vivo comes from studies of APP mutant transgenic mice with amyloid deposits in their hippocampus and cortex. For example, Chapman et al. [80] showed that long-term potentiation of hippocampal synaptic transmission is severely impaired in aged APP mutant transgenic mice compared to age-matched wild-type mice; this occurred despite normal basal synaptic transmission and short-term plasticity. Aβ may directly impair synaptic function in vivo as indicated by memory impairment in rats following injection of Aβ into the hippocampus [81]. It was reported that synaptic plasticity in the hippocampus is altered in PS1 mutant transgenic in a manner consistent with enhanced elevations of presynaptic calcium and glutamate release [82]. In another study of hippocampal synaptic function, it was shown that late afterhyperpolarizations in CA3 pyramidal neurons were larger in PS1 mutant transgenic mice compared to nontransgenic control mice [83]. The latter study further showed that calcium responses to depolarization were larger in hippocampal neurons in the PS1 mutant mice, and that potentiation of CA3-CA1 synapses was increased. Collectively, the emerging data suggest that synapses are a primary site of dysregulation of calcium homeostasis in AD.

5. A note on apolipoprotein E

Apolipoproteins shuttle cholesterol from the blood into cells. Individuals with one or two copies of the E4 isoform of apolipoprotein E are at increased risk for atherosclerotic cardiovascular disease and AD, while those with one or both of the other two isoforms (E2 and E3) are at reduced risk [84]. Hartmann et al. [85] reported that ApoE amplifies calcium signaling in lymphocytes, and [86] showed that a peptide derived from the receptor binding domain of ApoE stimulates calcium influx and release from ER in cultured cortical neurons, a neurotoxic effect. Tolar et al. [87] reported that a 22 kDa N-terminal thrombin-cleavage fragment of ApoE is neurotoxic, and that the mechanism involves calcium influx through NMDA glutamate receptor channels. In other studies, ApoEα were shown to modulate the effects of sAPP on calcium homeostasis in cultured rat hippocampal neurons, they enhanced the ability of sAPP to lower intracellular calcium levels with E3 being more effective than E4 [88]. The latter study provided evidence for direct interaction between sAPP and ApoE that accounted for the modulation of sAPP’s effects on calcium homeostasis.

While the data described above suggest that ApoEα may affect neuronal calcium homeostasis by direct actions on calcium-regulating proteins, other findings suggest the possibility that ApoEα can exert calcium-stabilizing effects indirectly as the result of antioxidant activities of the ApoEα. Miyata and Smith [89] showed that ApoEα can protect cultured cells from cell death induced by either hydrogen peroxide or Aβ, with E2 and E3 being more effective than E4. Based upon the facts that the three different ApoE isoforms differ at key cysteine residues (ApoE2 has two cysteine residues, ApoE3 has one cysteine residue, and ApoE4 has none), and that HNE (which is produced by lipid peroxidation in AD) covalently modifies cysteine residues, we determined whether the antioxidant activities of ApoEα were due to binding of HNE. We found that ApoE2 and 3 bind more HNE than does ApoE4, and that this HNE-binding activity is strongly correlated with the abilities of the different isoforms to protect neurons against the toxicities...
of HNE and Aβ [90]. Because HNE destabilizes neuronal calcium homeostasis by impairing membrane transporters (see above), ApoEs 2 and 3 may stabilize calcium homeostasis by binding and thereby detoxifying HNE. More recently, it was shown that ApoEs can modify nitric oxide production by microglia and neurons in an isoform-specific manner [91], in ways consistent with adverse effects of E4 on cellular calcium homeostasis. Further studies will be required to better understand how ApoEs modulate cellular calcium homeostasis, and how such actions may affect neurodegenerative cascades in AD.

6. Glial cell calcium homeostasis in Alzheimer’s disease

Neurons are not the only cell type in the brain that are affected in AD. Vulnerable brain regions exhibit activated microglial cells and astrocytes, which are often associated with amyloid deposits suggesting that the glial cells respond to Aβ [92]. Several effects of Aβ on cultured astrocytes and microglia have been reported. For example, Aβ and related lipid peroxidation impair glutamate transport [32], while sAPP enhances glutamate transport [93] in astrocytes. Aβ also induces the production of inflammatory cytokines in astrocytes [92]. Aβ is a potent activator of microglia, inducing them to produce cytotoxic substances such as nitric oxide and tumor necrosis factor [92,94,95].

6.1. Astrocytes

Calcium plays important roles in regulating several different functions of astrocytes including mitogenic responses to growth factors such as bradykinin and S100 beta [96,97] and responses to neurotransmitters such as glutamate and ATP [98,99]. Calcium regulates gene expression [100] and release of signaling molecules such as glutamate and ATP in astrocytes [101]. Moreover, intercellular calcium waves in astrocytes may also transfer signals to neurons that modulate their activity and survival [102,103]. Exposure of cultured astrocytes to Aβ alters calcium wave signaling, causing an increase in the amplitude and velocity of evoked calcium waves, and increasing the distance they travel (Fig. 5). Aβ may enhance calcium waves by increasing intracellular calcium levels and increasing the amount of ATP released from the astrocytes. This action of Aβ on the propagation of intercellular calcium signals in astrocytes suggests a possible contribution of altered astrocyte calcium signaling to the pathogenesis of AD.

6.2. Oligodendrocytes

Although the vast majority of research on the cellular and molecular pathogenesis of AD has focused on the degeneration of neurons in gray matter, it has been established that damage to white matter occurs in AD [104,105]. Oligoden-
Fig. 6. Alterations in glia cell calcium homeostasis may contribute to disease pathogenesis in Alzheimer’s disease. Alterations in astrocytes, microglia, and oligodendrocytes have been documented in studies of AD patients and in experimental models of AD. Aβ can induce cell activation and production of inflammatory cytokines in astrocytes and microglia, and can damage and kill oligodendrocytes; perturbed calcium homeostasis contributes to these effects of Aβ. Each type of glial cell expresses APP and presenilins (PSs) and are therefore be subject to adverse effects of altered APP processing and PS mutations on cellular calcium homeostasis.

7. Conclusions and implications for disease prevention and treatment

The identification of mutations in APP and presenilins as the causal factors in some cases of early-onset inherited forms of AD allowed numerous studies in which the mutant genes have been shown to result in a disruption of cellular calcium homeostasis, with synapses being particularly vulnerable to such adverse effects of the mutations. The evidence for the involvement of perturbed cellular calcium homeostasis in AD pathogenesis has led to clinical trials of a few drugs known to stabilize neuronal calcium homeostasis and which demonstrated in vitro and in vivo neuroprotective efficacy in models relevant to AD. AD patients in clinical trials of nimodipine, a blocker of L-type voltage-dependent calcium channels, exhibited modest improvements in some of their symptoms [112]. Memantine, an uncompetitive NMDA receptor antagonist, was reported to be beneficial in the treatment of patients with severe dementia [113]. Such results suggest a potential benefit of drugs that suppress calcium influx. However, these drugs may also compromise the normal functions of neurons that rely on calcium influx. The latter is a particularly important concern in a chronic neurodegenerative disorder such as AD which typically has a course of many years and, therefore, requires continuous treatment with the drug.

Because of the potential side effects of drugs that block specific calcium-regulating proteins, therapeutic strategies based on stimulating endogenous calcium-stabilizing mechanisms may therefore, prove to be more efficacious with fewer side effects. One such approach is to activate neurotrophic and neurogenic signal transduction pathways [114]. Several different neurotrophic factors have been shown to protect neurons against Aβ toxicity and other insults relevant to AD including basic fibroblast growth factor and sAPP [56,115,116]. These and other neurotrophic factors have been shown to stabilize intracellular calcium
levels by modulating the expression of calcium-regulating proteins such as calcium-binding proteins and glutamate receptor proteins [70]. Clinical trials of nerve growth factor in AD patients have been performed, with beneficial effects reported. However, such neurotrophic factors do not readily cross the blood–brain barrier and it is, therefore, necessary to infuse them directly into the brain parenchyma or cerebrospinal fluid. Another approach is to administer therapies that stimulate the production of endogenous neurotrophic factors. In this regard, it has been shown that both mental and physical exercise can stimulate the production of several neurotrophic factors including brain-derived neurotrophic factor (BDNF) and nerve growth factor in brain regions involved in learning and memory processes [117]. Interestingly, neurotrophic factor levels in the brain are also subject to modulation by dietary factors. Most notably, it has been shown that dietary restriction (reduced calorie intake or intermittent fasting) can induce the expression of BDNF in the hippocampus, cortex and striatum of rats and mice [118]. AD may be preventable in many individuals. Individuals with high calorie intakes and elevated homocysteine levels are at increased risk of AD, and studies of animal models of AD suggest that low calorie diets and dietary supplementation with folic acid (which lowers homocysteine levels) can protect neurons against neuronal dysfunction and degeneration [119,120–122]. Data reviewed recently [123,124] suggest that dietary restriction can stabilize neuronal calcium homeostasis and protect neurons against excitotoxicity and apoptosis by a mechanism involving activation of neurotrophic factor signaling and stimulation of production of stress resistance proteins such as heat-shock protein-70 and glucose-regulated protein-78. The latter stress resistance proteins have been shown to stabilize cellular calcium homeostasis [125,126]. By keeping homocysteine levels low, folic acid may prevent DNA damage and protect neurons against calcium-mediated injury. Dietary restriction has been shown to enhance learning and memory during aging [127], and can protect synapses against insults relevant to AD pathogenesis [128] suggesting an ability of this dietary manipulation to enhance synaptic calcium homeostasis. Finally, it has been reported that neurogenesis in the hippocampus and subventricular zone is impaired in experimental models of AD by a mechanism involving perturbed calcium homeostasis [129,130]. Dietary restriction and enriched environments can enhance hippocampal neurogenesis [124] suggesting that stimulation of neurogenesis may be another strategy for preventing and treating AD.

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