



From Brain Ischemia to Alzheimer-Like Neurodegeneration

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ABSTRACT

Latest studies have revealed a key role of ischemic brain episodes in Alzheimer-like neurodegeneration and dementia development. This review presents the current progress in understanding how brain ischemia may promote Alzheimer's disease pathological changes and cognitive impairment. It seems that brain ischemia promotes Alzheimer's disease-like neurodegeneration development through various mechanisms, including accumulation and aggravation of different parts of amyloid protein precursor, tau protein phosphorylation, dysregulation of Alzheimer-related genes, neuroinflammation, neuronal loss, synaptic dysfunction, white matter lesion and general brain atrophy. Progress in understanding key mechanisms of ischemia-induced changes of Alzheimer-phenotype will help develop preventing and treating strategies against sporadic Alzheimer's disease pathology and dementia generated by sublethal and/or silent ischemia.

Keywords

Alzheimer's disease, Brain ischemia, Amyloid protein precursor, Tau protein, Neurodegeneration, Genes

Introduction

Nowadays sporadic Alzheimer's disease presents the largest part of dementia in an aging society. Alzheimer's disease is described pathologically by progressive neurodegeneration which leads to development of cognitive impairment in patients with hippocampal atrophy. Characteristic elements of this disease comprise extraneuronal senile plaques produced by β -amyloid peptides 1-40 and 1-42 together with intraneuronal neurofibrillary tangles generated by phosphorylation of tau protein in the brain. There is no cure and current therapies are not effective in delaying progression of Alzheimer's disease. This disorder is a real medical, social, and economic burden in the present society for the reason that population is rapidly aging [1,2].

Postischemic Alzheimer-type dementia is the second most common form of dementia [3]. In fact, Alzheimer's disease and postischemic dementia often coexist in aging patients with dementia [4]. It is calculated approximately that circa 40% of Alzheimer's disease subjects have mixed dementia [3]. Patients with postischemic brain injury frequently have cognitive deficits to diverse degrees [5,6]. Experimental animals after ischemia-reperfusion exhibit cognitive deficits, too [7-10]. The key role of episodic brain ischemia in dementia development has appeared to the forefront of clinical investigation [11-21]. Investigations in the last 25 years have suggested that ischemic brain injury might promote Alzheimer-type neurodegeneration through generation of reactive oxygen species [20,22], by neuronal energy failure,

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development of inflammation through activated glial cells [22-25] and different parts of amyloid protein precursor accumulation [12,22] and tau protein pathology [26], that in turn, damage the neuronal cells especially in hippocampus and contribute to white matter lesions [27-30]. This review tries to present the current progress focusing on brain ischemia-reperfusion-induced Alzheimer's disease-like neurodegeneration and dementia.

Mechanisms of Action Triggering Ischemic Alzheimer-like Pathology

Alzheimer's disease comprises two forms: early-onset Alzheimer's disease with prevalence of circa 5% that is caused by mutations of genes encoding amyloid protein precursor and/or presenilins, and over 95% of late-onset Alzheimer's disease cases which are called of sporadic nature. The most important risk factor for sporadic Alzheimer's disease is aging, and lastly the most supported by a good number of scientists cause of Alzheimer's disease is brain ischemia closely associated with age [11-21]. Despite of years of expand, first theory of Alzheimer's disease cause, the amyloid cascade hypothesis, did not resolve the etiology and disease treatment and current studies suggest that ischemic brain injury promotes Alzheimer's disease-like neurodegeneration through numerous molecular mechanisms as presented below.

Accumulation of Amyloid after Brain Ischemia

β -amyloid peptides 1-40 and 1-42 which are components of amyloid plaques are produced from amyloid protein precursor through proteolytic cleavages by β - and γ -secretases. Amyloid deposits occur both in the brain tissue and in the walls of vessels in Alzheimer's disease and in the brains following ischemic injury in animals and humans [12,22,31-34]. Animals with short term survival (2-7 days) after ischemia-reperfusion brain injury, showed intense brain immunoreactivity to the C-terminal of amyloid protein precursor and to the β -amyloid peptide and to the N-terminal of amyloid protein precursor as well. The staining was identified intra- and extracellularly [12,22]. Different parts of amyloid protein precursor were noted within neuronal and glial cells. Staining was seen mainly in undamaged neurons. After 6-12 months following brain ischemia injury, an increased immunoreactivity only to β -amyloid peptide and C-terminal of amyloid protein precursor

was observed [22-24,35]. Extracellular various parts of amyloid protein precursor deposits ranged from widespread small dots to irregular diffuse plaques [12,22,36-40]. Widespread and multifocal diffuse plaques predominated in the hippocampus, entorhinal cortex, corpus callosum, around the lateral ventricles and thalamus. Glial and neuronal cells have been found frequently inside diffuse extracellular plaques. Time-dependent collection of β -amyloid peptide in the hippocampus, especially in the areas with open blood-brain barrier in rats, occurs after brain ischemia [27,28,41-45]. It should be emphasized that the β -amyloid peptide deposits as seen in animals up to 2 years after transient brain ischemia cannot be stained with thioflavine S [12,46] but in humans, the opposite situation after brain ischemia was present as regards thioflavine S staining [32]. Some of evidences have showed that brain ischemia upregulates β - and γ -secretase-mediated amyloid protein precursor cleavage [12,19,20,38,40,47-50]. It is possible that brain ischemia upregulates amyloid protein precursor processing and leads to β -amyloid peptide accumulation by activation of gene expression of β -secretase and presenilin 1 and 2, leading consequently to increases in the secretase level and its activity [50-52]. The amyloid accumulation in vessel walls caused by ischemic brain injury with vessel spasm could further induce ischemic lesion and develop a self-propelling vicious circle of ischemic episodes and finally lead to irreversible damage of brain tissue [22,53].

Hyperphosphorylation of Tau Protein after Brain Ischemia

The microtubule-associated tau protein becomes abnormally hyperphosphorylated in Alzheimer's disease patient's brains and finally generates intraneuronal neurofibrillary tangles which are crucial in progressing Alzheimer's disease pathology. Cyclin dependent kinase 5 (Cdk5) is involved in neurofibrillary tangle-like tauopathy induced by ischemic tau protein hyperphosphorylation [26] and tau protein phosphorylation at numerous Alzheimer's disease specific sites caused by experimental focal brain ischemia was observed, too [54]. Increased tau protein phosphorylation with parallel activation of Cdk5, calcium/calmodulin-dependent protein kinase II (CaMK-II), and glycogen synthase kinase-3b (GSK-3b), as well as inhibition of protein phosphatase 2A (PP2A) was noted in a rat model of focal brain ischemia

[55]. It is thus reasonable to suggest that the increased tau protein phosphorylation and β -amyloid peptide overproduction appear to be very sensitive to brain ischemia.

Dysregulation of Alzheimer's-Related Genes after Brain Ischemia

After transient focal ischemic brain injury, amyloid protein precursor gene was upregulated in the penumbra and infarct core during seven days of recirculation [56-58]. In the rat CA1 subfield of hippocampus, the expression of amyloid protein precursor gene was decreased below control value during 2 days following ischemic brain injury [50]. Seven and 30 days following brain ischemia, the amyloid protein precursor gene expression increased above control value [50]. In temporal cortex, the expression of amyloid protein precursor gene was reduced below control value 2 days after brain ischemia [51]. However, 7 and 30 days after ischemic injury, the amyloid protein precursor gene expression was increased above control [51].

In experimental ischemic brain injury, down expression of α -secretase gene was noted [59]. Ye et al. [60] noted the dysregulated expression of β -secretase gene after ischemic brain injury. This expression increased in the hippocampus and cortex during recirculation [60]. β -secretase gene expression increased above control value following brain ischemia in the rat CA1 area of hippocampus 2-7 days after injury [50]. But 30 days following brain ischemia, β -secretase gene expression decreased below control value [50]. β -secretase gene expression was upregulated in the temporal cortex 2 days following brain ischemia [51]. Seven and thirty days following temporal cortex ischemia, β -secretase gene expression was significantly down regulated [51].

The increased overexpression of presenilin-1 gene was observed on day 3 after transient brain ischemia in neurons of the CA3 area of gerbil hippocampus [61]. Expression of presenilins after local ischemic brain injury was upregulated in the rat hippocampus and cortex [62]. In the rat CA1 subfield of hippocampus, presenilin 1 and 2 gene expression was above control value 2 and 7 days following complete brain ischemia [50]. But 30 days following the ischemic injury, presenilin 1 and 2 gene expression decreased below control value [50]. In the temporal cortex, presenilin 1 gene expression decreased below control value but presenilin 2 increased above control 2 days

following brain ischemia [52]. Seven days after brain ischemia, presenilin 1 gene expression was down regulated and presenilin 2 was significantly elevated [52]. Thirty days, following brain ischemia presenilin 1 gene expression increased above control value and presenilin 2 was reduced below control [52].

It was found that autophagy gene in hippocampus CA1 area was not significantly modified 2, 7 and 30 days after brain ischemia. But mitophagy gene was significantly upregulated at day 2 and decreased below the basal values at days 7 and 30 [63]. The gene expression of caspase 3 in hippocampus CA1 area 2 days after ischemic brain injury increased by more than 300% comparing to the basal level. But 7 days after ischemia, its expression was close to the basal value. Thirty days after brain ischemic injury, in the above area the gene expression was reduced below the basal value [63].

In the temporal cortex, autophagy gene expression increased during 2-30 days following transient ischemic brain injury in rats [64,65]. But mitophagy gene decreased below normal value 2 days after brain ischemia. Seven and thirty days after ischemic injury, mitophagy gene expression increased above control values. Apoptotic gene caspase 3 expressions were reduced below normal value 2 days following brain ischemia. Seven and thirty days following ischemia, caspase 3 gene expression increased above control values [64].

Neuronal Loss after Brain Ischemia

Neuronal and synaptic loss in Alzheimer's disease cases correlates directly to the severity degree of dementia [66]. Hippocampus pathology with necrotic and apoptotic neuronal cells is seen in the CA1 subfield of hippocampus 2-7 days after brain ischemia [22,35]. At 2 days, neuronal loss was superimposed with damaged neuronal cells. In later stages (7 days and 6 months), the number of neuronal cells with abnormal changes was reduced being replaced by neurons loss. Above changes were localized mainly in hippocampus and third cortical layer. Borderline zones of the cerebral cortex were also the site of severe pathology. Six months following ischemic brain injury in addition to localized neuronal loss different types of pathological changes of neurons were noted. The first one took the form of chronic neuronal degeneration which was observed in the early stage after ischemia. Other changes were of a nature typical for the

early ischemic changes but they were observed in those areas of the brain that were not involved in early damage, e.g., the CA2, CA3, and CA4 subfields of hippocampus [22]. The neuronal death in the CA1 area, together with the decrease of acetylcholine level in the cortex and striatum is evident following focal brain ischemia, suggests that the neuronal disappearance might result from insufficiency of neuronal excitatory transmission [66,67].

Synaptic Dysfunction after Brain Ischemia

Synaptic integrity of brain is necessary for physiological functions, including memory and learning. Decreased levels of both synaptophysin and postsynaptic density protein 95 have been found in rat hippocampus following local brain ischemia [42,54]. Likewise, these rats presented synaptic ultrastructural changes in the CA1 area of the hippocampus. Other study has shown that ischemic brain injury generates an increase in synaptic autophagy and asymmetric synapses, which may be connected with neuronal death in the CA1 area of hippocampus after transient ischemia [65,68,69]. There are experimental evidences of isolated and persistent synaptic malfunction resulting from transient brain ischemia [70]. Depression of excitatory synaptic transmission in ischemic condition was shown in CA1 area of hippocampus [67]. The ischemia induced intracellular Ca^{2+} increase upregulates calpain's activity in neurons and calpain target proteins are present in GABAergic and glutamatergic synapses. In brain ischemia, calpains cleave pre- and post-synaptic proteins. Calpain-mediated protein cleavage contributes to neuronal death in brain ischemia [71].

White Matter Lesion and Inflammation after Brain Ischemia

White matter lesion and glia activation are seen in both animal and human brains following brain ischemia [22,25,27,28,35,72-74]. In rat models, brain ischemia appears to cause more severe white matter changes in the subcortical white matter and corpus callosum [22,27,28,75]. These findings are consistent with the glia activation in the corpus callosum after ischemic brain injury [76]. Brain ischemia promotes increased permeability of blood-brain barrier that facilitates the entry of inflammatory cells into the brain tissue and the release of a large number of serine proteases as well as β -amyloid peptides

from blood into brain parenchyma, what in turn leads to white matter lesion [25,41,44,77-80].

Ischemia-Induced Brain Atrophy

Some evidences indicate that transient ischemic brain injury in rats caused widespread neuronal loss, in structures belonging or not to selectively vulnerable areas of the brain [22,35]. The ischemic brain changes represent a gradually progressing process extending over a long period during reperfusion after the ischemic episode [22]. The nature of the neuropathological processes is indicated by the changes in the brain occurring during ischemic period and two years of survival [22]. They are characteristic not only for the early brain changes, but for an active pathological process in the late stage after ischemia as well. One/two year(s) after ischemia, the pathological process results in generalized brain atrophy [22,35,81]. Gross examination, conducted between 9 and 24 months after ischemic brain injury, demonstrated hydrocephalic hallmarks of brain [35,81]. Dilatation of the subarachnoid space around the brain hemispheres was observed, too [35]. Complete atrophy of hippocampus with massive pyramidal neuronal disappearance in the pyramidal layer of the hippocampal CA1 subfield and atrophy of the striatum were noted [35]. Cerebral cortex was narrow showing increased neuronal density. An additional feature of late brain atrophy was manifested as diffuse white matter lesions taking the form of rarefaction and cavitations, revealing advanced spongiosis. This phenomenon may be explained by massive neuronal loss with accompanying increased blood-brain barrier permeability occurring in the early and late stages following brain ischemia [41].

Conclusions

Brain ischemia is common in the old persons and frequently contributes to neurodegeneration, dementia, and probably to sporadic Alzheimer's disease development. As discussed in this review, many investigations have shown a causative role of ischemic brain episodes in Alzheimer-like neurodegeneration. On the other hand, there are data showing ischemic lesions in Alzheimer's disease brains and Alzheimer's lesions in experimental ischemic brains [4,82,83]. It should be emphasized that the brain ischemia-promoted neurodegeneration is connected with β -amyloid peptide generation and tau protein hyperphosphorylation suggesting that

the ischemic neurons degeneration/loss might be caused by or associated with abnormal β -amyloid peptide production and tau protein hyperphosphorylation [12,26,50,51,54,57,58]. This review presents evidences that the brain ischemia promotes solid dysregulation of Alzheimer's-related genes and proteins and neurodegenerative epigenetic markers, which may be part of additional neuropathogenic factors contributing to the neuropathology of ischemia and dementia with Alzheimer's phenotype [50,51,52,57,58,64]. In summary, experimental data on postischemic brain injury show that Alzheimer's disease-related peptides (e.g. β -amyloid peptide) and/or proteins (e.g. tau protein) render the brain tissue more susceptible to brain ischemic pathology, resulting in the generation of neurodegenerative abnormalities like dementia. Alzheimer's disease-related factors at the same time sensitize the brain to ischemic neurodegeneration and lower the threshold of ischemic brain pathology *in vivo*. We propose that ischemia-reperfusion processes in brain are the fountainhead of a cycle of genetic, molecular and cellular events that have neurodegenerative consequences, finally leading to Alzheimer's disease. We speculate that Alzheimer's disease may be caused by repeated sublethal and silent ischemia-reperfusion alterations that attack and slowly steal the minds of their victims. Ischemic changes in areas destroyed by Alzheimer's disease neuropathological processes may contribute to dementia of Alzheimer's disease individuals. It is tempting to speculate that Alzheimer's disease is a byproduct of ischemia-reperfusion-induced overexpression of amyloid protein precursor, β - and γ -secretase genes in the brain. Such data convinces us of the need for future study efforts in this exciting, interesting and new very significant field of experimental investigations. On the other hand, ischemic brain injury provides a bridge between clinical and experimental research that

greatly facilitates the interpretation of complex disorder processes including Alzheimer-type dementia.

Future studies should focus on searching for the major and more important molecular/genetic mechanisms by which brain ischemia causes cognitive impairment and neurodegeneration of Alzheimer's-type. This study has been intended to find potential treatment targets to prevent and cure ischemic dementia with Alzheimer-phenotype and possibly, also Alzheimer's disease. Whether brain ischemia is directly involved in the pathogenesis of Alzheimer's disease or acts indirectly as a contributor to the chain of negative events, needs to be established. Nevertheless, prevention and treatment of ischemic brain injury antecedents may have important implications for Alzheimer's disease. In view of the above-mentioned observations that cognitive decline is progressing after brain ischemia, there is a distinct possibility that we can prevent this decline by targeting the slowly progressing neurodegeneration, following the ischemic brain injury by aiming at molecular events now shown to be triggered by brain ischemia. These approaches could include individual or combined treatments, possibly targetting brain β -amyloid peptide generation, tau protein phosphorylation, brain inflammation and neuronal loss.

Conflict of Interest

Author declares no conflict of interest

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