Ageing Research Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Metal ions influx is a double edged sword for the pathogenesis of Alzheimer's disease

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ARTICLE INFO

Article history:
Received 25 June 2016
Received in revised form 8 September 2016
Accepted 17 October 2016
Available online xxx

Keywords:
Metal ions
Oxidative stress
Synaptic plasticity
Neurotoxicity
Autophagy
Apoptosis
Cognitive decline
Alzheimer's disease

ABSTRACT

Alzheimer's disease (AD) is a common form of dementia in aged people, which is defined by two pathological characteristics: β-amyloid protein (Aβ) deposition and tau hyperphosphorylation. Although the mechanisms of AD development are still being debated, a series of evidence supports the idea that metals, such as copper, iron, zinc, magnesium and aluminium, are involved in the pathogenesis of the disease. In particular, the processes of Aβ deposition in senile plaques (SP) and the inclusion of phosphorylated tau in neurofibrillary tangles (NFTs) are markedly influenced by alterations in the homeostasis of the aforementioned metal ions. Moreover, the mechanisms of oxidative stress, synaptic plasticity, neurotoxicity, autophagy and apoptosis mediate the effects of metal ions-induced the aggregation state of Aβ and phosphorylated tau on AD development. More importantly, imbalance of these mechanisms finally caused cognitive decline in different experiment models. Collectively, reconstructing the signaling network that regulates AD progression by metal ions may provide novel insights for developing chelators specific for metal ions to combat AD.

Contents

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http://dx.doi.org/10.1016/j.arr.2016.10.003
1568-1637/

1. Introduction

Alzheimer's disease (AD) is a common form of dementia that is characterized by a gradual loss of neuronal function. Epidemiological investigations have demonstrated that the number of AD patients in the US was 4.5 million in 2000 and that the risk of AD doubles in people over 65 years old. AD is an incurable disease, and its pathological hallmarks include amyloid β-protein (Aβ) deposition in senile plaques (SPs) and phosphorylated tau in neurofibrillary tangles (NFTs). Although genetic studies have indicated the relevance of Aβ and tau in the biochemistry of this disease (Goate, 2006), knowledge regarding the mechanisms of Aβ accumulation and tau hyperphosphorylation is quite limited.

Because the concept of an association between protein aggregation and AD has been established, the stimulators and mechanisms of protein misfolding and aggregation need to be summarized. Recently, the mechanism of abnormal metal metabolism has generated increased interest among AD investigators. For example, bioactive metals, such as iron (Fe), copper (Cu), and manganese (Mn), have been shown to play an important role in oxidative stress, particularly in mitochondria, as well as in protein misfolding and aggregation, ultimately leading to AD (Liu et al., 2006; Zatta et al., 2003). In addition, the role of metal dyshomeostasis in the pathogenesis of AD has been strongly corroborated by several key reports that have indicated that metal ion homeostasis restoration in the brains of both AD patients and AD transgenic mice can prevent Aβ aggregation, dissolve SPs and delay AD-related cognitive impairment (Adlard et al., 2008; Cherny et al., 2001; Opazo et al., 2003). Consistent with this trend, many studies have addressed the link between metal ion metabolism, Aβ deposition and tau phosphorylation.

Although biometals have been reported to be cofactors for AD progression, the mechanisms underlying this process remain unclear. In light of key roles of excessive Aβ deposition and tau hyperphosphorylation in the pathogenesis of AD, we reviewed the mechanisms that potentially contribute to AD development in metal ion-dependent processes, including oxidative stress, synaptic plasticity, neurotoxicity, autophagy and apoptosis. Specifically, this review is intended to provide a greater understanding of the pathogenesis of AD by examining the current data regarding the effects of metals, including zinc, iron, copper, aluminium, magnesium and calcium, on Aβ deposition and tau phosphorylation, as well as the mechanisms of these effects. Finally, potential therapeutic strategies that are based on these mechanisms are addressed.

1.1. The homeostasis of metal ions is modulated by different transporters that are involved in the effects of metal ions on AD development

In light of excess metal ions are able to aggravate AD, questions are easily raised regarding whether some specific molecules are involved in the transportation of metal ions or regulate the homeostasis of metal ions. To this end, we summarize the transporters of biometals, which may be responsible for the observed biological functions during AD development. As shown in Table 1, the Zrt-, Irt-like protein (ZIP) members (ZIP1-5 and 7–15) are thought to be the major uptake mechanism for Zn^{2+}. NMDAR, voltage-gated L-type Ca^{2+} (Koh and Choi, 1994), and Ca^{2+}-permeable AMPA/kainite channels (Jia et al., 2002) and Na^{+}/Zn^{2+} exchangers (Cheng and Reynolds, 1998) are also responsible for Zn^{2+} uptake. However, the transportation of Zn^{2+} is not unidirectional. Intracellular Zn^{2+} is sequestered or exported by the ZnT protein family. The ZnT family has eight members that are expressed in different cell types of the CNS and that are responsible for Zn^{2+} exportation (Table 1). Similar to Zn^{2+}, Cu^{2+} also has its own specific transporters. For example, ATP7A mediates Cu^{2+} influx into the Golgi apparatus, which allows copper absorption and distribution into other organs (Nyasae et al., 2007). Similar to ATP7A, ATP7B is a p-type ATPase that transports Cu^{2+} into the Golgi apparatus. However, ATP7B is predominantly expressed in the liver but not in other organs (Schilsky et al., 2000). Apart from these canonical Cu^{2+} transporters, CtR1 and NMDAR are also involved in Cu^{2+} penetration into cells (Ding et al., 2013; Schlief et al., 2006; Shemer et al., 2006). DMT1 is the only molecule with a known role in Fe^{2+} transportation into the cytosol (Ayton et al., 2013). In contrast, the mechanisms for Al^{3+}, Mg^{2+} and Ca^{2+} transport remain thoroughly unclear, although several transporters have been identified (Table 1). Considering the roles of metal ions in accelerating AD *via* their specific transporters, several reports have demonstrated the efficacy of metal ion chelators in improving AD. Although we could not negate the effects of chelators on ameliorating the symptoms of AD, the specificity of chelators has been questioned. For instances, clioquinol can chelate several metal ions, including Zn^{2+}, Cu^{2+} and Fe^{2+} (Table 1). Similar to clioquinol, desferrioxamine (DFO) also has multiple functions in chelating Cu^{2+}, Fe^{3+} and Al^{3+} (Ayton et al., 2013). Even though non-specificity of chelators, different groups have obtained positive therapeutic activity against AD. For example, metal chelators have shown the potential efficacy on treating AD via regulating the homeostasis of Cu^{2+} and Fe^{2+} in AD patients (Robert et al., 2015). In addition, a case has been reported that cliquinol treatment changed the concentration of p-tau and the ratio of $A\beta_{1\text{-}42}/A\beta_{1\text{-}40}$ in the CSF of patients with early onset of AD (Ibach et al., 2005). DFO was also implicated as effective agents for treating AD by inhibiting the phosphorylation and aggregation of tau (Savory et al., 1998). Nevertheless, the efficacy of these chelators need extensive clinical trials for future application.

1.2. Metal ions induce Aβ deposition and tau hyperphosphorylation, which result in the formation of amyloid plaques or neurofibrillary tangles during AD development

1.2.1. Zn^{2+}

In view of critical roles of Aβ deposition and tau hyperphosphorylation in AD development, we will next summarize the effects of metal ions influx on Aβ and tau procession. Bush et al. (Bush et al., 1993, 1994a,b,c; Damante et al., 2009) have reported that Zn^{2+} not only is responsible for APP processing but also can bind to Aβ, which results in Aβ deposition. Indeed, Zn^{2+} may also interfere with APP processing, which results in the abnormal cleavage of APP and Aβ deposits. For instance, 1) ADAM-10 requires zinc binding for proteolysis (Lammich et al., 1999), 2) zinc increases the expression of presenilin 1 (PS1) (Park et al., 2001), 3) zinc inhibits the activity of the γ-secretase complex (Hoke et al., 2005), and 4) zinc binding can protect Aβ from MMP degradation (Crouch et al., 2009) by masking the proteolytic cleavage sites (Bush et al., 1994b). In addition to Aβ deposition, Zn^{2+} treatment increases tau phosphorylation, which prompts NFT formation (Boom et al., 2009; Mo et al., 2009). Additionally, NMDAR, GABAR, GSK3b, PKB, ERK1/2, c-Jun and adenylate cyclase have been reported to be involved in Aβ deposition and

Please cite this article in press as: Wang, P., Wang, Z.-Y., Metal ions influx is a double edged sword for the pathogenesis of Alzheimer's disease. Ageing Res. Rev. (2016), http://dx.doi.org/10.1016/j.arr.2016.10.003