REVIEW

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Alzheimer's factors in postischemic dementia

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Abstract

The way for explanation postischemic dementia processes has been one fraught with a wide range of complications and frequent revisions with a lack of a final clear solution. Data from animal models of brain ischemia and human ischemic brains studies have demonstrated an overexpression of amyloid precursor protein and increase production of a β-amyloid peptide. Restoration brain activity following ischemic brain episode is delayed and not always complete due to an alteration related with increase in the level of the β-amyloid peptide. In this paper, we will propose our idea about production of the β-amyloid peptide from the amyloid precursor protein in ischemic brain lesions, and how this protein presents etiological and therapeutic targets that are now under consideration. Maturation of the ischemic brain tissue pathology may be caused not only by a neurodegeneration of selectively vulnerable neuronal cells destroyed following ischemia but also by acute and chronic pathology of resistant parts of the brain and chronic changes in the blood-brain barrier. We propose that in dementia following ischemia an initial ischemic episode precedes the brain tissue deposition of β-amyloid peptide, which in turn amplifies the vascular dysfunction after first episode of ischemia triggering next focal ischemic episodes as vicious cycle preceding final ischemic degenerative changes and may gradually over a lifetime, progress to brain atrophy and finally to postischemic dementia with Alzheimer's phenotype.

***Keywords*:** brain ischemia, postischemic dementia, hippocampus, β-amyloid peptide, blood-brain barrier, atrophy.

Introduction

The expression of amyloid precursor protein is especially high in the brain. Accumulation of β-amyloid peptide, which is processed from amyloid precursor protein, in the intra- and extracellular space is a neuropathological hallmark of Alzheimer's disease. In sporadic Alzheimer's disease very little is known about what causes β-amyloid peptide deposition in brain parenchyma. Growing evidence suggest that brain ischemia may play a role in the etiology of sporadic Alzheimer's disease [1–7]. Transient brain ischemia results in an acute increase in β-amyloid peptide production [1–7] through induced β-secretase overexpression [8]. In an analogous way, complete brain ischemia due to *cardiac arrest* in rat's results in deposition of different fragments of amyloid precursor protein in numerous brain regions mainly in the hippocampus [1, 7, 9]. In humans, an evident increase in β-amyloid peptide deposition was found in neurons in the hippocampus of patients who died following ischemic brain stroke [10]. Additionally, a neuropathological examination of patients brains after *cardiac arrest* have shown accumulation of β-amyloid peptide together with fibrillar and non-fibrillar β-amyloid peptide plaques development and strong staining for advanced glycation end-product receptors (RAGE) [11, 12]. In sum, ongoing interest in brain ischemia research has provided evidence showing that ischemia may be involved in the pathogenesis of Alzheimer's disease [13]. The profile of pathology that is observed in an experimental rat model of global brain ischemia due to *cardiac arrest* shares a commonality with neurodegeneration processes in Alzheimer's disease [1, 7, 9, 13]. The objective of this review was to further develop and characterize *cardiac arrest* model in rats [14], which provides practical way to analyze Alzheimer's disease pathogenesis.

Amyloid precursor protein after brain ischemia due to cardiac arrest

Following experimental brain ischemia due to *cardiac arrest* with a survival time up to one-year it was observed increased staining for different fragments of amyloid precursor protein in brain parenchyma [1, 15–17]. What is in agreement with human brain neuropathological studies following *cardiac arrest*, which have confirmed an increase in β-amyloid peptide level and its transporting receptor RAGE staining after ischemic brain episode [11, 12]. The data from above animal and human studies demonstrated β-amyloid peptide deposition in intra- and extracellular space in brain tissue [1, 11, 15]. Immuno-

reactivity of β-amyloid peptide was showed in neurons and glial cells [16, 18, 19]. The reactive astrocytes with collection of β-amyloid peptide in cytoplasm are involved in the formation of glial scar [18, 19]. Reactive astrocytes with abnormal level of β-amyloid peptide deposition are involved in postischemic insufficient repair of host tissue including astrocytic death [1, 19–21].

Abnormal deposition for β-amyloid peptide has been shown in periventricular and subcortical white matter following brain ischemia [22, 23]. Possibly, aforementioned pathology is connected with leukoaraiosis formation after brain ischemia [23]. Extracellular accumulation of β-amyloid peptide ranged from multifocal very small dots to fibrillar amyloid plaques [1, 9, 11, 15, 19, 24]. Multifocal and widespread diffuse and fibrillar amyloid plaques were noted frequently in hippocampus, brain cortex, and subventriculary in the ischemic brain [1, 7, 9, 15, 16, 22–25].

Blood-brain barrier after brain ischemia due to cardiac arrest

In short-term survival, following complete brain ischemia episode, blood-brain barrier microvessels presented plenty of abnormalities: increased numbers of endothelial microvillas, cellular invaginations, vasospastic events, microthromb formation and local permeability for uncellular and cellular blood components (Table 1) [1, 14, 26–28]. Instead, animals with long-term survival following brain ischemia episode showed chronic changes of blood-brain barrier for uncellular and cellular blood elements (Table 1). Permeability abnormalities were spotty and dispersedly and involved arterioles, microcirculation, venules and veins [24]. Blood-brain barrier alterations predominate in hippocampus, brain cortex and white matter.

Table 1 – ***Staining for horseradish peroxidase (HRP), rat's N- and C-terminal of amyloid precursor protein (NAPP, CAPP) and β-amyloid peptide (βA) and human β-amyloid peptide 1-42 (βA1-42) in perivascular space after experimental 10 minutes brain ischemia due to cardiac arrest***

Groups	HRP	NAPP	βA	CAPP	βA1-42
Control					
Short-term survival	-	-	-	-	-
Long-term survival	-	-	-	-	-
Cardiac arrest					
Short-term survival	+/++	++	++	++	+++
Long-term survival	+/++	-	+/++	+/++	+++

The staining intensity: - no staining; + a single and diffuse areas; ++ a few and diffuse areas; +++ many strong and diffuse areas.

Other studies showed platelets aggregates of varying sizes within both arterial and venous brain vessels after ischemic injury [24, 27]. Some platelets were noted outside brain vessels in the perivascular space [24, 27]. Pathologically aggregating platelets like blood-brain barrier changes were local, random, widespread and dispersedly. Alterations of blood-brain barrier and platelets dominated in vessel bifurcations and branches. Current data suggest that platelets play a major role in postischemic injury not only through thrombus development, but also through involvement in neuroinflammatory response. Platelets may contribute to the recruitment of inflammatory cells to brain tissue following ischemia as effect of short life and β-amyloid peptide source. Platelets pathology and microvascular insufficiency [29] was noted in patient's brains early during the course of Alzheimer's disease thus supporting a further link between related processes and Alzheimer's disease [30].

In short-term survival following ischemic brain injury multifocal and widespread diffuse C-terminal of amyloid precursor protein, β-amyloid peptide and N-terminal of amyloid precursor protein deposits in the perivascular space were noted (Table 1) mainly in the hippocampus, white matter and brain cortex [1]. Multiple, abundant, extracellular deposits embraced or adjoined the blood-brain barrier microvessels. Perivascular deposits formed irregular, often asymmetric, well-delineated areas that frequently encircled microvessels, forming round, perivascular cuffs or hallo [1]. Diffuse, broad, but faintly positive perivascular zones were also found. Endothelial and pericyte cells were stained, too. In long-term survival, following ischemic brain episode, perivascular deposits ranged from numerous small-diffused areas to irregular diffuse plaques [16, 24, 25]. Deposits in brain microvessels and around them stained only for β-amyloid peptide and C-terminal of amyloid precursor protein (Table 1) [16, 24, 25]. Strong staining in the perivascular space suggested diffusion of different fragments of amyloid precursor protein out of the vascular compartment. Especially staining for C-terminal of amyloid precursor protein in long-lived animals underscores the likely importance of the C-terminal of amyloid precursor protein in the neuropathogenesis of ischemia as in Alzheimer's disease [31].

In other, our studies it was tested permeability for human β-amyloid peptide 1–42 by open blood-brain barrier after single or repeated complete brain ischemia (Table 1). In above studies widespread and multifocal accumulation of β-amyloid peptide 1–42 around blood-brain barrier microvessels was seen (Table 1) especially in hippocampus, brain cortex and occasionally in white matter [32–35]. Amyloid peptide permeability involved arterioles, microcirculation and venules. Endothelial, pericyte, glial and neuronal cells were filled with human β-amyloid peptide 1–42 [32–35]. Direct evidence that β-amyloid peptide crosses the ischemic blood-brain barrier and enters the brain parenchyma from the circulation is thus provided.

Cells death after brain ischemia due to cardiac arrest

In brain ischemia, neuropathology focuses on the hippocampus abnormalities because it is part of the brain selectively vulnerable to ischemic injury like in Alzheimer's disease. Small areas of pyramidal neurons death were noted in the CA1 sector of hippocampus two days following ischemic injury in rats [15]. In these cases, complete disappearance of vulnerable neuronal cells in the CA1 area was observed from 7 to 14 days later. Moreover, about one third of brains following ischemic episode did not present complete disappearance

of CA1 area in short-term survival period [15]. Above animals developed death of all neurons of CA1 sector in very late stages [15, 16, 18, 19]. Additionally, some evidence presented distinct pathology in brain areas considered to be resistant to ischemic injury such as: CA2, CA3 and CA4 areas of hippocampus. Above sectors showed acute postischemic changes in neurons at 1, 6, 9, 12 and 24 months following ischemic episode [15, 16]. Pyramidal neurons in hippocampus have very long axons that connect different structures of the brain together through many synaptic connections. Neuropathology in pyramidal neurons may be of significant relevance to Alzheimer's disease development. Recently, it has become recognized that neuropathological processes in ischemic neurons continue well beyond the acute stage [15, 16, 18]. Evidences indicate that brain ischemia regardless of survival time is followed by acute neuronal cells changes in brain regions belonging or not to selectively vulnerable areas. In ischemic brain neurodegenerative changes in neuronal cells took the form of "burn faintly phenomenon" [15, 18].

Current investigations showed that astrocytes apoptosis may contribute to pathogenesis of many acute and chronic degenerative disorders like brain ischemia and Alzheimer's disease [21]. Common astrocytic reactions that occur in the ischemic brain and Alzheimer's disease are cellular swelling, proliferation (astrocytosis) and hypertrophy–hyperplasia (astrogliosis) [36]. It is widely believed that reactive astrocytes at the early stage of brain injury have a beneficial effect on neurons by participating in several biological processes such as the repair of the extracellular matrix, control of the blood-brain interface, and trophic support of neurons. However, whether prolonged reactive astrocytic response is beneficial in neuronal recovery is still controversial. Some studies showed following ischemic brain injury the early import from brain tissue and circulatory system to the astrocytes different fragments of amyloid precursor protein and in the late stage the export from astrocytes to the brain parenchyma of the neurotoxic C-terminal of amyloid precursor protein and β-amyloid peptide [19, 37, 38]. We considered that in early stages astrocytes through phagocytosis removed from neuronal cells and their neighborhood neurotoxic fragments of amyloid precursor protein. Next in astrocytes cytoplasm is going degradation of various fragments of amyloid precursor protein. In late stages when ischemic abnormal metabolism of amyloid precursor protein took chronic form and astrocytic metabolism beginning to be inefficient we can observe at first disruption of astrocyte processes [1, 19]. On other hand disruption of astrocytes processes indicated degradation of different neurotoxic fragments of amyloid precursor protein in the astroglial cytoplasm. The late observations of astroglial behavior support the idea that astrocytes produce amyloid precursor protein and are a source of β-amyloid peptide. When above process fully developed, at the same time atrophy of brain started. In an early stage following brain ischemia, it was noted vigorous incorporation of N-terminal of amyloid precursor protein into the developing astroglial scar around the ischemic area [4]. Functional recovery following brain ischemia may reflect the balance between degenerative processes and growth phenomena including a neuroinflammatory reaction [39] leading to glial scar development as well as the release of toxic elements like the C-terminal of amyloid precursor protein. At early stages of brain ischemia, the N-terminal of amyloid precursor protein may be synthesized by cells derived from the vascular endothelium, which became fragmented after injury [4]. Over time, these cells change shape and size to become incorporated into the glial scar in a close spatial relationship with astrocytes and surprisingly newly formed neurovessels that penetrated the scar. Concurrently with the expression of scar-forming N-terminal of amyloid precursor protein there is expression of potentially toxic fragment like C-terminal of amyloid precursor protein [40]. Evidence derived from mice overexpressing the C-terminal of amyloid precursor protein indicates that this fragment may promote synaptic degeneration and neuronal death [41]. Some experiments show that C-terminal of amyloid precursor protein steadily accumulates in neuronal cells in the ischemic region as the ischemia progresses the C-terminal of amyloid precursor protein staining become increasingly larger in the centre of ischemia even though the neurons are dying and the ischemic centre becomes largely acellular [4]. The same study suggests that C-terminal of amyloid precursor protein identified in microglia cells could be due to the phagocytosis of dead, C-terminal of amyloid precursor protein containing neurons by microglia [4]. Most interestingly there are current studies showing that astrocytes, but not microglia cells can take up β-amyloid peptide [20, 42]. Additionally, more recent work shows that C-terminal of amyloid precursor protein induces the death of astrocytes whereas the loss of neurons is a secondary consequence of the neuronal dependence on astrocytes for antioxidant protection [43]. The localization of some fragments of amyloid precursor protein to astrocytes may be of significant relevance to Alzheimer's disease in which chronic astrocytosis is thought to play a key role in the evolution of amyloid plaques and in repairing host tissue through development of glial scars. The study of astrocytes is particularly important considering the co-existence of the apoptotic death of neuronal cells and astrocytes in ischemic brain [44] and neurodegenerative disorders. Furthermore, significant astrocytes death occurs after reactive astrocytosis and dying astrocytes kill neighboring cells in ischemic brain injury.

Brain atrophy after brain ischemia due to cardiac arrest

Gross examination of experimental brains performed up to one-year following ischemic injury revealed dilatation of brain ventricles and subarachnoid space between and around the hemispheres [16, 24, 37, 38]. Additionally, atrophy of the dorsal hippocampus was found following brain ischemic injury [15, 19, 32]. The presence of new infarcts in experimental ischemic brain injury model with very long survival of animals has been shown [24]. Generally, cortex of brain was narrow expressing increased neuronal density. White matter was narrow and in some places with advanced spongiosis

[15, 22, 23]. Finally, atrophic brain is indicative of an active progressing neurodegenerative processes.

Functional consequences after brain ischemia due to cardiac arrest

In addition to ischemic neuropathological changes in brain neurobehavioral abnormalities have been observed [45]. Brain ischemia due to *cardiac arrest* does not result in long-lasting neurological deficits in animals [45]. Spontaneous recovery of sensorimotor function has been observed after ischemic brain injury [45]. Following brain ischemia, a locomotor hyperactivity has been noted [45] as in Alzheimer's disease patients. The hyperactivity was positive correlated with increased neuronal changes in hippocampus [9, 46, 47]. Ischemic brain injury results in reference and working memory deficits [45]. Moreover, ischemic brain injury in experimental animals leads to progression spatial memory for one-year and more [45]. Neuro-cognitive impairment progression has been presented consistently following brain ischemia [45]. Moreover, data from repetitive brain ischemia in gerbils has been shown persistent locomotor hyperactivity, reduced anxiety and severe neuro-cognitive deficits [48]. Above abnormalities were connected with significant brain atrophy [15, 16, 19] associated with diffuse neuronal loss in the brain cortex and in CA1 sector of hippocampus [9, 16]. Alertness and sensorimotor capacities are affected for 1–2 days whereas the deficits in learning and memory seem to be rather long-lasting [45]. Taken together supporting evidences from both experimental and clinical studies indicated that the progressive neuro-cognitive activities decline could not be explained only by the direct contribution of the primary ischemic brain injury, rather a progressive consequence of the additive effects of the ischemic lesions, Alzheimer's factors and aging [6, 49, 50]. This data suggests that ischemia enhances amyloid precursor protein mRNA expression, which may contribute to the progression of neuro-cognitive impairment in postischemic injury [3, 51, 52]. At last, the production of β-amyloid peptide in brain following ischemia increases and impairs the memory. The functional alterations were shown within the areas of selective vulnerability to ischemia and they precede the neurons death. Additionally, other regions of brain those which are devoid of ischemic neuronal injury display functional abnormalities. These changes mainly seem to be due synaptic changes, because of connections neuronal cells within sectors with ischemically damage and death neurons.

Conclusions and future perspectives

The accumulation of β-amyloid peptide in neurons and in astrocytes probably is important in chronic ischemic brain mechanisms, which develop neurodegenerative pathways including postischemic dementia [1, 19, 51]. Moreover, the aforementioned protein accumulation suggests that above protein can start synaptic alterations and finally trigger retrograde neuronal cells death after brain ischemia episodes [16]. The above evidence shows that the chronic amyloid deposition after brain ischemia injury may start a secondary pathological progression that could worsen the ischemic intellectual brain outcome by further neurons death in vulnerable and resistant sectors of the brain [15, 16]. After ischemic brain episodes, β-amyloid peptide is produced because of neuronal injury in brain [2], and at the same time is taken from systemic circulatory system and probably appears its effects, influencing ischemic neuronal cells as dementia. It is accepted that β-amyloid peptide participates in neurons death in vulnerable and resistant areas of the brain [53]. The β-amyloid peptide is a neurotoxin peptide and entangles within an ischemic processes in glial cells, which lead finally neuronal and glial cells to death [54] and postischemic dementia with Alzheimer's phenotype.

The main factors of Alzheimer's disease pathology in ischemic brain are specific proteins abnormal metabolism, blood-brain barrier changes, different kinds of plaques and neuronal death with full-blown dementia. New data are suggesting that brain ischemia starts neuronal death and ischemic blood-brain barrier starts plaques development with detected hippocampus atrophy and increased volume of lateral ventricles [16], hemorrhagic damage of temporal lobe [55] finally ended with impairment in spatial working memory [45]. The data of Alzheimer's phenotype following brain ischemia led us to the rival theory that Alzheimer's disease etiology may be attributed to the ischemia in human brain.

In summary, we are presenting a good model for Alzheimer's disease investigation using animal's ischemic brains. By use of brain ischemia model, we may elucidate the pathogenesis of Alzheimer's disease. Recent knowledge regarding the neuropathophysiology, neurochemistry and neuropathology of brain ischemia and Alzheimer's disease indicates that similar processes contribute to neuronal death, amyloid accumulation and brain parenchyma disintegration.

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