Postischemic dementia with Alzheimer phenotype: selectively vulnerable versus resistant areas of the brain and neurodegeneration versus β-amyloid peptide

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Abstract

The road to clarity for postischemic dementia mechanisms has been one fraught with a wide range of complications and numerous revisions with a lack of a final solution. Importantly, brain ischemia is a leading cause of death and cognitive impairment worldwide. However, the mechanisms of progressive cognitive decline following brain ischemia are not yet certain. Data from animal models and clinical pioneering studies of brain ischemia have demonstrated an increase in expression and processing of amyloid precursor protein to a neurotoxin oligomeric β-amyloid peptide. Functional and memory brain restoration after ischemic brain injury is delayed and incomplete due to a lesion related increase in the amount of the neurotoxin amyloid protein. Moreover, ischemic injury is strongly accelerated by aging, too. In this review, we will present our current thinking about biogenesis of amyloid from the amyloid precursor protein in ischemic brain injury, and how this factor presents etiological, therapeutic and diagnostic targets that are now under consideration. Progressive injury of the ischemic brain parenchyma may be caused not only by degeneration of selectively vulnerable neurons destroyed during ischemia but also by acute and chronic damage of resistant areas of the brain and progressive damage in the blood-brain barrier. We propose that in postischemic dementia an initial ischemic injury precedes the cerebrovascular and brain parenchyma accumulation of Alzheimer disease related neurotoxin β-amyloid peptide, which in turn amplifies the neurovascular dysfunction triggering focal ischemic episodes as a vicious cycle preceding final neurodegenerative pathology. Persistent ischemic blood-brain barrier insufficiency with accumulation of neurotoxin β-amyloid protein in the brain tissue, especially in extracellular perivascular space and blood-brain barrier microvessels, may gradually, over a lifetime, progress to brain atrophy and to full-blown ischemic dementia with Alzheimer phenotype.

Key words: *brain ischemia, postischemic dementia, Alzheimer's factors, hippocampus, β-amyloid peptide.*

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Introduction

Brain tolerance to ischemia

Despite significant progress in the understanding of the neuropathophysiology, neurochemistry and neuropathology of experimental and human brain ischemia, the processes of the full outcome of the brain remains a topic of huge disagreement. In the classic view, clinical and experimental observations of cardiac arrest recommend that brain ischemia of 6 minutes ends in irreversible brain damage and leads finally to death. This point of view was challenged by Hirsch and coworkers [18], who noted recovery of brain bioelectrical activity after 10 minutes of brain ischemia produced by inflating a cuff around the animal's neck without interfering with heart activity. They suggested that the shorter period of brain ischemia after cardiac arrest was due to the fact that the recovery period of the heart should be added to the period of brain ischemia. Later, Ames and coworkers [2] noted that even without heart insufficiency after ischemia, recirculation was a serious limiting factor of brain recovery. They discovered that after 7.5 minutes of brain ischemia a considerable volume of the brain was not completely recirculated and they called that process a "no-reflow phenomenon". They suggested that recirculation disturbances were probably responsible for the short time of the brain ischemia. If this idea is correct, prolongation of the ischemic time of the brain can be possible under conditions in which development of the "no-reflow phenomenon" is prevented and/or stopped. It has been proved that sufficient therapy of ischemic recirculation pathology leads to recovery of brain bioelectric activity of the cortex and vasomotor and respiratory centers following complete brain ischemia in cats and rabbits as long as 1 hour duration [19,49]. In one cat, permanent restitution of integrative central nervous function returned after a very long period of ischemia [20]. However, integrative central nervous function is not predictable following short and prolonged brain ischemia and an increasing number of disturbances delaying recovery after ischemia have been identified. These include ischemia-induced dysregulation of cerebral blood flow [52], calcium- and glutamate-mediated pathology [40,51,75], changes of the blood-brain barrier [62-64,66] and even secondary depression of previously noted activities [49].

Maturation phenomenon following brain ischemia

Ito and coworkers [24] created the term "maturation phenomenon" for the progressive development of brain pathology following ischemia. It was also pointed out by the above group that the delay of maturation increased inversely with the time period of ischemia. Additionally, they showed that neurons in selective vulnerable areas like the hippocampus are going to die by neuronal delayed death within 4 days following 5 minutes of ischemia [31]. The above observations were made during the two first stages of brain ischemia investigations, which were focused on the hemodynamic and molecular effects *in vivo* and *in vitro* generally following acute brain ischemia with a short-term survival. Moreover, in the above studies little attention was given to chronic complicating side effects resulting from primary brain ischemia such as dementia [26,32].

Course of postischemic dementia

Postischemic dementia connected with chronic delayed secondary injury occurs in individuals suffering from focal or global brain ischemia in a progressive manner [26,59,67,70]. The chronic postischemic deficits, including dementia, have received far less attention in experimental and clinical investigations of brain ischemic injuries. Similarly, the processes involved in neuronal selective vulnerability should be clearly differentiated from those occurring in the neurons in more resistant areas of the brain [59,67]. Differentiation of probably similar and different processes in vulnerable and resistant sectors of the brain [59] is of particular importance for the establishment of pathways which in the acute pathway cause damage in the selectively vulnerable regions and probably further impair the damage in the resistant areas with the help of the Alzheimer neurotoxin β-amyloid peptide [67] and vice versa as a vicious circle. Some changes appear after a maturation interval, which may be longer than the usual duration of an acute experiment [24,31,59,67]. For this reason, failure to observe neuropathological or behavioral abnormalities shortly postischemia does not exclude the possibility that such lesions may develop at a later time after ischemic brain injury. At present, there are indirect explanations of the mechanisms involved in postischemic dementia. Below, the new available direct information will be reviewed and discussed mainly from a chronic and

unique animal model of complete brain ischemia with rat survival after ischemia of up to 2 years [67]. It is the only chronic model of brain ischemia due to cardiac arrest utilized by experimental neuroscience. This model of complete brain ischemia provides a practical way to analyze Alzheimer neurotoxin involvement in ischemic neurodegeneration and postischemic dementia. In this review, we will present our current thinking about biogenesis of the β-amyloid peptide from the amyloid precursor protein in ischemic brain injury, and how this factor presents etiological and therapeutic targets that are now under consideration.

Selectively vulnerable regions of the brain

Neurons located in the following areas of the brain are considered to be selectively vulnerable to ischemic brain injury: the limbic system, including pyramidal neurons in the CA1 area of the hippocampus, small and medium sized neuronal cells of the striatum, layers 3, 5 and 6 of the cortex and Purkinje cells. The lower limit of selective ischemic damage to CA1 pyramidal neuronal cells is less than 5 minutes [31] and a longer period is 1 hour [19,49]. The data from human clinical practice presenting injury to the selectively vulnerable hippocampal neurons have been disappointingly limited, without main conclusions. Disappearance of the neuronal CA1 sector does not provoke any major neurological deficits, especially motor deficits [32]. Kiryk and coworkers [32] observed high impairment of learning behavior deficits, which were parallel to the maturation process in the neuronal CA1 area of the hippocampus and striatum.

Resistant regions of the brain

All areas of the brain whose neurons are not selectively vulnerable can be defined as resistant (e.g. CA2, CA3 and CA4 areas of the hippocampus). As mentioned above, the "no-reflow phenomenon" may limit recovery following brain ischemia but appropriate therapy of this reperfusion side effect of ischemia can influence progressive recovery of some brain activities, following complete brain ischemia lasting up to 1 hour [19,20,49]. An important factor which has to be taken into account is the latency of the recovery following ischemia. The latency after brain ischemia recovery depends, on the one hand, on the duration of the ischemic episode and, on the other hand, on the reappearance of the neurochemical, neurophysiological and functional processes. Acute, short lasting animal

experiments therefore bear the risk that an injury may be erroneously considered to be irreversible because the latency time for the return has not elapsed. In addition, transient return during maturation of an irreversible injury is also possible and in this case the recovery may be erroneously interpreted as an indicator of functional recovery, although the same function/activity may develop to a late stage or disappear at a later survival time [49]. Global resistance to ischemic brain injury in consequence exceeds by far the lower number of damaged and/or dead neurons in the selectively vulnerable sectors of the brain.

Mechanisms from the first stage of ischemic brain studies

The history of brain ischemia research can be divided into two stages. During the first stage, studies described the hemodynamic, electrophysiological and biochemical changes in animal models, designed to replicate characteristic features of clinical brain ischemia [2,19,49,52]. The main conclusion from these studies was that brain tissue exhibited a much greater tolerance to circulatory arrest than previously assumed, provided microcirculatory disturbances were prevented during the recirculation phase after ischemia. Only in circumscribed, anatomically defined "selectively vulnerable" regions [31] may delayed neuronal cell death [24] evolve despite adequate postischemic recirculation. Later, evidence was provided that a similar type of delayed neuronal death may occur after complete brain ischemia [31] and in the peripheral penumbra of an evolving brain infarct after permanent occlusion of a major brain artery [21], or in the center of the vascular territory after transient vascular occlusion [12]. Based on the above, it is clear that mechanisms of action in different models of brain ischemia are complementary and are shared. Since delayed neuronal death in these regions cannot be readily explained by hemodynamic disturbances, research has drifted into so-called molecular mechanisms of neuronal ischemic injury that are thought to provoke cell death despite adequate blood flow and energy metabolism [50,53].

Mechanisms from the second stage of ischemic brain studies

The second stage of brain ischemia research has relied heavily on cell biological concepts of cellular injury, derived from different disease models. Examples of these are cytotoxic effects mediated by glutamate and Ca^{2+}

[40,51,75], nitric oxide, as well as suicidal genomic responses triggered by subcellular injury to mitochondria and endoplasmic reticulum [49,50,53]. However, the validity of these concepts has been tested in customized experimental models of ischemia that do not always replicate the clinical neuropathophysiology of brain ischemia. It is obvious that this incongruence is the main reason for the fact that so far all neuroprotective drugs derived from such experiments have failed to prove successful in clinical trials [16]. We, therefore, propose to initiate a third stage of brain ischemia research in which genetically/translationally controlled cell biological changes are screened without any prior mechanistic input before proceeding to the finer analysis of putative mechanisms of disease evolution or repair. Obviously, the multitude of molecular abnormalities in brain ischemia does not allow the *prima vista* distinction between causal and epiphenomenal contributions to neuronal death or repair. The major challenge of this novel research strategy is, therefore, the identification of those disease relevant genomic/translational responses that require therapeutic intervention to improve the final outcome. Our expected achievements will be to initiate and to provide a robust scientific basis for a third generation of research into brain ischemia that is timely and expected to lead to the identification of completely novel mechanisms and therapeutic strategies against the ischemic consequences.

In summary, after brain ischemia a few recirculation disturbances were observed: the "no-reflow phenomenon", postischemic hypoperfusion, microcirculatory compression by swollen perivascular glia [49], formation of endothelial microvilli and disseminated intravascular coagulopathy [54,55]. Problems with recovery and/or secondary suppression of energy metabolism may be the consequence of circulatory disturbances, following primary brain ischemia [55]. During and following ischemic brain injury, severe disturbances of water (brain edema), ion homeostasis (e.g. calcium) and neurotransmitters (e.g. glutamate) occur with developing acidosis [40,51,75]. During global brain ischemia, protein synthesis is inhibited but the inhibition of protein synthesis is reversible [19]. In the vulnerable regions, protein synthesis initially recovers as fast as in the other parts of the brain but after a delay, which depends on the time of ischemic injury, it is secondarily suppressed [19]. The exact mechanism responsible for the delayed suppression of synthesis is still under investigation [67].

Mechanisms from the third stage of ischemic brain studies

After ischemic brain injury, amyloid precursor protein mRNA increases by as much as 200% in the brain [1,30,34,78]. The aforementioned data support the evidence that ischemic brain episodes trigger a cascade, which increases the amyloid precursor protein mRNA level, contributing to the progression of cognitive deficits following brain ischemia lesions [1,34,78], and could be related to neurodegeneration and activation of astrocytes in the cascade of ischemic brain injury [30].

Following brain ischemia with a survival time up to 1 year, there was observed increased β-amyloid peptide staining in brain [25,56-59,67,71]. This is in agreement with clinical pioneering neuropathological studies, which have demonstrated an increase in β-amyloid peptide accumulation and its transporting receptor RAGE immunoreactivity, following brain ischemia [27,42,73,82]. The data from aforementioned experimental and clinical investigations demonstrated β-amyloid peptide accumulation in intracellular and extracellular space in the brain [27,38,39,56,59,71,73,79,82,85]. Staining of β-amyloid peptide was shown in neurons, astrocytes, microglia and oligodendrocytes [5,6,43,46,60,61,67]. Reactive astrocytic cells with accumulation of β-amyloid peptide in the cytoplasm are involved in glial scar formation [5,43,60,61]. Reactive astrocytes with abnormal levels of amyloid accumulation are involved in postischemic insufficient repair of host tissue, including astrocytic death [56,60,61,80,83].

Abnormal staining for β-amyloid peptide has been shown in subcortical and periventricular white matter after brain ischemia episodes [64,66]. Different types of amyloid deposits are formed in the ischemic tissue, e.g. diffuse, primitive and classic deposits [27,73,82]. Probably they have different pathological origins. The more intense the lesions, following brain ischemia, of white matter are, the more extensive is the staining of β-amyloid peptide in these areas [84]. Probably, the above neuropathology is associated with leukoaraiosis development, following ischemic brain lesions [66]. Extracellular deposits of β-amyloid peptide range from multifocal, widespread, very small dots to regular amyloid plaques [27,56,59,61,62,65,69,73,82]. Multifocal and widespread amyloid plaques were noted mainly in ischemic hippocampus, cortex, corpus callosum, and subventricularly in the ischemic tissue [56,59,62-64,66-69,71,73].

The deposition of amyloid in ischemic neurons and in astrocytic cells is important in late ischemic brain processes during the development of neurodegeneration with dementia [5,56,61,85,86]. It is possible that once β-amyloid peptide formation is triggered, there may be cell-to-cell transfer of β-amyloid peptide along anatomical pathways [59-61,67,77]. Additionally, the above protein accumulation suggests that this protein may trigger synaptic degeneration alterations and finally start retrograde neuron death, following ischemic episodes [44]. The aforementioned data indicate that the progressive β-amyloid peptide accumulation following ischemic brain episodes may trigger a secondary neuropathological process that could deteriorate the ischemic functional and intellectual brain outcome by additional neuronal cell death in vulnerable and resistant areas of the brain [59,67]. Following brain ischemia, β-amyloid peptide is produced as a result of neuronal injury in the brain [23] and systemic circulatory system alterations and probably exerts its effects, influencing ischemic neuronal and glial cells as dementia. It is accepted that β-amyloid peptide participates in neuronal cell death in vulnerable and resistant areas of the brain [11]. The β-amyloid peptide is a neurotoxin protein and entangles within ischemic processes in glial cells, which finally leads to neuronal and glial cell death [14].

Dementia following brain ischemia

In addition to neuropathological and neuropathophysiological effects, cognitive decline has been shown following ischemic brain injury in humans and in animals [26,32,37]. Human brain ischemia can cause neurological deficits in a number of neurological activities, most commonly in motor activity, cognitive decline and dementia [17]. Postischemic dementia is characterized by progressive cognitive deterioration including language, reasoning and memory. Of those patients suffering from brain ischemia lesions, less than 50% will return to independent living during the following year. Even among those who regain functional independence, many brain ischemia patients continue to manifest significant deficits, limitations and changes in their cognitive functioning and behavior. As such, ischemic brain injury is one of the leading causes of disability and experiencing a brain ischemia episode results in a two-fold increase in the risk of developing dementia. Other data show that 1 in 10 will have dementia soon after the first ischemic episode,

and over 1 in 3 will be demented after recurrent brain ischemic injury [71]. A more serious consequence of ischemic brain injury is postischemic dementia [26], which is also associated with severe disability and huge cost [13]. Dementia is the worst consequence for patients after an ischemic brain episode, being responsible for about 50% depending on the diagnostic criteria, population demographics and geographic location [37]. At present, it is becoming clear that postischemic dementia shares risk factors in common with Alzheimer dementia. Indeed, brain ischemia lesions may precede the onset of this form of dementia, strongly suggesting that brain ischemia injury may trigger different forms of neurodegenerative dementias. Postischemic dementia is associated with chronic and progressive injury [68], which occurs in patients suffering from brain ischemia in a progressive manner [26].

Cognitive decline is associated with brain areas of selective vulnerability to ischemia and they are revealed before final neuronal disappearance. Additionally, other "resistant" brain regions, which are theoretically devoid of ischemic primary neuronal injury, display some functional abnormalities, e.g. amygdala and perirhinal cortex [7]. These troubles mainly seem to be due to synaptic pathology. Ischemic brain lesions do not result in long-term neurological deficits in animals following brain ischemia [32,76]. Some spontaneous reappearance of sensorimotor activities has been demonstrated following brain ischemia [85]. Intensive locomotor hyperactivity has been observed immediately after ischemic brain insult [28,35,47]. Hyperactivity following brain ischemia was directly associated with its neuronal pathology in the specific ischemic parts of the hippocampus and amygdala and perirhinal cortex [7,32,35], which is typical for Alzheimer's disease. Longer lasting brain ischemia and, as its effect, longer locomotor hyperactivity is significantly associated with huge hippocampus neuronal cells loss [9] and in other "resistant" brain regions [7,59]. Following a brain ischemia episode, impairment in habituation, as revealed by longer exploration time, was observed [10]. Animals after brain ischemia show reference and working memory deficits [32,33,36,76]. Moreover, ischemic brain injury in animals leads to progressive deterioration of spatial memory during 1.5 years of observation [8,29,32]. Deficits of cognitive impairment have been noted to increase for the entire time of reperfusion [29,32,36,74,76]. Additionally, data on repetitive ischemic brain injury have shown persistent

locomotor hyperactivity, reduced anxiety, and severe cognitive deficits [22]. The above behavioral deficits were associated with brain atrophy, which additionally was connected with diffuse neuronal loss in the CA1 area of the hippocampus and in the brain cortex and amygdala and perirhinal cortex [7,22,59]. Alertness and sensorimotor capacities are affected for 2 days, whereas deficits in learning and memory seem to be persistent and progress with time [32,36,76].

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 second only to age [15,65]. Dementia, which is observed following ischemic injuries, is associated with intellectual impairment and finally brain atrophy [32,81] and in the end with huge cost [15]. Strong epidemiological trends show that areas of brain injury due to ischemic damage also increase with age, and these areas of ischemic damage are known as leukoaraiosis. Leukoaraiosis is a strong predictor of postischemic dementia [66]. It is also strongly associated with cognitive changes and cognitive decline in individuals who have not yet progressed to dementia [45]. Taken together, strong evidence from both basic research and epidemiological studies indicates 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, including recurrent ischemic lesions, aging and Alzheimer's factors [71,72].

Conclusions

The available clinical and experimental evidence indicates that the vulnerability of brain cells to ischemia is determined by both ischemia and post-ischemia recirculation. Ischemic brain pathology is a function of the duration of stopped circulation and catabolic processes, being more evident the longer ischemic injury lasts. At present, there are at least three processes considered to be of unique importance for the development of full brain ischemia injuries, which are rather independent of the time of ischemia: brain tissue acidosis, intracellular flooding with calcium and amyloidogenesis. If these processes are responsible for ischemic neuronal death, it would be understandable that vulnerable neurons are irreversibly damaged during short-term survival following a brain ischemia episode, whereas the resistant ones can develop

acute and chronic pathological changes [59,67] after long-term survival of the above episode. During ischemia and immediately postischemia, and during recirculation, abnormal processes are of great importance for the development of irreversible injury in vulnerable and resistant brain neurons. Among them one has to distinguish global and local disturbances. The most significant disseminated and irregular disturbance is the "no-reflow phenomenon". This particular phenomenon is not responsible directly for selective neuronal vulnerability but its presence is a prerequisite for further pathology of the resistant neuronal areas of the brain, following an ischemic episode. Generally, the above process is of equal importance for vulnerable and resistant neuronal regions because it appears following a variable duration of ischemia and it affects all areas of the brain to a similar degree. The development during this phenomenon of recurrent focal ischemic episodes can influence especially clearance from the brain of metabolic waste, including β-amyloid peptide, e.g. through perivascular space and across the blood-brain barrier [3,4,70]. Pathology resulting from the aforementioned mechanisms finally depends on the postischemic metabolic and functional state of each individual brain area. The injury may happen immediately at the time of the injury but there may also be continued damage after recirculation is reestablished [59,67,71].

The role of primary brain ischemia injury and molecular mechanisms emerging from recurrent ischemic lesions and permanent ischemic blood-brain barrier permeability seems to be crucial for step-by-step development of postischemic dementia [59,67,70,77]. Brain ischemia activates inflammatory processes, which are closely associated with glia activation and induce amyloidogenic amyloid precursor protein processing [3,4,36,67]. Data from animal investigations have revealed that long-term survival after an ischemic brain episode may result in permanent repeated focal ischemic lesions with progressive neuronal pathology in vulnerable and resistant areas of the brain with triggering of constant inflammatory processes [36,43, 46,55,56,59-61,67]. These changes are associated especially with increased expression and pathological metabolism of amyloid precursor protein [1,34,57-59, 67-69,71,78], the number of activated reactive astrocytic and microglial cells [6,43,46,60,61,67], loss of hippocampal neurons with detected hippocampus and brain atrophy [20,59,67,69], and hemorrhagic tempo-

ral lobe damage [48], and finally result in cognitive decline with Alzheimer phenotype [32,67]. A far-sighted vision of the neuropathology pathways that result in postischemic dementia reveals several vicious cycles within a larger vicious cycle, that is to say a number of interactive paths that all, once set in motion, amplify their own pathways, thus accelerating the development of postischemic dementia with Alzheimer phenotype [32,67]. Several lines of evidence suggest that production of amyloid oligomers reduces neuroplasticity and contributes to neuron degeneration and alterations in neurogenesis [36,41,47,71,77].

We propose that in postischemic dementia an initial brain ischemia episode precedes the cerebrovascular and brain tissue accumulation of Alzheimer disease related neurotoxin β-amyloid peptide, which in turn amplifies the neurovascular dysfunction, producing, in a vicious circle, repeated focal brain ischemic episodes, which precede the final irreversible neurodegenerative pathology. In summary, the long-term consequences of brain ischemia lesions in animals and humans may include cognitive and behavioral deficits with final full-blown dementia of Alzheimer phenotype.

Acknowledgements

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