# Genes associated with Alzheimer's disease affecting ischemic neurodegeneration of the hippocampal CA3 region

**Ryszard Pluta*, Marzena Ułamek-Kozioł**

**Neurodegeneration in the brain after ischemia with reperfusion mimicking the neuropathology of Alzheimer's disease:** Brain ischemia with reperfusion, which is one of the main causes of morbidity and mortality in the world, triggers various neuropathological changes characteristic for Alzheimer's disease (AD) such as increased blood-brain barrier permeability, excitotoxicity, necrosis, autophagy, mitophagy, apoptosis, neuroinflammation, amyloid plaques, neurofibrillary tangles, cerebral vessel pathology, and brain atrophy that lead to the death of neurons, deteriorating motor, sensory and cognitive functions (**Figure 1**) (Kato et al., 1988; Wisniewski et al., 1995; Van Groen et al., 2005; Kocki et al., 2015; Ułamek-Kozioł et al., 2016, 2017, 2019). Brain ischemia is recognized as a major contributor to the dysfunction of an aging brain and the development of neurodegenerative diseases, including AD (Pluta, 2019). The explanation of the final mechanisms of post-ischemic neurodegeneration progress and etiology of AD as well as the development of causal treatment for both diseases seems to involve complicated and complex procedures which require endless revision (Kametani and Hasegawa, 2018; Pluta, 2019). This is partly due to the fact that neurodegenerative processes leading to dementia after both ischemia and AD are not well understood yet. Therefore, there is no causal treatment or adequate criterion for early diagnosis of dementia. Recently, an etiological link has been proposed between dementia following ischemia and dementia due to Alzheimer's disease (**Figure 1**) (Salminen et al., 2017; Pluta, 2019). Our article presents facts supporting the idea that neuropathological mechanisms after cerebral ischemia contribute to the development of the genotype and phenotype of AD. The main goal is to broaden knowledge about the overall ischemia processes underlying neuronal death and their impact on regeneration and functional recovery during neurodegeneration of the AD type, and what follows, their relationship with neuronal processes involved in the possible development of AD (**Figure 1**). Therefore, the main challenge of this new research strategy is to identify genomic and proteomic changes that are common for both ischemia and AD and can be cured. In particular, we are looking for evidence linking the expression of genes associated with AD after ischemia with their role in the regulation of AD proteins in the ischemic brain. Furthermore, we try to understand the role of expression of AD genes along with their proteins during the clinical progress and maturation of post-ischemic brain neurodegeneration with the association of the genotype and phenotype of AD. In this perspective, we combine the importance of cerebral ischemia-induced AD genes expression with a presentation of the final relevant ischemic, genetic mechanism of protein placement in the brain and its reference to the progression of AD. These findings are likely to lead to the development of much-needed new causal therapies and early dementia diagnostic methods in both incurable diseases.

Although numerous classical neuropathological processes associated with cerebral ischemia and AD including apoptosis, autophagy, mitophagy, neuroinflammation, blood-brain barrier changes and brain atrophy (**Figure 1A**) have been characterized in recent decades, the possibility of discovering new mechanisms arises with the development of neurobiology in such areas as genomics and proteomics, thus transferring the issues of brain ischemia to a new level. The analysis of new data reveals that genes associated with AD change after brain damage due to ischemia and reperfusion. Moreover, they are directed at the translation of proteins that modulate autophagy, mitophagy, apoptosis, and generation amyloid as well as at the development of neurofibrillary tangles in age-related ischemic encephalopathy. The illustration below shows the latest data from an ischemic brain injury study in rats that focuses on the ischemia-induced genotype of AD in the CA3 region of the hippocampus, which is associated with memory and learning. In this article, we highlight the possible relationship between amyloid and tau protein with irreparable neurodegeneration after experimental ischemia and full-blown dementia of the AD phenotype. It should be emphasized that, despite the fact that cerebral ischemia and AD are the main causes of disability, dementia and mortality in the world, there is no effective treatment that would primarily improve the structurally irreversible effects of these disorders, either.

**Behavior of genes associated with amyloid production after experimental ischemia in the hippocampal CA3 area in rats:** In the CA3 area of hippocampus, the expression of the *amyloid protein precursor* gene was recorded by RT-PCR above the control values within 2–30 days post-ischemia (**Figure 1B**) (Pluta et al., 2020). However, *α-secretase* during 2–30 days was noted below the control values after ischemia. Expression of the *β-secretase* gene decreased below the control value 2–7 days during recirculation and after 30 days it increased above the control values. Two and seven days after ischemia, *presenilin 1* gene expression increased above the control value. Thirty days post-ischemia, the expression of the above gene was below the control values. There was a decreased expression of the *presnilin 2* gene in the hippocampal CA 3 region during 2–7 days following ischemic brain injury (Pluta et al., 2020). Thirty days post-ischemia, the *presnilin 2* gene expression was significantly higher (**Figure 1B**).

**Reaction of the *tau protein* gene to hippocampal ischemia in rats:** On the second day post-ischemia in the hippocampal CA3 area, the expression of the *tau protein* gene decreased in relation to the control values (**Figure 1B**) (Pluta et al., 2020). On the seventh and thirtieth day post-ischemia, the expression of the above gene was above the control values (**Figure 1B**). Tau protein in post-ischemic brain was phosphorylated at multiple sites and hyperphosphorylation of tau protein was linked to the formation of neurofibrillary tangles associated with AD. Elevated levels of tau protein were noted in human blood and CSF after acute ischemic stroke, which correlated with severity of brain damage and poor outcome. It can therefore be suggested that the generation of the amyloid with the increased dysfunction of the tau protein appears to be a very important consequence of post-ischemic brain resulting in increased sensitivity of the neurons to the episode of ischemia (**Figure 1B**) (Kocki et al., 2015; Pluta et al., 2020).

**Challenges:** Dementia following ischemia and AD is a symptom of unknown end mechanisms that are probably very complex. Both diseases are considered debilitating ones that cannot really be subjected to causal treatment. In addition, there has long been a debate on the criteria for early diagnosis of dementia in both diseases, with no definitive clues that could be beneficial on the one hand and unfavorable on the other. Actually, triggering such a debate reflects a growing interest in these disorders, which can lead to a better understanding of disease mechanisms in the near future, and thus to the causal treatment options for these cases. Particular circumstances indicate that

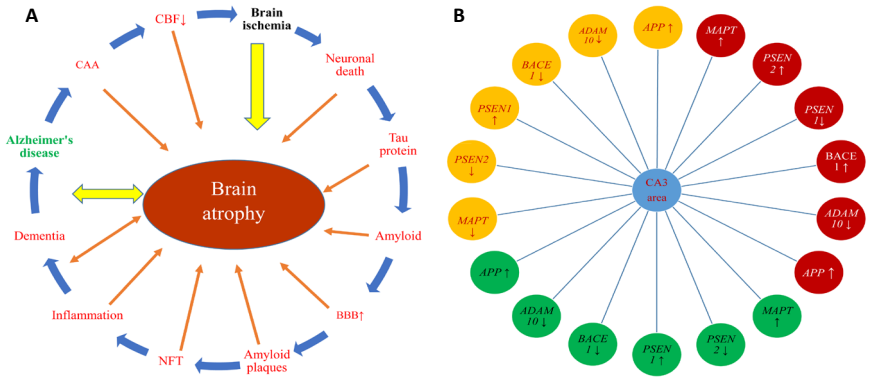


**Figure 1** | **Development of Alzheimer's disease lesions after brain ischemia.**
(A) Post-ischemic changes with possible impact on the development of Alzheimer's disease. ↑: Increase; ↓: decrease; BBB: blood-brain barrier; CAA: cerebral amyloid angiopathy; CBF: cerebral blood flow; NFT: neurofibrillary tangles. (B) Changes in the expression of genes associated with Alzheimer's disease in the CA3 region of the hippocampus as assessed by RT-PCR at various times after experimental cerebral ischemia. Color: Yellow: 2 days post-ischemia; green: 7 days post-ischemia; red: 30 days post-ischemia; *APP*: amyloid protein precursor; *ADAM10*: α-secretase; *BACE1*: β-secretase; *PSEN1*: presenilin 1; *PSEN2*: presenilin 2; *MAPT*: tau protein.

ischemic brain injury simultaneously initiates neuropathology and gene expression associated with AD, the development of amyloid plaques and neurofibrillary tangles, as well as the atrophy of the hippocampus, which is crucial for the development of AD dementia (**Figure 1A**) (Kato et al., 1988; Van Groen et al., 2005; Pluta, 2019). Data on the genotype and phenotype of AD after ischemic brain injury seem to directly support the ischemic theory of AD (Pluta, 2019). Knowledge of typical genetic and molecular processes that are the cause of brain neurodegeneration after ischemia, and possibly the development of AD, gives new possibilities to understand the final etiology of dementia of both disease entities. Understanding the processes underlying the association of ischemic induction genes and proteins associated with AD and the risk of neuropathology for AD development and dementia will provide the most significant goals for future causal treatment. Therefore, gene overexpression associated with AD and the presence of amyloid after ischemia in brain tissue is probably a vicious self-driving wheel that explains the development of neurodegeneration in AD with dementia (**Figure 1A**) (Pluta, 2019). Although the exact molecular mechanisms of neurodegeneration and ischemic susceptibility of neurons are ultimately unknown, decreased regulation of α-secretase gene expression in the ischemic hippocampal CA3 region makes neurons less resistant to damage (Pluta et al., 2020). The current challenge is to find ways to increase the patient's adaptation reserve to combat ischemic deficiencies and support neuronal survival. In the future, it is likely that the mere control of ischemia and ischemia-induced genes and their proteins will provide new hope for generating causal therapies urgently needed to prevent or treat neurodegenerative diseases. In this perspective, we present the hard-won preliminary data on the induction through ischemia genes in the hippocampus, i.e. an amyloid protein precursor, amyloidogenic secretases and tau protein, which play a key role in sporadic AD (**Figure 1B**). In this study we summarize our recent observations confirming the hypothesis that genes associated with AD and their proteins play an important role in brain damage due to ischemia-reperfusion with dementia and that the ischemic episode is a necessary and leading provider of the onset and progression of AD neuropathology and dementia (Pluta, 2019). For this reason, it is essential to study the effect of cerebral ischemia episodes on the development of sporadic AD using an experimental ischemia model to clarify its etiology.

*This work was supported by the Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland (to RP).*

**Ryszard Pluta*, Marzena Ułamek-Kozioł**
Laboratory of Ischemic and Neurodegenerative Brain Research, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
***Correspondence to:** Ryszard Pluta, MD, PhD, pluta@imdik.pan.pl.
https://orcid.org/0000-0003-0764-1356 (Ryszard Pluta)
**Date of submission:** May 26, 2020
**Date of decision:** June 30, 2020
**Date of acceptance:** August 10, 2020
**Date of web publication:** December 12, 2020

**https://doi.org/10.4103/1673-5374.300982**
**How to cite this article:** *Pluta R, Ułamek-Kozioł M (2021) Genes associated with Alzheimer's disease affecting ischemic neurodegeneration of the hippocampal CA3 region. Neural Regen Res 16(7):1392-1393.*


## References

Kametani F, Hasegawa M (2018) Reconsideration of amyloid hypothesis and tau hypothesis in Alzheimer's disease. Front Neurosci 12:25.
Kato T, Hirano A, Katagiri T, Sasaki H, Yamada S (1988) Neurofibrillary tangle formation in the nucleus basalis of Meynert ipsilateral to a massive cerebral infarct. Ann Neurol 23:620-623.
Kocki J, Ułamek-Kozioł M, Bogucka-Kocka A, Januszewski S, Jabłoński M, Gil-Kulik P, Brzozowska J, Petniak A, Furmaga-Jabłońska W, Bogucki J, Czuczwar SJ, Pluta R (2015) Dysregulation of amyloid precursor protein, beta-secretase, presenilin 1 and 2 genes in the rat selectively vulnerable CA1 subfield of hippocampus following transient global brain ischemia. J Alzheimers Dis 47:1047-1056.
Pluta R (2019) Brain ischemia: Alzheimer's disease mechanisms. New York: Nova Science Publishers, Inc.
Pluta R, Ułamek-Kozioł M, Kocki J, Bogucki J, Januszewski S, Bogucka-Kocka A, Czuczwar SJ (2020) Expression of the tau protein and amyloid protein precursor processing genes in the CA3 area of the hippocampus in the ischemic model of Alzheimer's disease in the rat. Mol Neurobiol 57:1281-1290.
Salminen A, Kauppinen A, Kaarniranta K (2017) Hypoxia/ischemia activate processing of amyloid precursor protein: impact of vascular dysfunction in the pathogenesis of Alzheimer's disease. J Neurochem 140:536-549.
Van Groen T, Puurunen K, Maki HM, Sivenius J, Jolkkonen J (2005) Transformation of diffuse beta-amyloid precursor protein and beta-amyloid deposits to plaques in the thalamus after transient occlusion of the middle cerebral artery in rats. Stroke 36:1551-1556.
Ułamek-Kozioł M, Kocki J, Bogucka-Kocka A, Petniak A, Gil-Kulik P, Januszewski S, Bogucki J, Jabłoński M, Furmaga-Jabłońska W, Brzozowska J, Czuczwar SJ, Pluta R (2016) Dysregulation of autophagy, mitophagy and apoptotic genes in the medial temporal lobe cortex in an ischemic model of Alzheimer's disease. J Alzheimers Dis 54:113-121.
Ułamek-Kozioł M, Kocki J, Bogucka-Kocka A, Januszewski S, Bogucki J, Czuczwar SJ, Pluta R (2017) Autophagy, mitophagy and apoptotic gene changes in the hippocampal CA1 area in a rat ischemic model of Alzheimer's disease. Pharmacol Rep 69:1289-1294.
Ułamek-Kozioł M, Czuczwar SJ, Kocki J, Januszewski S, Bogucki J, Bogucka-Kocka A, Pluta R (2019) Dysregulation of autophagy, mitophagy, and apoptosis genes in the CA3 region of the hippocampus in the ischemic model of Alzheimer's disease in the rat. J Alzheimers Dis 72:1279-1286.
Wisniewski HM, Pluta R, Lossinsky AS, Mossakowski MJ (1995) Ultrastructural studies of cerebral vascular spasm after cardiac arrest-related global cerebral ischemia in rats. Acta Neuropathol 90:432-440.

*P-Reviewer: Dimitriadis SI; C-Editors: Zhao M, Li JY; T-Editor: Jia Y*