6

Alzheimer's Factors in Ischemic Brain Injury

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1. Introduction

Aging nations are growing worldwide and now one in four of us may expect to experience an ischemic brain injury by the age 85. Stroke is the third most common cause of death and the second most common cause of dementia in industrialized societies with a mortality rate of circa 30% and an incidence of about 250–400 in 100,000. Stroke affects circa 700,000 people each year in the US alone, and about 50% of these individuals will experience lasting functional dysfunctions including sensory problems and cognitive deficits (Hillis 2006). It is estimated that ischemic stroke is responsible for approximately half of all patients hospitalized for acute neurological disorders. As outlined earlier, it can cause neurological dysfunctions in a number of neurological functions most commonly in the motor activity, cognitive decline, and dementia. Postischemic dementia is characterized by progressive cognitive deterioration including language, reasoning and memory. Of those individuals suffering from ischemic brain injury less than 50% will return to independent living during the following year. Even among those who regain functional independence, many stroke patients continue to manifest significant deficits, limitations and changes in their cognitive functioning and behavior. As such, stroke is one of the leading causes of disability and experiencing a stroke results in two-fold increase in risk for dementia. Other data showed that 1-in-10 developing dementia soon after first stroke, and over 1-in-3 being demented after recurrent stroke. The brain has limited responses to different kind of neuropathogens. Similar neuropathological features are observed in different cerebrovascular diseases and Alzheimer's disease (Kalaria 2000; Pluta 2004a; Pluta 2004b; De la Torre 2005; Pluta 2006a; Benarroch 2007; Niedermeyer 2007; Pluta 2007c; Bell, Zlokovic 2009). Brain stroke is the leading cause of cognitive impairment worldwide. These data are supported by observations in clinical as well as in experimental studies, which suggest that ischemic brain injury is a major risk factor of dementia ranking only second to age (Gorelick 1997; Pluta 2006a; Pluta 2007c). Dementia, which is observed following different brain ischemic injuries, is associated with intellectual impairment and finally brain atrophy (Hossmann et al., 1987; Loeb et al., 1988; Tatemichi et al., 1990; Pluta 2002b; Kiryk et al., 2011). Amyloid plaques, which are the main pathological hallmarks of Alzheimer's disease, account for about 90% of dementias including ischemic-type dementia (Jendroska et al., 1995; Wisniewski, Maslinska 1996; Shi et al., 1998; Pluta, 2007a; Qi et al., 2007). The relationship between brain ischemic injury dementia and Alzheimer's disease type dementia is recently much debated. The mechanisms of the progressive cognitive decline after ischemic brain injury are not yet clear

but animal investigations have demonstrated an increase in expression and processing of amyloid precursor protein to β-amyloid peptide (Pluta et al., 1994b; Pluta et al., 1997b; Pluta et al., 1997c; Pluta et al., 1998b; Lin et al., 1999; Shi et al., 2000; Lin et al., 2001; Badan et al., 2004; Pluta et al., 2009) and an increase in the phosphorylation of tau protein (Dewar, Dawson 1995; Wen et al., 2004b; Wen et al., 2004c, Wen et al., 2007). Moreover, the common mechanism that links progressive cognitive decline after ischemic brain injury and during Alzheimer's disease is neuroinflammation (Koistinaho et al., 2002), which can cause gradual neurodegeneration during prolonged face of injury. However, the link between ischemic brain injury and delayed progressive cognitive decline opens a new area for potential treatment in that the onset of the progressive cognitive decline after ischemia is delayed. The above data raise the question whether Alzheimer's related proteins affect ischemic brain tissue. The details of Alzheimer's protein-related mechanisms, which probably mediate ischemic brain cell damage and neurotoxicity (Mattson et al., 2000; Malm, Koistinaho 2007) and involvement of these proteins in brain accumulation will be reviewed. This chapter summarizes some of the findings, which suggest that ischemic overexpression of amyloid precursor protein renders the brain more vulnerable to ischemic episodes (Koistinaho et al., 2002) and describes the factors that are involved in increased neuronal susceptibility to ischemic injury (Mattson et al., 2000; Malm, Koistinaho 2007).

1.1 Consequences of ischemic brain injury

Brain ischemic injury is the most common chronic cause of disability around world and has generally a negative influence on the individuals it affects, caregivers and society as a whole (Flynn et al., 2008). Ischemic stroke survivors suffer from chronic progressing neurological disabilities that significantly influence their ability to return to society. A more insidious consequence of brain ischemia is a post-stroke dementia (Jellinger 2007) that is also associated with severe disability. Worldwide brain vascular disorders like ischemia are responsible for 5.4 million deaths every year (Flynn et al., 2008). Circa 3% of total healthcare finances are attributable to brain ischemia. Cost of ischemic stroke to the EU economy is estimated at 21 billion euro and to USA economy at 2.2 trillion dollars (Fillit, Hill 2002, Flynn et al., 2008). The global scale of the problem and the enormous associated costs it is clear that there is an urgent need for advances in the prevention of ischemic brain injury and its consequences like postischemic dementia. Dementia is the worst consequence for survivors following brain ischemia and being responsible for approximately 20% of all confirmed dementias (Fillit, Hill 2002). Globally cerebrovascular diseases dementia varies from 10 to 50% depending on the diagnostic criteria, geographic location and population demographic (Leys et al., 2002). Recently it is becoming clear, that cerebrovascular diseases dementia in fact shares many risk factors in common with Alzheimer's disease. Indeed ischemic brain injuries may precede the onset of this form of dementia strongly suggesting that brain ischemic episodes may trigger neurodegenerative dementias. Postischemic dementia connected with chronic delayed secondary injury occurs in individuals suffering from focal or global brain ischemia in a progressive manner (Jellinger 2007). The chronic postischemic injury including dementia has received far less attention in clinical and experimental stroke investigations. Vascular dementia incorporates cognitive dysfunction with cerebrovascular diseases.

1.2 Epidemiology of postischemic dementia

Epidemiological studies have shown that the prevalence of dementia in ischemic brain injury patients is nine-fold higher than controls at 3 months (Madureira et al., 2001;

Pohjasvaara et al., 1998; Tatemichi et al., 1992) and 4-12 times higher than in controls 4 years after a lacunar infarct (Loeb et al., 1992). Different patterns of cognitive decline as effect of ischemia brain injury have been shown by longitudinal epidemiological, studies which have suggested a progressive course of dementia following ischemic stroke. Tatemichi et al., (1990) presented that the incidence of dementia was 6.7% among patients directly after 1 year of survival in a group of 610 subjects who were initially free of dementia following stroke. Bornstein et al., (1996) reported that 32% individuals who were initially free of dementia directly after stroke developed incidental dementia during 5 years of survival following first ischemic episode. Henon et al., (2001) observed a sample of 169 patients who had been free of dementia before stroke and reported that the cumulative proportion of individuals with incidental dementia was 21.3% after 3 years of survival. Altieri et al., (2004) examined 191 free of dementia stroke patients for a 4 years, and noted that the incidence of dementia increasing gradually with 21.5% subjects had developed dementia by the end of the follow-up time. In population-based investigations of stroke and dementia subjects, Kokmen et al., (1996) checked the medical records of 971 patients who were nondemented before first stroke. The incidence of dementia was 7% at 1 y, 10% at 3 y, 15% at 5 y and 23% at 10 y. Desmond et al., (2002) performed functional assessments annually on 334 ischemic brain injury patients and 241 ischemia free control individuals, all of whom were free of dementia in baseline examinations, and noted a progressive course of dementia with the incidence rate of 8.94/100 person/year in the ischemic group and 1.37/100 person/year in the control group. In two studies based on subjects presenting with a lacunar infarction as their first ischemic stroke, Samuelsson et al., (1996) found that 4.9% and 9.9% of 81 patients had dementia after 1 and 3 years of observation, respectively, and Loeb et al., (1992) reported that 23.2% individuals had dementia during an average of 4 years of survival.

Removal of the above deficits/abnormalities is a topic to which a neurologist and scientists devotes little time. In different patients, some spontaneous functional restoration is noted during weeks/months after ischemic brain injury. However, in general, this spontaneous recovery is incomplete. Moreover, ischemic brain injury often leaves its victims functionally devastated and as such is the leading cause of permanent disability requiring long-term institutional care in our nations. The loss of life quality years and health care resources are staggering. The situation is even aggravated by the fact that unlike many other neurological diseases, no safe, effective therapy is available for the majority of patients with acute ischemic brain injury. The burden after ischemic brain injury on our societies is dramatically increasing. Thus, an understanding of the underlying progressing pathological processes/cascades is urgently needed. This chapter tends to summarize the neuropathological changes of chronic postischemic brain injury and reveal the convinced mechanisms.

2. Amyloid precursor protein and β-amyloid peptide after ischemia

After brain ischemia, amyloid precursor protein mRNA had enhanced till 200% in the brain during the seventh day of reperfusion. The above data suggest that local ischemic brain injury increases amyloid precursor protein mRNA level, which may contribute to the progression of cognitive impairment in ischemic brain injury (Abe et al., 1991; Koistinaho et al., 1996; Shi et al., 1998; Shi et al., 2000). Above studies also show that focal ischemic brain injury alters Kunitz protease inhibitor amyloid precursor protein/amyloid precursor protein 695 ratios in brain and this shift in precursor isoforms could be related to degeneration and activation of astrocyte following the ischemic injury (Kim et al., 1998). In permanent local

brain ischemia injury, amyloid precursor protein mRNA species, which contain a Kunitz-type protease inhibitor domain, were expressed in the cortex by day 21 of survival but the net amount of precursor mRNA did not change. This investigation suggests a selective role of amyloid precursor protein species that contain the Kunitz protease inhibitor domain in cascade of focal brain ischemia (Abe et al., 1991). After local ischemia amyloid precursor protein 770 and amyloid precursor protein 751 mRNAs were increased during 7 days in the brain (Koistinaho et al., 1996).

Animals after focal and global ischemic brain injury with a survival time up to 1 year presented increased brain immunoreactivity to the β-amyloid peptide and as well as to the N- and C-terminal of amyloid precursor protein. The staining was observed extracellularly and intracellularly (Pluta et al., 1994b; Hall et al., 1995; Tomimoto et al., 1995; Horsburgh, Nicoll, 1996a; Ishimaru et al., 1996a; Yokota et al., 1996; Pluta et al., 1997b; Pluta et al., 1998b; Lin et al., 1999; Pluta 2000; Lin et al., 2001; Sinigaglia-Coimbra et al., 2002; Fujioka et al., 2003; Yang, Simpkins 2007). Different fragments of amyloid precursor protein were noted in astrocytes, neurons, oligodendrocytes, and microglia (Banati et al., 1995; Palacios et al., 1995; Pluta et al., 1997b; Nihashi et al., 2001; Pluta, 2002a; Pluta2002b; Badan et al., 2003; Badan et al., 2004). Animals with long survival after ischemic brain injury from 0.5 to 1 year showed pathological brain staining only to the β-amyloid peptide and to the C-terminal of amyloid precursor protein (Pluta et al., 1998b; Pluta 2000). The reactive astrocytes with deposition of different fragments of amyloid precursor protein might be involved in the development of glial scar (Nihashi et al., 2001; Pluta 2002a; Pluta 2002b; Badan et al., 2003; Badan et al., 2004). Reactive astrocytic cells with pathological level of β-amyloid peptide deposition might be involved in pathological repair of host tissue after ischemic brain injury including astrocytes death (Pluta et al., 1994b; Pluta 2002b; Wyss-Coray et al., 2003; Takuma et al., 2004).

Pathological amyloid precursor protein staining especially for β-amyloid peptide and C-terminal has been observed in periventricular and subcortical white matter after ischemic brain injury (Pluta et al., 2006, Pluta et al., 2008). The more intense postischemic brain injury of white matter is, the more extensive is the staining of different parts of amyloid precursor protein in this region (Yam et al., 1997). In contrast, in our unpublished studies, the data are opposite. We noted ischemic time-independent intensity of immunostaining, shorter ischemic brain injury stronger reactivity. Probably, this kind of abnormalities is responsible for leukoaraiosis formation after ischemic brain injury (Pluta et al., 2008). Extracellular accumulation of different fragments of amyloid precursor protein ranged from multifocal widespread very small dots to regular amyloid plaques (Pluta et al., 1994b; Pluta et al., 1998b; Pluta 2000; Pluta 2002b; Pluta 2003). Multifocal and widespread different kinds of amyloid plaques were observed mainly in the ischemic hippocampus, brain and entorhinal cortex, and corpus callosum, and subventriculary (Pluta et al., 1994b; Pluta et al., 1997b; Pluta et al., 1998b; Pluta 2000; Pluta 2003; Pluta 2005; Pluta et al., 2006; Pluta et al., 2008; Pluta et al., 2009; Pluta et al., 2010).

The accumulation of the β-amyloid peptide in astrocytes and the C-terminal of amyloid precursor protein in ischemic neurons underline the likely importance of these two proteins in ischemic brain injury cascade of degeneration (Pluta et al., 1994b; Yokota et al., 1996; Pluta 2002b; Badan et al., 2003; Badan et al., 2004). Moreover, the above parts of precursor deposits suggest that these fragments of precursor may initiate synaptic pathology and finally promote retrograde neuronal death after ischemic injury (Oster-Granite et al., 1996). The

aforementioned observations indicate that the late neurotoxic β-amyloid peptide and C-terminal of amyloid precursor protein deposition after ischemic brain injury may represent a secondary injury process that could deteriorate the ischemic brain outcome by unexpected additional neurons death (Pluta et al., 1997c, Pluta et al., 1998b). Following ischemia β-amyloid peptide is produced as a result of neurons injury (Ishimaru et al., 1996a) and probably appears its effects, influencing ischemic neurons and glia as dementia. It is generally received that β-amyloid peptide takes part in neurons death (Cotter et al., 1999). The β-amyloid peptide is a toxic protein and entangles within an ischemic process in astrocytes, oligodendrocytes, and microglia that lead neurons and glia finally to death (Giulian et al., 1995).

3. Amyloid precursor protein secretases after ischemia

The amyloid precursor protein is cleaved by α-secretase and it is not pathological pathway in brain. Ischemic brain injury results in the downregulation of α-secretase mRNA and decreases its net activity (Nalivaeva et al., 2004; Yan et al., 2007). In the pathological pathway called amyloidogenic precursor is cleaved by β-secretase and γ-secretase to form β-amyloid peptide. The formation of β-amyloid peptide in the brain after ischemic injury increases and impairs the memory (Yan et al., 2007). Current investigations have shown that brain ischemia stimulates the formation and activity of β-secretase in brain tissue (Wen et al., 2004a; Chuang et al., 2008). Presenilin, which is overexpressed after ischemic brain injury (Tanimukai et al., 1998; Pennypacker et al., 1999), is involved in ischemic β-amyloid peptide synthesis by γ-secretase (Polavarapu et al., 2008).

4. Amyloid precursor protein intracellular domain after ischemia

Important brain trigger, which initiates amyloid precursor protein cleavage, is ischemic episode. The main proteolysis is performed by α- or β-secretase that produce large soluble N-terminal parts called respectively soluble N-terminal domain of amyloid precursor protein α (sAPPα) or soluble N-terminal domain of amyloid precursor protein β (sAPPβ). These fragments are release into the extracellular space. Remaining C-terminal domains are bind with membrane and called respectively C-terminal fragment 83 or 99 (CTF83/CTFα or CTF99/CTFβ). The second cleavage occurs in the intramembrane area by γ-secretase, which depending on where the first proteolysis was made and finally releases either the β-amyloid peptide or p3 fragment. This phenomenon seems to be largely nonselective occurring in at least 3 different sites of the amyloid precursor protein like V636, A638 and L645 (ε-cleavage site) (Sastre et al., 2001; Yu et al., 2001). The final products are β-amyloid peptide 40/42 and an intracellular 50 aa C-terminal of amyloid precursor protein domain (5kDa) (Pinnix et al., 2001). Amyloid intracellular domain is very labile and can be further disintegrated by the insulin degrading enzyme or proteasome. Amyloid intracellular domain with specific binding proteins initiating a signal cascade, which subsequently migrates to the cell nucleus to become a component of a transcriptional process but the adaptor protein FE65 rescues the amyloid intracellular domain from rapid proteolysis.

5. Tau protein after ischemia

Tau protein overexpression in neurons was observed in the hippocampus (Geddes et al., 1994) and the brain cortex (Dewar et al., 1993; Dewar et al., 1994) after ischemic brain injury

(Sinigaglia-Coimbra et al., 2002). Moreover, an increase of tau immunostaining was noted in glia and oligodendrocytes following local brain ischemia (Dewar, Dawson 1995; Irving et al., 1997). Additionally pathological tau protein was found in microglia around the ischemic core (Uchihara et al., 2004). The above data indicate that only some neurons display pathologically changed tau protein following ischemic brain injury (Dewar, Dawson 1995), which may reflect an early alterations state of the degenerative processes in these cells (Irving et al., 1997). Another study noted a complete dephosphorylation of tau protein after ischemic brain injury (Mailliot et al., 2000). The dephosphorylation of tau protein may influence its transportation between axon and cell body and affects its susceptibility to proteolysis (Shackelford, Yeh 1998). Some other study noted that tau protein itself blocks transport of amyloid precursor protein from the neuron body into axon and dendrites causing amyloid precursor accumulation in the neuron body (Stamer et al., 2002). The recent studies show that after ischemic brain injury, hyperphosphorylated tau protein accumulates in cortical neurons and colocalizes with signs of apoptosis. This process may be important element in the etiology in ischemic brain degeneration. The above observations indicate that neuron ischemic apoptosis is connected with tau protein hyperphosphorylation (Wen et al., 2004b; Wen et al., 2007). Wen et al. (2004c, 2007) noted that reversible brain ischemia is associated with neurofibrillary tangle-like tauopathy formation in the brain. These data provide groundwork for the cause of dementia after ischemic brain injury (Wen et al., 2004c).

6. Presenilins after ischemia

Ischemic brain injury overexpression of presenilin 1 gene in neurons of the CA3 sector and dentate gyrus was noted (Tanimukai et al., 1998). In above study, increased expression of presenilin 1 mRNA was the highest at day 3 of reperfusion in affected regions. The above data suggest that the overexpression of presenilin 1 mRNA may be associated with some responses of neurons injured by ischemic pathology. In another study, the increased expression of presenilin mRNA was found in the hippocampus, striatum, cortex, and cerebellum following local ischemic brain injury (Pennypacker et al., 1999). Generally presenilin mRNA exhibited the highest expression in the hippocampus and brain cortex. The expressions were higher on the contralateral side to the local ischemic brain injury. This difference may reflect a loss in brain cells e.g. neurons expressing presenilin genes on the ipsilateral side. Staining of presenilin was more expressed in glia than in neurons and in a trace of the pyramidal neurons of hippocampus after ischemic brain injury (Pluta 2001). Presenilin 1 increases neuron vulnerability to ischemia by increasing intracellular calcium (Mattson et al., 2000; Pluta et al., 2009). A current investigation presented that presenilin 1 and intracellular calcium regulates neuron glutamate uptake (Yang et al., 2004). Taken together, above data indicate that presenilins and intracellular calcium may play an important role in regulating glutamate uptake, and therefore they may influence glutamate toxicity in the ischemic brain injury.

7. Apolipoproteins after ischemia

Astrocytic apolipoprotein E mRNA overexpression with the highest level at day 7 after ischemic brain injury was found, which suggests that ischemic neuron injury results in the induction of certain genes in the brain within reactive astrocytes and this induction may

contribute to amyloidogenesis following brain ischemia (Ali et al., 1996). Apolipoprotein E mRNA overexpression in glia but not in neurons was noted in ischemic penumbra with a peak on 21st day. In ischemic core apolipoprotein E mRNA overexpression was observed in macrophages (Kamada et al., 2003). Overexpression of clusterin mRNA was shown in the penumbra in permanent focal brain ischemia. In these studies, reactive astrocytes in the cortex were stained abnormally for apolipoprotein J. It was suggested that local expression of clusterin mRNA might contribute to the neuroinflammation, which representing a main factor in secondary injury processes after focal ischemic brain episodes (Van Beek et al., 2000). After moderate ischemic brain injury a time-dependent deposition of clusterin was noted in pyramidal neurons of the CA1 and the CA2 sector in the hippocampus undergoing delayed neuronal death. Overexpression of apolipoprotein J mRNA in contrast to neuronal protein staining appeared to be glial in origin with increases in mRNA the hippocampus fissure and only a very weak signal over the CA1 and the CA2 pyramidal neuron layer. The above results support the idea that clusterin is synthesized in the astrocytes, secreted outside and next taken up by dying neurons (Nishio et al., 2003). Clusterin deposition was observed in neurons destined to die by apoptosis. Moreover, pathological overexpression of clusterin suggests that the synthesis of this protein was a result of selective delayed neuronal death rather than involvement in the pathological cascade of events that cause it (Walton et al., 1996).

The pathological immunostaining for apolipoproteins A1, E, and J was shown extracellularly and intracellularly (Hall et al., 1995; Kida et al., 1995; Pluta et al., 1995a; Horsburgh, Nicoll 1996a, Horsburgh, Nicoll 1996b; Ishimaru et al., 1996b; Pluta 2000; Kamada et al., 2003). Intracellular staining was noted in damaged neurons exhibiting features of ischemic injury (Pluta 2000). Less often immunostaining for above proteins was observed in glia (Kamada et al., 2003). Extracellular accumulations of apolipoproteins were irregular and well delineated and mainly diffuse. Strong staining was noted also in acellular, necrotic, irregular and spider-like foci (Kida et al., 1995; Pluta et al., 1995a; Ishimaru et al., 1996a). It is important to notice that accumulations of apolipoproteins colocalize with aggregates of different parts of amyloid precursor protein (Kida et al., 1995; Pluta et al., 1995b). Apolipoprotein E promotes the deposition of β-amyloid peptide into the oligomeric and the fibrillar form. Clusterin is engaged in transport of β-amyloid peptide through the blood-brain barrier. The main activity of apolipoproteins A1, E and J is controlling the level of soluble β-amyloid peptide in the intracellular and the extracellular space of brain tissue as well as their influence on fibrillar β-amyloid peptide conversion. Apolipoprotein E induces β-amyloid peptide increased lysosomal leakage and finally apoptosis in neuronal cells (Ji et al., 2002). Apolipoproteins A1, E, and J influence the deposition, structure and neurotoxicity of the β-amyloid peptide in brain ischemia. Additionally, in β-amyloid peptide production apolipoproteins E and J are involved prior to its accumulation. The above studies show principal roles of apolipoproteins E and J in β-amyloid peptide accumulation and that they play an important role in it extracellular β-amyloid peptide metabolism independent of β-amyloid peptide synthesis. These observations indicate that apolipoproteins A1, E and J deposition following ischemic brain injury may be a secondary damaging phenomenon, which could deteriorate healing of ischemic neurons indirectly influences development of ischemic-type dementia.

8. α-synuclein after ischemia

Brain ischemia provoked changes in a presynaptic protein α-synuclein in the ischemic hippocampus (Ishimaru et al., 1998; Kitamura et al., 2001). Intense α-synuclein

immunostaining was found in the perivascular neighborhood of the CA1 sector in experiments with long-term survival following ischemic brain injury (Kitamura et al., 2001). In degenerating regions after brain ischemia glia presented intense reactivity for α-synuclein (Ishimaru et al., 1998). The above results suggest that α-synuclein may be essential protein in the neuropathological ischemic cascade (Goedert 2001). Abnormal α-synuclein accumulation might disrupt synaptic function, resulting in cognitive deficits (Hashimoto, Masliah 1999). The pathology of α-synuclein disturbs the synaptic activity that finally causes retrograde neurons loss in the ischemic brain injury (Goedert 2001).

9. Platelets after ischemia

Pluta et al., (1994c) for the first time directly presented the involvement of platelets in pathological processes after ischemic brain injury. They documented a key role of platelets during repeated vessels occlusion following ischemic brain injury (Pluta et al., 2009). These authors observed augmented thrombocytes aggregations and adhesiveness to vessel endothelium, which very well correlated with ischemic brain disease progression. Other study presented increased platelet microparticles and membrane remnants during reperfusion after ischemic brain damage (Mossakowski et al., 1993; Horstman et al., 2009). Next some study reported circulating platelets complexes and platelets-leukocytes aggregates in systemic circulation following brain ischemia injury (Ritter et al., 2005). Thus chronic abnormal platelets activity following brain ischemia injury now is established as an important pathological phenomenon. It may be suggested that platelets activity after ischemic insult is directly connected with development of general inflammation reply. However, the founding of platelets outside brain vessels after ischemic brain injury (Pluta et al., 1994c; Pluta 2003; Pluta 2006b; Pluta 2007a; Pluta 2007b) comes to evidence of platelets involvement in complex processes of neuroinflammtion and neurodegeneration. Different elements of coagulation system have been noted in brain ischemia episodes including collagen in perivascular space (Pluta et al., 1994c). Above findings, together with other direct evidences suggest that platelets interaction with white blood cells and next with the blood-brain barrier vessels is responsible for leukocyte passage through ischemic blood-brain barrier. Platelets are capable of directly activating lymphocytes and are responsible for synthesis of immunoglobulins (Cognasse et al., 2007). In addition it is suggested involvement of platelet-activating factor in disruption endothelial tight junctions what means opening of the blood-brain barrier (Callea et al., 1999; Brkovic, Sirois 2007; Adamson et al., 2008; Knezevic et al., 2009). We feel that above observations are important in understanding the etiology of ischemic brain neurodegeneration with dementia and Alzheimer's disease etiology.

10. Neuropathology after ischemia

Most of the experiments with reference to ischemic brain injury were conducted on small rodents. The reproduction of overlapping pathological mechanisms in small rodent models is a suitable approach to unravel of causal relationships. Studies were conducted to support the hypothesis that the anatomy of the brain vasculature in small rodents is not different from that of humans. The preference to perform brain ischemia studies on rodents are also supported by pragmatic reasons including a high homogeneity due to inbreeding, accessibility and lower costs. For several reasons, the favored brain region for the study of

ischemic injury is the hippocampus. First, the hippocampus is the part of brain, which displays the same pathology as human ischemic brain. Second, the hippocampus is implicated in spatial learning and memory. Third, the hippocampus, especially its area CA1 is one of the brain sectors very sensitive to ischemic injury like in humans. Finally, the distinct laminar organization of the hippocampus and its final mapped synaptic connections allow exact layer-type or cell-type investigations. With respect to the above observations and metabolism, cerebral blood flow and pathology few models of brain ischemia, which mimicked human condition have been presented (Kirino 1982; Pulsinelli et al., 1982; Smith et al., 1984; Pluta et al., 1991). In these models selective ischemic pyramidal neurons death was noted in the CA1 sector of the hippocampus (Kirino 1982; Pulsinelli et al., 1982; Pluta 2000; Pluta 2002b). Loss of neurons develops during 7 days after ischemia and is called delayed neuronal death (Kirino 1982). Three min of ischemic brain injury in gerbils and 10 min in rats are sufficient to start this characteristic hippocampal pathology (Kirino 1982; Pulsinelli et al., 1982; Pluta 2000; Pluta 2002b). Prolongation of ischemic brain injury in rats to 10-20 min results in complete neurons death in the CA1 sector of the hippocampus and neuronal injury in the brain cortex and striatum (Pulsinelli et al., 1982; Kiryk et al., 2011).
Prolongation of recirculation time ends in neuronal alterations in hippocampal regions of nonselective vulnerability (Pluta et al., 2009). Striatal pathology is mainly noted in the dorsolateral area and influence medium-sized neurons (Pluta 2002b). In the brain cortex, the layers 3, 5 and 6 presented neuronal changes (Pulsinelli et al., 1982; Pluta 2000; Pluta 2002b). Within these regions of selective neurons pathology strong activation of astrocytes and microglia were showed (Petito et al., 1990; Schmidt-Kastner et al., 1990; Gehrmann et al., 1992; Morioka et al., 1992; Orzyłowska et al., 1999; Pluta 2000; Pluta 2002b). In brain areas with neuronal disappearance and neuronal cobweb interruption brain ischemic atrophy finally develops (Hossmann et al., 1987; Pluta 2002b; Pluta 2004b; Pluta, Ulamek 2006) with all neurodegenerative consequences.

11. Neuroinflammation after ischemia

Ischemic brain injury is associated with both acute and chronic neuroinflammatory reactions, involving activation, hypertrophy and proliferation of astrocytes and microglia. Ischemically activated astrocytes in the CA1 area of the hippocampus overexpress cytokines (Orzylowska et al., 1999). These data show that upregulation of neuroinflammatory mediators by astrocytes are directly connected with selective vulnerability of neuronal cells in ischemic brain injury (Orzylowska et al., 1999; Touzani et al., 2002). The above data suggest that neurons in vulnerable sectors in ischemic brain are targets of astrocytes interleukin-1β. This idea is supported by overexpression of neuronal interleukin-1 receptor (Touzani et al., 2002). In addition, it was confirmed that interleukin-1β is the important factor in brain ischemia cells damage and edema formation (Yamasaki et al., 1995). Chronic synthesis by ischemic brain neuroinflammatory factors may start a self-sufficient cycle that shifts ischemic pathology into hallmarks typical for Alzheimer's disease. In ischemic brain interleukin-1 is a key factor, which motivates neurons to pathological cleavage of amyloid precursor (Griffin et al., 1998) and emits inflammatory mediators. All these events result in neuronal abnormal function and finally their death. Neuronal loss arises from neuroinflammatory factors, which induce neuronal damages that trigger microglia activity with further self-propagation of the neuroinflammatory events. Additionally, evidence has been showed that β-amyloid promotes the release of neuroinflammatory pathogens by microglia (Giulian et al., 1995). In the

hippocampus glia activity precedes neurons alternations and persists for long time after ischemic brain injury. Initially, this activity was combined with repair responses at the site of the brain injury, but currently it has been shown that neuroinflammatory reaction is a key play in the evolution processes of ischemic brain pathology (Stoll et al., 1998).

Considerable evidence indicates that neuroinflammatory cascade modulates both the synthesis factors and proliferation reactions of activated astrocytes (Smith, Hale 1997), which exert both beneficial and harmful effects during repair mechanisms in the injured brain (Stoll et al., 1998). The reactive glia produce cytokines, which next stimulate glia, cytokine production and gliosis in a self-propagating, cycle (Barone, Feuerstein 1999). Neuroinflammatory genes overexpression peaks 24 h in the damage area, then decrease (Schroeter et al., 2003). Additionally, ischemic brain injury not only causes tissue cell injury, but also engages neuroinflammatory reactions that include the movement and depositions of leukocytes, macrophages, monocytes and different serum proteins due to open of the blood brain barrier (Danton, Dietrich 2003). In addition to the core ischemic injury neuroinflammatory reactions in the remote region to the primary ischemic injury have also been observed. Using the focal model of brain ischemia degeneration was noted in thalamus and substantia nigra in areas which are supplied by opened cerebral arteries and these areas showed no sign of ischemia (Danton, Dietrich 2003). Neurodegeneration in thalamus and substantia nigra were preceded by TNFα overexpression, supporting the role of neuroinflammation in the remote region to the ischemic brain lesion (Danton, Dietrich 2003). Other authors additionally reported a transient overexpression of IL-6 in the substantia nigra following focal brain ischemia (Dihne, Block 2001). Increased number of neuronal progenitor cells has been noted in the hippocampus following focal (Takasawa et al., 2002) and global (Jin et al., 2001) brain ischemia and in subventricular zone after *cardiac arrest* in rats (Andjus et al., 2010), with a considerable number of cells differentiating into astrocytes that support the neuroinflammatory reaction in the remote area distal to the primary deadly injury. Finally focal or global brain ischemic can induce a general inflammatory reaction both in the brain and peripheral body system. Inflammatory markers such as interleukin-6 and matrix metalloproteinases-9 are significantly elevated in blood plasma following brain ischemia (Castillo, Rodriguez 2004).

Neuroinflammation has also been implicated in the neuropathogenesis of dementia. In dementia patients neuroinflammation is often combined with β-amyloid peptide accumulation and neurofibrillary tangles development (Moore, O'Banion 2002). Neuronal cells in the hippocampus are peculiarly vulnerable to the influence of chronic inflammation (Hauss-Wengrzyniak et al., 2000; Wenk, Barnes 2000). In addition, hippocampus, the center involved in learning and memory, which demonstrates the greatest early activation of microglia in the different diseases, finally shows the highest degree of neuropathology and atrophy (Hossmann et al., 1987; Cagnin et al., 2001; Pluta 2002b; Pluta 2004b; Pluta, Ulamek 2006). A large number of different experimental and clinical treatment studies presented that reactive microglia and proinflammatory factors are present at areas of β-amyloid plaques accumulation and anti-inflammatory therapy decreases the progression of the diseases connected with amyloid pathology in own etiology (McGeer et al., 1996; Kalaria 1999; Akiyama et al., 2000).

12. Ischemic brain cells and β-amyloid peptide

In the ischemic brain, the main pathological focus is concentrated on pyramidal neurons in hippocampus because this region of the brain is selectively vulnerable to ischemia. In

generally, complete loss of vulnerable neurons in the CA1 sector was noted during 7 days following brain ischemia (Butler et al., 2002). Moreover, one third of subjects with ischemic brain injury did not present full loss of neurons in CA1 sector following ischemia with long-term survival (Sadowski et al., 1999; Pluta 2000). In some cases, complete disappearance of all neurons of CA1 area was observed in very late stages after ischemia (Pluta 2000; Pluta 2002a; Pluta 2002b; Pluta et al., 2009). Some investigations presented marked neuropathological alterations in pyramidal neurons considered to be completely resistant to ischemic injury such as: in areas CA2, CA3, and CA4 of hippocampus and dentate gyrus (Pluta 2000; Pluta et al., 2009). These regions presented unexpectedly acute ischemic changes in neuronal cells from 1 to 24 months after ischemic brain injury (Pluta 2000; Pluta et al., 2009). Currently was noted that neuropathological processes in ischemic neurons continue well beyond the acute stage of insult (Pluta 2000; Pluta 2002a; Pluta et al., 2009; Kiryk et al., 2011). In these situations, enduring ischemic blood–brain barrier opening (Pluta 2003; Pluta 2005; Pluta 2006b; Pluta 2007b, Pluta et al., 2010) probably leads to enhanced ischemic neurons vulnerability to β-amyloid peptide (Koistinaho et al., 2002).

Some investigations reported that astrocytic apoptosis may contribute to the neuropathogenesis of different diseases such as ischemic brain injury (Koistinaho et al., 2004; Takuma et al., 2004; Pluta 2006a). Astrocytic abnormal activities observed in the ischemic brain injuries: swelling, astrogliosis, and astrocytosis (Bernaudin et al., 1998; Stoltzner et al., 2000). In ischemic brain some animal studies showed the early import of different parts of amyloid precursor protein from brain tissue and systemic circulatory to the astrocytes and in the late stages the export of the toxic β-amyloid peptide and C-terminal of amyloid precursor protein from dead astrocytes to the brain parenchyma (Pluta et al 1994b; Pluta 2002b; Koistinaho et al., 2004; Pluta 2004a; Pluta 2004b).

At early stages of ischemia-reperfusion brain injury, the N-terminal of amyloid precursor protein (Pluta et al., 1994b) may be produced by vascular endothelium that became damaged following injury (Badan et al., 2004). This hypothesis is supported by the overexpression and synthesis of β-secretase after brain ischemia (Wen et al., 2004a; Sun et al., 2006; Zhang et al., 2007). Furthermore presenilin overexpressed in postischemic brain (Tanimukai et al., 1998; Pennypacker et al., 1999; Pluta 2001) is involved in the cleavage of amyloid precursor protein to synthesize β-amyloid peptide through the γ-secretase complex (Wolfe et al., 1999). This secretase is involved in amyloidogenic cleavage of amyloid precursor protein. At the first step, amyloid precursor protein is cut at the N-terminal of the β-amyloid peptide fragment by protease called β-secretase. In the second step, the metabolite of β-secretase is cut by γ-secretase to form soluble β-amyloid peptide. Endothelial cells change structural features like: shape and size during time to become incorporated into the amyloid plaques in a close spatial relationship with damaged and dead astrocytes. The same investigations show that C-terminal of amyloid precursor protein aggregates in neurons following local brain ischemia and as the infarct increases, the C-terminal of amyloid precursor protein staining become increasingly larger in the core even though the neurons are dying and the core becomes largely acellular (Badan et al., 2004). The same and other studies reported that β-amyloid peptide and C-terminal of amyloid precursor protein noted in microglia could be due to the phagocytosis of dead neurons remnants containing β-amyloid peptide and C-terminal of amyloid precursor protein by microglia (Badan et al., 2004; D'Andrea et al., 2004). Moreover, there are data demonstrating that astrocytes but not microglia can swallow up β-amyloid peptide (Matsunaga et al., 2003; Wyss-Coray et al., 2003; Pluta 2006a). Other studies show that C-terminal of amyloid

precursor protein triggers the loss of astrocytes whereas the death of neurons is a secondary and result of the neuronal dependency on astrocytes for antineurotoxic amyloid guard (Abramov et al., 2003; Pluta 2006a). The accumulation of some parts of amyloid precursor protein in astrocytes may be important in promotion of amyloidosis in ischemic brain tissue in which chronic astrocytosis is probably play a key role in the occurrence of different kinds of amyloid plaques.

13. Blood–brain barrier after ischemia

Ischemic brain injury provoked a number of vessel abnormalities, which are open tight junctions and blood–brain barrier, diffuse leakage through necrotic vessels and vasospasm (Petito et al., 1982; Mossakowski et al., 1993; Mossakowski et al., 1994; Pluta et al 1994a; Wisniewski et al., 1995; Gartshore et al., 1997; Shinnou et al., 1998; Lippoldt et al., 2000; Ueno et al., 2002; Pluta 2003; Pluta 2005; Pluta et al., 2006b). Till one year after ischemic brain injury brain white and gray regions contained many diffuse and focal sites of horseradish peroxidase and gadolinium extravasations (Mossakowski et al., 1994; Pluta et al., 1994a; Pluta 2003; Pluta 2005; Pluta et al., 2006; Andjus 2010). Horseradish peroxidase leakage involved capillaries, venules, veins and arterioles. The above leakage was observed in hippocampus, cortex, thalamus and basal ganglia, and cerebellum. In summary in ischemic brains were chronic blood–brain barrier abnormalities.

Short-term survival after ischemic brain injury, animals presented within gray and white matter around blood-brain barrier vessels staining for all parts of amyloid precursor protein (Pluta et al., 1994b). On the contrary, after long-term survival immunostaining only for the neurotoxic β-amyloid peptide and to the C-terminal of amyloid precursor protein was noted (Pluta et al., 1997b; Pluta 2000; Pluta 2003; Pluta 2005; Pluta et al., 2010). Multiple and abundant β-amyloid peptide and C-terminal of amyloid precursor protein staining embraced or adjoined the blood-brain barrier vessels. Diffuse deposits of β-amyloid peptide and C-terminal of amyloid precursor protein like "puff of smoke" were also noted. Immunostaining inside capillaries with a halo of β-amyloid peptide and C-terminal of amyloid precursor protein staining around vessels (Pluta 2005; Pluta et al., 2009) indicated diffusion of this part of amyloid precursor and β-amyloid peptide across the blood-brain barrier vessels. Above deposits were observed mainly in the hippocampus, entorhinal and brain cortex.

The above observations were supported by *i.v.* injection of human β-amyloid peptide 42 into animals with *cardiac arrest*, which accumulated amyloid in the ischemic brain white and gray matter in perivascular space (Pluta et al., 1996; Pluta et al., 1997a; Pluta et al., 1999). β-amyloid peptide 42 can be moved by the blood–brain barrier receptor mediated system (Deane et al., 2003; Deane et al., 2004a; Deane et al., 2004b) and by blood–brain barrier leakage caused by ischemic brain injury (Pluta et al., 1996; Pluta et al., 1997a; Pluta et al., 1999; Pluta et al., 2000) or β-amyloid peptide toxicity on blood–brain barrier after ischemia (Thomas et al., 1996; Fiala et al., 1998; Farkas et al., 2003; Paris et al., 2004a; Paris et al., 2004b).

The pathological immunostaining for apolipoproteins A1, E and J was observed mainly around vessels (Kida et al., 1995; Pluta 2000). Perivascular deposits of above proteins were well delineated and irregular. Diffuse, broad, but faint areas were also seen. Extracellular apolipoproteins E and J staining were strongly labeled by antibody to apolipoprotein A1, stronger than by apolipoprotein E antibody (Kida et al., 1995; Pluta et al., 1995a). They were

immunostained stronger by antibody to apolipoprotein E than apolipoprotein J (Kida et al., 1995; Pluta et al., 1995a). It is important to notice that deposits around vessels of apolipoproteins colocalize with deposits of different parts of amyloid precursor protein (Kida et al., 1995; Pluta et al., 1995a). Apolipoprotein E can promote the aggregation of β-amyloid peptide into the fibrillar formation. Clusterin is involved in transport of β-amyloid peptide through the blood–brain barrier. The general role of apolipoproteins is controlling the content of β-amyloid peptide in the extracellular space of brain tissue as well as their control on amyloid plaques development. These data demonstrate significant additive effects of apolipoproteins on controlling β-amyloid peptide accumulation around blood-brain barrier vessels and that they play a main role in influencing extracellular brain β-amyloid peptide metabolism/clearance independent of β-amyloid peptide formation. Another activity, for apolipoprotein E in ischemic brain tissue is the proposed extracellular clearance of ischemic brain parenchyma by reverse movement of amyloid into blood (Pluta et al., 2000). Delayed clearance may exacerbate healing of the ischemic blood–brain barrier. Above data point out that around vessels apolipoproteins deposition following ischemic brain injury represents a secondary injury processes that could hamper healing and outcome of ischemic brain.

After brain ischemia injury thrombocytes are forming aggregates, which adhere to the endothelium lining of blood–brain barrier vessels (Pluta et al., 1994c; Pluta 2003; Pluta 2005). As an effect of this pathology the "no-reflow phenomenon" is developing (Mossakowski et al., 1993; Pluta et al., 1994c; Pluta 2003). Moreover, trombocytes were noted on the abluminal side of vessels following ischemic brain injury (Pluta et al., 1994c; Pluta 2003; Pluta 2005). This kind of pathology was observed in capillaries, venules, veins and arterioles independently of time after ischemic brain injury. Some study suggests that brain ischemia results in development platelet-leukocytes aggregates (Ishikawa et al., 2004) in the peripheral circulatory system (Ritter et al., 2005). Another study showed strong platelet-leukocyte-endothelium reactions following focal ischemic brain injury (Ishikawa et al., 2004). An increasing body of evidence has supported the idea that white cells can play an additional pathological function in brain ischemia injury (Caceres et al., 1995; Gidday et al., 2005). White blood cells matrix metalloproteinase-9 recruited to the brain ischemic tissue next white blood cells to the same brain regions in a positive feedback manner and influence chronic opening of blood–brain barrier following a primary ischemic injury (Gidday et al., 2005). Investigation by electron microscopy of ischemic blood–brain barrier presented leukocytes adhering to the endothelial cells of capillaries and venules (Caceres et al., 1995). This observation is suggested probable movement of leukocytes across blood-brain barrier vessels. Endothelial cells alterations and white blood cells aggregation and finally their adherence to vessel wall also reflect a "no-reflow phenomenon".

14. Ischemic blood–brain barrier and β-amyloid peptide

In ischemic blood-brain barrier vessels damaged endothelium presented ruptures of endothelial membranes (Caceres et al., 1995). Other studies of ischemic endothelium presented an increased number of endothelium microvilli and deep crater-like pits, and enlarged junctional ridging with undulations of basement membrane (Pluta et al., 1991). As an effect of presented alterations, platelets developed microthrombi, which attached to the vessel wall and caused a permanent supply of neurotoxic constrictors such as β-amyloid peptide (Chen et al., 1995; Thomas et al., 1996). Final effect of above phenomenon is

pathological vasoconstriction during reperfusion (Wisniewski et al., 1995; Ohtake et al., 2004). Recent data suggest that thrombocytes are the main ischemic factor in recirculation injury, not only through thrombus formation but also as cause of inflammation in cooperation with leukocytes (Nishijima et al., 2004). Due to the fact that β-amyloid peptide causes vasoconstriction (Thomas et al., 1996; Niwa et al., 2000) and endothelium damage (Thomas et al., 1996), a role for β-amyloid peptide in vasoconstriction and blood–brain barrier pathology has been proved. During reperfusion after brain ischemia, islets of necrotic endothelial cells in blood-brain barrier were noted (Petito et al., 1982; Mossakowski et al., 1994; Pluta et al., 1994a). Necrotic blood–brain barrier characterizes diffuse leakage of blood elements (Petito et al., 1982; Mossakowski et al., 1994; Pluta et al., 1994a; Pluta et al., 1994c) and different parts of amyloid precursor protein from blood serum (Pluta et al., 1994b; Pluta et al., 1996). This process is probably due to senescent endothelium and this phenomenon is increased during recirculation and is augmented by β-amyloid peptide toxicity (Mossakowski et al., 1994). Senescent endothelium is a common feature of vessel aging (Erusalimsky, Kurz 2005) and is also influenced by ischemic episodes (Mossakowski et al., 1994). Another problem during reperfusion with senescent endothelium is covering it with β-amyloid peptide where β-amyloid peptide acts as antiangiogenic factor (Paris et al., 2004a; Paris et al., 2004b). Ischemic brain insults together with β-amyloid peptide have harmful effects on astrocytes and pericytes (Lupo et al., 2001; Anfuso et al., 2004) and can influence blood–brain barrier vessel angiogenesis and finally can regulate the blood–brain barrier activity (Ramsauer et al., 2002).

15. Disabilities after ischemia

In addition to pathological and pathophysiological effects, cognitive abnormalities have been showed after ischemic brain injury (Block 1999; Kiryk et al., 2011). The cognitive abnormalities were found in regions of selective vulnerability to ischemic injury and they come before neuronal death. In addition, other brain areas, which are devoid of ischemic primary neurons lesions, display some functional changes. These abnormalities mainly seem to be due synaptic damage. Ischemic brain injury does not result in long-lasting neurological deficits in ischemic animals (Block 1999; Kiryk et al., 2011). Some spontaneous recovery of sensorimotor function has been demonstrated after brain ischemia (Yang, Simpkins 2007). Following ischemic brain injury a locomotor hyperactivity has been noted for 7 days (Kuroiwa et al., 1991; Karasawa et al., 1994). Hyperactivity was directly connected with neuronal alterations in the ischemic hippocampus (Kuroiwa et al., 1991; Kiryk et al., 2011). Longer ischemia and longer locomotor hyperactivity is significantly associated with increased hippocampal neurons changes (Block 1999). After ischemic brain injury, impairment in habituation up to 6 months as revealed by longer exploration time was noted (Mileson, Schwartz 1991; Colbourne, Corbett, 1995). Brain ischemia results in reference and working memory deficits (Davis et al., 1986; Kiyota et al., 1991; Kiryk et al., 2011). In addition, brain ischemia in animals leads to deterioration of spatial memory for up to 1.5 year (Block, Schwarz 1998; Karhunen et al., 2003; Kiryk et al., 2011). Deterioration of cognitive impairment has been observed consistently during reperfusion (Roof et al., 2001; Karhunen et al., 2003; Kiryk et al., 2011). Besides, data on repetitive ischemic brain injury have shown persistent locomotor hyperactivity, reduced anxiety, and severe cognitive deficits (Ishibashi et al., 2006). Above pathology was associated with brain atrophy, which connected with diffuse neurons loss in the CA1 sector of the hippocampus and in the brain

cortex (Ishibashi et al., 2006). Alertness and sensorimotor capacities are affected for 2 days, whereas deficits in learning and memory seem to be rather long lasting (Kiryk et al., 2011). Taken together strong evidence from both basic research and epidemiological studies indicated that the deterioration of cognitive activities could not be explained only by direct primary ischemic brain injury, but rather by a progressive consequence of the additive effects of the ischemic episodes, aging and Alzheimer's factors (Pasquier, Leys 1997; Popa-Wagner 2007).

16. New guarding of ischemic brain injury

16.1 Anti-amyloid therapy

1998 is a turning point in the new history of novel strategies in ischemic brain injury and Alzheimer's disease treatment (Pluta et al., 1998a). At first the full success against human β-amyloid peptide 42 *i.v.* immunization in rats with brain ischemic injury (Pluta et al., 1998a; Pluta et al., 1999) and second moderate effect by intraperitoneal immunization in transgenic mouse overexpressing amyloid precursor (Schenk et al., 1999) and third peripheral administration antibodies against β-amyloid peptide (Bard et al., 2000) led to the fast development of new therapies against amyloid pathology.

Human β-amyloid peptide removal/treatment has remarkable effects in ischemic brain injury (Pluta et al., 1998a; Pluta et al., 1999; Pluta, Ulamek 2008) and less effect in mice with overexpressed amyloid pathology (Schenk et al., 1999). Experience in patient's vaccination was less convincing (Nicoll et al., 2003; Lemere et al., 2006; Hawkes, McLaurin 2007). Trials in cases with amyloid pathology were stopped when 6% of immunized patients developed meningoencephalitis (Nicoll et al., 2003; Orgogozo et al., 2003; Gilman et al., 2005). Moreover, only 20% of patients synthesized antibody against amyloid (Gilman et al., 2005). Patients treated with autovaccine in *post mortem* examination had less amyloid plaques in brain, as well as occurrence of T-cell lymphocytes. Recently, it has been proved that antibodies against β-amyloid are in normal human immunoglobulin that in particular recognize and inhibit the toxic hallmarks of β-amyloid peptide (Dodel et al., 2004). Within the past decade treatments have been concerned on inhibitors of γ- and β-secretases responsible for cleavage β-amyloid peptide from amyloid precursor protein (Dovey et al., 2001; Selkoe 2001; Roberts 2002). Reduction of β-amyloid peptide in the brain parenchyma of aged rats after oral administration of the γ-secretase inhibitors has been noted result in decrease levels of β-amyloid in both cerebrospinal fluid and brain tissue (Best et al., 2006; El Mouedden et al., 2006). Another recent study was used antibody anti-β-secretase in which decrease of amyloid was shown in transgenic model of amyloid pathology (Rakover et al., 2007). This decrease correlated very well with improvement of cognitive function. Two single-chain antibodies have been shown to possess α-secretase activity supplying a novel use of vaccine (Rangan et al., 2003; McCarty 2006). Another group of scientists have used small particle libraries to screen for substances that either interfere with assembly of β-amyloid particles into fibrils (Lashuel et al., 2002; De Felice et al., 2004) or disaggregate them (Soto 2001; Gong et al., 2003; Blanchard et al., 2004).

Neprilysin is β-amyloid peptide degrading enzyme in the brain (Kanemitsu et al., 2003). Human neprilysin gene transfer into brain leads to a remarkable decrease of β-amyloid deposits in transgenic mice with amyloid pathology (Marr et al., 2003). These observations proved that the deficient metabolism of β-amyloid caused by decrease level of neprilysin might contribute to pathological amyloidogenic cascades including ischemic brain injury.

Ischemic brain injury results in the downregulation of α-secretase mRNA and decreases its net activity (Nalivaeva et al., 2004; Yan et al., 2007). Insulin degrading enzyme is another enzyme for β-amyloid clearance in the brain (McCarty 2006). Overexpression of above enzyme reduces β-amyloid levels and retards or completely prevents amyloid plaques development in the brain (Leissring et al., 2003). Some other enzymes like endothelin converting enzyme and angiotensin converting enzyme degraded/metabolized β-amyloid peptide, too (Eckman et al., 2003, Hemming, Selkoe 2005).
Treatment by gelsolin a molecule that has high affinity for β-amyloid reduced the level of β-amyloid in the brain intra- and extracellular space by peripheral action (Matsuoka et al., 2003). Other β-amyloid drug curcumin can moved across blood-brain barrier and reduce amyloid level and amyloid plaque burden in transgenic mice with amyloid pathology (Yang et al., 2005). The enoxaparin β-amyloid drug significantly reduced β-amyloid aggregates in cortex and the total amyloid cortical concentration by combining the blood serum β-amyloid peptide in systemic circulatory (Bergamaschini et al., 2004). In compliance with the sink hypothesis molecules, which are combining β-amyloid peptide in inactive complexes in the blood serum decreases the level of blood β-amyloid peptide, which then increase a net efflux of β-amyloid peptide from the brain into blood plasma (DeMattos et al., 2001; DeMattos et al., 2002).
Recently endogenous receptor for advanced glycation-end-products peptides and β-amyloid peptide antibodies has been found in sick and healthy subjects (Mruthinti et al., 2004). These observations suggest that naturally occurring antibodies for β-amyloid peptide and receptor for advanced glycation-end-products control β-amyloid peptide level in brain and peripheral blood.

16.2 Anti-tauopathy therapy

A novel therapy has been directed against hyperphosphorylated tau protein either by inhibiting various protein kinases or promoting phosphatase activities (Lau et al., 2002; Iqbal, Grudke-Iqbal 2004; Klafki et al., 2006). Recent *in vitro* studies shown particles, which inhibited tau protein fibrillization making these molecules a promising candidate to test them in experimental conditions (Chirita et al., 2004). A new interesting data concerning therapy against amyloid have been presented lastly in animals in which triple transgenic mice were injected with β-amyloid peptide antibodies (Oddo et al., 2004). β-amyloid peptide antibodies inducted *i.v.* lead to clearance of early hyperphosphorylated tau protein deposits (Oddo et al., 2004).
Some study showed that memantine reversed hyperphosphorylation of tau protein in hippocampal slices (Li et al., 2004) and this effect of memantine occurred by disinhibition of the activity of protein phosphatase 2A (Chohan et al., 2006) that earlier was noted to be downregulated in brains with amyloid pathology (Gong et al., 1993). Based on above data it was shown in humans that treatment amyloid pathology by memantine during one year significantly decreases hyperphosphorylated tau in cerebrospinal fluid (Gunnarsson et al., 2006).

16.3 Suppressing neuroinflammation

In ischemic brains the microglia are presented as neuroinflammatory invaders, which adding additional events *via* synthesis of cytokines designed to answer to primary neuropathology. This activity may lead to significant progression of brain ischemia cases

through neurons loss. Epidemiological studies suggest that long use of anti-inflammatory treatment in amyloid and neuroinflammatory disease like Alzheimer's disease can prevent its development (Moore, O'Banion 2002; Szekely et al., 2004). From these observations considerable studies were undertaken to investigate the influence of anti-inflammation treatment in ischemic and amyloid brain diseases. These studies include nonsteroidal anti-inflammatory therapy (Morihara et al., 2005), cannabinoids (Ramirez et al., 2005) and peroxisome proliferator-activated receptor-γ agonists (Sastre et al., 2003; Echeverria et al., 2005; Heneka et al., 2005; Sastre et al., 2006). Current results from transgenic model of amyloid pathology was presented data that therapy against β-secretase decreases reaction of neuroinflammation in brain (Rakover et al., 2007).
Delivery umbilical cord blood cells 48 h after ischemic brain injury are developing neuroprotection by blocking the neuroinflammatory reactions (Willing et al., 2007). Above cells show protective activities *via*: modulating the neuroinflammatory response, stopping the apoptotic events and enhancing neurogenesis and angiogenesis. Activation of sigma-1 and -2 receptors *via* 1,3-di-*0*-tolylguanidin injection 24 h after ischemic brain injury is impressive in reducing ischemic damage (Willing et al., 2007). Above substance is protective by reducing inflammatory reaction and decreasing intracellular calcium in neurons and by stopping the synthesis of cytokines. In ischemic brain informations from the damaging neuronal cells trigger immune cells for an inflammatory activity, with overproduction of cytokines. Whether the cause is known or not, neurological disorders present similar cellular neuronal abnormalities and inflammation. These treatments approaches may not only be beneficial for therapy of ischemic brain injury (Willing et al., 2007) but also other neurological disorders. Above presented treatments act in a similar manner by increasing neurons survival and inhibiting the activity of general immune system (Willing et al., 2007).

16.4 Protecting blood-brain barrier

The natural activity of the brain is associated with the coupling between cerebral blood flow and transport *via* the blood-brain barrier and neurons activity. Cerebral blood flow controls the neuronal physiological environment not only by regulation of local blood flow but also by regulating focal transport through blood-brain barrier. The blood-brain barrier is an energetic system with two sites of transport by its blood- and brain-facing sites. Structure and function of the blood facing side allows entry of nutrients products but opposite brain facing eliminate metabolites such as β-amyloid peptide from brain (Pluta et al., 2000; Deane et al., 2004a; Deane et al., 2004b; Zlokovic 2005). A main role of the blood-brain barrier is control of the brain pool of pathological β-amyloid peptide. The aim of this part of chapter is to analyze knowledge of the association of the ischemic blood-brain barrier with final ischemic brain injury, especially with regards to the formation different amyloid plaques (Pluta 2006a; Pluta 2006b; Pluta 2007a; Pluta 2007b) and to develop a consensus on whether blood-brain barrier changes are a valid target for brain ischemia treatment (Pluta 2006a; Pluta 2006b; Pluta 2007a; Pluta 2007b; Pluta, Ulamek 2008).
According to the new ischemic blood-brain barrier maturation idea of ischemic brain injury (Pluta 2006a) all parts of blood-brain barrier such as endothelium, basal lamina, pericyte and astrocyte cells are main targets for treatment of above disorder (Sohrabji 2007). The current idea states that pathological blood-brain barrier activity caused by ischemic injury at its abluminal and luminal sides for β-amyloid with damaged neurons by ischemic insult are responsible for full-blown late onset ischemic-type dementia (Pluta 2004b; Pluta 2006a; Pluta 2006b; Pluta 2007a; Pluta 2007b). In this way a novel and more effective therapy approaches

can be formulated and more data on different kind amyloidosis can be gathered. Aforementioned data suggest that reducing movement of β-amyloid peptide from blood to brain tissue (Dickstein et al., 2006) and significantly improving reverse transport from brain into blood plasma (Pluta et al., 2000; Bell et al., 2009) and preventing ischemic events in neurons (Pluta 2007c see for references) are principal main future points in treatment of ischemic brain injury (Iwata et al., 2001; Moore, O'Banion 2002; Cheng et al., 2003; Deane et al., 2003; Borlongan et al., 2004; Deane et al., 2004a; Deane et al., 2004b; Guo et al., 2004; Kalback et al., 2004; Koistinaho et al., 2004; Tanzi et al., 2004; Pluta, Ulamek 2008]. Current data provide new information that injection with β-amyloid peptide reduces blood-brain barrier leakage, amyloid burden and microgliosis in transgenic model of amyloid pathology (Dickstein et al., 2006). It was presented that the blood-brain barrier is damaged in amyloid diseases and after β-amyloid peptide delivery the immune system clears amyloid from the brain as it would in peripheral organs lacking barriers. Once β-amyloid is cleared the activity of the blood-brain barrier is restored (Dickstein et al., 2006). This study directly proves that the blood-brain barrier is disrupted in amyloid brain diseases (Bowman et al., 2007; Sohrabji 2007; Zipser et al., 2007; Pluta et al., 2009) and that vaccination with β-amyloid peptide heals the sides of damage blood-brain barrier in transgenic mice with amyloid pathology (Dickstein et al., 2006) and ischemic brain injury (Pluta et al., 2000). Earlier my laboratory has proved that *i.v.* immunization with human β-amyloid peptide 42 in brain ischemia heals blood-brain barrier leakage for β-amyloid peptide 42 (Pluta et al., 2000) and prevent disease neuroprogression (Pluta et al., 1998a; Pluta et al., 1999). Possible explanation of the reparation of the blood-brain barrier is that the vaccination leads to the decrease in the level of circulating β-amyloid peptide (Dickstein et al., 2006), which could directly and/or indirectly damage the blood-brain barrier (Farkas et al., 2003; Marco, Skaper 2006; Bell et al., 2009). For example inflammatory factors (Boutin et al., 2001) that stimulate angiogenesis (Grammas, Ovase 2001) and β-amyloid peptide have been shown to influence an increase of some angiogenic factors like VEGF and TGF-β (Tarkowski et al., 2002; Pogue, Lukiw 2004). It can be proposed that with the removal of information provided by β-amyloid peptide the endothelial cells behave normally and tight junctions are closed, thereby restoring a natural blood-brain barrier function. Increased concentration in plasma β-amyloid peptide has been observed in a transgenic mice with amyloid pathology after active amyloid vaccination and *i.v.* delivery of molecules with an affinity to β-amyloid peptide (DeMattos et al., 2002; Matsuoka et al., 2003) and after active immunization (Pluta et al., 1998a; Pluta et al., 1999) of non-human primates (Lemere et al., 2004). It is proposed that molecules that sequester blood serum β-amyloid peptide may decrease or prevent brain amyloidosis (Matsuoka et al., 2003). In addition studies with antibodies anti-intercellular adhesion molecule-1 (Zhang et al., 1994) or platelet-endothelial cell adhesion molecule-1 (Rosenblum et al., 1994) have presented that blockage of adhesion molecules and leukocyte adhesion or platelets (>90% of β-amyloid peptide is stored in blood platelets) attachment respectively reduces ischemic brain damage after effects.

Several different ways have been suggested to remove β-amyloid peptide by blood-brain barrier including: receptor-mediated β-amyloid peptide transport by blood-brain barrier, enzyme mediated β-amyloid peptide metabolism and β-amyloid peptide bindable molecules that mediated β-amyloid peptide clearance. Receptor mediated transport of β-amyloid peptide by blood-brain barrier is responsible for both influx and efflux of β-amyloid peptide. Lipoprotein receptor-related protein mediates efflux of β-amyloid peptide from brain tissue into blood (Deane et al., 2004a; Deane et al. 2004b; Bell et al., 2009).

The interaction between lipoprotein receptor-related protein and β-amyloid peptide mediates amyloid blood-brain barrier vessels binding, endocytosis and transcytosis through blood-brain barrier into circulatory system (Herz 2003). Moreover, p-glycoprotein has been proposed to be engaged in amyloid movement by blood-brain barrier (Lam et al., 2001). Currently some data noted that the neonatal Fc receptor at the blood-brain barrier has an important role in IgG-assisted β-amyloid peptide removal from the brain (Deane et al., 2005). Receptor for advanced glycation-end-products mediates influx of β-amyloid peptide from blood into brain tissue (Deane et al., 2003; Deane et al., 2004b). Decrease of receptor for advanced glycation-end-products can reduce influx of β-amyloid peptide into brain (Deane et al., 2003). Glycoprotein 330/megalin probably is involved in receptor-mediated transport of apolipoprotein J alone and in a complex with amyloid at the blood-brain barrier (Zlokovic et al., 1996). Lipoprotein receptor-related protein and receptor for advanced glycation-end-products play opposing roles in amyloid transport through blood-brain barrier (Deane et al., 2004b). For now the most important way would be to look for new drugs, which influence the function or overexpression of β-amyloid peptide transport receptors by blood-brain barrier. The reduced function of receptor for advanced glycation-end-products and increased activity of lipoprotein receptor-related protein in ischemic blood-brain barrier might readjust the movement equilibrium for β-amyloid peptide by increasing its net efflux from brain into blood plasma. Statins, which increased lipoprotein receptor-related protein in blood-brain barrier, might facilitate the movement of β-amyloid peptide from brain tissue (Deane et al., 2004a). It is worth noting that receptor for advanced glycation-end-products blockades using receptor for advanced glycation-end-products specific IgG (Mruthinti et al., 2004) can also increase the expression of lipoprotein receptor-related protein (Deane et al., 2004b).

16.5 Therapy by estrogens

The incidence of ischemic brain injury is gender related (Pluta 2006a) and the risk of ischemic brain injury in aged women is greater than in men. The cumulative risk for ischemic brain insults in women is higher because of a lack of estrogen after menopause (Pluta 2006a). Estrogen treatment has been noted as blood–brain barrier function control through intercellular junction proteins (Kang et al., 2006) and/or intracellular transport elements and through protective effects on the cell elements of barrier such as endothelium, pericyte and astrocyte cells (Yang et al., 2005), cells which are vulnerable to influence of ischemia and aging together in the context of natural blood–brain barrier action (Sohrabji 2007; Zipser et al., 2007). Pathological opening of the blood–brain barrier can expose ischemic brain tissue to different cellular and plasma elements from blood that indirectly or directly impair neurons and press other pathological cascades. Age-related events in different sectors of the brain can have far reaching consequences for cognitive deficits e.g. after ischemic brain injury (Kiryk et al., 2011). Most scientists have taken the approach of studying estrogen effects on pathology related to ageing disorders (Simpkins et al., 1997; Dubal et al., 1998; Shi et al., 1998; Chi et al., 2002; Chi et al., 2005). Estrogens exert protective activity in animals ischemic brain injury (Simpkins et al., 1997; Dubal et al., 1998; Shi et al., 1998; Chen et al., 2001; Chi et al., 2002; Yang et al., 2005), but the mechanisms of their protection are not understood. These hormones may guard neuronal integrity (Chen et al., 2001) by readjusting the physiological activity of the blood–brain barrier (Chi et al., 2002; Chi et al., 2005). Another probable mechanism is that estrogens decreases overexpression of amyloid precursor protein messenger RNA in ischemic brain injury (Shi et al., 1998). The

protective effects of estrogens are observed in all of the neurovascular elements like: endothelial, pericyte, astrocyte and neuron cells and microglia (Chen et al., 2001; Yang et al., 2005). In addition after ischemic brain injury estrogens increase cerebral blood flow and decrease secondary ischemic episodes (McCullough et al., 2001). Prevention of ischemic brain injury and treatment of repeated ischemic episodes after primary ischemic insult may have important implications for delayed postischemic pathology like dementia. In view of the earlier data that cognitive deficits are progressing after ischemic brain injury (Kiryk et al., 2011), there is the distinct possibility that we can stop this decline by targeting the gradually progressing degenerative events, which follows ischemic brain injury by aiming at molecular processes now shown to change after brain ischemia.

17. Conclusion

The complex of overlapping events, which potentially lead to neurons death and finally dementia in ischemic brain injury, start with neuronal energy shortages due to the stopped delivery of nutrients products during ischemic episodes. The energy failure during ischemic brain injury is reflected by a fast and rapid depletion of ATP. Ischemic loss of ATP is followed by the dysfunction of ion pumps and depolarization of the neural cells, and the production of high level of reactive oxygen species, which are dangerous for neurons. Reactive oxygen species initiate lipid peroxidation and generation of lipid peroxides, which are metabolized to pathological products (Muralikrishna Adibhatla, Hatcher 2006). Parallel to these events, the activities of antioxidants decrease following ischemic brain injury (Nita et al., 2001). During recirculation a marked increase in the neurotoxic β-amyloid peptide, C-terminal of amyloid precursor protein and neuroinflammatory factors were noted. The β-amyloid peptide and C-terminal of amyloid precursor protein can act as glia stimulants. The presence of large numbers of astrocytes associated with the β-amyloid peptide and C-terminal of amyloid precursor protein deposits, in particular around vessels of the hippocampus, suggest that these amyloid deposits generate chemotactic mediators, which stimulate recruitment of next astrocytes. This suggests that astrocytes gradually accumulate β-amyloid peptide and the amount of accumulation correlates very well with the extent of pathology in the hippocampus and the survival time after ischemic brain injury. β-amyloid peptide within astrocytes appears to be of blood origin, possibly deposited by phagocytosis of locally opened blood-brain barrier (Pluta et al., 1996). In contrast, current results suggest that astrocytes could also act as a source for β-amyloid peptide, because they overexpress β-secretase in response to long-term pathology (Rossner et al., 2005). Although it remains unclear to which degree astrocytes contribute to β-amyloid peptide synthesis or its clearance, it seems apparent that astrocytes contribute to neuroinflammation cascades. In addition, microglia has been associated with amyloid plaques, which indicates that plaques development and the degree of microglia activation are interrelated. β-amyloid peptide stimulates a nuclear factor kappa B dependent pathway that is important for cytokine gene transcription, reactive astrocytes and activated microglia. Moreover, other Alzheimer proteins involved in the ischemic metabolism of amyloid precursor protein have also been implicated in neuroinflammatory reactions. Evidence suggests that neurons themselves are capable of synthesizing neuroinflammatory factors. Thus, neurons can serve as a source of cytokines including tumor necrosis factor-α and interleukin-1β (Orzyłowska et al., 1999; Heneka, O'Banion 2007). It is possible that the neurons proper may exacerbate local neuroinflammatory activities and thus contribute to own progressive distraction in ischemic

brain injury. A study with a transgenic model of amyloid pathology supports the notion that cytokines influence brain deposition of serum amyloid (Guo et al., 2002). It has been suggested that neuroinflammatory factors either raise the susceptibility for β-amyloid peptide deposition or directly influence amyloid precursor protein cleavage. Additionally, cytokines are able to transcriptionally upregulate β-secretase mRNA and its enzymatic activity (Sastre et al., 2003). β-secretase and γ-secretase are key enzymes for β-amyloid peptide synthesis. The above data can be linked to the increased overexpression and activity of β-secretase and γ-secretase noted in animal ischemic brain (Wen et al., 2004a; Polavarapu et al., 2008). Finally, interleukin-1β has been shown to significantly increase amyloid precursor protein production in astrocytes (Rogers et al., 1999). Moreover, cytokines may be involved in neurofibrillary tangle formation. The idea that interleukin-1 is the common link between β-amyloid peptide production, microglia activation and tau phosphorylation has recently been supported by a study in a triple transgenic animal model of amyloid pathology (Oddo et al., 2006). In this study, tau phosphorylation precedes β-amyloid peptide accumulation. Because the β-amyloid peptide and C-terminals of amyloid precursor protein and cytokines, such as interleukin-1β and tumor necrosis factor-α, directly impair neuronal activity, focal neuroinflammatory events may contribute to neurons dysfunction before neurons death. Neuroinflammatory mediators may directly contribute to ischemic brain degeneration like in Alzheimer's disease. β-amyloid peptide is formed by β- and γ-secretases from the amyloid precursor protein. Above reaction is called amyloidogenic cascade. In nonamyloidogenic process mediated by α- and γ-secretases amyloid precursor protein is cleaved within the β-amyloid peptide fragment. In both pathways is the synthesis of a 5 kDa fragment called the amyloid precursor protein intercellular domain that is proposed to contribute the progressing neuropathology in degenerative diseases including ischemic brain episodes (Muller et al., 2008). Scientists during the last 15 y have suggested the important role of amyloid precursor protein and its enzymatic processing in the neuropathology of ischemic brain injury. Above is also highlighted by the fact of noted overexpression of mRNA amyloid precursor protein (Shi et al., 1998; Shi et al., 2000), mRNA presenilins (Tanimukai et al., 1998; Pennypacker et al., 1999) and mRNA β-secretase following brain ischemia (Wen et al., 2004a; Chuang et al., 2007). The amyloid precursor protein intercellular domain is synthesized intracellular following enzymatic processing from the plasma membrane-derived amyloid precursor protein and probably might have a more direct influence on ischemic pathology than extracellular β-amyloid peptide. Over the past decade the participation of amyloid precursor protein intercellular domain in cell events have been presented including modulation in gene expression, apoptosis, cytoskeletal dynamics and suppression of neurogenesis (Muller at al., 2008). All these processes initiate and contribute to a *vicious cycle* of the disease process, resulting in progressive synaptic and neuronal dysfunction and loss in ischemia with dementia (Pluta et al., 2009; Kiryk et al., 2011).

Primary brain ischemia creates secondary repeated, transient and silent focal ischemic episodes, which are sufficient to sustain chronic/gradual oxidative stress and other events that could be the reason for the creepy and progressive neurons damage and death (Pluta et al., 2009; Pluta et al., 2010). Evidence derived from mice overexpressing the C-terminal of amyloid precursor protein, indicates that this part of the amyloid precursor protein may promote synaptic degeneration and retrograde neurons death (Oster-Granite et al., 1996), and finally dementia (Nalbantoglu et al., 1997). Moreover, ischemic brain injury is age-dependent (Oster-Granite et al., 1996; Popa-Wagner 2007).

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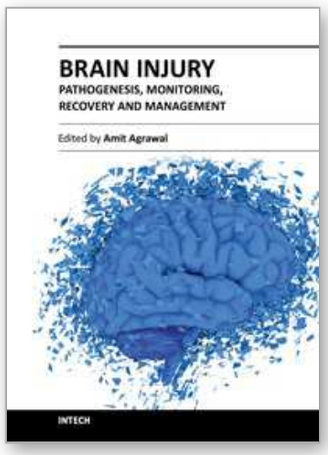

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The present two volume book "Brain Injury" is distinctive in its presentation and includes a wealth of updated information on many aspects in the field of brain injury. The Book is devoted to the pathogenesis of brain injury, concepts in cerebral blood flow and metabolism, investigative approaches and monitoring of brain injured, different protective mechanisms and recovery and management approach to these individuals, functional and endocrine aspects of brain injuries, approaches to rehabilitation of brain injured and preventive aspects of traumatic brain injuries. The collective contribution from experts in brain injury research area would be successfully conveyed to the readers and readers will find this book to be a valuable guide to further develop their understanding about brain injury.

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