Review paper

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Amyloid pathology in the brain after ischemia

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Abstract

As the population is aging all over the world, the economic burden of ischemic brain injuries is constantly increasing. Human brain ischemia is one of the leading causes of premature death, significant morbidity and physical and mental disabilities, resulting in a lower quality of life and unusually high costs of health and social care. One of the most difficult problems associated with the pathology of the brain after ischemia is progressive dementia observed in people who survived the stroke. More recently, brain ischemia has been shown to elicit Alzheimer's disease neuropathologic change, possibly facilitating the development of dementia due to the amyloidogenic processing of Alzheimer's disease-related amyloid protein precursor into amyloid. The main purpose of this review is to present the development of Alzheimer's disease neuropathologic change in the brain after human and experimental ischemia, with a particular emphasis on proteins and genes involved in the amyloidogenic processing of the amyloid protein precursor to amyloid.

Key words: *brain ischemia, ischemic stroke, amyloid protein precursor, amyloid, β-secretase, presenilin 1, presenilin 2, cognitive decline, dementia, protein, gene.*

Introduction

Brain ischemia is more and more common in aging societies in both developing and developed countries. Ischemic stroke is the second cause of death and the third cause of disability and may soon become the leading cause of death in the world [6,10,39] and the development of the Alzheimer's disease [9,20,28,38,73]. Epidemiological research indicates that approximately 17 million patients are diagnosed with an ischemic stroke each year [6,9]. About 6 million stroke patients die every year around the world [6]. Currently, the number of patients who survived ischemic stroke has reached 33 million [6,9]. According to epidemiological forecasts, this number will increase to 77 million in 2030 [6]. Physical damage after the stroke usually improves to a greater or lesser extent, but for unknown reasons, the decline in cognitive activity is slowly progressing. Recent reports on the burden of ischemic stroke in relation to incidence, prevalence, disability-adjusted life-years loss, loss of work efficiency, dependence in daily life activities and mortality have shown a growing economic burden with regard to the high costs of health and social care and clinical practice of people who suffered a stroke [16-18]. Information on the increased incidence of ischemic stroke in 18-50-year-old patients which has been recently released indicates that the incidence of stroke in adults is more than 2 million

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cases per year [5]. Therefore, it should not come as a surprise that cognitive impairment due to injury after the stroke, which eventually turns into dementia, accounts for a significant part of the costs related to health care, clinical practice and social services. The total annual cost of an ischemic stroke in Europe was around 64 billion euros in 2010 [42]. The occurrence of dementia after the first stroke is estimated at 10% of survivors and after recurrent stroke at 33-41% [44]. In a long-term study on the incidence of stroke-related dementia, cumulative incidence over 25 years was estimated at 48% [32]. Other authors argue that if the trend of problems with ischemic stroke continues, by 2030 about 12 million people will die, 70 million people will be after a stroke and more than 200 million disability-adjusted life-years loss will be noted annually worldwide [18]. It has been shown that focal cerebral ischemia in humans, caused by unilateral carotid stenosis, causes an increased accumulation of amyloid in the brain confirmed by positron emission tomography, which suggests a relationship between ischemic stroke and Alzheimer's disease-related amyloid [23]. Data from experimental studies have shown that the presence of a high level of amyloid in the brain after ischemia increases the neuroinflammatory response and the size of the infarct [77,83,87]. The aim of this review is to present the generation of amyloid in the brain after human and experimental ischemia, with a particular emphasis on proteins and genes involved in amyloidogenic processing of the amyloid protein precursor to amyloid.

Amyloid in brain and blood after brain ischemia

In humans

In the human brain after ischemia, amyloid accumulation in various brain structures has been demonstrated [26,27,37,88]. Observations have shown both diffuse and senile amyloid plaques in areas of the brain prone to ischemia, in the cerebral cortex and in arterial border zones after brain injury due to ischemia and reperfusion [26,27,37,88]. The amount of amyloid plaques in various areas of the brain correlated well with the age of the patient who had an ischemic event [26,27]. In addition, in the white and grey matter, immunological staining of amyloid in the perivascular space that surrounded the vessels was found [88]. The accumulation of amyloid in the perivascular space looked like cuffs. Amyloid deposits in the perivascular space of the blood-brain barrier microvessels suggest that amyloid originated from serum [48,52,53,56]. Evidence confirming this idea comes from a clinical study in which plasma amyloid is found to be elevated (approximately a 70-fold increase) in patients after a brain ischemia-reperfusion episode [33,91]. Neurons from the hippocampus and cortex were very strongly stained on amyloid. Epithelial and ependymal cells also stained on the amyloid. In the cells of the choroid plexus, epithelium and the lining cells bordering the cerebral ventricles, the receptor for advanced glycation end-products was found [37]. The data showed that the choroid plexus epithelium and the lining cells, equipped with a receptor for advanced glycation end products, play not only a significant role in the accumulation of amyloid in brain tissue, but also are a place where amyloid can be removed [52,53]. According to another research article, the immunoreactivity of amyloid 1-40 and 1-42 in the human hippocampus after ischemia was observed in the intra- and extracellular space [74].

In animals

Various parts of the amyloid protein precursor have been reported in the intra- and extracellular space of the hippocampus, white matter, cortex and around the lateral ventricles, after an episode of ischemia of the brain with reperfusion in animals [19,21,24,25,35,36,46,49-51,57,60,61,80,84,90]. Numerous extracellular depositions of various fragments of the amyloid protein precursor were noted around the microvessels of the blood-brain barrier. Perivascular deposits of all parts of the amyloid protein precursor formed well-marked, irregular, diffuse plaques that regularly surround the vessels and resemble a perivascular hallo or cuff [46]. Accumulation of all fragments of the amyloid protein precursor, such as N- and C-terminal and β-amyloid peptide, in neuronal, glial, pericyte, endothelial and ependymal cells was also observed [2-4,41,43,46,50,54,55]. Deposition of amyloid as diffuse plaques in response to experimental ischemia-reperfusion injury of the brain does not appear to be a temporary phenomenon because diffuse amyloid deposits have been shown to convert to the senile plaque at approximately 9 months after ischemic damage [85].

mRNA of the amyloid protein precursor in the brain after experimental ischemia

After experimental brain injury due to ischemia and reperfusion, the mRNA of the amyloid protein precursor was induced in penumbra and in the core, up to 200% and 150%, respectively [78,79]. After focal ischemic brain injury with recirculation, the amyloid 751 and 770 protein precursor mRNA also increased within one week [31].

mRNA of enzymes processing the amyloid protein precursor in the brain after experimental ischemia

α-secretase mRNA, which metabolizes the amyloid protein precursor by non-amyloidogenic processing [14], decreased after experimental brain damage due to ischemia-reperfusion [40]. In amyloidogenic processing, the amyloid protein precursor is metabolized by β- and γ-secretase [14], whose mRNA and activity are stimulated by the ischemic episode in the cerebral cortex and the hippocampus to produce the β-amyloid peptide [8,11,12,62,86,87]. In other studies, the maximum increase in presenilin 1 mRNA was recorded in the hippocampus, cortex and striatum after ischemic brain injury with recirculation [45,82].

Genes involved in the production of amyloid in the brain after experimental ischemia

CA1 region of the hippocampus

Expression of the amyloid protein precursor gene dropped below the control values in the CA1 hippocampal region 2 days after brain ischemia with recirculation [30]. But at that time, the expression of the β-secretase and presenilin 1 and 2 genes was maximal [30]. Expression of the amyloid protein precursor, β-secretase and presenilin 1 and 2 genes increased above the control value 7 days after ischemic brain injury [30]. Expression of the amyloid protein precursor gene increased above the control value, while the β-secretase and presenilin 1 and 2 genes decreased below control values 30 days after ischemic cerebral episode [30]. Modifications of the mean level of expression of the amyloid protein precursor, β-secretase and presenilin 2 genes were statistically significant between 2 and 7, between 2 and 30 and between 7 and 30 days after brain injury as a result of ischemia-reperfusion [30]. Changes in the mean level of expression of the presenilin 1 gene were statistically significant between 2 and 30 and between 7 and 30 days after the ischemic episode [30].

Medial temporal cortex

Expression of the amyloid protein precursor gene in the medial temporal cortex decreased below control values 2 days after cerebral ischemia with recirculation [63]. But at that time, the expression of the β-secretase gene increased maximally [63]. Seven and thirty days after ischemic brain injury, the expression of the amyloid protein precursor gene has risen above the control value, and the expression of the β-secretase gene has been reduced below the control values [63]. Expression of the presenilin 1 gene was within the control limits on days 2, 7 and 30 after brain injury by ischemia-reperfusion [64]. On the second day after ischemia, the expression of the presenilin 2 gene was maximal, but on days 7 and 30 of the recirculation the expression was within the control limits [64]. Changes in the mean level of gene expression of the amyloid protein precursor, β-secretase and presenilin 2 were statistically significant between 2 and 7 and between 2 and 30 days after brain injury due to ischemia-reperfusion [63,64]. Changes in the mean level of expression of the presenilin 1 gene were not statistically significant at all the time after ischemia [64].

Discussion

The presented data support the thesis that ischemia-reperfusion injury of the brain plays a key role in the amyloidogenic processing of the amyloid protein precursor to amyloid in the ischemic brain and blood [30,33,46,57,62,65,70,76,91]. The amyloid protein precursor is metabolized by β-secretase, whose gene expression [30,65,66], mRNA and protein level [12,86,89] increases in the brain after ischemia-reperfusion injury. Expression of presenilin genes and their levels of mRNA and proteins that are increased following ischemic brain injury [30,40,64,82] are involved in the production of the β-amyloid peptide by the γ-secretase complex [62,65]. After brain injury due to ischemia and reperfusion, the amyloid level rises as a consequence of neuronal death after ischemia [24] and it is highly likely that neurotoxic amyloid activity additionally exacerbates ischemic neuronal damage. The above data help to understand

acute and chronic neuronal loss and brain atrophy after the ischemia-reperfusion episode in the brain [7,20,22,54,57-59] and slow, progressive accumulation of amyloid plaques in the brain tissue after the ischemia episode [26,27,46,57,85,88]. After ischemic brain injury, an increase in blood amyloid levels was observed in humans [33,91]. The level of serum amyloid growth correlated negatively with the clinical improvement after ischemia-reperfusion brain injury, which in turn reflected the severity of ischemic injury [91] and/or the development of recurrent ischemic stroke [47]. We can conclude that the proteomic and genomic changes associated with Alzheimer's disease contribute to brain ischemia-reperfusion neurodegeneration [72] with the development of the dementia [7,9,13,15,28,29,34,75,81].

Brain injury after ischemia seems to favour the development of ischemic neurodegeneration of the Alzheimer's disease neuropathologic change [1] by neuronal damage and death [54], neuroinflammation [77], accumulation of all parts of the amyloid protein precursor, especially amyloid [46,58], tau protein dysfunction [67,68] and dysregulation of proteins associated with Alzheimer's disease and their genes [30,63,64], changes in the white matter and general brain atrophy with final development of dementia [66,71,75]. Therefore, it is now required to know the mechanisms underlying the progressive development of irreversible effects in the brain after ischemia. Here we present new pathways in ischemia-reperfusion neurodegeneration with the phenotype and genotype of Alzheimer's disease, focusing on the expression of genes involved in the metabolism of the amyloid protein precursor to amyloid. Increased expression of the amyloid protein precursor and its amyloidogenic processing genes and proteins after ischemic brain damage sheds new light on a better understanding of the role of amyloid as an additional factor in neuropathology after ischemia. In addition, dysregulation of genes involved in amyloid production, such as the amyloid protein precursor, β-secretase and presenilin 1 and 2 in the hippocampus and medial temporal cortex after brain ischemia, has been documented, and these genes and proteins are important in the development of sporadic Alzheimer's disease. It has also been shown that ischemic-reperfusion injury of the brain induces neuronal damage in the hippocampus and temporal cortex in an amyloid-dependent manner [30,63,64], thus determining a new and important way to regulate the survival or death of neurons. Although important advances have recently been made in research on neuropathogenicity of amyloid after cerebral ischemia, the basic pathways/mechanisms induced by amyloid after ischemia with the reperfusion of irreversible neurodegeneration are still unclear. The high prevalence of dementia in survivors of ischemic stroke remains a challenge for both the scientific and the clinical community [69]. It seems clear that future research should focus on preventing the development of Alzheimer's disease neuropathologic change [1] in the brain after ischemia associated with proteins characteristic for Alzheimer's disease and their genes, which may result in better neurological outcomes after the ischemic episode.

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Disclosure

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