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Review

Significance of metallothioneins in aging brain

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ABSTRACT

Aging is an inevitable biological process, associated with gradual and spontaneous biochemical and physiological changes, and increased susceptibility to diseases. Chronic inflammation and oxidative stress are hallmarks of aging. Metallothioneins (MTs) are low molecular weight, zinc-binding, anti-inflammatory, and antioxidant proteins that provide neuroprotection in the aging brain through zinc-mediated transcriptional regulation of genes involved in cell growth, proliferation, and differentiation. In addition to Zn^{2+} homeostasis, antioxidant role of MTs is routed through –SH moieties on cysteine residues. MTs are induced in aging brain as a defensive mechanism to attenuate oxidative and nitrative stress implicated in broadly classified neurodegenerative α-synucleinopathies. In addition, MTs as free radical scavengers inhibit Charnoly body (CB) formation to provide mitochondrial neuroprotection in the aging brain. In general, MT-1 and MT-2 induce cell growth and differentiation, whereas MT-3 is a growth inhibitory factor, which is reduced in Alzheimer's disease. MTs are down-regulated in homozygous weaver (wv/wv) mice exhibiting progressive neurodegeneration, early aging, morbidity, and mortality. These neurodegenerative changes are attenuated in MTs over-expressing wv/wv mice, suggesting the neuroprotective role of MTs in aging. This report provides recent knowledge regarding the therapeutic potential of MTs in neurodegenerative disorders of aging such as Parkinson's disease and Alzheimer's disease.

Contents

1. Introduction

Aging is a major risk factor for neurodegenerative disorders, including cerebrovascular disease, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS: Lou Gehrig's disease), multiple sclerosis (MS), transmissible spongiform encephalopathy, and cancer (Mocchegiani et al., 2000; Niccoli and Partridge, 2012). Aging is accompanied with structural, chemical, functional, neuropsychological, and genetic changes, with increased susceptibility to diseases and cognitive impairments.

Abbreviations: AD, Alzheimer's disease; GFP, green-fluorescence protein; H_2O_2, hydrogen peroxide; 6-OH-DA, 6-hydroxy dopamine; MT, metallothionien; MT_{dko}, metallothionein double knock out; MT_{trans}, metallothionein transgenic; α-Syn-MT_{tko}Mice, α-synuclein-MTs triple knockout mice; wv/wv-MTs Mice, MTs over-expressing weaver mice; MicroPET, micro-positron emission tomography; RhO_{mgko}, mitochondrial genome knock out; SIN-1, 3-morpholinosydnonimine; MPTP, 1, methyl 4-phenyl, 1,2,3,6, tetrahydropyridine; MPP^+, 1-methyl, 4-phenyl, pyridinium ion; NO, nitric oxide; NOS, nitric oxide synthase; PD, Parkinson's disease; PNs, Parkinsonian neurotoxins; $ONOO^-$, peroxynitrite ion; ROS, reactive oxygen species; SAGE, serial analysis of gene expression; TNF-α, tumor necrosis factor-α.

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Alterations in inflammatory/immune response and antioxidant depletion lead to loss of mobility and agility in aging (Mocchegiani et al., 2010). The aging can be delayed by preventing loss of neurons and brain plasticity, thinning of cortex, neuronal morphology, neurofibrillary tangles, oxidative stress, 8-OH, 2dG accumulation, DNA damage, reduction in telomer length, reductions in glutamate, dopamine, and 5-HT; their receptors and transporters (Mattson and Magnus, 2006).

The primary objective of neurochemical research is to investigate various aspects of aging brain, and develop novel therapeutic strategies to preserve brain compensatory mechanisms to prevent the onset of neurodegenerative diseases (Mattson, 2009). Most importantly, metal-ion dyshomeostasis plays a crucial role in neurodegenerative diseases of aging (Bonda et al., 2011). MTs are implicated in neurodegenerative diseases such as: Parkinson's diases (PD), Alzheimer's disease (AD), prion disease, brain trauma, brain ischemia, and psychiatric diseases (Hozumi, 2013). MT induction in cell therapy may provide protection by serving as antioxidant, anti-inflammatory, antiapoptotic agents, and by augmenting Zn^{2+}-mediated transcriptional regulation of genes involved in growth, cell proliferation, and differentiation (Sharma et al., 2013a). Furthermore, MTs inhibit Charnoly body (CB) formation by serving as free radical scavengers (Sharma et al., 2013b). Hence it is important to elucidate the molecular mechanisms of MTs in cell signaling, neurotransmission, protein transport and storage in the aging brain.

In general, MTs sequester and disperse metal ions, participate in the regulation of metalloproteins, particularly Zn^{2+}-dependent transcription factors; and protection from ROS, ionizing radiation, anticancer drugs, mutagens, and metals. Aschner et al. (2006) provided a brief review on various MT isoforms, their structure and abundance in the brain, their ability to potentiate or attenuate neurodegenerative diseases, with special emphasis on the etiology of AD. In this review, we have highlighted most recent findings from our and other labs on MTs-mediated neuroprotection in neurodegenerative disorders of aging, such as PD and AD.

1.1. Molecular biology of MTs

MTs constitute a superfamily of highly conserved, low molecular weight polypeptides; characterized by high contents of cysteine and metal ions, and were discovered >50 years ago. MT isoforms were discovered for the first time in our labs in the rat brain (Itoh et al., 1983). MTs exist ubiquitously in almost all forms of life (Kägi et al., 1993; Vasak and Kägi, 1994) and occur in bacteria, fungi, plants, and eukaryotes (Hidalgo et al., 2001; Aschner and West, 2005). The molecular weight of MTs is 6–7 kDa, with 60+ amino acid residues (20 cysteines), and synthesized primarily in the liver and kidneys. The synthesis of MTs depends on the bioavailability of dietary Zn^{2+}, Cu^{2+}, Se^{2+}, and amino acids, histidine and cysteine. MTs bind Zn^{2+}, Cu^{2+}, regulate metal ion metabolism, detoxify Cd^{2+}, Ag^{+}, Cu^{2+}, Hg^{+}, and protect cells against ROS, and alkylating agents (Nordberg, 1998). MTs are abundant in fibrous and protoplasmic astrocytes in the CNS (Aschner, 1996). MTs maintain the low intracellular concentration of essential metals, regulate transcription, replication, protein synthesis, metabolism, and Zn^{2+}-dependent molecular events. Higher organisms contain genes, which encode four major isoforms of MTs: MT-1, MT-2, MT-3, and MT-4 (Davis and Cousins (2000). All mammalian MTs are monomeric proteins, containing two metal-thiolate clusters (Vašák and Meloni, 2011). MT-1 and MT-2, as widely expressed isoforms are regulated in all mammalian tissues and are induced by various stimuli, including metals, drugs, and inflammatory mediators. The MT-3 gene is differentially regulated as compared to MT-1 and MT-2 and its transcription is non-metal-induced (Palmiter et al., 1992). MT-3 and MT-4 are tissue-specific (Fowler et al., 1987; Kägi et al., 1993). MT-3 is brain-specific and is expressed primarily in the Zn^{2+}-containing neurons of the hippocampus, amygdala, and cerebral cortex (Nordberg, 1998). MT-4 is localized primarily in the squamous cell epithelium. MT-3 mRNA was detected in Zn^{2+}-enriched neurons (Masters et al., 1994) and in astrocytes (Hozumi et al., 1999; Hozumi et al., 1996). MT-3 is known as a growth inhibitory factor (GIF) and inhibits the survival and neurite formation of the cultured neurons in vitro (Uchida et al., 1991; Zheng, 1998). MT-3 mRNA and protein are up-regulated following brain injury (Hozumi et al., 1999) and down-regulated in AD (Uchida et al., 1991; Yu et al., 2001; Colangelo et al., 2002), suggesting its role in CNS repair (Hozumi et al., 1999; Hozumi et al., 1988). MT-3 prevents neuronal sprouting in vitro and MT-3 knockout mice are highly sensitive to Kainate-induced seizures; suggesting its involvement in Zn^{2+} regulation during stimulation of glutamatergic neurotransmission (Erickson et al., 1997). The down-regulation of MT-3 is associated with the neuropathology of AD (Uchida et al., 1991; Yu et al., 2001; Colangelo et al., 2002). The growth-inhibitory ability of MT-3 is related to its ·OH radical scavenging property (Uchida et al., 2002).

MTs synthesis is induced in the reactive glia in response to pathogen or disorder in the CNS. MTs are involved in host-defense reactions and protection during neuropathological conditions to prevent inflammation and secondary tissue damage (oxidative stress, neurodegeneration, and apoptosis) to promote repair and regeneration (angiogenesis, neurogenesis, neuronal sprouting, and tissue remodeling). Recent studies have distinguished receptor-mediated actions from those arising from zinc binding ability and antioxidant properties of MTs (Cecília et al., 2012). MTs can regulate metal-containing transcription factors, zinc-finger proteins, and p-53. MTs protect neurons by signal transduction through the low-density lipoprotein (LDL) family of receptors involving lipoprotein receptor-1 (LRP1) and megalin (LRP2) in order to regulate lipid metabolism (Pedersen et al., 2009). Wyman et al. (1999) described Zn^{2+}-inducible MTs promoter for the expression of nerve growth factor (NGF) in rodent brain transplants and suggested that these promoters may provide regulated gene expression for therapeutic strategies in the neurodegenerative disorders of aging.

1.2. Induction and translocation of MTs

It is now established that MTs are induced in response to environmental neurotoxicity, infectious diseases, drug resistant malignancies, and nutritional stress. The induction and translocation of MTs in the nucleus is to protect from DNA damage, apoptosis, and regulate gene transcription during certain stages of the DNA cell cycle (Cherian and Apostolova, 2000). MTs may react directly with $ONOO^{-}$ ions to prevent DNA and lipoprotein damage (Cai et al., 2001). Zn^{2+}- induced MTs protect against DNA damage by free radicals. MT-3 protects against DNA damage induced by Fe^{3+} and H_2O_2, which is inhibited by allkylation of –SH groups by treatment with EDTA and N-ethylmelameide. MT-3 also scavenges ROS and superoxide anions generated by xanthine/xanthine oxidase (You et al., 2002). During oxidative and nitrative stress of aging, MTs are induced and translocated in the nuclear region, whereby donating Zn^{2+}, regulate the transcriptional activation of complex-1, glutathione peroxidase, and redox-sensitive genes involved in neuroprotection (Sharma and Ebadi, 2008a,b). Upon exposure to either $FeSO_4$, or MPP^{+}; MT-1 is translocated in the endonuclear region to prevent apoptosis and protect dopaminergic (SK-N-SH) neurons against MPP^{+} and SIN-1-induced oxidative and nitrative stress (Ebadi and Sharma, 2003; Sharma and Ebadi, 2003).

1.3. MTs and metal ion homeostasis in aging

Since $[Zn^{2+}]_i$ concentrations are mediated by complexing with apothionein to form MTs, there has been interest in exploring