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Review article

Expression of Alzheimer's disease risk genes in ischemic brain degeneration

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ABSTRACT

We review the Alzheimer-related expression of genes following brain ischemia as risk factors for late-onset of sporadic Alzheimer's disease and their role in Alzheimer's disease ischemia-reperfusion pathogenesis. More recent advances in understanding ischemic etiology of Alzheimer's disease have revealed dysregulation of Alzheimer-associated genes including amyloid protein precursor, β-secretase, presenilin 1 and 2, autophagy, mitophagy and apoptosis. We review the relationship between these genes dysregulated by brain ischemia and the cellular and neuropathological characteristics of Alzheimer's disease. Here we summarize the latest studies supporting the theory that Alzheimer-related genes play an important role in ischemic brain injury and that ischemia is a needful and leading supplier to the onset and progression of sporadic Alzheimer's disease. Although the exact molecular mechanisms of ischemic dependent neurodegenerative disease and neuronal susceptibility finally are unknown, a downregulated expression of neuronal defense genes like alfa-secretase in the ischemic brain makes the neurons less able to resist injury. The recent challenge is to find ways to raise the adaptive reserve of the brain to overcome such ischemic-associated deficits and support and/or promote neuronal survival. Understanding the mechanisms underlying the association of these genes with risk for Alzheimer's disease will provide the most meaningful targets for therapeutic development to date.

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Introduction

Alzheimer's disease is a heterogeneous disease and the most widespread type of dementia in the world neuropathologically defined by massive neuronal loss mainly in hippocampus. The main pathologic features of Alzheimer's disease are the intra- and extracellular β-amyloid peptide deposits in the brain and intra-neuronal accumulations of hyperphosphorylated tau protein, furthermore referred to as neurofibrillary tangles. Genetic, neurochemical, and pathologic data suggest that β-amyloid peptide aggregation and deposition is important in Alzheimer's disease pathogenesis [1]. On the other hand, tau protein pathology strongly correlates with neuronal dysfunction and progression of the clinical stage of Alzheimer's disease [2]. The clinical stage of Alzheimer's disease is also related to selective neuronal death especially in hippocampus, synaptic and neurotransmitter loss, and neuroinflammation [2].

Brain ischemia in animals causes progressive and irreversible dementia with Alzheimer's phenotype [3–5]. Additionally, the progressive injury in the hippocampus [6–9] and the white matter destruction [7,10,11] were evident after ischemic brain episode. Temporary brain ischemic insult resulted in a tricky delayed death of specific vulnerable neuronal cells inside the CA1 area of the hippocampus, related to neuroinflammation [6–8,12]. Rarefaction of white matter was found a couple of months after ischemia and noticeably increased 1 year following ischemic brain episode [7,10,11]. It should be emphasized that the white matter alterations are typical for elderly persons and subjects with cognitive impairment. The above alterations also appear in sporadic Alzheimer's disease individuals, suggesting that brain ischemia can be dealt with as an useful model for development of mechanisms responsible for the progression of Alzheimer-type dementia. The finding of β-amyloid peptide, presenilin 1 and 2, apolipoproteins, alfa-synuclein and hyperphosphorylated tau protein immunoreactivity in experimental ischemic brains [13–17], in patient brains following episodes of ischemic injury [18–22] and presence of these proteins in sporadic Alzheimer's disease have indicated shared molecular mechanisms of neurons loss, aberrant proteins accumulation and advancement of dementia in both post-ischemic brain and sporadic Alzheimer's disease. For that reason, it is of significance to investigate the effects of brain ischemia on sporadic Alzheimer's disease development through experimental ischemic model in order to unravel the etiology of Alzheimer's disease [4,6,23]. Regarding the latest exciting findings, in this review we try to combine the results together from a genetic point of view. It is hoped that the newest important findings will provide some view into the multifaceted interaction between ischemic influence on Alzheimer-related genes and β-amyloid peptide production in progressing from the injury following brain ischemia to dementia with Alzheimer's phenotype.

In complex, heterogeneous diseases such as Alzheimer's disease, novel approaches to integrate genetic changes and epigenetic data into organized molecular networks may facilitate our understanding of the underlying disease pathogenesis. It is likely that sporadic Alzheimer's disease arises from a complex interplay between ischemic brain injury and specific genetic susceptibility for an ischemic factor. This review will present the hard-earned data connected with ischemic induction of amyloid protein precursor, secretases, autophagy, mitophagy and apoptosis genes playing key roles in sporadic Alzheimer's disease generation. Here we summarize the latest studies supporting the theory that Alzheimer-related genes play an important role in ischemic brain injury and that ischemia is a needful and leading supplier to the onset and progression of sporadic Alzheimer's disease.

Amyloid precursor protein gene

The gene coding amyloid protein precursor is located on chromosome 21. After transitory local brain ischemia, amyloid protein precursor mRNA was upregulated to a maximum of 2 fold change in the penumbra and 1.5 fold change in infarct core during seven days following injury [24–26]. Selective induction of Kunitz-type protease inhibitor field-containing amyloid protein precursor mRNA after persistent focal ischemia in rat brain cortex was observed through 21 days post-ischemia [27]. Noteworthy, the increased expression of amyloid protein precursor mRNA 770 and 751 after transient focal brain ischemia during 7 days was noted after injury [28]. In the rat selectively vulnerable CA1 area of hippocampus, the expression of amyloid protein precursor gene decreased to a minimum of −0.5 fold change 2 days after ischemic brain injury [29]. Seven and thirty days after complete brain ischemia, the amyloid protein precursor gene increased to a maximum of 0.8 and 0.6 fold change, respectively [29]. In medial temporal lobe cortex, the expression of amyloid protein precursor gene was reduced to a minimum of −0.7 fold change two days following complete brain ischemia [30]. But seven and thirty days following ischemia, the amyloid protein precursor gene expression was increased in temporal lobe to a maximum of 0.5 and 1.0 fold change, respectively [30]. Treatment with estrogen of rodents with experimental transient focal brain ischemia attenuates over-expression of amyloid protein precursor messenger RNA [25]. These data clearly show that estrogen can decrease the over-expression of amyloid protein precursor mRNA after brain ischemia.

α and β-secretase genes

The amyloid protein precursor is cleaved by α-secretase and it is the non-amyloidogenic pathway. In experimental brain ischemia, down regulation of α-secretase mRNA was noted [31]. The mechanism, in which amyloid protein precursor is cleaved by β- and γ-secretases, represents amyloidogenic pathway which finally generate β-amyloid peptide [32]. The gene coding β-secretase is located on chromosome 11. Ye et al. [33] demonstrated the dysregulation in β-secretase mRNA expression in mice ischemic brain. This expression increased in the cortex and hippocampus during recirculation period [33]. Specifically, during 4 h of recirculation, a significant rise of β-secretase mRNA level was noted in the cortex (1.8 fold change) and hippocampus (1.9 fold change) [33]. At 7 days and 1 month after ischemia, the β-secretase mRNA induction dropped systematically but was still above the control level [33]. β-secretase gene expression increased to a maximum of 3.9 fold change after complete brain ischemia in the rat CA1 subfield of hippocampus with 2 days survival [29]. Seven days after ischemia, β-secretase expression increased to a maximum of 1.0 fold change [29]. But thirty days after complete brain ischemia, β-secretase gene expression decreased to a minimum of −0.7 fold change [29]. β-secretase gene expression rose to a maximum of 4.0 fold change in the medial temporal lobe cortex 2 days after complete brain ischemia [30]. Seven and thirty days after temporal lobe ischemia, β-secretase gene expression was diminished to a minimum of −0.7 and −0.9 fold change, respectively [30].

Presenilin 1 and 2 genes

The genes coding presenilin 1 and 2 are located on chromosomes 14 and 1, respectively. Presenilins are involved in the amyloidogenic processing of amyloid protein precursor to generate β-amyloid peptide through the γ-secretase complex [34–36]. The highest over-expression of Alzheimer-related presenilin-1 gene was demonstrated on day 3 post-ischemia in neurons of the CA3 subfield of gerbil hippocampus [37]. Induction of presenilins after