

● PERSPECTIVE

The role of degenerative pathways in the development of irreversible consequences after brain ischemia

Ischemic stroke and irreversible consequences: Ischemic stroke in humans is the second most common cause of death in the world (Mozaffarian et al., 2016). The outcomes after a stroke are often dependent on complications, including motor disorders, depression and dementia (Pluta et al., 2018a), which causes a high risk of re-hospitalization and/or palliative care. This is also the main reason for long-term disability in people after stroke, with up to half of those who survived the stroke will not regain their independence until the end of their lives (Mozaffarian et al., 2016). According to epidemiological forecasts, human ischemic stroke will soon become the dominant cause of death worldwide (Bejot et al., 2016) as well as dementia with the phenotype of Alzheimer's disease (AD; Kim and Lee 2018). It is suggested that human ischemic stroke and experimental brain ischemia in animals are associated with the possible development of AD neuropathology (Pluta et al., 2018a). Epidemiological observations have shown that brain ischemia is a contributing factor to the development of AD and *vice versa*. Below we present the latest advances in the investigation of brain ischemia-reperfusion injury, focusing on ischemia-induced of the AD phenotype and genotype in humans and animals. We focus in this report on the very likely association between β -amyloid peptide and tau protein in humans (Qi et al., 2007) and animals with post-ischemic irreversible neurodegenerative processes and development dementia. It should be emphasized that despite the fact that stroke in humans is one of the main causes of disability, dementia and death in the world, it has no effective therapy improving outcome of the functional and structural irreversible consequences of this disease.

A new look on post-ischemic brain: Brain ischemia is undoubtedly one of the most common multifactorial forms of neurodegeneration, including a number of abnormal molecular mechanisms occurring during ischemia and at different times during recirculation and gradually spreading to various brain structures. The ischemic episode seems to favor the development of neurodegenerative changes of AD type by neuronal death, neuroinflammation, accumulation of different fragments of the amyloid protein precursor, tau protein dysfunction and dysregulation of AD-related genes, changes in the white matter and general brain atrophy (Pluta et al., 2018a). Progress in understanding new key processes induced by brain ischemia like changes in the phenotype and genotype of the AD type which are not yet fully explained will help develop strategies for prevention and treatment against neurodegeneration and dementia induced by ischemia.

Neuropathology: In the hippocampus and cortex, the death of neuronal cells was demonstrated in the CA1 region and in 3, 5, and 6 cortical layer within 2–7 days after brain ischemia (Pluta et al., 2018a). In later times, after ischemic brain injury, in different brain structures, apart from local loss of neurons, various types of changes in neurons were observed. The lesions of the white matter and the activation of glial cells in brain tissue have been reported in both animals and humans after ischemia. Brain ischemia promotes the increased permeability of the blood-brain barrier, which facilitates the penetration of inflammatory cells into the brain, the β -amyloid peptide as well as tau protein from the circulatory system into the brain tissue, which in turn leads to increased changes in the white matter and progressive brain atrophy (Pluta et al., 2018c). Amyloid accumulation is observed both in the brain tissue and in the cerebrovascular walls after ischemia in animals (Pluta et al., 2018a) and humans (Qi et al., 2007). Extracellular amyloid deposits occur mainly as irregularly distributed diffuse amyloid plaques. In humans, amy-

loid plaques stained with thioflavin S, while in experimental animals they did not (Pluta et al., 2018a). Accumulation of amyloid in the walls of the cerebral vessels due to ischemia with cerebral vasospasm may additionally cause recurrent ischemic changes and develop a self-driving vicious circle of additional repeated ischemic episodes, ultimately leading to irreversible brain damage and atrophy.

Amyloidogenic pathway in post-ischemic brain: In the hippocampus and temporal cortex, the expression of the amyloid protein precursor gene was recorded below the control values within 2 days after brain ischemia (Kocki et al., 2015; Pluta et al., 2016b). However, on days 7 and 30 after ischemia, the increased expression of the amyloid protein precursor gene was observed above the control values in both brain structures. Expression of the β -secretase and presenilin 1 and 2 genes increased above the control values in the rat hippocampus 2–7 days after ischemic injury. Thirty days after ischemia, the expression of above genes was below the control values. There was an increased expression of the β -secretase gene in the temporal cortex 2 days after brain ischemia (Pluta et al., 2016b). Seven and thirty days after ischemia, the β -secretase gene expression was significantly reduced. In the temporal cortex there was a decrease in the presenilin 1 gene expression below control values, whereas presenilin 2 expression was above control values 2 days after brain ischemia (Pluta et al., 2016a). Seven days after ischemia still reduction of presenilin 1 gene expression was observed, but presenilin 2 was significantly elevated. Thirty days after the end of ischemia, the expression of the presenilin 1 gene increased and the presenilin 2 decreased below the control values. The course of events in the medial temporal lobe cortex seems slower and/or less pronounced in relation to the events in the hippocampus.

Tau protein in post-ischemic brain: Microtubule-associated tau protein is hypophosphorylated in ischemic brain injury in humans as well as in experimental animals resulting in neuronal development of neurofibrillary tangles in humans and/or neurofibrillary tangle-like tauopathy in animals (Pluta et al., 2018c) that are characteristic for neuropathology of the AD type. On the second day after experimental ischemia in the hippocampus, the expression of the tau protein gene increased approximately 3-fold in relation to the control values (Pluta et al., 2018b). On the seventh and thirtieth day after ischemia, the expression of the tau protein gene oscillated in the range of control values. It can therefore be suggested that the overproduction of the β -amyloid peptide with the increased hyperphosphorylation of the tau protein appears to be a very important consequence of brain ischemia resulting in increased sensitivity of the neuronal cells to ischemia. Expression of the tau protein gene correlates with the increase in the tau protein level in the blood in humans after ischemic episode and accumulation in the extracellular space after brain injury, as well as the hyperphosphorylation of tau protein following brain ischemia (Pluta et al., 2018c). Additionally, the level of tau protein in serum predict neurological outcome in patients after ischemic brain injury due to cardiac arrest.

Genes responsible for autophagy, mitophagy and apoptosis in post-ischemic brain behave as in AD: It was found that the expression of the autophagy gene in the hippocampus did not undergo significant modification within 2–30 days after ischemic brain injury (Ułamek-Kozioł et al., 2017). But the expression of the mitophagy gene was significantly elevated on day 2 and decreased below the control values on days 7 and 30. Expression of the caspase 3 gene in the hippocampus 2 days after ischemia increased more than 3-fold compared to the control value (Ułamek-Kozioł et al., 2017). But 7 days after ischemia, its expression was close to the control value and was reduced below the control on the 30th day. In the temporal cortex, autophagy gene expression was increased within 2–30 days after brain ischemia (Ułamek-Kozioł et al., 2016). Expression of the mitophagy gene decreased below control values within 2 days after ischemia. But during 7–30 days after ischemia, the expression

of the mitophagy gene increased above control values. Expression of the caspase 3 apoptosis gene was reduced below the control values 2 days after ischemia. Seven and thirty days after ischemia, the expression of caspase 3 gene increased significantly above control values (Ułamek-Kozioł et al., 2016).

Conclusion and future perspective: Thus, the knowledge of the underlying progressive neuropathological mechanisms in the irreversible consequences development after brain ischemia is urgently required. Here, we discuss new pathways of ischemic neurodegeneration with AD phenotype, focusing on the expression genes of amyloid protein precursor and enzymes that metabolize this protein to the β -amyloid peptide and the tau protein post-ischemia. Increased expression of the tau protein gene and level of its protein, and the amyloidogenic pathway after brain ischemia sheds new light on a better understanding role of dysfunctional tau protein and β -amyloid peptide as the additional cause of pathology in post-ischemic brain. Although significant advances have recently been made in studies on the pathogenicity of β -amyloid peptide and tau protein following ischemia, the underlying mechanisms of amyloid and tau protein-induced post-ischemic irreversible neurodegeneration are yet unclear. In addition, dysfunction of genes for autophagy, mitophagy and apoptosis after ischemia has been found, which genes are important factors in the development of AD. The explanation of the final mechanisms of action of the above factors after brain ischemia requires further intense research, when at present we only touched the top of the iceberg. Therefore, understanding new additional phenomenon associated with the death of neurons after brain ischemia is critical to the development of effective treatment of ischemic stroke with irreversible consequences. This type of research can help determine the requirements for the implementation of new therapies for post-stroke consequences and may be important in guiding and assessing future prevention priorities.

Research should continue on a new “mass approach” aimed at identification and understanding the hitherto unknown metabolic pathways to minimize the consequences after brain ischemia. This interesting and innovative way of recognizing events after brain ischemia should be based on international cooperation using modern equipment for genetic and proteomic research and well characterized experimental models of brain ischemia. These observations will help to explain progressive brain damage following ischemia, accumulation of amyloid and slow development of AD type neuropathology that spreads from ischemic hippocampus to temporal cortex and further to other brain structures. Furthermore, the data show that ischemic brain injury activates neuronal death in the hippocampus and temporal cortex involving amyloid and tau protein (Kocki et al., 2015; Pluta et al., 2016b, 2018b), thus defining a new phenomenon regulating neuronal survival and/or death after ischemia. In addition, processes in which autophagy, mitophagy and caspase 3, amyloid and tau protein together or separately induce neuronal death are not completely understood and require a quick explanation. However, we believe that the understanding of above processes and the minor changes that are taking place in ischemia is the key to successful development treatment strategies that will facilitate recovery at all stages post-ischemic injury.

In vivo monitoring AD related genes and their proteins using well define our model of brain ischemia in rats opens the way to a better understanding neuropathology and the development dementia post-ischemia. Although, role of amyloid and tau protein after ischemia is generally complex and requires further explanation, and the amyloid and tau protein represents a relatively under-investigated factors in ischemic brain. We have reason to believe that determining the role of the amyloid and tau protein in stroke may contribute to understanding the basis for developing a new target for the treatment post-ischemic brain in humans. Finally, regulation of amyloid and tau protein behavior can be considered as potential new therapeutic targets after brain ischemia. Embarking on this path, it should be further addressed what aspects of harmful or beneficial signaling by amyloid and tau protein are dysregulated after brain ischemia, which can affect the neuron's network.

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