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·Review·

Environmental factors in the development and progression of late-onset Alzheimer's disease

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Late-onset Alzheimer's disease (LOAD) is an age-related neurodegenerative disorder characterized by gradual loss of synapses and neurons, but its pathogenesis remains to be clarified. Neurons live in an environment constituted by neurons themselves and glial cells. In this review, we propose that the neuronal degeneration in the AD brain is partially caused by diverse environmental factors. We first discuss various environmental stresses and the corresponding responses at different levels. Then we propose some mechanisms underlying the specific pathological changes, in particular, hypothalamic-pituitary adrenal axis dysfunction at the systemic level; cerebrovascular dysfunction, metal toxicity, glial activation, and Aβ toxicity at the intercellular level; and kinase–phosphatase imbalance and epigenetic modification at the intracellular level. Finally, we discuss the possibility of developing new strategies for the prevention and treatment of LOAD from the perspective of environmental stress. We conclude that environmental factors play a significant role in the development of LOAD through multiple pathological mechanisms.

Keywords: Alzheimer's disease; environmental factors; corticotrophin-releasing factor; cerebrovascular; metal toxicity; glia; astrocyte; microglia; Aβ; kinase; phosphatase; tau; hyperphosphorylation; epigenetic modification; DNA methylation; histone acetylation

Introduction

The most important feature of organisms is their adaptability to external environmental changes by modulating their internal metabolism or external behaviors. But when the environmental variations exceed a certain level, environmental stress, a term originating from ecology, is induced[1]. For example, life-forms under disadvantageous environmental conditions exhibit poor growth and responses different from those under fertile conditions[2]. Excessive environmental stress or abnormal responses to environmental factors can induce morbidity and even death[3, 4]. Human beings are also influenced by numerous natural, psychological, and social factors from birth.

The cerebrovascular system, especially the blood-brain barrier (BBB), plays an essential role in the transport and excretion of environmental factors. Besides, the environment of neurons, constituted by neurons themselves and glial cells[5, 6], markedly impacts their functional status and fate[7, 8]. Thus, environmental factors may participate in aging or aging-related diseases[9, 10], including late-onset Alzheimer's disease (LOAD)[11].

To better understand the relationship between environmental factors and LOAD, we decided to explore LOAD pathophysiology from a new direction in this review. To date, many environmental factors have been proposed as risks of LOAD, including metals[12, 13], air pollution[11, 14], pesticides[15-17], chronic psychological stress[18-20],

starvation[21, 22], hyperthermia/ hypothermia[23-25], and brain trauma[26-28]. However, their intracellular and/or extracellular mechanisms of inducing LOAD are still controversial. Although previous studies have reported many mechanisms to interpret the pathological alterations in LOAD patients[29-31], some intermediate components that link the systemic level with intracellular level are still lacking. Here we propose that dysfunction of the hypothalamic-pituitary adrenal (HPA) axis at the systemic level; cerebrovascular dysfunction, glial activation, metals malmetabolism, and extracellular Aβ toxicity at the intercellular level; and intracellular pathways, including kinase/phosphatase imbalance, epigenetic modifications, and oxidative stress, are the main mechanisms involved in the effects of environmental factors on the pathogenesis of LOAD.

Effects of Environmental Factors on LOAD Pathogenesis at the Systemic Level

Mammals generally respond to environmental stimuli at the whole-individual level through complicated mechanisms, such as the activation of HPA axis and autonomic system[32, 33], to direct and control multiple reflex activities to deal with environmental pressures. At the systemic level, behavioral stress induced by external stimulation is the leading process associated with LOAD.

Kirby and co-workers demonstrated that acute stress increases the proliferation of hippocampal cells, neurogenesis, and the expression of astrocytic fibroblast growth factor 2 (FGF2)[34]. A behavioral study focusing on the memory functions of the hippocampus has also shown that moderate acute stress enhances memory performance[35]. In contrast to acute stress, chronic behavioral stress suppresses cell proliferation and differentiation of new neurons in the adult dentate gyrus[36]. Unpredictable chronic mild stress preferentially reduces cell proliferation and neurogenesis in the ventral hippocampus, and the reductions can be reversed by fluoxetine[37]. Cumulative evidence demonstrates that the release of stress hormones is responsible for the brain changes caused by chronic behavioral stress. Chronically stressed rats show enhanced corticosterone feedback on acute stress-induced HPA activity[38] and the attenuated stress response of adrenocorticotropic hormone (ACTH) after chronic morphine treatment is associated with enhanced sensitivity to glucocorticoids[39]. Kim *et al*. (2008) reported that corticotrophin-releasing factor (CRF) mRNA expression in the hypothalamus and ACTH levels in serum are significantly increased by chronic administration of corticosterone[40]. Some investigators reported similarly increased CRF gene transcription in the paraventricular nucleus, consistent with other reports that chronic stress upregulates CRF mRNA expression[41-43].

Effects of Environmental Factors on LOAD at the Intercellular Level

Abnormality of the cerebrovascular system, especially disruption of the BBB, is an important factor associated with the transport of environmental factors[44]. Recent studies have shown co-morbidity between AD and cerebrovascular disease[45], and that AD is associated with atherosclerosis[46, 47], amyloid angiopathy[48, 49], and cerebral microvascular pathology[50, 51]. Extracelluar Aβ causes inflammation[52, 53], apoptosis[54, 55], oxidative stress[56, 57], and excitotoxicity[56, 58]. Metals are also associated with neuronal malfunction in AD, though the effects of iron, aluminum, zinc, and copper remain inconclusive[12, 59]. Most of these metals induce oxidative stress and increase Aβ accumulation[12, 13]. Surrounding glia may influence neuronal function by secreting inflammatory factors[60-62], participating in the clearance of amyloid and exacerbating Aβ accumulation[63-65].

External factors also influence neuronal micro-environment through multiple pathogenic mechanisms. Air pollution is one of the most common sources of environmental toxins. Since various air pollutants lead to ROS production, and as the human population exposed to air pollution increases, the risk of LOAD increases[66]. In a related study, exposed urbanites displayed differential regulation of apolipoprotein E (APOE) genes and tau hyperphosphorylation with pre-tangle material, while 51% had diffuse Aβ plaques[14]. Correspondently, air pollution accelerates Aβ42 accumulation[67]. Traumatic brain injury (TBI) is recognized as one of the most detrimental environmental risk factors for the later development of cognitive impairment[68, 69]. Repetitive neurotrauma can lead to the development of a progressive form of dementia reminiscent of early onset LOAD[70, 71]. Aβ plaques have also been identified in patients following a single TBI[72, 73], even in children[74]. Similarly, Uryu *et al*. (2002) reported

increased Aβ levels and urine isoprostanes in Tg2576 mice, together with induced cognitive impairments after mild TBI[75]. Anesthesia is another risk factor associated with LOAD. It is linked to cognitive dysfunction and acceleration of senile dementia[76, 77]. The commonly-used inhaled anesthetic sevoflurane induces caspase activation and apoptosis, and also increases the levels of β-site APP-cleaving enzyme (BACE), leading to elevated Aβ levels both in H4-APP cells and mice[78]. Other anesthetics, such as isoflurane[79], isoflurane with hypoxia[80], desflurane with hypoxia[81], and isoflurane with nitrous oxide[82], also alter APP processing and subsequently increase Aβ production.

Effects of Environmental Factors on LOAD at the Intracellular Level

Nutrient deficiency plays a significant role in glucose metabolism dysfunction in LOAD. In a recent review[58], we illustrated thiamine deficiency as an important contributor to the induction of dysfunctional glucose metabolism. Deficiency of folate and vitamin B_{12} also influences neuronal metabolism by inducing hyperhomocysteinemia and decreasing S-adenosylmethionine (SAM) levels. Under conditions of energy deficiency, the balance between kinases and phosphatases, protein aggregation and clearance, as well as oxidative stress and reduction capacity, also tends to be disturbed, which further leads to Aβ accumulation, tau hyperphosphorylation, and neuronal death[58].

Overall, exposure to environmental insults or stressors such as psychological stress[83, 84], environmental toxins[11], hypothermia[24, 25], anesthesia[84, 85], brain trauma and injury[75, 86], heat[87], starvation and glucose hypometabolism[22, 58], can induce tau hyperphosphorylation, and Aβ aggregation and oligomerization, which are tightly linked to LOAD pathogenesis. Here we propose that multiple mechanisms at different levels mediate the pathological roles of environmental factors in LOAD. At the systemic level, HPA axis dysfunction is the main mechanism to induce a LOAD phenotype by behavioral stress[88, 89]. At the intercellular level, cerebrovascular dysfunction, Aβ accumulation[57, 90], glial activation[91-93], and metal toxicity[11-13] are generally responsible for an abnormal microenvironment surrounding neurons, and contribute to their dysfunction. Imbalance between the activities of tau-related kinases and phosphatases induced by environmental stimuli or insults leads to the highly-phosphorylated form of tau protein in LOAD[94, 95]. Furthermore, intracellular epigenetic modification through experience, especially DNA methylation and histone acetylation, also plays a vital role in LOAD[96-98], as discussed in detail below. In all, complicated pathological networks at different levels are correlated with LOAD (Fig. 1).

Environmental Factors in the Development of LOAD

HPA Axis Dysfunction at the Systemic Level

Some studies have shown that behavioral stress promotes the pathological changes in animal models of LOAD. Lee *et al*. (2009) demonstrated that behavioral stress aggravates LOAD pathology through the generation of metabolic oxidative stress and down-regulation of MMP-2, which may be mediated by corticotropin-releasing hormone receptor (CRFR)[100]. Rissman *et al*. (2012) showed that CRFR1 and CRFR double-knockout mice do not show repeated stress-induced alterations in tau-P or solubility, indicating that CRF-induced tau phosphorylation is CRFR1-dependent[19]. Consistently, CRF antagonism inhibits stress-induced Aβ deposition within the cortex of transgenic mice. Kang *et al*. (2007) demonstrated that behavioral stressors rapidly increase interstitial fluid Aβ through neuronal activity, which is mimicked by exogenous CRF administration but not corticosterone[101]. In addition, stress-level glucocorticoid administration exacerbates Aβ accumulation by increasing the levels of APP and β-APP-cleaving enzyme[102]. Glucocorticoids also augment tau accumulation, indicating that this hormone accelerates the development of neurofibrillary tangles (NFTs)[89]. Catecholamines may be also involved in AD phenotype, which is demonstrated by the fact that blockade of β-adrenergic receptors (β-ARs) prevents the release of IL-1β during acute stress, and stimulation of β-ARs induces the release of IL-1β and IL-6[103-105]. By injecting the β2-AR-selective agonist clenbuterol hydrochloride, acute stress-induced Aβ production is enhanced, while injecting the β2-AR-selective antagonist ICI 118,551 reduces Aβ production[105]. All of this evidence suggests that stress hormones are directly related to pathological changes.

Tran *et al*. (2011) found that chronic psychological

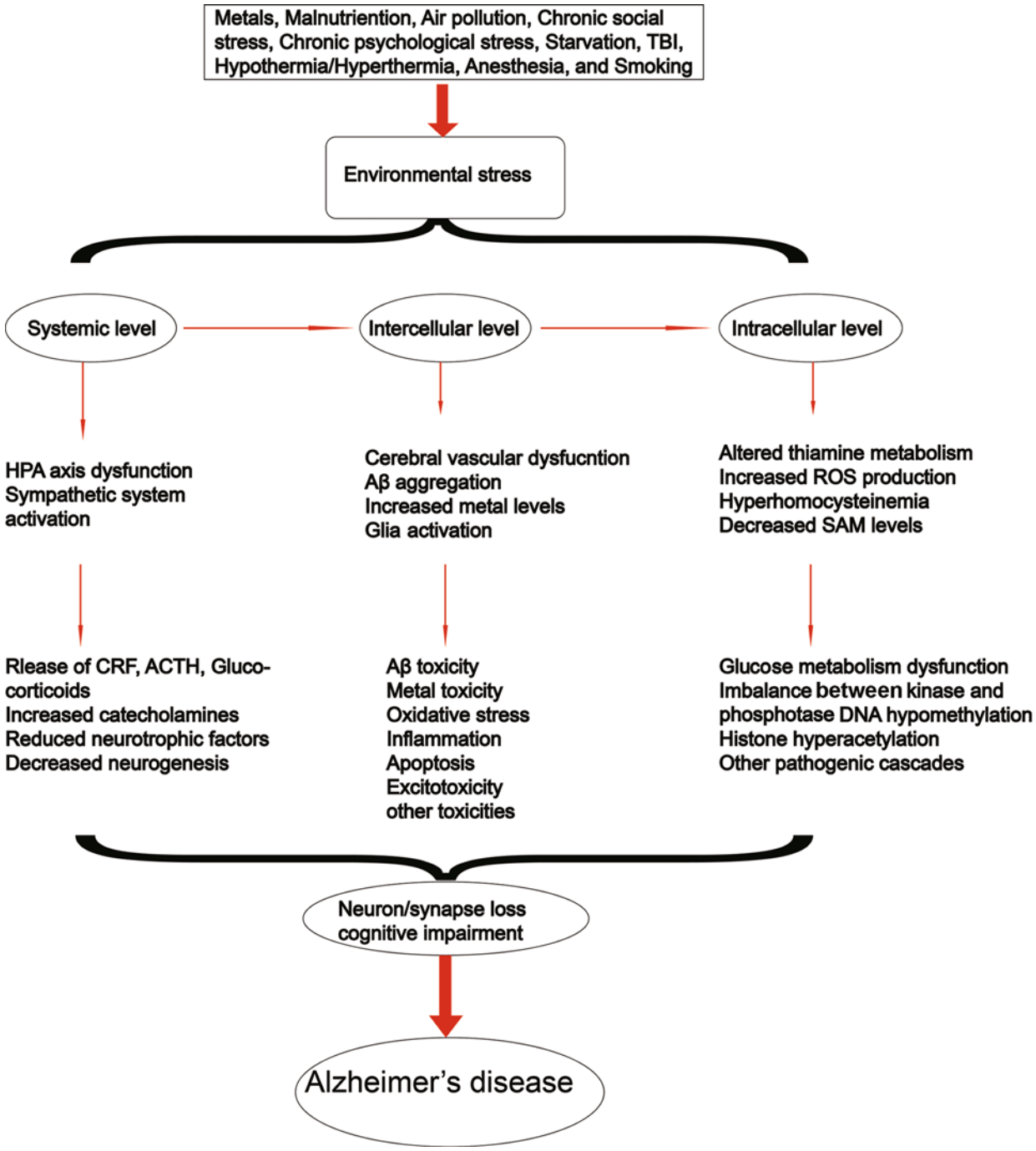

Fig. 1. Environmental factors in the development and progression of late-onset Alzheimer's disease (LOAD). Multiple mechanisms at different levels mediate the pathological roles of environmental factors in LOAD. At the systemic level, HPA axis dysfunction is the main mechanism to induce AD phenotype[42, 88, 89]. At the intercellular level, cerebrovascular dysfunction, Aβ accumulation[57, 90], glial activation[91-93, 99], and metal toxicity[11-13] are responsible for creating an abnormal microenvironment around neurons. At the intracellular level, the imbalance between the activities of tau-related kinases and phosphatases[29, 94, 95], and abnormal epigenetic modification, especially DNA methylation and histone acetylation[96-98], are associated with neuronal dysfunction in LOAD. ACTH, adrenocorticotropic hormone; CRF, corticotrophin-releasing factor; HPA axis, hypothalamic-pituitary adrenal axis; ROS, reactive oxygen species; TBI, traumatic brain injury.

stress leads to lower scores in the radial arm water maze, impairs long-term potentiation (LTP), enhances long-term depression, and increases total CaMKII and calcineurin in a rat AD model[18, 106]. Other investigators also found that chronic stressors, like social isolation, are associated with abnormalities in LTP and dendritic branching, and decreased cued and contextual memory[107]. Hippocampal neurogenesis is also impaired by isolation stress in APPsw (Tg2576) mutant mice[108]. Other chronic stressors, including exposure to predator odor[109], psychosocial stress[110, 111] and restraint [112, 113], as well as direct corticosterone administration[114], all lead to impaired adult neurogenesis in the hippocampus. Even in neurologically normal individuals, excessive adverse stress causes cognitive impairment[115]. Hence, there is no doubt that HPA axis dysfunction induces LOAD pathology and cognitive impairment (Fig. 2).

Environmental Factors at the Intercellular Level

Cerebrovascular dysfunction Recent findings indicate that neurovascular dysfunction contributes to cognitive decline and neurodegeneration in AD. To begin with, the BBB is responsible for the clearance of Aβ through receptors for advanced glycation end products (RAGE) and low-density lipoprotein receptor-related protein (LRP)[44, 116]. Acting as a cell-surface receptor for Aβ[117], RAGE binds monomeric, oligomeric, and aggregated Aβ[118, 119]. RAGE also mediates Aβ-induced neurotoxicity directly by inducing oxidative stress and indirectly by activating microglia[117]. RAGE leads to mitochondrial dysfunction *via* intraneuronal Aβ transport[120]. LRP also transports Aβ *via* the BBB[121, 122]. Reduced LRP levels in brain microvessels are correlated with endogenous Aβ deposition in a chronic hydrocephalus model in rats[123]. In addition, the formation of capillaries by brain capillary endothelial cells is greatly reduced in the Tg2576 mouse model of AD[124], and high concentrations of the β-sheet form of Aβ are anti-angiogenic[125]. Decreased length of brain capillaries in the CA1 region correlates well with increasing dementia rating scores[51]. Zlokovic (2005) proposed that senescence of the neurovascular unit severely reduces the normal responses of neurovascular cells to physiological and pathophysiological stimuli, which in turn may disrupt normal BBB functions[116]. Furthermore, glucose transporters (GLUTs) in the BBB are responsible for the transport of sufficient glucose to astrocytes and then neurons[58]. Reduced GLUTs such as GLUT1 and GLUT3 have been found in AD[126, 127]. Thus BBB dysfunction leads to an abnormal brain energy supply, and hence induces the regional hypometabolism revealed by imaging techniques[58].

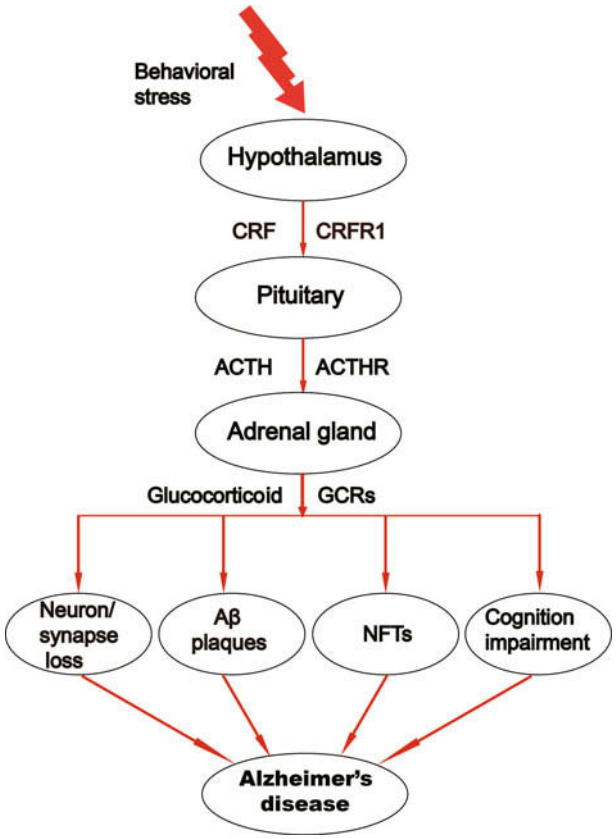

Fig. 2. Hypothalamic-pituitary adrenal axis dysfunction mediates the induction of LOAD-like pathology through behavioral stress. Behavioral stress causes HPA abnormality by producing excessive corticotrophin-releasing factor (CRF), corticotropin, and catecholamines and their receptors, which further leads to LOAD pathology, such as Aβ accumulation and neuronal and synaptic loss. ACTH, adrenocorticotropic hormone; ACTHR, adrenocorticotropic hormone receptor; CRF, corticotrophin-releasing factor; CRFR1, corticotropin-releasing hormone receptor 1; GCRs, glucocorticoid receptors; NFTs, neurofibrillary tangles.

Glial activation Reactive astrocytes have been suggested to participate in the clearance and degradation of Aβ in LOAD. Actually, activated astrocytes located close to senile plaques accumulate in the brains of transgenic APP mice, and astrogliosis parallels the increase of the expression of neprilysin, one of the enzymes responsible for Aβ clearance[128]. Thus it seems that astrocytes are activated to protect neurons from Aβ toxicity. However, it is also possible

that the excessive inflammatory factors or cytokines secreted by astrocytes stimulated by Aβ lead to a malignant microenvironment that further impairs neuronal functions. Besides, astrocytes are responsible for the metabolism of glucose/lactate, glutamate/glutamine, and glutathione precursors/glutathione; when these mechanisms are impaired, neuronal functions are compromised[129].

Apart from astrocyte activation, microglial activation has received much attention and is recognized as an early event in LOAD. Imaging targeted at microglial activation has been explored for early diagnosis of AD. Microglia clusters are located in Aβ deposits in the brains of LOAD patients and APP transgenic mice[53]. In addition, cultured microglia secrete Aβ and catalyze APP in a manner that promotes Aβ deposition[130]. Furthermore, many laboratories have shown that microglia, both *in vivo* and *in vitro*, phagocytose exogenous fibrillar Aβ[114, 115], indicating that microglia participate in Aβ clearance.

CD45 (also known as leukocyte common antigen) is a transmembrane protein tyrosine phosphatase and plays an essential role in modulating immune responses. CD45 is expressed on microglia in the frontal cortex and hippocampus of normal aging subjects, and markedly increases in the regions close to Aβ plaques in LOAD patients and transgenic animal models of LOAD[131, 132]. Wilcock *et al*. (2001) showed that increased CD45 expression is positively correlated with reduced Congo red staining of compact plaques[133]. Zhu *et al*. (2011) found elevation of both cerebral intracellular and extracellular soluble oligomeric Aβ, insoluble Aβ, and the microglial neurotoxic cytokines tumor necrosis factor-α and IL-1β in PSAPP/CD45$^{-/-}$mice compared with CD45-sufficient PSAPP littermates[131]. This further indicates that reduced CD45 activity leads to the accumulation of neurotoxic Aβ oligomers and validates the CD45-mediated microglial clearance of oligomeric Aβ as a novel therapeutic target for LOAD[132].

Aβ deposition Previous evidence has shown that Aβ leads to oxidative stress[57], mitochondrial dysfunction[134, 135], excitotoxicity[136, 137], and inflammation[138, 139]. However, the role of Aβ seems to be a mystery in the field of LOAD pathophysiology, though many mechanisms have been proposed. Studies have shown that Aβ accumulation in mitochondria precedes extracellular amyloid deposition and increases with age in LOAD patients and animal models[140, 141]. Soluble Aβ oligomers also cause neuronal damage or mitochondrial dysfunction by disturbing the functions of the respiratory chain[142] and other mitochondrial components, including cyclophilin D[143], Aβ-binding alcohol dehydrogenase[144], and TOMM40[145]. Most previous studies indicated that Aβ is a negative component in the pathogenesis of LOAD. Nevertheless, some studies found that picomolar or low nanomolar levels of Aβ are neurotrophic or neuroprotective[146] and physiological concentrations of Aβ efficiently increase hippocampal LTP[147]. From our perspective of environmental stress, Aβ tends to be recognized as an abnormal response to environmental stress and also acts as an environmental insult that results in the abnormal interstitial changes surrounding the neurons, which may be also associated with glial abnormalities, including astrocytic and microglial activation. Besides, based on the above discussion, the entire pathogenic pathway induced by environmental stress may contribute to Aβ production and accumulation. Thus, Aβ toxicity would also be the common link among different mechanisms.

Metal toxicity Iron (Fe) accumulation has been demonstrated in cells associated with neuritic plaques in LOAD[148, 149]. Fe regulates α-secretase activity to influence APP cleavage[150]. Besides, congenital Fe overload (hemochromatosis or HFE) has been linked to LOAD[71]. The occurrence of HFE mutations in LOAD indicates that HFE mutation is also a risk factor for LOAD[151, 152]. More importantly, HFE mutations are associated with increased oxidative stress and the progression of disease[153]. Furthermore, the transferrin subtype C2 increases in LOAD patients[154]. The presence of transferrin subtype C2 may have additive effects on the risk of LOAD with APOE ε4 and HFE mutations[154]. The combined data on transferrin subtype C2 and HFE mutation indicate that an Fe metabolism-related genotype may increase the risk of LOAD.

The involvement of aluminum (Al) neurotoxicity in LOAD neurodegeneration is supported by considerable evidence. Compared with normal controls, the Al level is elevated in necropsy and biopsy samples from LOAD brains confirmed by histopathology[155]. Besides, the risk of LOAD is correlated with increased Al levels in drinking water[156, 157]. Evidence also supports that Al participates in the formation of NFTs and neuritic plaques[158-160]. By intracisternal injection of Al phosphate into rabbits, Forbes

et al.(2002) showed that Al causes pathological lesions similar to NFTs[161]. With the same method, Vasudevaraju *et al*. (2008) showed that Al causes apoptosis in neurons[162]. Other laboratory work further showed that Al-induced lesions share biochemical similarities with NFTs in LOAD, especially the presence of tau protein[163, 164]. The role of Al in LOAD pathogenesis remains to be explored; further experiments need to be designed.

A relationship between zinc (Zn) and LOAD has been suggested, and Zn seems to be a key component of amyloid plaques and the cerebral amyloid angiography observed in LOAD[165]. First, Zn is responsible for the aggregation of Aβ. At pH 7.4, Aβ is rapidly aggregated by Zn-induced resistance to cleavage[166]; this differs from the pH range for Fe- and copper (Cu)-induced Aβ aggregation and toxicity. More importantly, Zn participates in the formation of toxic small oligomer intermediates, associated with the condensation of Aβ oligomers on the neuronal surface[167, 168]. Previous evidence appears to indicate that Zn causes synaptic disruption induced by Aβ accumulation. Deshpande *et al*. (2009) have demonstrated that Zn promotes the binding of Aβ to NR2B, an N-methyl-*D*-aspartate receptor subunit that is responsible for the induction of excitotoxicity[169]. By sequestering Zn, Aβ seems to affect the metabotropic ZnR (GPR39) and TkB receptors, resulting in LTP impairment[170]. Moreover, several Zn-dependent metalloproteinases, such as neprilysin, insulin-degrading enzyme, and matrix metalloproteinases, degrade Aβ in the extracellular milieu, which may offer a possible interpretation of the inverse relationship between cerebrospinal fluid (CSF) Zn and Cu levels and CSF Aβ levels found in normal healthy people[171]. Furthermore, Zn induces tau hyperphosphorylation in neuronal cell lines, and intracellular Zn increases in NFT-bearing neurons[172].

It is well known that acute exposure to arsenic impairs brain functions[173, 174]. Exposure to the heavy metal arsenic results in a 4-fold increase in tau phosphorylation at many of the sites that are hyperphosphorylated in paired helical filament tau[175]. Further, tau is a major substrate for the enzymatic activities affected by arsenic. The arsenic-containing compound phenylarsine oxide induces tau phosphorylation within its microtubule-binding domain *in situ* by a staurosporine-sensitive protein kinase in cultured cells[176].

Apart from the above-mentioned metals, Cu is also thought to be involved in LOAD, but it is still unknown whether deficiency or overload occurs. Some studies have shown that Cu deficiency is associated with LOAD, and excessive dietary Cu on a high-cholesterol diet in rabbits and in a mouse model of LOAD induces LOAD-like pathology[177]. Another study also indicated that chronic Cu exposure contributes to LOAD in humans[178]. There is strong evidence that low-dose lead (Pb) exposureive is causally associated with deficits in cognition[179]. Coincidentally, the highest levels of Pb in the brain have been found in the hippocampus and cerebral cortex, areas associated with learning and memory[180]. Recently, Pb-induced impairment of learning and memory has been attributed to over-expression or over-activation of serine/threonine protein phosphatases, suggesting a novel mechanism of Pb neurotoxicity[181]. Further studies are needed to explore the role of metal malmetabolism in AD pathogenesis.

Kinase–Phosphatase Imbalance and Epigenetic Modification at the Intracellular Level

Phosphatase hypoactivity Accumulating studies suggest that an imbalance of kinase-phosphatase is intimately associated with the pathophysiology of LOAD. Previous studies have shown that the brain protein phosphatases (PPs) PP1, PP2A, PP2B, and PP5 dephosphorylate the hyperphosphorylated tau *in vitro*, but PP2C does not dephosphorylate at any of the sites studied[182-184]. Hyperphosphorylated tau in LOAD brain is mainly dephosphorylated by PP2A and PP2B and at a lesser extent by PP1. PP2A is the main phosphatase that regulates tau phosphorylation, accounting for 71% of the total tau activity in the human brain, with PP1, PP5, and PP2B accounting for 11%, 10%, and 7%, respectively[184]. The PP2A and PP5 activity and expression are downregulated in the LOAD brain and this results in aberrant phosphorylation of tau and neurofilament proteins[185, 186]. The enzymatic activity levels of PP2A and PP5 are reduced by 50% and 20%, respectively, in the LOAD brain[187, 188]. A minor reduction in the PP2A methylation rate is related to tau hyperphosphorylation and increased Aβ production[189]. In the LOAD brain, the neocortical levels of the endogenous inhibitors of PP2A, I_1PP2A and I_2PP2A, are significantly increased[190]. In addition, transgenic mice expressing the negative form of the PP2A catalytic subunit show increased tau phosphorylation[191]. These findings imply that a downregulation of tau phosphatases in the LOAD brain

might underlie the abnormal hyperphosphorylation of tau and other neuronal proteins.

Kinase hyperactivity Recent *in vitro* studies have shown that several protein kinases are involved in tau phosphorylation at specific sites[192]. These include proline-directed kinases such as glycogen synthase kinase-3 (GSK-3)[193], cycle-independent kinase 5[192], mitogen-activated protein kinase/extracellular signal regulated-kinases (MAPK/ERK)[194], AMP-activated protein kinase[195], stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK)[196], p-38 kinase (p38)[197], microtubule affinity-regulating kinases (MARKs)[198], cAMP-dependent protein kinase (PKA)[182], Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)[199], tyrosine-specific kinases, and Src family kinases such as c-Abl kinase[200] and Ick[201]. In addition, JNK kinase 1, an upstream activator of JNK/SAPK[202], and mitogen-activated kinase kinase 6, an upstream activator of p38[203], are also activated in LOAD. Based on the literature, GSK-3β, also known as tau protein kinase 1, seems to be the most important enzyme in determining tau phosphorylation status[184].

Tau hyperphosphorylation The hyperphosphorylation of tau is one of the key pathogenic features of LOAD. It has been hypothesized that it is induced by the over-activation of kinase or the inactivation of phosphatase. Thus kinases such as MARKs, PKA, CaMKII, and checkpoint kinase 2, which phosphorylate tau on Ser^{262} *in vitro*[204], or GSK-3β[205, 206], CDK5[207, 208], and other kinases are all responsible for tau hyperphosphorylation. Abnormal interactions between kinase and phosphatase produce an imbalance of phosphorylation and dephosphorylation, which could be the fundamental mechanism for abnormal tau hyperphosphorylation (Fig. 3). Some studies have shown that the disruption of the balance between kinase and phosphatase induces tau hyperphosphorylation. In the study by Leclerc *et al*. (2001), it was proposed that GSK-3β and CDK5 are responsible for most of the abnormal hyperphosphorylation in LOAD, and indirubins from a traditional Chinese herbal formula (Danggui Longhui Wan) inhibit GSK-3β and CDK5/P25 and hence reduce abnormal tau phosphorylation[205]. When the brain is exposed to acidosis, asparaginyl endopeptidase is released from lysosomes into the cytoplasm, which inhibits PP2A and promotes tau hyperphosphorylation, indicating that acidosis triggers tau hyperphosphorylation[209]. Calcyclin-binding

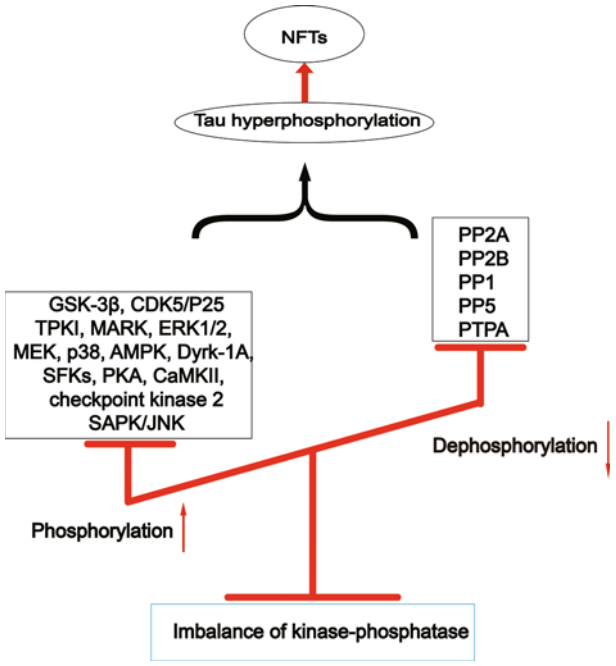

Fig. 3. Imbalance between tau-related kinases and phosphatases causes tau hyperphosphorylation. Hyperphosphorylation of tau is induced by the over-activation of kinases such as GSK-3β and MARK, or the inactivation of phosphatases like PP2A, which further promotes the formation of neurofibrillary tangles.

protein and Siah-1-interacting protein (CacyBP/SIP) play a role in the organization of microtubule[210]. Wasik *et al*. (2013) showed that in LOAD patients, CacyBP/SIP is almost exclusively present in neuronal somata, while it occurs in the somata and processes in control patients. Besides, they found a similar pathogenic distribution of CacyBP/SIP in tau transgenic mice, but not in APP/PS1 mice[210]. Further research is needed to understand the role of abnormal kinases and phosphatases in the development of LOAD.

Epigenetic Modifications Induced by Environmental Stress in LOAD

DNA methylation Because of the diversity of individual genetic backgrounds and life experiences, factors late in life may influence the susceptibility and progression of LOAD through epigenetic modification by DNA methylation or histone acetylation[96, 211, 212]. Based on previous data, it is quite possible that abnormal DNA methylation is induced by deficiency of vitamins B_6, B_{12}, and folic acid, and this may be involved in gene transcription associated

with AD pathology. In the review by Marques *et al*. (2011) it was hypothesized that nutrient deficiency leads to hyperhomocysteinemia and further induces a consequent decrease in the levels of SAM, a key donor of methyl groups in DNA methylation[211]. Thus, low SAM levels could demethylate DNA and result in the activation and overexpression of genes involved in LOAD pathology. A study has shown that the deficiency of folate and vitamin B_{12} in culture medium decreases the SAM levels, up-regulates PSEN1 and BACE, and leads to more Aβ production[213]. PSEN1, APOE, methylenetetrahydrofolate reductase, and DNA methyltransferases (DNMT1), which are all responsible for methylation homeostasis, show significant inter-individual epigenetic variability in the brain and lymphocytes of LOAD patients[182, 214]. One finding suggested that APP promoter hypomethylation could be a risk factor for LOAD. Particularly, Aβ40 accumulation induces abnormal methylation patterns such as global hypomethylation and hypermethylation of specific loci, including the promoter of neprilysin[215]. Infantile exposure to Pb causes increased BACE1 and Sp1 transcription, and their levels parallel the DNMT1 activity, indicating that the toxicity of Pb may be mediated by DNMT1 by increasing Aβ levels through hypomethylation of BACE1 or Sp1[216]. In the TGCRND8 model, Sp1 is also regulated by its methylation pattern in response to metabolic stimuli, such as vitamin B deficiency and SAM administration[214]. Oxidative stress may cause DNA damage and related deficiencies in Ogg1, which is thought to be a significant factor in the process of aging-related diseases such as LOAD[96].

Histone modification Recent studies have shown the association of histone acetylation with the AD pathology, and this seems to be a new field to be explored. One of the most exciting studies to date was led by Li-Huei Tsai and André Fischer. They reported that a drug that promotes histone acetylation improves learning and memory in a mouse model of AD[217]. Besides, specific overexpression of histone deacetylase 2 (HDAC2) in mouse neurons, reduces dendritic spine density, synapse number, synaptic plasticity, and memory formation, but not of HDAC1[217]. On the contrary, HDAC2 knockout results in elevated synapse number and memory facilitation. Correspondently, oral administration of an HDAC inhibitor (HDACi)[218] to the 3×Tg-LOAD mouse model clearly prevents cognitive deficits and reduces tau hyperphosphorylation[219]. Consistent with this study, treatment with the HDACi sodium 4-phenylbutyrate for 5 weeks also reverses the memory impairment and improves spatial learning in a transgenic mouse model (Tg2576) of LOAD[220]. Environmental enrichment increases histone acetylation and furthermore enables the rescue of impaired learning and memory in another mouse model of LOAD[217]. In a similar study, the HDACi sodium butyrate helps with the maintenance and recovery of long-term memory in the same model[217, 221]. Trichostatin A, another HDACi, also rescues the memory defects and hippocampal synaptic dysfunction in APP/PS1 mice, as well as reducing tau hyperphosphorylation, but does not disrupt the interaction between HDAC6 and tau[222]. By quantification with targeted proteomics, Zhang *et al*. (2012) showed that histone acetylation is significantly lower in the LOAD temporal lobe than in aged controls[223]. Overall, the role of histone acetylation is still an area to be explored, and further studies are needed.

New Perspectives on the Management of LOAD

As described in our review of glucose metabolism in LOAD[58], previous studies seem to have led to a frustrating impasse in LOAD research. Considering that most studies have long been focused on the two pathological hallmarks, their related mechanisms and consequences, we argue that it is time to understand the disease from an ecological perspective, using the concept of environmental stress. In this review, we admit that the typical pathological changes play a significant role in understanding LOAD; however, we tend to focus on the precedents of the pathology, and emphasize environmental risk factors and their pathological pathways in LOAD. This new orientation changes the concepts underlying LOAD management, such that early prevention of environmental risk factors and blocking the intermediate pathological pathways induced by environmental stress are the most attractive treatment. Based on this concept, we argue that avoidance or reduction of exposure to environmental factors is the first step in LOAD prevention and treatment. Metals, nutrients, air pollution, pesticides, and chronic psychological stress can all be controlled by individual or social measures. Though there is no confirmed evidence to support the sufficiency of AD prevetion from environmental factors, this seems to be a practical and effective mean of reducing

the occurrence or initiation of LOAD. Besides, blocking the intermediate pathological pathways based on the mechanisms proposed here is a potential approach to prevent the initiation and progression of the disease. By modulating the HPA axis, repairing the cerebrovascular system, balancing the activities of phosphatases and kinases, reducing metal exposure, regulating DNA methylation or histone acetylation, inhibiting inflammatory factors, and antagonizing Aβ toxicity, the initial pathological cascades may be blocked and LOAD would not occur. However, further studies are required to test the efficacy of these new mechanisms as LOAD research progresses.

Conclusions

Most previous studies have focused on the mechanisms and consequences of the internal pathological changes occurring in neurons in LOAD. In this review, we explore a new field based on the concept of environmental stress. We conclude that environmental stress may produce a microenvironment that induces neuronal dysfunction in LOAD *via* multiple pathological mechanisms, including HPA axis dysfunction, cerebrovascular dysfunction, imbalance of kinases and phosphatases, metal toxicity, epigenetic modification, glial activation, and Aβ toxicity. This perspective of environmental stress may shed new light on understanding the etiology, pathophysiology, prevention, and treatment of LOAD.

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