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Alzheimer's Disease Associated Genes and their Products in Brain Ischemia: Impact of Ischemia on the Pathogenesis of Alzheimer's Disease

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ABSTRACT

Ongoing interest in brain ischemia research has provided data showing that ischemia may be involved in the etiology of Alzheimer's disease. Brain ischemia in animals leads to metabolic and structural changes within the special brain areas like in Alzheimer's disease it is in the hippocampus. Ischemia is the second naturally occurring pathology, including the Alzheimer's disease, which causes neurons death in the CA1 region of the hippocampus. Brain ischemia has been found as the most effective predictor for the development of Alzheimer's-type dementia. Postischemic dementia might be the result of direct influence of ischemia, ischemic white matter changes and Alzheimer's-type neuropathology, or combinations of these three. Animals after ischemia with short-term survival up to 6 months showed strong intracellular staining to the N-terminal of amyloid protein precursor and to the β-amyloid peptide and as well as to the C-terminal of amyloid protein precursor. But after 6 months, animals demonstrated strong intracellular staining only to the β-amyloid peptide as well as to the C-terminal of amyloid protein precursor. Extracellular metabolite of amyloid protein precursor deposits especially in hippocampus ranged from numerous widespread small dots to irregular diffuse plaques. Recent knowledge regarding the activation of Alzheimer's-related genes and proteins as well as neuropathology of both brain ischemia and Alzheimer's disease indicate that similar processes contribute to neuronal death and brain parenchyma disintegration and finally dementia. We present the concept that Alzheimer's-associated genes and their proteins can contribute to and/or trigger postischemic brain pathology, including dementia of Alzheimer's phenotype. Over time, some brain regions, especially the hippocampus would become increasingly at risk of chronic ischemia, leading to progress the neuropathological changes of Alzheimer's-type. Nevertheless, altered by ischemia brain predisposes to progressive neuronal damage, dysfunction and death, induction of Alzheimer's-related genes and proteins and finally lead to acute or chronic neuropathology, including full-blown dementia of Alzheimer's phenotype. Ischemia indicates a vascular system as probable factor that induces neurodegeneration and full-blown dementia in Alzheimer's disease.

Key words: Brain ischemia, Alzheimer's disease, gene, protein, amyloid protein precursor, presenilin 1 and 2, beta-secretase, tau protein, autophagy, mitophagy, apoptosis

INTRODUCTION

Alzheimer's disease is a progressive and irreversible disease with changes in behavior and personality and with final diagnosis available post mortem after brain autopsy. Although there are rare cases with familial form (circa 5%) of Alzheimer's disease, the majority of patients have the sporadic form (>95%) of the disease. This disease is the most important cause of dementia in world aged society (~75%). The continuing neuronal death in vulnerable brain regions e.g. in hippocampus and progressive dementia in individuals with Alzheimer's disease are related with the presence of extracellular diffuse and senile amyloid plaques and intraneuronal neurofibrillary tangles in diseased brains neurons. The recent calculation for population suffering from Alzheimer's disease is between 15-20 million patients' worldwide [Hu et al., 2007]. As the world population grows and mean life spans go on to lengthen, the incidence of Alzheimer's disease is calculated to be between 30-40 million worldwide by 2050 [Hu et al., 2007]. In 2014, the direct cost of Alzheimer's disease for payers in the USA

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alone was estimated to be $214 billion [Winblad et al., 2016]. The neuropathological changes associated with Alzheimer's disease begin decades before the emergence of clinical symptoms. The cause of sporadic Alzheimer's disease is unclear. The series of events that lead to neuronal death especially in hippocampus during disease is not clearly understood. As a result of above, no etiology, no diagnosis ante mortem and no causal therapy stopping the progression of this devastating disease is actually present [Pluta et al., 2013]. The road to clarity of Alzheimer's disease etiology, early final ante mortem diagnosis and causal treatment has been one fraught with a wide range of complications and numerous revisions with a lack of a final solution.

Alzheimer's disease is the one of the great health-care challenges of the 21st century. In December 2013, the G8 stated that dementia including Alzheimer's disease type dementia should be made a global priority and their ambition that a cure or a disease-modifying therapy should be available by 2025 [Scheltens et al., 2016]. Alzheimer's disease etiology so far is an unresolved issue, as can be seen by the Alzheimer's disease Research Contest announced by the US Department of Defense at the end of 2017. While the study of Alzheimer's disease etiology to date have focused on "amyloid hypothesis" without final conclusion, other etiology approaches may be necessary. We propose as first an alternative idea to the "amyloid hypothesis", the "ischemic theory" of Alzheimer's disease [Pluta et al., 1994b, Pluta 2007, Pluta et al., 2009]. At present, the involvement of brain ischemia in the pathogenesis of sporadic Alzheimer's disease has attracted considerable interest.

Vessel pathology in the first case of Alzheimer's disease

Alois Alzheimer in the first case of Alzheimer's disease reported that in the brain of Augusta D. he had noted that "a growth appears on the endothelia, in some places also a proliferation of vessels" and "the larger vascular tissues show arteriosclerosis changes" [Alzheimer 1907]. It seems that the endothelial proliferation and revascularization were a direct consequence of the brain ischemia-reperfusion injury. Endothelial proliferation and blood-brain barrier vessel angiogenesis and moderate arteriosclerosis in the brain arteries of the first case provide strong evidence that neurovascular pathologies were also evident in the original case of Alzheimer's disease [Alzheimer 1907].

Small vessel pathology in Alzheimer's disease

Microvascular changes have been consistently observed in almost all-human Alzheimer's disease brains examined post mortem and in brain biopsy tissue from patients with Alzheimer's disease [Kalaria 2002]. Capillary degenerations appear more prevalent in the hippocampus, a sector that is linked to learning and memory and is primary target for Alzheimer's disease and brain ischemia neuropathology [Pluta 2000, Pluta et al., 2009]. Additionally, microvascular pathology in Alzheimer's disease patients did not correlate to the degree of the disease development and suggest that capillary changes are not a consequence but cause of neuropathology in Alzheimer's disease [De Jong et al., 1999]. The different types of cerebrovascular lesions that have been associated with Alzheimer's disease include: 1) presence of cerebral small vessels amyloid angiopathy, 2) microvascular degeneration (endothelial and pericytes degeneration, basement lamina thickening, collagen accumulation, tortuosity, fibrohyalinosis, lipohyalinosis), 3) changes of the blood-brain barrier, 4) white matter lesions and lacunas, 5) large brain infarcts and microinfarcts and presence of intracerebral hemorrhages [Kalaria 2002]. Post mortem examination has presented a very strong correlation between brain capillary amyloid angiopathy and both β-amyloid peptide plaque accumulation and development of Alzheimer's disease neuropathology [Attems, Jellinger 2004]. Experimental ischemic study revealed that almost identical capillary alterations, as such in Alzheimer's disease patients, could be formed in animals with prevalence in CA1 sector of hippocampus [De Jong et al., 1999]. The role of microvascular pathology in Alzheimer's disease is to this very day a matter of confusion and controversy.

Dementia

Dementia is a general term for symptoms exhibited by people with different kinds of cognitive impairment. These symptoms may include impaired mental functioning in areas such as memory, learning, judgment, attention, concentration, language and thinking. They are often accompanied by personality and behavioral changes. There seem to be peaks in the incidence of dementia - one in patients in their early 40's and 60's and another in patients in their 70's and 80's.

Postischemic dementia of Alzheimer's disease phenotype

In Humans

A more insidious consequence of ischemic brain injury in humans is a progressive postischemic dementia that is also linked with severe disability [Pluta 2007, Pluta et al., 2013, Frisch et al., 2017, Sherzai et al., 2018]. Epidemiological studies have shown that the prevalence of dementia in postischemic brain injury individuals is 9-fold higher than in controls after 3 months and 4–12 times higher than in controls 4 years after a lacunar infarct [Pluta 2007, Yang, Simpkins 2007, Kim, Lee 2018]. Different patterns of cognitive decline, as a result of postischemic injury, have been evident by longitudinal epidemiological studies, which have demonstrated a progressive course of dementia with the incidence rate of 9/100 persons/year. Dementia is the worst consequence for survivors following brain ischemia and it is responsible for approximately 20 % of all confirmed

dementias [Pluta 2007, Yang, Simpkins 2007, Pluta et al., 2013]. Globally, dementia, following ischemic stroke, varies from 10 % to 50 % depending on the diagnostic criteria, geographic location and population demographic [Pluta 2007, Yang, Simpkins 2007, Pluta et al., 2013]. In fact, it is becoming clear that postischemic dementia has many risk factors in common with sporadic Alzheimer's disease. Indeed, brain ischemic injuries may precede the onset of this form of dementia, strongly suggesting that brain ischemic episodes may trigger neurodegenerative dementias. Postischemic dementia associated with chronic delayed secondary injury occurs in patients suffering from focal, lacunar and salient brain ischemia in a progressive manner [Pluta 2007, Yang, Simpkins 2007, Pluta et al., 2013]. The progressive postischemic injury has received far less attention in clinical and experimental dementia studies.

In Animals

In addition to ischemic neuronal lesions in animals after brain ischemia, behavioral changes have been shown, too [Bara de la Tremblaye, Plamondon 2011, Kiryk et al., 2011, Li et al., 2011, Cohan et al., 2015]. Following ischemic brain injury, locomotor hyperactivity has been observed [Ishibashi et al., 2006] as in Alzheimer's disease individuals [Pluta et al., 2013]. Longer ischemia and longer locomotor hyperactivity, which are positive, correlated with increased pyramidal neurons loss in hippocampus [Ishibashi et al., 2006]. After ischemic brain injury, impairment in habituation, as revealed by an increase in exploration time, was observed. Brain ischemia results in reference and working memory deficits [Kiryk et al., 2011]. Moreover, ischemic brain injury in animals leads progressively to spatial memory deficits during the survival period [Kiryk et al., 2011]. In addition, evidence from repetitive ischemic brain injury has shown persistent locomotor hyperactivity, severe cognitive deficits and reduced anxiety [Ishibashi et al., 2006]. The behavioral changes in animals, mentioned above, were associated with significant brain atrophy and neuronal loss in the CA1 subfield of hippocampus, brain cortex, caudate nucleus, amygdala, and perirhinal cortex [Ishibashi et al., 2006, Pluta et al., 2009, Barra de la Tremblaye, Plamondon 2011, Kiryk et al., 2011, Li et al., 2011, Pluta et al., 2013]. Alertness and sensorimotor capacities are affected for 1–2 days whereas the deficits in learning and memory seem to be irreversibly progressing and lasting for good [Kiryk et al., 2011, Pluta et al., 2013].

Possible factors contributing to cognitive impairment

Removal of the above abnormalities is an issue that neurologists and scientists devote little time to. Ischemic brain injury often leaves its victims functionally devastated and, as such, is the leading cause of permanent disability requiring long-term institutional care. The loss of life quality for years and health care resources are staggering. The situation is even aggravated by the fact that unlike many cases of other neurological diseases, no safe, causal and effective therapy is available for the patients with postischemic dementia. The social burden after brain ischemia is dramatically increasing. Thus, understanding of the underlying progressing neuropathological processes is urgently needed.

Taken together, supporting evidences from both clinical and experimental investigations showed that the progressive decline of cognitive activities could not be explained only by the direct contribution of the primary ischemic brain injury, but rather by a progressive consequence of the additive effects of the postischemic injury, Alzheimer's disease associated factors and aging [Pluta et al., 2013, Popa-Wagner et al., 2018]. The available data suggest that brain ischemia enhances amyloid protein precursor expression and metabolism, which may be partly involved in the progression of cognitive impairment in the postischemic period [Pluta et al., 2009, Pluta et al., 2013, Kocki et al., 2015, Pluta et al., 2016a, Pluta et al., 2016b, Ułamek-Kozioł et al., 2016, Ułamek-Kozioł et al., 2017]. At last, the generation of β-amyloid peptide in postischemic brain parenchyma increases which impairs the memory [Pluta et al., 1991, Pluta et al., 1994b, Badan et al., 2004, Pluta et al., 2009]. Also overexpression of tau protein gene and its product was shown after ischemia-reperfusion brain injury [Tanimukai et al., 1998, Pennypacker et al., 1999, Pluta 2001, Pluta et al., 2018]. Additionally, pathological postischemic accumulation of α-synuclein might disrupt synaptic activity, resulting in cognitive suffering [Pluta et al., 2013]. The functional abnormalities precede the neuronal degeneration within the areas of selective vulnerability to ischemia. What is more, areas of brain, which are devoid of ischemic neuronal injury, display functional abnormalities. The above alterations seem to be mainly due to synaptic insufficiency in connections of neuronal cells within areas with ischemically damaged or dead neurons.

Brain ischemia as possible trigger of sporadic Alzheimer's disease

Alzheimer's disease is characterized by loss of neurons, amyloid plaques, neurofibrillary tangles, cerebral amyloid angiopathy and dementia development. In Alzheimer's disease, there is a positive correlation between areas with heavy β-amyloid peptide deposition and those which are damaged in the brain [Pluta et al., 2013]. On the other hand, quantitative measure of β-amyloid peptide level did not correlate with Alzheimer's disease duration [Pluta et al., 2013]. This may be interpreted as follows: it seems that β-amyloid peptide could not continue accumulating in the brain during the disease development. Although the extent of neuronal death is directly correlated with the intensification of dementia [Pluta et al., 2013], the mechanism leading to the neuronal cells loss still remain unclear. It is a matter of controversy whether the pathological cascade of β-amyloid

peptide in Alzheimer's disease is primarily triggered by intraneuronal or extracellular accumulations of β-amyloid peptide and will contribute directly or indirectly, if at all, to Alzheimer's disease development with massive neuronal loss. Investigation on transgenic animals demonstrates that the mechanism of neuronal death did not correlate with the presence of tau protein filament formation within individual neurons which are going to die, suggesting that neuronal death can occur independently of generation of neurofibrillary tangles [Andorfer et al., 2005]. Moreover, there is evidence to support the above results that some neurons in Alzheimer's disease may die without forming neurofibrillary tangles [Armstrong 2006, Pluta et al. 2013]. It can be concluded that there is no relationship between amyloid plaques and neurofibrillary tangles and developing dementia in Alzheimer's disease, and amyloid plaques and neurofibrillary tangles may arise as independent alterations and can result from a neurodegenerative processes rather than being their cause. These seem to provide an additional conclusion that neuronal death may not result directly and/or primarily from amyloid plaques and formation of neurofibrillary tangles but rather it might be associated with other pathological factor(s). Another important pathological element in Alzheimer's disease is β-amyloid peptide accumulation in brain small blood vessels. The β-amyloid peptide deposition in brain small blood vessels causes wall pathology in vascular network and results in blood–brain barrier changes and focal "no-reflow phenomenon". The collapse of such a barrier leads to spread of blood β-amyloid peptide into the surrounding brain parenchyma [Pluta et al., 1996]. Examination of amyloid plaques made by using serial sections of Alzheimer's disease brains by both electron and light microscopy in order to observe the relationship between plaques and microvessels can be summarized as follows: (1) The cores of the typical senile plaques appear in tight contact with the microvessels and the β-amyloid peptide spread into the surrounding brain parenchyma [Armstrong 2006]. The composition of senile plaques core includes complement factors and immunoglobulin's [Armstrong 2006]. The presence of immune proteins within the plaques core suggests that blood immunological components could be entangled in the structure of β-amyloid peptide deposits. (2) Different types of plaques have a close link to the capillaries. (3) Both confocal laser scanning microscopy and scanning electron microscopy demonstrated a direct link between the β-amyloid peptide and vascular network, especially β-amyloid peptide 1–40. Additionally, confocal laser scanning microscopy has demonstrated that β-amyloid peptide 1–40 depositions occur in and around neurovessels. The above mentioned results seem to indicate that some changes of the blood–brain barrier can induce transport of blood β-amyloid peptide 1–40 into the brain parenchyma of Alzheimer's disease patients. (4) The global atrophy of the brain, especially of the hippocampus and alterations of astrocytic cells (vascular end-feet) are common hallmarks in Alzheimer's disease [Armstrong 2006]. From this point of view, dysfunction of the blood–brain barrier is an important element with regard to the neuropathological damage observed in Alzheimer's disease brains.

The discovery of mutations within amyloid protein precursor gene led to the suggestion of primary pathological role for metabolite of amyloid protein precursor in Alzheimer's disease. This data has supported the formulation of the "amyloid hypothesis" of Alzheimer's disease in which the deposition of β-amyloid peptide is the trigger of neuropathological events in Alzheimer's disease and of all subsequent pathologies. Nevertheless, the etiology based on "amyloid hypothesis" of sporadic Alzheimer's disease has not yet been cleared up and probably is baseless. The results presented so far suggest that amyloid protein precursor and presenilin genes overexpression may not be the direct cause of different forms of Alzheimer's disease cases but probably they could influence the neurochemical components of a resulting pathology, and therefore indirectly affect the levels of neurotoxicity and extent of secondary neurodegeneration [Pluta et al., 2013, Kocki et al., 2015, Pluta et al., 2016a, Pluta et al., 2016b, Ułamek-Kozioł et al., 2017, Pluta et al., 2018]. Conversely, in transgenic animal brains, with high blood levels of β-amyloid peptide in systemic circulation, no detectable depositions of β-amyloid peptide appeared [Pluta et al., 2013]. Basing upon evidence of no difference in the level of blood β-amyloid peptide 1–40 and β-amyloid peptide 1–42 among cases of sporadic Alzheimer's disease and control individuals, finding out that more numerous deposits of β-amyloid peptide 1–40 and β-amyloid peptide 1–42 were noted in brains of Alzheimer's disease patients than in controls strongly suggests that a certain dysfunction of the blood-brain barrier could induce an abnormal passage of β-amyloid peptides from systemic circulation to the brain tissue in Alzheimer's disease patients [Pluta et al., 1996]. Additionally, plaque-like degeneration of arteries and capillaries and considered that the core of senile plaques might consist of material that had permeated from the circulatory network was observed [Armstrong 2006]. Therefore passage to and accumulation of serum β-amyloid peptide into the surrounding brain parenchyma and vessel wall may require interrupted blood–brain barrier. Some risk factors for Alzheimer's disease development like brain ischemia are known to disrupt blood–brain barrier integrity and thereby can allow transportation of peripheral β-amyloid peptide into the surrounding brain parenchyma [Pluta et al., 1996]. For this reason, a detailed study on the role of ischemic factor in sporadic Alzheimer's disease should be carried out as a priority. It should be mentioned that there is still controversy whether ischemic-type dementia is a different entity from Alzheimer's disease dementia or merely two extreme descriptions of the same clinical condition. Currently, a considerable and growing body of evidence suggests that ischemic mechanism(s) in combination with overexpression of Alzheimer's disease-connected genes are present in Alzheimer's disease

development [Pluta et al., 2013, Kocki et al., 2015, Pluta et al., 2016a, Pluta et al., 2016b, Ułamek-Kozioł et al., 2016, Ułamek-Kozioł et al., 2017, Pluta et al., 2018]. Lately, brain ischemia has been recognized as a factor lowering the threshold of neuronal death. Neuropathological post mortem examinations of Alzheimer's disease brains have shown that 30% of patients showed evidence of postischemic injury [Kalaria 2002] and the cases with both Alzheimer's disease and brain ischemia demonstrated more severe cognitive impairment than those without brain ischemia [Snowdon et al., 1997, Li et al., 2011]. Some studies from transgenic mice demonstrated that neuronal death, a common feature of Alzheimer's disease, is not dependent on β-amyloid peptide [Armstrong 2006]. Other studies indicate that β-amyloid peptide is generated as a response to ischemic neuronal injury which is supported by overexpression genes of amyloid protein precursor, presenilin1 and 2, and beta-secretase [Kocki et al., 2015, Pluta et al., 2016a, Pluta et al., 2016b]. In addition, the genes of autophagy, mitophagy, apoptosis and tau protein were overexpressed following brain ischemia [Ułamek-Kozioł et al., 2016, Ułamek-Kozioł et al., 2017, Pluta et al., 2018]. In human cases with brain ischemia, β-amyloid peptide was found in neuronal bodies and around dystrophic neurites and accumulation of β-amyloid peptide was similar to depositions seen in Alzheimer's disease [Qi et al., 2007]. Thus, the increased staining of different parts of amyloid protein precursor may be a reaction of the brain to ischemic neuronal injury [Pluta et al., 1994b, Badan et al., 2004, Pluta et al., 2009, Pluta et al., 2013]. On the other hand, increased synthesis and metabolism of amyloid protein precursor in patients with brain ischemia may be an acute response of the genes and proteins to brain ischemic injury leading to the massive deposition of β-amyloid peptide [Qi et al., 2007]. We propose that amyloid protein precursor/β-amyloid peptide is involved in the course of the disease as a secondary pathological factor. Tau protein pathology can also be a part of the neuronal reaction to brain ischemia which is supported by overexpression of tau protein gene following ischemic brain episode [Wen et al., 2007, Pluta et al., 2018]. Experimental brain ischemia-reperfusion injury has also resulted in overexpression of amyloid protein precursor gene in the brain cortex and hippocampus, implying that the production and metabolism of amyloid protein precursor may be a characteristic response to loss of functional activity by ischemic brain [Kocki et al., 2015, Pluta et al., 2016a, Pluta et al., 2016b]. To support these conclusions, different parts of amyloid protein precursor were found in ischemic neuronal bodies, axonal swellings and dystrophic neurites [Pluta et al., 1994b, Badan et al., 2004, Pluta et al., 2009, Pluta et al., 2013]. In ischemic brain, diffuse plaques are connected with field of clusters of neuronal perikarya and the shape of staining frequently covered dendrite area. In Alzheimer's disease, the predominance of neuronal mRNAs in individual plaques was observed, which suggests that the amyloid plaques develop in the areas where neurons die [Pluta et al., 2013, Kocki et al., 2015]. The demonstrated data support the idea that amyloid protein precursor gene and its protein is upregulated in brain as an effect of neuronal injury and/or loss of functional innervations, and therefore, that the early development of diffuse plaques in Alzheimer's disease may be a result of neuronal degeneration [Kocki et al., 2015, Pluta et al., 2016a, Pluta et al., 2016b]. Different studies support a general conclusion that the formation of amyloid plaques and neurofibrillary tangles is a reactive alteration that appears in response to neuronal ischemic injury and is not strictly related to dementia [Armstrong 2006]. Nevertheless, β-amyloid peptide is a neurotoxin when produced and may start processes of secondary neuronal injury. Other data also suggest that tau protein hyperphosphorylation with overexpression of its gene is a result of neurodegenerative changes [Wen et al., 2007, Majd et al., 2016, Fujii et al., 2017, Pluta et al., 2018]. It can be concluded that amyloid plaques and tau protein changes arise independently. However, once initiated, pathological processes can mutually cooperate. If β-amyloid peptide and tau protein alterations are the product of neurodegeneration thus, probably, these two proteins are hallmarks of late stages in sporadic Alzheimer's disease development. We would like to put forward a theoretical scheme that fits very well with ischemia basis of sporadic Alzheimer's disease. According to our theory, Alzheimer's disease would start to develop when at least two pathological events converge: brain ischemia and ischemic chronic insufficiency of blood–brain barrier for β-amyloid peptide [Pluta et al., 1996, Pluta et al., 2013]. These two pathologies create two main characteristic features of Alzheimer's disease, brain ischemia is responsible for acute and delayed neuronal death in hippocampus and dysfunctional, dying and dead neurons in other areas affected by ischemically induced β-amyloid peptide of the brain with global brain atrophy, and ischemic chronic blood–brain barrier insufficiency creating mainly amyloid pathology in surrounding brain tissue [Pluta et al., 1996]. The magnitude and extent to which the blood–brain barrier is exposed appears to be minimal since acute alterations such as microinfarcts were not easily observed. Still, these neuropathology remains of great consequence to the brain tissue and appears to be cumulative over time. Transgenic mice that accumulate β-amyloid peptide without neuronal loss in hippocampus support directly the above idea [Armstrong 2006]. The neuropathology of Alzheimer's disease is rooted in ischemic pathology what is indicated by evidence growing recently [Pluta et al., 1994a, Qi et al., 2007, Wen et al., 2007, Pluta et al., 2009, Kocki et al., 2015, Majd et al., 2016, Pluta et al., 2016a, Pluta et al., 2016b, Ułamek-Kozioł et al., 2016, Fujii et al., 2017, Salminen et al., 2017, Ułamek-Kozioł et al., 2017, Pluta et al., 2018]. The "amyloid hypothesis" of Alzheimer's disease and the "ischemic theory" of Alzheimer's disease may together explain Alzheimer's-type neurodegeneration in the brain. Therefore, overexpression of amyloid protein precursor gene

and increased staining of its different parts in brain after ischemia and ischemia alone probably constitute a vicious cycle that leads to neurodegeneration with dementia. We hypothesize that initial acute upregulation of different parts of amyloid protein precursor in the ischemic brain is the effect of neuronal death as a response to ischemic injury by genes associated with Alzheimer's disease [Kocki et al., 2015, Pluta et al., 2016a, Pluta et al., 2016b, Ułamek-Kozioł et al., 2016, Ułamek-Kozioł et al., 2017, Pluta et al., 2018]. However, long-term overexpression of amyloid protein precursor gene in brain may contribute to neurotoxicity. Progressing death of neurons after ischemia–reperfusion injury may be caused not only by degeneration of neurons destroyed during primary ischemic insult but also by ischemic opening of blood–brain barrier with accumulation and influence of cytotoxic fragments of amyloid protein precursor on ischemic neurons.

Ischemic brain injury in animals causes progressive and irreversible cognitive impairment with Alzheimer's disease genotype and phenotype induction, dysfunction of learning new information in the short term survival postischemia, and memory loss in the long term survival postischemia, suggesting that those deficits are due to impairment of memory retention or the memory recall process [Berra de la Tremblaye, Plamondon 2011, Kiryk et al., 2011, Li et al., 2011, Cohan et al., 2015]. Also, the progressive damage in the hippocampus and the white matter with general brain atrophy were found, following brain ischemia [Pluta 2000, Pluta et al., 2009]. Transient brain ischemia resulted in an insidious delayed death of specific vulnerable pyramidal neurons within the CA1 subfield of the hippocampus, associated with inflammation [Sekeljic et al., 2012]. Rarefaction of white matter was noted a few months following ischemia and markedly increased 1 year after ischemic brain injury. White matter changes are characteristic for elderly persons and individuals with cognitive impairment. The above changes also appear in sporadic Alzheimer's disease patients, suggesting that brain ischemia can be regarded as a useful model for understanding mechanisms responsible for the development full-blown dementia of Alzheimer's-type [Pluta et al., 1991, Pluta et al., 1994a, Pluta et al., 2009, Pluta et al. 2013].

CONCLUSIONS

This review presents facts that support the hypothesis that common pathological mechanisms to both brain ischemia and sporadic Alzheimer's disease are contributing to cognitive impairment and Alzheimer's-type dementia [Berra de la Tremblaye, Plamondon 2011, Kiryk et al., 2011, Li et al., 2011, Cohan et al., 2015, Sherzai et al., 2018]. The main objective of this review is to increase the knowledge on the neuronal processes underlying brain damage and their influence on activity following neurodegeneration and their relationship with those neuronal processes involved in cognitive decline and finally dementia. Brain ischemia and Alzheimer's disease share apparently common features: characteristic genes overexpression, proteins generation, aggregation and depositions, and specific vulnerability of certain classes of neurons, mainly in the hippocampus and long incubation period [Pluta et al., 1994a, Pluta et al., 1994b, Pluta 2000, Pluta 2001, Pluta et al., 2009, Pluta et al. 2013, Kocki et al., 2015, Pluta et al., 2016a, Pluta et al., 2016b, Ułamek-Kozioł et al., 2016, Ułamek-Kozioł et al., 2017, Pluta et al., 2018]. Development of this fast moving and expansive field, we can study to what extent these features reflect common etiological mechanisms. The major challenge of this novel research strategy is, therefore, the identification of those disease relevant molecular abnormalities and genomic and proteomic responses in the brain and blood that require therapeutic intervention to improve the final outcome and have influence on final ante mortem diagnosis of Alzheimer's disease.

In future we should study the role of pathways that are invoked during ischemia–reperfusion injury and may potentially develop neurodegeneration in Alzheimer's disease brain. The fundamental message of this review is that the neuropathology seen in Alzheimer's disease is a continuous process starting from the initial ischemic neuronal damage to the well-established production and extravasations of β-amyloid peptide from blood across dysfunctional ischemic blood–brain barrier, with overexpression of Alzheimer's disease-associated genes and their products in the brain and blood, culminating in the formation of amyloid plaques and neurofibrillary tangles and finally with development full-blown dementia of Alzheimer's disease phenotype.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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