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Review Article

Time sequence of oxidative stress in the brain from transgenic mouse models of Alzheimer's disease related to the amyloid-β cascade

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ABSTRACT

Alzheimer's disease (AD) is a multifactorial disorder characterized by the presence of amyloid plaques and neurofibrillary tangles (NFTs). Rare early-onset forms of AD are associated with autosomal dominant mutations in the amyloid precursor protein gene, presenilin 1 gene, or presenilin 2 gene. The late-onset form of the disease (LOAD) is the most common form. The causes of LOAD are not yet clarified, but several environmental and genetic risk factors have been identified. Numerous studies have highlighted a role for free radical-mediated injury to brain regions of this illness. In addition, studies from mild cognitive impairment patients suggest that oxidative stress is an early event in the pathogenesis of AD. The associations between these markers of free radical damage and the pathogenic cascades involved in AD are complex. Over the past 2 decades, a number of mouse models have been created to recapitulate the major neuropathological hallmarks of AD, namely amyloid plaques and NFTs. These mice recapitulate many, although not all, of the key features of AD. Some strains of transgenic mice develop amyloid plaques, some accumulate NFTs, and some do both. Here we review the evidence for increased free radical-mediated damage to the brain with particular attention to the stage of the disease in various transgenic models of AD related to the amyloid-β cascade.

Contents

Abbreviations: AD, Alzheimer's disease; ABAD, amyloid binding alcohol dehydrogenase; APOE, apolipoprotein E; APP, amyloid precursor protein; Aβ, amyloid beta; COX, cytochrome c oxidase; DP, decoy peptide; FAD, familial forms of Alzheimer's disease; GPX, glutathione peroxydase; GR, glutathione reductase; HNE, 4-hydroxynonenal; LOAD, late-onset form of Alzheimer's disease; MCI, mild cognitive impairment; NFTs, neurofibrillary tangles; PDGF, platelet derived growth factor-β; PDH, pyruvate dehydrogenase; PrP, prion protein; PS, presenilins; RCR, respiratory control ratio; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances.

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Introduction

Alzheimer's disease (AD) is a multifactorial disorder characterized clinically by progressive cognitive decline and neuropathologically by synaptic and neuronal loss and the presence of amyloid plaques and neurofibrillary tangles (NFTs). Rare early-onset forms of AD are caused by highly penetrant autosomal dominant mutations in one of three genes: amyloid precursor protein (APP) gene, presenilin (PS) 1, or PS2 [1]. The common late-onset form of the disease (LOAD) affects currently more than 10 million individuals worldwide and represents a significant and growing public health burden [2]. The causes of LOAD are not yet clarified, but several environmental and genetic risk factors have been identified; the most potent of these, other than age, is the inheritance of the ε4 allele of the apolipoprotein E gene [3]. It is important to note that, although familial forms of AD (FAD) have a much earlier onset than sporadic AD, the neuropathology associated with both forms of AD is similar, although LOAD or the sporadic form of AD is not associated with any known mutations in APP or the enzymes that cleave it to release the amyloid-β peptide (Aβ).

Abundant in vitro and in vivo data now support the notion that accumulation of Aβ-containing senile plaques and that of paired helical filament tau-containing NFTs in brain are linked in a complex pathogenic cascade that includes earlier formation of abnormal Aβ aggregates [4]. This cascade induces a series of overlapping events such as disturbed cell signaling, innate immune activation, mitochondrial dysfunction, excitotoxicity, abnormal glycation, and altered metabolism of metal ions, among others. All of these events can directly or indirectly produce free radical stress, which in turn promotes further Aβ synthesis and aggregation and consequently the pathogenic cascade [5]. Oxidative stress can increase β-secretase expression and tau phosphorylation, through c-Jun amino-terminal kinase/p38 mitogen-activated protein kinase [6] and glycogen synthase kinase 3 [7], respectively. On the other hand, free radicals are generated early in the Aβ aggregation process, when oligomers and protofibrils are formed [8].

Numerous studies have highlighted the role of free radical-mediated injury to brain regions in this illness, with the elevation of lipid [9], protein [10], and nucleic acid oxidation [11,12]. In addition, studies from mild cognitive impairment patients suggest that oxidative stress is an early event in the pathogenesis of AD [13,14]. The associations between these markers of free radical damage and the pathogenic cascades involved in AD are complex [15] and remain to be clarified.

Therefore, it is crucial to develop animal models to better understand the overlapping events involved in the pathogenesis of AD. Over the past 2 decades, a number of mouse models have been created to recapitulate the major neuropathological hallmarks of AD, namely amyloid plaques and NFTs. These mice recapitulate many, although not all, of the key features of AD and have been widely used in AD research. At the present time, there are numerous types of transgenic mice available for the study of AD, many of which have been characterized to some extent in terms of neuronal loss, neuropathological, and/or behavioral impairment. Some strains of transgenic mice develop Aβ plaques, some accumulate NFTs, and some do both. The age of onset and the magnitude of pathologic change also vary across mouse strains. These mice recapitulate many key aspects of AD, including amyloid neuropathology, cerebral amyloid angiopathy, synaptic loss, dystrophic neurites, and reactive gliosis, as well as impairments in synaptic plasticity, learning, and memory. Such mouse models exhibit these characteristics to varying extents and are widely used to investigate the roles of APP, Aβ, and amyloid pathology in the pathogenesis of AD. Mice expressing mutant human APP develop Aβ plaques at about 10–12 months of life, but do not develop NFTs. Mice that express both mutant APP and mutant human PS1 accumulate Aβ plaques at a younger age, but do not develop NFTs. Accumulation of NFTs is achieved in mice carrying mutant human tau genes, which are associated with frontotemporal dementia, but these mice do not develop Aβ plaques. The development of both Aβ plaques and NFTs has been achieved in a "triple transgenic" mouse expressing APP, PS1, and the mutant tau protein and also with conditional neuronal expression of SV40 T antigen [16].

Although none of the current genetically engineered mouse models of AD fully recapitulates the comprehensive neuropathology of the human AD brain, these individual AD mouse models offer great advantages toward the understanding of particular proteins, pathological pathways, and lesions in the pathogenesis of AD. These different transgenic mouse models exhibit varying ages of onset of impairments. Here we review the evidence for increased free radical-mediated damage to brain with particular attention to the stage of the disease in various transgenic mouse models of AD (Table 1). All of the transgenic mouse models reviewed below are based on genetic manipulation of the Aβ cascade and therefore represent inherited forms of AD, so extrapolations to LOAD should be made with caution. The role of oxidative damage in each of these transgenic mouse models has been examined to varying extents. This review concentrates on transgenic mouse models related to the Aβ cascade and sheds light on the role of oxidative stress in the pathophysiology of AD.

Transgenic mouse models based on the mutation and overexpression of APP

Transgenic mice overexpressing wild-type human APP exhibit only subtle increases in Aβ and little amyloid pathology [17]. Therefore many transgenic mouse models were developed that overexpress human APP carrying at least one familial mutation and show robust age-dependent increases in Aβ levels and amyloid pathology similar to those observed in humans. The common features of these models are based on the production of elevated levels of Aβ, amyloid plaques, dystrophic neuritis, and gliosis.

The Tg2576 mouse model

The most widely studied transgenic mouse model is the Tg2576 with a Swedish FAD mutation (K670N/M671L) driven by a hamster prion protein (PrP) promoter that drives its expression widely in the nervous system. The expression of the human APP was fivefold above the levels of the endogenous APP, the expression of $A\beta_{1-40}$ and $A\beta_{1-42}$, and the amyloid deposition increased with age, along with gliosis and dystrophic neuritis. Amyloid plaques appeared between 11 and 13 months. These mice also displayed spatial memory impairment by 9–10 months of age [18]. The slope of increase in cerebral cortical β-secretase (BACE1) activities in Tg2576 mice between the ages of 9 and 13 months was significantly higher compared to that of the α-secretase, whereas the expression levels of BACE1 protein and mRNA did not change with age [19]. Modifications of peroxisomal oxidative markers were observed in these transgenic mice at as early as 3 months of age, with significant increase in catalase and glutathione peroxidase (GPX) proteins in the neocortex and decrease in the hippocampus. The activity of catalase was increased in the neocortex and decreased in hippocampus, whereas GPX activity was decreased in both structures of the brain at 3 months of age. Superoxide dismutase (SOD) 1 protein and mRNA were decreased in both structures, whereas SOD2 protein and activity were significantly increased in the neocortex. Markers of oxidative damage such as protein-bound acrolein in the neurons and nucleic acid oxidation in the neocortex and the CA1 pyramidal cells were elevated [20]. By 8 months of age, before amyloid plaque formation, the cerebral cortex and hippocampus of Tg2576 mice had significantly higher isoprostane 8,12-*iso*-iPF2a-VI levels than those of wild-type mice, and this difference became increasingly significant at 12 months of age. These values also directly correlated with plasma and urinary levels