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Iron dysregulation in Alzheimer's disease: Multimodal brain permeable iron chelating drugs, possessing neuroprotective-neurorescue and amyloid precursor protein-processing regulatory activities as therapeutic agents

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Abstract

Considering the multi-etiological character of Alzheimer's disease (AD), the current pharmacological approaches using drugs oriented towards a single molecular target possess limited ability to modify the course of the disease and thus, offer a partial benefit to the patient. In line with this concept, novel strategies include the use of a cocktail of several drugs and/or the development of a single molecule, possessing two or more active neuroprotective-neurorescue moieties that simultaneously manipulate multiple targets involved in AD pathology. A consistent observation in AD is a dysregulation of metal ions (Fe^{2+}, Cu^{2+} and Zn^{2+}) homeostasis and consequential induction of oxidative stress, associated with beta-amyloid aggregation and neurite plaque formation. In particular, iron has been demonstrated to modulate the Alzheimer's amyloid precursor holo-protein expression by a pathway similar to that of ferritin L-and H-mRNA translation through iron-responsive elements in their 5′UTRs. This review will discuss two separate scenarios concerning multiple therapy targets in AD, sharing in common the implementation of iron chelation activity: (i) novel multimodal brain-permeable iron chelating drugs, possessing neuroprotective-neurorescue and amyloid precursor protein-processing regulatory activities; (ii) natural plant polyphenols (flavonoids), such as green tea epigallocatechin gallate (EGCG) and curcumin, reported to have access to the brain and to possess multifunctional activities, such as metal chelation-radical scavenging, anti-inflammation and neuroprotection.

Keywords: Alzheimer's disease; Aβ-peptide; Iron homeostasis; APP mRNA; Multi-functional drugs; Iron-chelator

Contents

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; Aβ, beta-amyloid peptide; β-CTF, beta-C-terminal fragment; EGCG, epigallocatechin gallate; DFO, desferrioxamine; ERK1/2, extracellular signal-regulated kinases 1 and 2; GAP-43, growth-associated protein-43; HFE, haemochromatosis; HO-1, heme oxygenase; HIF, hypoxia-inducible factor; IREG-1, iron regulated transporter protein-1; IRP, iron regulatory protein; NFT, neurofibrillary tangles; PHFτ, hyperphosphorylated τ; OS, oxidative stress; PD, Parkinson's disease; PKC, protein kinase C; sAPP α, soluble APPα; ROS, reactive oxygen species

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1. Introduction

Alzheimer's disease (AD) is clinically characterized by a progressive loss of cognitive abilities and dementia, being closely related to the degree of neuronal and synaptic loss (Hardy, 1997; Mattson, 1997; Selkoe, 1996). The main key features of the disease are the involvement of senile neuritic plaques (extracellular insoluble β-amyloid peptide (Aβ) aggregates) and neurofibrillary tangles (NFT, intracellular lesions consisting of paired helical filaments formed of hyperphosphorylated cytoskeletal protein τ,) (Hardy and Selkoe, 2002; Iwata et al., 2000; Jellinger and Bancher, 1998; Masters et al., 1985; Selkoe, 2000; Sivaprakasam, 2006; Younkin, 1995). In the past decade, a significant body of evidence has pointed to the "amyloid cascade" event as the major causative factor in AD, with Aβ providing the initial insult. Aβ is a cleavage product of a larger protein named the amyloid beta precursor protein (APP) and is generated by the combined actions of the proteolytic enzymes β- and γ-secretases, a process that occurs normally under physiological conditions (Hardy and Allsop, 1991; Hardy and Higgins, 1992; Selkoe, 1991). Aβ spontaneously self-aggregates in the presence of divalent metals (Fe^{2+}, Cu^{2+}, Zn^{2+}) into neurotoxic amyloid fibrils in the neocortex (Atwood et al., 2003; Bush, 2003). In this respect, it is accepted that in AD and other neurodegenerative diseases, including Parkinson's disease (PD), Huntington's chorea, Friedreich's ataxia, amyotrophic lateral sclerosis (ALS), aceruloplasminemia and neurodegeneration with brain iron accumulation Type 1 (NBIA1), iron is accumulated in specific brain regions of the pathology, in a cell- and time-specific manner (Barnham et al., 2004; Doraiswamy and Finefrock, 2004; Zecca et al., 2004). Given its essentiality in multitude metabolic processes, it is not surprising that iron is sophisticatedly regulated, and that its dysregulation results in detrimental consequences for neuronal function.

Additional neuropathologies in AD include increased expression of apoptotic protein features (Caricasole et al., 2003; Tamagno et al., 2003), impaired ubiquitin-proteasome system (Hol et al., 2005; Song and Jung, 2004), and oxidative stress (OS) (Moreira et al., 2005; Smith et al., 2000), as well as cholinergic, dopaminergic and serotonergic dysfunctions (Jellinger, 2006). Thus, AD is considered poly-etiological in origin, where a complex set of multifactorial reactions act independently or cooperatively, leading eventually to the demise of neurons. This has led to an emerging concept of designing drug ligands that would modulate multiple targets identified for AD.

This review will focus on two separate scenarios concerning multi-drug therapy that share in common the implementation of iron chelating activity: (i) the use of novel brain penetrating bi-/multi-functional iron chelator-neuroprotective compounds, and (ii) the potential of natural, non-toxic plant-derived polyphenols, reported to possess potent transitional metal (iron and copper) chelating/radical scavenging activities.

2. Iron and AD

Iron is one of the most essential transition metals involved in the formation of oxygen-free radicals, owing to its interaction with hydrogen peroxide through Fenton chemistry. Free radical-related OS causes molecular damage that can lead to critical failure of biological functions and ultimately cell death (Halliwell, 2001; Sayre et al., 2001). It has become apparent that iron progressively accumulates in the brain with age, as well as in the affected brain areas of neurodegenerative disorders. (Bartzokis et al., 2004; Zecca et al., 2004). Analysis of AD brains indicates iron accumulation within specific brain regions displaying selective vulnerability to neurodegeneration, such as the hippocampus and cerebral cortex (Lovell et al., 1998; Pinero et al., 2000; Pinero et al., 2001). Using an *in situ* iron detection method, Sayre and colleagues (Sayre et al., 2000; Sayre et al., 1999) found redox-active iron associated with both NFT and senile plaques. More recently, non-invasive MRI in living APP transgenic mice showed association of iron with neurite plaques (Vanhoutte et al., 2005). Moreover, raman spectroscopy and micro-particle-induced X-ray (μ-XRF) emission studies revealed an abnormal enrichment of biometals (Fe^{2+} Cu^{2+} and Zu^{2+}), associated with insoluble Aβ amyloid plaques from post-mortem AD brains (Lovell et al., 1998) and purified senile plaque cores (Liu et al., 2006; Lovell et al., 1998). High levels of iron have also been reported in the amyloid plaques of the Tg2576 mouse model for AD, resembling those seen in the brains of AD patients (Smith et al., 1998a). In addition to the accumulation of iron in senile plaques, it was reported that the amount of iron present in AD neuropil doubles that found in the neuropil of non-demented brains (Lovell et al., 1998). Further studies have suggested that accumulated iron supports the AD pathology as a possible source of OS-dependent reactive oxygen radicals, demonstrating that neurons in AD brains experience high oxidative load (Casadesus et al., 2004; Castellani et al., 2004; Honda et al., 2004; Moreira et al., 2005). Post-mortem analysis of Alzheimer patient brains has revealed activation of two enzymatic indicators of cellular OS: heme oxygenase (HO-1) (Takeda et al., 2000) and NADPH oxidase (Shimohama et al., 2000). Also, HO-1 was greatly enhanced in neurons and astrocytes of the hippocampus and cerebral cortex of Alzheimer subjects, co-localizing to senile plaques and NFT (Schipper, 2000). A recent study reported that ribosomal RNA provided a binding site for