
Common Proteomic and Genomic Contribution to Ischemic Brain Damage and Alzheimer's Disease

Ryszard Pluta¹ • Marzena Ułamek-Kozioł^{1,2} • Sławomir Januszewski¹ • Stanisław J. Czuczwar³

¹Laboratory of Ischemic and Neurodegenerative Brain Research, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland; ²First Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland; ³Department of Pathophysiology, Medical University of Lublin, Lublin, Poland

Author for correspondence: Ryszard Pluta, Laboratory of Ischemic and Neurodegenerative Brain Research, Mossakowski Medical Research Centre, Polish Academy of Sciences, 02-106 Warsaw, Pawińskiego 5 Str., Poland. Email: pluta@imdik.pan.pl

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Abstract: Ischemic brain damage is associated with the deposition of folding proteins, such as all fragments of the amyloid protein precursor and tau protein, in the intra- and extracellular spaces of neurons. In this chapter, we summarize the protein changes associated with Alzheimer's disease and their gene expression (amyloid protein precursor and tau protein) after cerebral ischemia and their role in the ischemic etiology of Alzheimer's disease. Recent advances in understanding the ischemic etiology of Alzheimer's disease have revealed dysregulation of *amyloid protein precursors*, *β-secretase*, *presenilin 1 and 2*, *autophagy*, *mitophagy*, *apoptosis*, and *tau protein* genes after ischemic brain injury. However, reduced expression of mRNA of the α-secretase in cerebral ischemia causes neurons to be less resistant to injury. In this chapter, we present the latest evidence that Alzheimer's disease-related proteins and their genes play a key role in brain damage with ischemia-reperfusion and that ischemic episode is an essential and leading provider of Alzheimer's disease development. Understanding the underlying processes of linking Alzheimer's disease-related proteins and their genes in brain ischemia

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injury with the risk of developing Alzheimer's disease will provide the most significant goals for therapeutic development to date.

Keywords: Alzheimer's disease; amyloid; brain ischemia; secretases; tau protein

INTRODUCTION

Newer studies show that brain ischemia with reperfusion can be associated with a fully developed Alzheimer's disease (1, 2). It is generally suggested that cerebral ischemia triggers Alzheimer's disease, and an ischemic change in the permeability of the blood–brain barrier additionally causes amyloid transportation from the blood to the brain, and this is the last element that causes the full-bloom sporadic Alzheimer's disease (3, 4). Ischemic human stroke and experimental ischemia-reperfusion brain injury are serious, life-threatening neuropathological episodes with severe complications such as post-ischemic cognitive impairment and physical disability (5–12). The evidence to date suggests that there is a potential compatibility among neuropathogenesis of brain ischemia and Alzheimer's disease. First, clinical observations have shown that Alzheimer's disease is a contributing factor to the development of ischemic brain damage and vice versa (13). Second, ischemic brain injury and Alzheimer's disease have the same risk factors like hypertension, hyperlipidemia, diabetes, and age. Third, experimental ischemia-reperfusion brain injury produces a stereotypical pattern of selective death/loss of neurons in the hippocampus with severe brain atrophy, which is similar to the neuropathology observed in Alzheimer's disease, indicating active, slowly progressive neuropathological processes (14–18). Fourth, inflammatory changes appear to play a key role in the progression of brain ischemia and Alzheimer's disease (19). Fifth, the data indicate that ischemic brain damage can cause the pathology of proteins typical for Alzheimer's disease by inducing the generation and deposition of the β -amyloid peptide and other fragments of amyloid protein precursor (16, 20–22). Finally, studies show that tau protein dysfunction also plays a key role in regulating brain ischemia-reperfusion episodes (23–33). Together, these results point to common proteomic and genomic factors in ischemic brain injury and Alzheimer's disease in the neuropathological processes.

In this chapter, we present the current knowledge about the dysregulation of genes involved in the amyloidogenic processing of the amyloid protein precursor, which is associated with the generation of the β -amyloid peptide in the brain after ischemia. In addition, we pay attention to whether the signal pathway of the amyloid protein precursor is involved in the induced ischemic death of neurons in the CA1 area of the hippocampus and medial temporal cortex. Also, we take into account the importance of ischemic gene expression associated with Alzheimer's disease, such as autophagy, mitophagy, and apoptosis during clinical onset, progression and maturation of brain injury after ischemia in the etiology of Alzheimer's disease. With regard to the latest exciting discoveries after brain ischemia injury, we combine data from the proteomic and genomic point of view. In recent years, several researchers have documented that brain ischemia-reperfusion episode is an important element in the development of Alzheimer's disease and plays a key role in proteomic and genomic (e.g., amyloid protein precursor, amyloid

processing secretases, autophagy, mitophagy, caspase 3, and tau protein) changes of this disorder (1, 2, 31). Below we summarize the latest evidence that Alzheimer's disease-related proteins and their genes play an essential role in brain ischemia-reperfusion injury, and ischemic episode is a necessary and most important supplier for the start and progress of the full development of sporadic Alzheimer's disease.

AMYLOID STAINING AND BLOOD LEVEL AFTER BRAIN ISCHEMIA

Although a significant progress has been made in research on the pathogenicity of amyloid in Alzheimer's disease, the underlying molecular amyloid machinery affecting neurodegeneration after ischemic brain injury is unclear. Herein we present the existing facts regarding amyloidogenic processing of the amyloid protein precursor into amyloid during brain injury due to ischemia and reperfusion, which is associated with the production and accumulation of the N- and C-terminal of amyloid protein precursor and amyloid in the brain. The appearance of an elevated level of β -amyloid peptide in the blood and its staining in the brain after ischemic injury sheds new light on a better understanding of the role of amyloid in the development of neurological deficits following an ischemic episode.

In animals

Different fragments of the amyloid protein precursor staining were observed in the extra- and intracellular spaces after experimental ischemic brain injury (15, 20, 34–37). In animals that survived up to 6 months after brain ischemia with recirculation in the extracellular space of the hippocampus, brain cortex, white matter, and around the lateral ventricles, the N- and C-terminal deposits of the amyloid protein precursor and the β -amyloid peptide were observed (16, 20). The accumulation of different parts of the amyloid protein precursor in various cells, such as the neuronal, glial, microglia, oligodendrocyte, endothelial, pericyte, and ependymal cells, has also been found (15, 20, 38–42). Especially astrocytes around microvessels showed intense staining of many very long, thin processes that adhered to or embraced capillaries. More than 6 months of survival after cerebral ischemia, only the C-terminal staining of the amyloid protein precursor and the β -amyloid peptide was observed (16). Accumulation of β -amyloid peptide in response to transient focal ischemic brain injury does not appear to be a temporary phenomenon, as diffuse β -amyloid peptide deposits turn into plaque about 9 months after ischemic episode (43). After ischemia-reperfusion brain injury, the β -amyloid peptide arises as a result of neuronal ischemic damage (34), and it is likely that this peptide with its own neurotoxic activity further affects ischemic neurons.

In humans

Examination of human ischemic brains has shown that ischemia is associated with the accumulation of β -amyloid peptide in brain tissue (44–46). Studies have

shown both diffuse and senile β -amyloid peptide plaques in areas of the brain prone to ischemia, at arterial border zones and cortex after focal and global cerebral ischemia (44–46). The middle layers of the cerebral cortex, which are very susceptible to ischemic injury, were most commonly affected by amyloid (44–46). The number of amyloid plaques in brain tissue correlated positively with age (44–46). In brains after global cerebral ischemia with a survival of up to 1 month, strong staining of the β -amyloid peptide in neurons and perivascular areas was found (45). The staining of neurons depended on the area of the brain. Neurons from the cerebral cortex and hippocampus were the most intensely stained. The ependymal and epithelial cells were also stained on the β -amyloid peptide. Not all brains had senile amyloid plaques in the cerebral cortex. The cerebral white and gray matter vessels were surrounded by β -amyloid peptide deposits. Deposits in the perivascular space looked like cuffs. In some brains, the walls of the meningeal and cortical vessels were stained for the β -amyloid peptide. Accumulation of amyloid in the perivascular blood vessel space of the blood–brain barrier suggested that the β -amyloid peptide was derived from blood. Some evidence to support this hypothesis comes from clinical studies showing that the β -amyloid peptide in the blood has been elevated in patients after ischemic brain injury (22, 47). According to another study, β -amyloid peptides 1–40 and 1–42 staining were found in the human hippocampus after ischemia (21). This intense staining of various β -amyloid peptides may contribute to the progression of ischemic hippocampus neurodegeneration.

In the brains of patients after global cerebral ischemia caused by cardiac arrest, the immunostaining of the receptor for advanced glycation end products was located both in the cells of the choroid plexus epithelium and in the ependymal cells bordering the brain ventricles (48). These cells form both the cerebrospinal fluid–brain barrier and the blood–cerebrospinal fluid barrier. The β -amyloid peptide was noted by staining in the blood vessels of the choroid plexus and in the basal membrane of the choroid plexus epithelium (48). 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 the β -amyloid peptide in the brain parenchyma but also are a place where amyloid can be removable.

After ischemic brain injury in humans due to cardiac arrest, approximately 70-fold increase in beta-amyloid peptide 1–42 in the serum was found (22). The level of amyloid growth correlated negatively with the complete clinical outcome after ischemic brain injury, which in turn probably reflects the severity of ischemic damage (22). The data confirm that brain ischemia may play a key role in the amyloidogenic processing of the amyloid protein precursor.

TAU PROTEIN STAINING, PHOSPHORYLATION, AND BLOOD LEVEL AFTER BRAIN ISCHEMIA

Although there has been significant progress recently in research on the pathogenicity of the tau protein in Alzheimer's disease, the basic molecular processes associated with the tau protein that affect neurodegeneration after ischemic brain trauma have not been finally clarified. In this analysis, we show that both

ischemia–reperfusion brain damage and the permeability of the blood–brain barrier after ischemia induce tau protein dysfunction. As a result, we suggest that modifications of the tau protein by phosphorylation are dangerous for microtubule activity, especially in neurons, and are involved in the development of irreversible neuropathology in the ischemic brain with Alzheimer's disease dementia.

In animals

Early experimental studies documented tau protein staining in neuronal and glial cells in the hippocampus, thalamus, and cortex after permanent and focal brain ischemia (36, 49–53). The modified tau protein was also observed in microglial cells both in ischemic penumbra and in brain tissue, respectively, after focal and global cerebral ischemia (29, 54). The above data showed that some neuronal and glial cells had changes in the tau protein after ischemic brain damage (52), which may be the main pathological stage of ischemic processes in these cells (53). Another study revealed that tau protein alone can block the transport of amyloid protein precursor in neurons, which leads to the accumulation of the amyloid protein precursor in the body of neuronal cells (55).

Studies have also shown that the phosphorylation patterns of tau protein differed in different models of cerebral ischemia (32). The tau protein was dephosphorylated after total and focal cerebral ischemia (51, 52, 56). During total brain ischemia, the tau protein was dephosphorylated, and during recirculation, it was re-phosphorylated and accumulated in the brain tissue (56). Transient local ischemic brain injury in rats with 24-h recirculation induces site-specific hyperphosphorylation of tau protein (57). An experimental combination of reversible total brain ischemia with hyperhomocysteinemia resulted in an approximate 700-fold increase in the number of hyperphosphorylated positive tau protein neurons in the cerebral cortex compared to control conditions (31). Recent studies indicate that following brain ischemia, hyperphosphorylated tau protein in cortical neurons is integrated with apoptosis (24, 27, 29, 30, 54, 57, 58). Khan et al. (30) showed an increase in the production of paired helical filaments of tau protein after forebrain ischemia in mice. Wen et al. (24, 57, 58) provided evidence that brain ischemia with recirculation is involved in neurofibrillary tangle-like development after local ischemic cerebral injury. Finally, tau protein dysfunction, a typical hallmark of Alzheimer's disease, worsens experimental ischemic brain damage *via* tau protein-mediated iron export (59) and excitotoxicity depending on the tau protein (28, 60).

In humans

Early studies have shown that tau protein staining in neurons and glia is present in the hippocampus, thalamus, and cerebral cortex in the human brain after ischemia (61–63). The modified tau protein was also observed in microglial cells (63). It was noted that microglial cells' tau protein passes independent of phosphorylation modification following cerebral ischemia with recirculation in humans (63). Finally, in one of the studies, many neurofibrillary tangle-bearing neurons were observed in the nucleus basalis of Meynert ipsilateral to a massive focal cerebral infarction (23).

Tau protein was detected in human plasma after complete ischemic brain injury with two peaks after 2 and 4 days, which probably indicates the degree of neuronal damage after ischemia–reperfusion episode (25). The observed bimodal changes in the tau protein in the blood are consistent with the 2 types of neuronal death: first, by necrosis, and second, by delayed neuronal death (26). The presented research suggests that the increase in blood tau protein can be used as a biomarker to assess neurological damage to the brain after ischemia (25, 26).

mRNAs ASSOCIATED WITH THE AMYLOID PROTEIN PRECURSOR AFTER BRAIN ISCHEMIA

Due to the fact that there are some new data in the literature in human and animal studies regarding changes in amyloid protein precursor following ischemia–reperfusion brain damage in this part of the review, we present the first steps in mRNA studies related to the metabolism of the amyloid protein precursor after various types of brain ischemia. This indicates that there is urgent need for data on the new causative pathological role of amyloid in cerebral ischemia, which molecule presumably has an irreversible effect on the post-ischemic outcome.

mRNA of the amyloid protein precursor

After experimental focal ischemic brain damage with reperfusion, the mRNA level of the amyloid protein precursor increased both in the core and in the penumbra, by 150 and 200%, respectively, in 1 week of recirculation (64, 65). In addition, after permanent local ischemic brain injury without recirculation, the mRNA domain of the Kunitz-type protease inhibitor domain-containing amyloid protein precursor in the cortex of the brain was induced for 3 weeks (66). Also after transient local cerebral ischemia, the amyloid protein precursors, 770 and 751 mRNAs, were induced within 1 week of recirculation (67). In addition, 1 h after local ischemic brain damage in ovariectomized rats, the increased mRNA level of the amyloid protein precursor was observed in ischemic brain structures (64). In contrast, estrogen treatment reduces the mRNA level of the amyloid protein precursor in the ischemic brain (64). These data suggest that estrogen therapy can be used to lower the mRNA of the amyloid protein precursor after the ischemic episode.

mRNA of enzymes metabolizing the amyloid protein precursor

The amyloid protein precursor is metabolized by α -secretase, and this process is a non-amyloidogenic process. After experimental ischemic brain injury, the level of α -secretase mRNA decreases (68, 69). The second process is called amyloidogenic process, and the amyloid protein precursor is metabolized by β -secretase and γ -secretase to produce the β -amyloid peptide (70). Some studies have demonstrated that ischemic episode of the brain activates the production and activity of β -secretase after ischemia (71–74). Another study showed changes in mRNA levels of three enzymes that metabolize the amyloid protein precursor: β -secretase,

cathepsin B, and glutaminyl cyclase, which increased in the cortex and hippocampus after ischemia (75).

Three days after ischemic brain injury, the highest level of presenilin 1 mRNA was observed in the neuronal cells of CA3 area of the hippocampus (76). This observation suggests that an elevated level of presenilin 1 mRNA probably is associated with the response of neuronal cells to ischemia. In another study, the increased level of presenilin 1 mRNA showed the maximum growth in the striatum, cortex, and hippocampus after focal ischemic brain damage (77). In the above study, the increased level of presenilin 1 mRNA was greater on the side opposite to local ischemic brain injury. This observation may reflect the disappearance of brain neurons on the ipsilateral side. The mRNA of presenilin 1, which increased after brain ischemia (76, 77), is involved in the production of the β -amyloid peptide by the γ -secretase complex (70, 78). The above data will help understand the progressive neuronal disappearance following the ischemia–reperfusion episode of the brain and the slow, prolonged accumulation of the β -amyloid peptide in ischemic brain tissue (16).

EXPRESSION OF GENES INVOLVED IN THE PRODUCTION OF AMYLOID AFTER BRAIN ISCHEMIA

The ischemic–reperfusion episode of the brain is undoubtedly one of the most common multifactorial forms of neurodegeneration, including many pathological processes occurring during ischemia and recirculation and gradually spreading to various areas of the brain. It seems that the ischemic event in humans and animals is associated with the development of Alzheimer's disease type of neurodegenerative pathology, such as the accumulation of all parts of the amyloid protein precursor after its processing in the amyloidogenic process and dysregulation of Alzheimer's disease-related genes involved in this process. Progress in understanding new proteomic and genomic processes caused by ischemic brain damage in various brain structures that have not yet been fully elucidated will result in new strategies for the treatment of neurodegeneration of the Alzheimer's disease type with full-blown dementia due to ischemia.

CA1 area of the hippocampus and medial temporal cortex

In the CA1 region of the hippocampus and temporal cortex, the expression of the *amyloid protein precursor* gene was below the control value within 2 days after ischemia (79, 80). In the above areas, 7 and 30 days after cerebral ischemia–reperfusion, the expression of the *amyloid protein precursor* gene was above the control value (79, 80). The expression of the β -secretase gene increased above the control value following brain ischemia injury in the CA1 area of the hippocampus 2 to 7 days after recirculation (79). But, 30 days after brain ischemia, the expression of the β -secretase gene was below the control value (79). The expression of the β -secretase gene was above the control value in the temporal cortex after 2 days from ischemic episode (80). The expression of the β -secretase gene was reduced in the temporal cortex 7 and 30 days after

ischemia (80). In the CA1 region, the expression of the *presenilin 1* and 2 gene was increased 2 and 7 days after ischemia (79). But, 30 days post-ischemic injury, the gene expression of *presenilin 1* and 2 was below the control value (79). In the temporal cortex, *presenilin 1* gene expression was lowered below the control value, but *presenilin 2* was above the control value 2 days after ischemia (81). Seven days after ischemia, the gene expression of *presenilin 1* was reduced, and *presenilin 2* was elevated (81). Thirty days post-ischemia, the expression of *presenilin 1* gene was above the control value, and *presenilin 2* was below the control value (81).

EXPRESSION OF THE *TAU* PROTEIN GENE IN THE CA1 AREA AFTER BRAIN ISCHEMIA

In the neurons of CA1 area of the hippocampus, the tau protein encoding gene expression increased above the control value on the 2nd day after brain ischemia (33). On the 7th day of reperfusion after ischemic episode, the gene expression oscillated in the range of control values (33). On the 30th day of recirculation after brain ischemia, the expression of the *tau protein* gene was below the control value (33). The statistical significance of changes in the expression of the *tau protein* gene after brain ischemia–reperfusion injury in rats was between 2 and 7, and 2 and 30 days of recirculation (33).

EXPRESSION OF GENES INVOLVED IN THE DIRECT DEATH OF NEURONS AFTER BRAIN ISCHEMIA

One of the risk factors of Alzheimer's disease is aging, and for that reason, a large number of scientists believe that the main cause of Alzheimer's disease is brain ischemia closely related to age. It seems that brain injury caused by ischemia and reperfusion facilitates the development of irreversible neurodegeneration similar to Alzheimer's disease as a result of neuronal death, synaptic dysfunction, inflammatory changes, white matter damage, and general brain atrophy, which changes are closely related to genes involved in neuronal death in Alzheimer's disease. Despite the years of expansion, the amyloid Alzheimer's disease theory has not solved the etiology of the disorder (82), and the current research suggests that brain ischemia leads to neurodegeneration of Alzheimer's disease through numerous terminal events, such as dysregulation of genes that cause cell death in various brain structures of varying intensity. Understanding the basic pathological pathways causing proteomic and genomic changes associated with Alzheimer's disease and induced by cerebral ischemia will help in the development of neurodegenerative dementia treatment after ischemia.

CA1 area of the hippocampus

Expression of the *autophagy* gene in the CA1 region of the hippocampus after brain ischemia with 2, 7, and 30 days of recirculation was within the control

limits (83). Two days after ischemic brain injury, the expression of the *mitophagy* gene in the CA1 region increased above the control value. Seven and 30 days after ischemia–reperfusion injury of the brain, the gene expression was within the control range. Overexpression of the *caspase 3* gene in the CA1 region was observed after 2 and 7 days of recirculation. However, 30 days after ischemic brain injury, the gene expression was below the control value.

Medial temporal cortex

Two days after ischemic brain injury, *autophagy* gene expression increased above the control value in the medial temporal cortex (84). However, 7 and 30 days after ischemia–reperfusion brain injury, *autophagy* gene expression decreased. Two days after cerebral ischemia, *mitophagy* gene expression decreased below the control value (84). Nevertheless, 7 and 30 days after ischemic brain injury, the expression of the *mitophagy* gene increased above the control value. Two days after cerebral ischemia, the expression of *caspase 3* gene decreased below the control value (84). However, 7 and 30 days after brain injury due to ischemia and reperfusion, *caspase 3* gene expression increased above the control value.

THE RELATIONSHIP BETWEEN IRON DYSHOMEOSTASIS AND AMYLOIDOGENESIS

Both the amyloid protein precursor and iron play a key role in brain neurodegeneration due to Alzheimer's disease and cerebral ischemia (59, 85–88). Alzheimer's disease is primarily characterized by the deposition of amyloid plaques and the formation of neurofibrillary tangles which co-localize with iron (88). Under physiological conditions, the amyloid protein precursor is processed primarily on the non-amyloidogenic pathway by α -secretase, thereby producing the neuroprotective ectodomain of the soluble amyloid protein precursor α and the carboxy-terminal fragment α . Alternatively, a small pool of amyloid protein precursor is processed by the amyloidogenic pathway using β -secretase, thereby producing a soluble amyloid protein precursor β and carboxy-terminal fragment β . The carboxy-terminal fragment β is further cleaved by γ -secretase, resulting in β -amyloid peptides.

Iron is gradually deposited in selected areas of the brain during Alzheimer's disease, as well as in the course of ischemic neurodegeneration (59, 85–88). In the brain, iron is present in neurons, oligodendrocytes, astroglia, and microglia cells. Excess iron is associated with oxidative stress and neuronal damage because iron accumulation in neurons can cause free radical production and mitochondrial dysfunction and ultimately lead to neuronal death. In addition, iron can induce hyperphosphorylation and aggregation of tau protein. Deficiency of tau protein leads to iron accumulation, which is associated with impaired transport of the amyloid protein precursor to the cell membrane (59, 87). Therefore, iron accumulation in brain cells must be strictly regulated to maintain basic cellular function and avoid cytotoxicity. The evidence obtained confirms the role of the amyloid protein precursor in maintaining iron homeostasis

in brain tissue (86). It has been demonstrated that the amyloid protein precursor and soluble amyloid protein precursor α facilitate iron outflow by stabilizing the iron exporter ferroportin 1 on the cell membrane (86, 87). In contrast, ablation of the amyloid protein precursor in neurons causes iron retention (87), while the knockout of the amyloid protein precursor in mice causes iron accumulation in the brain (86). While the amyloid protein precursor affects iron export, the inverse is also true because iron modulates the metabolism of the amyloid protein precursor (86). Iron and interleukin 1 levels in cells regulate translation of the amyloid protein precursor by acting on an iron-responsive element found in the 5' untranslated region of the amyloid protein precursor mRNA (87, 89). Iron has also been shown to affect the processing of the amyloid protein precursor and the production of β -amyloid peptides. In addition, the activation of α -secretase and β -secretase is proteolytically modulated by furin; furin protein levels are reduced under conditions of excess iron, which promotes β -secretase activity, thereby promoting amyloidogenesis (87). Iron and inflammation promote amyloid toxicity (87). Recent experimental studies showed that: (i) iron overload increased retention in the neurons of the soluble amyloid protein precursor α , (ii) iron overload reduced the extracellular levels of the soluble amyloid protein precursor α and β -amyloid peptide, and (iii) the direct molecular target of iron is β -secretase (86).

Given the key physiological and pathological role of the amyloid protein precursor and its cleavage products in the brain, it is likely that iron overload may affect neuronal activity, interfering with the normal processing of the amyloid protein precursor. Although it is unclear what mechanism causes abnormal intracellular retention of the soluble amyloid protein precursor α , there is evidence that cell accumulation of the soluble amyloid protein precursor α may be due to intracellular cleavage of the amyloid protein precursor by α secretase or the internalization of the extracellular soluble amyloid protein precursor α by cell surface receptors (90, 91). Together, evidence of the beneficial role of the secreted soluble amyloid protein precursor α indicates that iron overload mediates the decrease in secreted soluble amyloid protein precursor α , which can lead to harmful consequences. This possibility is particularly important in neurological diseases, given that the secretion of the soluble amyloid protein precursor α affects many brain disorders, including Alzheimer's disease and cerebral ischemia (85–88). In addition, it has recently been suggested that the loss of β -amyloid peptide function, rather than its accumulation, plays a pathogenic role in Alzheimer's disease (92). In summary, iron overload affected non-amyloidogenic as well as amyloidogenic metabolism of the neuronal amyloid protein precursor. In addition, it was confirmed that the soluble amyloid protein precursor α is an endogenous inhibitor of β -secretase activity, potentially affecting the production of β -amyloid peptide (86). As iron directly inhibits β -secretase activity, it is likely that increased iron primarily inhibits β -secretase and the amyloidogenic pathway and promotes the non-amyloidogenic pathway and retention of the soluble amyloid protein precursor α . β -secretase activity is then inhibited by the growth of the soluble amyloid protein precursor α (86). These abnormal iron-induced changes form a *vicious circle* that leads to dysregulation of the processing of amyloid protein precursors in neurons.

CONCLUSION

Although there are reasonable doubts about the effects of cerebral ischemia on the development of Alzheimer's disease, the mounting evidence on the ischemic theory of Alzheimer's disease should not be ignored. Ignoring the numerous scientifically substantiated clinical and experimental data on the connection between brain ischemia and Alzheimer's disease will hamper not only the proper understanding of the disease mechanism but also the development of complementary and alternative strategies for the treatment and management of Alzheimer's disease. The conclusions drawn from the study of ischemia-induced Alzheimer's disease-associated proteins and their genes in the hippocampus and the medial temporal cortex, which contribute to the death of neurons, the production of the β -amyloid peptide, and neurofibrillary tangle-like formation, are important for the development of treatment goals in the therapy of Alzheimer's disease. As deposits of amyloid and tau protein may not be the cause in the pathogenesis of Alzheimer's disease, further research is needed in this field. Animal models of cerebral ischemia seem to be a useful experimental approach in determining the role of folding proteins and their genes in the neurodegenerative process of sporadic Alzheimer's disease.

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