Review paper

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Consideration of the ischaemic basis and treatment of Alzheimer's disease

Dedicated in Honor of my Mother Antonina Pluta (1922-2009) and Assistant Professor Irmina Zelman my Mentor and Friend (1927-2010)

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Abstract

Victims of Alzheimer's disease (AD) develop a progressive dementia over years, accompanied by development of neurofibrillary tangles and finally neuronal death, accumulation of amyloid plaques and deposition of amyloid in neurovessels. Currently AD is the major form of dementia and the fourth leading cause of death in aged population. The investigation of etiology and therapy of AD, now more than ever, needs an infusion of new concepts. The aims of this review are to analyze knowledge of the influence of ischaemic and amyloid pathology on the final development of AD, especially with regards to the etiology of AD plaques, to develop a consensus on whether ischaemic blood-brain barrier permeability for amyloid peptide or both are a valid target for AD therapy. Reviewing experimental models of AD, we will address the issue whether plaques of amyloid persist, develop with time or both in animals during different forms of experimental therapy. Based on above suggestions recent direct evidence that amyloid plaques and neurofibrillary tangles can be cleared from the brain is thus provided in experimental condition. Moreover, recent study provides data that immunization with β-amyloid peptide decreases blood-brain barrier permeability for β-amyloid peptide or restores blood-brain barrier integrity. This review summarizes the latest advances in this area focusing on investigations based on in vivo animal studies.

Key words: Alzheimer's disease, ischaemic etiology, amyloid therapy, tau protein therapy, blood-brain barrier therapy, inflammation therapy, gene therapy, immunotherapy.

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Introduction

Around 6.2 million people in Europe are estimated to suffer from dementia of which Alzheimer's disease (AD) accounts for around three quarters of the cases. Taking into account their careers and families for whom caring often becomes a heavy personal and financial burden, some 20 million people are affected, i.e. around 4% of the European population. The number of patients with AD doubles every 5 years beyond age 65. Alzheimer's disease affects more than 25% of the age 85 and 40% of those aged 90 and over. Alzheimer's disease is the most common of dementias, accounting for over 60% of all cases over age 65. Now the population of Poland aged ≥65 years is 6.5 million. It is estimated that about 260 thousands individuals suffer from Alzheimer dementia in our country. The second most common form of dementias is vascular dementia, usually resulting from vascular brain diseases. Late onset AD is not caused by ageing, nor is it an inevitable part of the ageing process, it is age-related [6,169]. Alzheimer's disease affects circa 19 million people worldwide without developing countries with a prevalence of approximately 1 percent in the total population, although the risk of being afflicted with AD increases with age [6,132,169]. By 2025 the population of world aged 65 years and older will exceed one billion with more than 700 million living in developing countries. Now when the lifespan quickly increases, the number of sporadic AD cases increases dramatically, too. Actually almost 30 million individuals in around the world suffer from Alzheimer's dementia and this number of sick persons in the next century will multiply several fold unless treatments to prevent, or cure the disease that currently are unavailable will be found. Alzheimer's disease is already responsible for a huge social and economic costs projected to rise exponentially in the coming decades [157] as the elderly part of the society continues to increase [27].

Now it is clear that AD is multifactor [50,72,76, 119,168] and thus heterogeneous disease [50,71, 81,105]. Alzheimer's disease can affect different people in different ways but the most common symptom pattern begins with gradually worsening difficulty in remembering new information. This is because disruption of brain cells network, which usually begins in areas involved in the forming new memories. As the damage spreads, patients also experience confusion, disorganized thinking, impaired judgment, trouble expressing themselves and disorientation with regard to location, time and space that may lead to unsafe wandering and socially inappropriate behavior. In advanced AD, patients need help bathing, dressing, using the bathroom, eating and carrying out other daily activities. Those in the final stages of the disease, lose their ability to communicate, fail to recognize loved ones and become bedbound and reliant on continual care. Alzheimer's disease is finally fatal. The course the disease takes and how fast changes occur vary from case to case. On average, sporadic AD patients live almost 10 years after they are diagnosed, though the disease can last for as many as 20 years [167].

Despite ongoing experimental and clinical interest in AD, the cause of the disease in sporadic cases is not known [7,67,109,144]. It is postulated that more than one pathogenetic pathway is involved in AD etiology. Owing to the involvement of more than one trigger factor in development Alzheimer's pathology it is important for the discovery specific therapies to prevent and treat this disease. Development of therapies requires the ability to correctly diagnose disease and knowledge about its neuropatogenesis. Diagnosis in AD patients is always late. The study of etiology and therapy [15] of sporadic AD, now more than ever needs an infusion of a new proposals. In 2007 approximately US$ 5.5 billion was spent on the symptomatic treatment of AD. The vast majority of this expense was generated by just four drugs within two main classes, the acetylcholinesterase inhibitors [53] and N-methyl-D-aspartate receptor antagonists [148,165, 173]. Since all currently available treatments are symptomatic treatments, aimed at alleviating the symptoms of the disease and trying to slow the deterioration of the patients, there is a significant current need for improved drugs that can modify the underlying course of the disease. New concepts are needed as current obligatory treatment directed at symptomatic relief in AD patients has shown to be marginally effective or even a lack of efficacy has been demonstrated [2,15,53,116,148,173,178,179]. Despite of several expensive drugs worldwide for therapy of AD, the disease still robs millions aged individuals of both their memory and their live. New science is identifying many of the novel pathways [13,129,135,136,166, 168,169], which contribute to this damaging live disease, providing unprecedented opportunity for the discovery new therapies aimed at the root causes of AD [82,83,94,103]. More effective therapies directed

at the cause of disease are needed. The genomic and ischaemic basis of AD will be defined completely in the near future, and corresponding molecular therapy targets will be identified. Ischaemic and genomic theories in brain degeneration have arrived and their application to resolving AD is our best hope.

The future front runner is autoimmunization, although this too is facing challenges in development. It may be some time before the first disease modifying agents emerge, which could revolutionize the way AD is treated. In 1998 [123], scientific interest in a new treatment approach to the therapy of AD was ignited after ischaemic model of AD investigation [120,122, 125], which indicated that it might be possible to immunize against the damaging properties of human β-amyloid peptide 1-42, [123,124] which led to accumulation and aggregation of this danger peptide in intra- and extracellular space of brain tissue [120,121, 124,126]. Pluta and colleagues [123] first presented that active immunization with human β-amyloid peptide 1-42 completely removed full-length amyloid from ischaemic rat brain [123,124]. This finding next has been partially confirmed and extended in other models of AD using both active [154] and passive [10] immunization. The main aim of this review is on the novel treatments for AD with a special emphasis on delivering against Alzheimer's proteins strategies. The expected epidemic number of AD cases in the next century makes the progress and discovery of effective therapy a matter of greatest importance and urgency. Presented review is good reason for revolutionary changes in future therapy of AD.

Ischaemic hypothesis of Alzheimer's disease

Recent study on transgenic AD animals with overexpression of amyloid precursor protein presented that cerebral blood flow is impaired in the animal models even before development of amyloid plaques and/or vascular amyloid deposition [69]. At least one third of brains with Alzheimer type dementia exhibit different neurovascular disorders [77]. In brains of AD cases, micro or macro intracerebral infarctions and white matter ischaemic damage [131,139] are evident [77]. Approximately 40% of cases with vascular type dementia had Alzheimer's-type pathology such as different kind of plaques [74,182], neurofibrillary tangles [80], hemorrhages [31,118] and neuronal death in hippocampus [75,76]. The presence of ischaemic changes seems usually ignored and regarded by scientists as insignificant or considered incidental in AD neuropathology. Interestingly, that Alzheimer in his original case of AD had made a note that besides "storage of peculiar material in the cortex, one sees endothelial proliferation and also occasionally neovascularisation" [3]. Endothelial proliferation with angiogenesis in the brain vessels of first patient provides data that ischaemic pathology was also present in the first case of AD. Above data suggest that we have overlap between vascular dementia and Alzheimer dementia [75,132] and that cerebrovascular pathology [13] plays a main role in the pathogenesis of AD. Aforementioned data raised the question what was the first: neurovascular disorder as a starter of AD [132] or degeneration of Alzheimer's-type itself [40]? Recent data propose a triggering and significant role for ischaemic mechanisms contributing to the degenerative processes in AD [13,77,113,125, 129,132,135,137,141,180,193]. Collected findings suggest that neuronal death following ischaemia with amyloid peptide from ischaemic circulatory system modulate ischaemic brain injury *via* molecular events in common with Alzheimer-type pathology [137 see for references]. These data indicate that brain ischaemia might be a key factor in the formation the full picture of Alzheimer dementia over years.

The brain has a limited response to different pathogens. For example similar neuropathological features are noted in the brain with ischaemia and that of AD. The pathogenesis of and a relationship between ischaemic dementia and Alzheimer's dementia are lastly much debated [40,76,113,119,128,137]. The role of both ischaemic brain injury and ischaemic blood-brain barrier changes in the pathology of AD is now more important than has long been assumed [19,22,113,119,125-130,133,135,136,163,191]. It is currently accepted that vascular dementia and AD share the same risk factors [132 see for references]. Cellular processes that lead to neurons demise in both disorders are known and are shared, too. Recently increasing information is mounting that pathological features of both disorders often occur concomitantly in individual cases. In fact mixed dementia may not represent two single co-occurring disorders but rather a single disease in which ischaemic hallmarks in neurons interact with focal ischaemic amyloid precursor protein metabolic alterations in characteristics brain regions. In contrast to the classical hypothesis of AD [6] new results indicate directly that brain ischaemia

contributes to the progression of AD pathology [177]. Ischaemia is well known factor of neurons death, blood-brain barrier abnormalities, inflammatory response, tangles and plaques formation and finally dementia development [5,7,13,14,19,22,33,35,38,40, 50,51,58,68,74,76,78,80,86,113,137,161,162,177,180, 182,187,191,192]. Importantly aforementioned results showed those lesions, which mimic the biochemical and neuropathological changes as you can see in AD and they induce tau protein [180,187] and amyloid peptide pathologies and slow progressive cognitive impairment development [187].

Post mortem AD brain examination confirmed commonly present cerebrovascular alterations [5,185] that suggested ischaemic pathology. Epidemiological studies have presented a synergistic and spatial connection between neurovascular pathology and AD pathology [5] in formation the clinical evidences of dementia. For example nuns, who had neurovascular pathology, were more demented than those with tau pathology and a big number of amyloid plaques but without neurovascular pathology [161,162]. Additionally human Rotterdam investigation presented that clinically silent ischaemic brain injuries doubled the risk of dementia and had a direct connection with rapid cognitive decline as compared to individuals without ischaemic episodes [177]. Above data are supporting of the hypothesis that silent ischaemic injuries contribute to the Alzheimer phenotype dementia [132,177]. In summary, many AD cases had silent ischaemic episodes [177], which represent cause of neurons death, blood-brain barrier changes, inflammation response, neurofibrillary tangles and amyloid plaques formation and finally full-blown Alzheimer's dementia [5,7,13,14,19,22,33,35,38,40,50,51,58,68,74, 76,78,80,86,113,137,161,162,177,180,182,187,191,192].

Pathogenesis for AD neurodegeneration include: changes in calcium concentration [184], triggering of specific receptors affecting cell homeostasis, activation of oxidative processes [47], disruption of membrane integrity [96,175,176] and changes in lipid, influence of glutamate connected neurons death, inflammatory response, tau pathology [6,29,109] and pathological amyloid precursor protein processing [6,29,55,61,88,96,104,109,111,159] and aging [30,32, 98,155] or a combination of two or more of above processes. All above presented mechanisms you can observe in brain ischaemia. It has been suggested that ischaemic brain injury and ischaemic blood-brain barrier changes may have an important role in formation brain degeneration with severe dementia [136 see for references]. It is well known that neurons death is occurring in brain ischaemia according to necrosis and apoptosis in brain sectors characteristic for AD such as entorhinal cortex and hippocampus [125,142]. These areas of the brain are involved in memory, thought and language. Most signaling factors, which trigger neurons death are known in ischaemia and are recognized as a ubiquitous signaling network, which links specific cell-surface receptors with the cell nucleus. In this rival theory, ischaemia of the brain is responsible for neurons death and ischaemic changes of blood-brain barrier for amyloid peptide movement from circulatory system into the brain and finally amyloid plaques formation [133,134,136,140 see for references]. It means that cross talk between ischaemic neuronal death and ischaemic blood-brain barrier injury exists in AD brain and could have significant implications for the triggering and maturation of AD [129,132,140-142]. Moreover, AD decreased length of capillaries in hippocampus correlates well with clinical pathology of Alzheimer dementia [9]. Oligomeric form of amyloid peptide through ischaemic neuronal toxicity and ischaemic vasculotoxic properties may provide an important link between AD and ischaemic neurodegeneration processes of this type of dementia [38,39,69,119-121,193]. Amyloid influence on blood-brain barrier vessels [1] is therefore one possible mechanism of blood-brain barrier damage [4] in AD [19,51,52,97,99,163]. Some studies indicate that 90% of human's amyloid plaques [80] and 80% of amyloid plaques in the transgenic AD models [43] are in direct contact with blood-brain barrier neurovessels [31,141,142] and they have spatial correlation with circulation network [5]. The reasons for AD are not known, but recent evidence strongly suggests that neurovascular ischaemic alterations play an important role in development this kind of disorder [12,14,38,40,68,69,76,78,86,113,122,125,128,129,132,13 3,135]. Some data from experimental models indicates that neurovascular insufficiency may be a trigger in AD and could provide link between this disorder and ischaemic brain injury [14,69,125,132,133]. β-amyloid peptide 1-42 influences the production of occludin and claudin tight junction proteins potentially affecting blood-brain barrier permeability [99]. In transgenic AD model with amyloid precursor overexpression amyloid positive microvessels showed endothelial cells apoptosis. Interesting findings in transgenic models of AD suggested that this disorder

had not only a neurodegenerative but also neurovascular elements [69]. Brain hypoperfusion and changes in blood-brain barrier transport could impair amyloid peptide clearance [12] and lead to increased level of both soluble and oligomeric amyloid peptides in brain tissue [69,127,130,131,142]. In addition brain hypoperfusion can trigger ischaemic injury, which may act synergistically with AD elements [69,131,138] to exacerbate slowly a cognitive deficit. Alzheimer's disorder is associated with severe neuropathology in vessels [9,77,191,193], changes in function [69] and functional MRI [156] that suggest that changes in the cerebral blood flow may be a predictor for AD development [91]. Recently it is important to look for new, rival hypothesis such as ischaemic theory, which designs new strategies for AD etiology and finally treatment [14,40,68,69,76,113,119,132,138]. Ischaemic processes in neuropathogenesis of AD may have significant implications for therapy of neurons loss in this disorder. In this rival hypothesis neurotoxicity of amyloid peptide [6] will contribute partially, if at all to Alzheimer's disease brain degeneration.

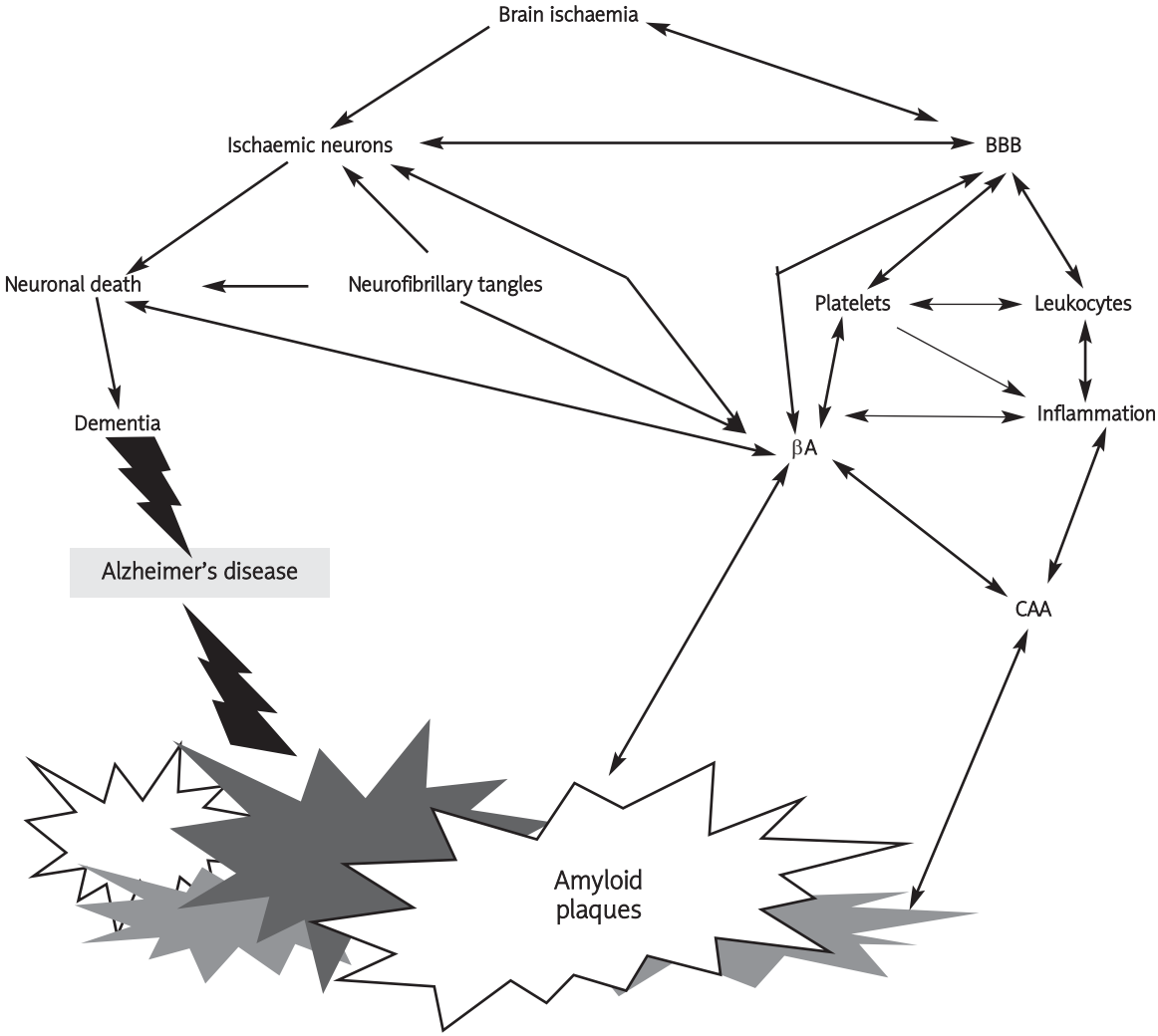
In summary the start of AD pathology involves an initial neurons changes triggered by ischaemia [69,74,182], which leading to enhanced neurons vulnerability to β-amyloid peptide [84] and the ischaemic changes of the blood-brain barrier [97,120] vessels with leakage of serum borne amyloid peptide [120,160] into the brain parenchyma, activation of amyloid peptide dependent neurons injuries [84] and finally culminating in the development of different amyloid plaques [74,120,182] and end in full-blown AD [132,141,177,180,187] (Fig. 1). It is proposed that AD may be caused by silent ischaemic episodes [177] that attack and slowly steal the minds of its victims. Moreover, ischaemia increases the toxicity of amyloid peptide. Next possibility is that ischaemia increases the vulnerability of primarily ischaemic neuronal cells to β-amyloid peptide neurotoxicity or accumulation of β-amyloid peptide increased ischaemic vulnerability [84]. According recent data the brain ischaemia age's brain 3.6 years each hour without treatment [153] and that explain age-dependent progression of Alzheimer's disease.

Anti-amyloid treatment

1998 is a turning point in the new history of novel idea in AD therapy [123]. At first the full success against human β-amyloid peptide 1-42 immunization in ischaemic rats [123,124] and second moderate effect in transgenic mouse model overexpressing amyloid precursor protein [154] and third passive immunization against β-amyloid peptide [10] led to the fast development of immunotherapies in animals and clinical trials in human AD. In the past decade investigations on immunization had led to the formation of new experimental proposals as well as alternative routs of vaccine delivery to amyloid plaques in AD brain [27,62,64,82,83,94,103,164,165,172].

Human β-amyloid peptide clearance therapy had remarkable effects in ischaemic AD model [123,124] and less effect in transgenic AD model [154]. In human clinic, vaccination results were less conclusive [62,94,112]. Trials in patients with AD were prematurely stopped when 6% of vaccinated cases developed aseptic meningoencephalitis [54,112,117]. In addition only 20% of cases produced antibody against amyloid peptide [54]. Brains treated with vaccine presented *post mortem* less plaques in different brain regions, as well as presence of T lymphocytes. Moreover, antibody responders presented any improvement in clinical memory tests. Above results showed that vaccine therapy against β-amyloid peptide might still be a viable option for the treatment of individuals with AD. Currently, it has been observed that antibodies against β-amyloid peptide are present in human immunoglobulin that specifically recognize and inhibit the neurotoxic effects of β-amyloid peptide [44].

Over the past ten years ideas of therapy have been focused on inhibitors of β- and γ-secretases responsible for the production β-amyloid peptide from parent amyloid precursor protein [45,149,158]. Decrease of different forms of β-amyloid peptide in the brain of old rats after oral delivery of the γ-secretase inhibitors has been shown to reduce levels of β-amyloid peptides in both brain parenchyma and cerebrospinal fluid [17,49]. Another new line of investigation is the use of antibody against β-secretase in which reduction of different amyloid forms was observed in transgenic animals [145]. This reduction correlated with some improvement of cognitive activity. Two single-chain antibodies have been presented to possess α-secretase activity providing a novel use of immunotherapy [103,147]. Other scientists have used small particle libraries to screen for molecules, which either interfere with assembly of β-amyloid peptide particles into fibrils [37,89] or disaggregate existing fibrils [18,57,164].



βA – β-amyloid peptide, BBB – blood-brain barrier, CAA – cerebral amyloid angiopathy

Fig. 1. Ischaemic basis for sporadic Alzheimer's disease neuropathogenesis.

Neprilysin gene transfer into the brain leads to a remarkable reduction of β-amyloid peptide deposits in transgenic AD model [79,100]. Above data suggest that the deficient degradation of β-amyloid peptide caused by a low levels of neprilysin might contribute to the AD development. Insulin degrading enzyme is another major enzyme for β-amyloid peptide degradation in the brain [103]. Overexpression of this enzyme decreases level of β-amyloid peptide and retards or completely prevents amyloid plaques formation in the brain tissue [92]. Another two enzymes, angiotensin converting enzyme and endothelin converting enzyme degrade β-amyloid peptide, too [47,63].

Therapy by gelsolin, an agent that has a high affinity for β-amyloid peptide decreased the level of β-amyloid peptide in the brain tissue probably *via* a peripheral action [102]. Other β-amyloid peptide bindable drug, curcumin can cross blood-brain barrier and bind amyloid plaques and decrease amyloid concentration and plaque burden in transgenic model of AD [186]. The enoxaparin β-amyloid peptide bindable agent delivered peripherally significantly lowered β-amyloid peptide deposits in cortex and the total amyloid peptide cortical level probably by sequestering the serum β-amyloid peptide peripherally [16]. According to the peripheral sink theory [41,42], β-amy-

loid peptide bindable substances sequester serum β-amyloid peptide that leads to clearance of amyloid peptide by promoting a net efflux of a rapidly mobilized soluble pool of β-amyloid peptide. The peripheral sink theory was proposed by DeMattos *et al*., [41] and was based on results obtained by passive immunization transgenic mice. These investigators proposed a model where sequestering of β-amyloid peptide in immune complexes in the plasma decreases the level of soluble β-amyloid peptide, which then contributes to a net efflux of amyloid peptide from the brain into blood [41,42].

Currently endogenous autoantibodies against β-amyloid peptide and receptor for advanced glycation-end-products peptides have been noted in healthy persons and individuals with AD [108]. Above data suggests that physiologically occurring autoantibodies against amyloid peptide and receptor for advanced glycation-end-products might be effective to β-amyloid peptide clearance from brain and blood.

Anti-tau treatment

Experimental treatments have been directed against hyperphosphorylated tau protein either by inhibiting various protein kinases or promoting phosphatase activities [70,83,90]. Current *in vitro* investigation shown small particles, which inhibited tau protein filament nucleation and fibrillization, making this substance a promising candidate to test in animal models of AD [25]. A new interesting observation about amyloid peptide vaccination has been presented lastly in experiments in which triple transgenic mice were passively immunized with antibodies against β-amyloid peptide [115]. β-amyloid peptide immunization leads to clearance of early but not late hyperphosphorylated tau protein aggregates *via* the proteasome [115].

Some investigation presented that memantine reversed hyperphosphorylation of tau protein in hippocampal slices [95] and this effect of memantine occurred by disinhibition of the function of protein phosphatase 2A [26] that earlier was noted to be downregulated in brains of AD patients [56]. Based on above information's, it was presented in human clinic that therapy of AD cases by memantine [148,173] during one year significantly decreases hyperphosphorylated tau in cerebrospinal fluid [59].

Anti-inflammatory treatment

In AD brains, the microglial cells behaved as inflammatory invaders, which cause an unintended pathology *via* release of cytokines designed to answer to primary brain pathology. This reaction may lead to a progression of AD through neurons death. Epidemiological observations suggest that long use of nonsteroidal anti-inflammatory therapy may prevent AD development [106,170]. Based on the above data, studies were undertaken to investigate the effects of anti-inflammation treatment in AD models [47]. These investigations include nonsteroidal anti-inflammatory drugs [107], peroxisome proliferator-activated receptor-γ agonists [46,65,152] and cannabinoids [146]. Another new data from transgenic model of AD showed that immunotherapy against β-secretase decreases development of inflammation in brain injury [145].

Umbilical cord blood cells delivered *i.v.* 48 hours after stroke are able to decrease neurodegeneration by providing neuroprotection and blocking the inflammatory reaction [181]. Injected cells appear to do this *via* multiple mechanisms: providing neuroprotection, modulating the inflammatory response, interrupting the apoptotic cascade, and enhancing neurogenesis and angiogenesis. Activation of sigma-1 and sigma-2 receptors *via* 1,3-di-*O*-tolylguanidin delivery 24 hours after stroke is equally impressive in reducing stroke injury [181]. Above molecule is neuroprotective by decreasing intracellular calcium in neuronal cells and inflammatory response by blocking the production of cytokines from brain immune cells. In brain the ischaemia and AD signals from the degenerating neuronal cells trigger immune cells for an inflammatory response, with increased production of cytokines. Whether the cause is known or not, all neurological diseases show similar intracellular neuronal signaling and inflammation reactions. The aforementioned therapeutic approaches may not only be beneficial for therapy of ischaemic stroke [181] but also for AD. Aforementioned two therapies act in a similar manner by inhibiting the peripheral immune system and promoting neuronal survival [181].

Blood-brain barrier treatment

The morphological and functional integrity of the brain depends on the coupling between cerebral blood flow and transport *via* the blood-brain barrier and neuronal function. In literature there are data

that neurovascular unit insufficiency may be triggered sporadic AD development [14,113,125,132, 137,163,193]. Possible etiological role of ischaemia in the development of AD have been presented in detail by several investigators [40,69,76,113,125,132,137]. Brain blood flow maintains a control of the neuronal environment not only by autoregulation of local blood flow but also by influencing transport by blood-brain barrier. The blood-brain barrier is a highly energetic system with different forms of transport *via* both its blood- and brain-facing sites. Structure of the blood facing side allows entry of nutrients products but opposite brain facing eliminate toxic products such as β-amyloid peptide from brain [34,35,126,193]. Among others an important role of the blood-brain barrier is control of the brain pool of β-amyloid peptide. The aim of this section of review is to analyze knowledge of the connection of the ischaemic blood-brain barrier with final formation AD, especially with regards to the development of amyloid plaques [132,136,137] and to develop a consensus on whether blood-brain barrier alterations are a valid target for AD treatment [135-138] and to stimulate scientists' discussion on the most important part of rival theory with regards to maturation of AD [132,133]. According to the ischaemic blood-brain barrier maturation theory of AD [133] all elements of blood-brain barrier such as endothelium, basal lamina, pericytes and astrocytes are main targets for therapy of AD [163]. The current idea states that injured blood-brain barrier transport system by ischaemia at its luminal and abluminal sides for β-amyloid peptide with damaged neurons by ischaemia are responsible for full-blown sporadic AD [128,129,133,135,136,140-142]. In this way new and more effective therapy approaches can be developed and more data on different amyloidosis can be gathered. Above observations suggest that stopping leakage of β-amyloid peptide from blood to brain tissue [43] and increasing reverse transport from brain into blood [12,126] and preventing ischaemic processes in neurons [137 see for references] are principal main points in treatment AD [20,24,33-36,60,73,78,85,106, 138,172]. Current studies provide data that active immunization with β-amyloid peptide reduces blood-brain barrier permeability, amyloid burden and neuroinflammation as microgliosis in transgenic model of AD [43]. It was proved that the integrity of the blood-brain barrier is disrupted in AD models and following β-amyloid peptide immunization the immune system clears amyloid peptide from sources in the brain tissue as it would in peripheral organs lacking barriers. Once β-amyloid peptide is removed, the integrity of the blood-brain barrier is restored [43]. Above investigation clearly proves that the blood-brain barrier is disrupted in AD brain [22,163,191] and that immunization with β-amyloid peptide repairs the damage blood-brain barrier in transgenic AD model [43]. Earlier we have proved that active immunization with human β-amyloid peptide 1-42 in ischaemic model of AD reverses the ischaemic blood-brain barrier permeability for β-amyloid peptide 1-42 [126] and prevent further disease progression [123,124]. One possible explanation of the restoration of the blood-brain barrier is that the active immunization leads to the reduction in the level of circulating β-amyloid peptide [43], which could directly or indirectly influence the activity of the blood-brain barrier [12,51,99]. For example, inflammatory factors such as IL-1β, IL-6 and TNF-α [21,151] that stimulate angiogenesis [58] and β-amyloid peptide have been noticed to influence an increase of some angiogenic factors like TGF-β and VEGF [143,174]. It can be concluded that with the removal of informatory substances provided by β-amyloid peptide, the endothelium become intact and tight junctions closed, thereby restoring a physiological blood-brain barrier activity. Increased level of β-amyloid peptide in plasma has been observed in a transgenic model of AD after active immunization with amyloid and *i.v.* delivery of molecules with an affinity to β-amyloid peptide [42,102] and after active immunization [123,124] of non-human primates [93]. It is proposed that molecules that sequester serum β-amyloid peptide may decrease or prevent brain amyloidosis [102]. Finally investigations with antibodies against intercellular adhesion molecule-1 [189] or platelet-endothelial cell adhesion molecule-1 [150] have shown that blockage of adhesion molecules and/or leukocyte adhesion [28] or platelets (> 90% of β-amyloid peptide in blood is stored in platelets) attachment respectively reduces brain neurodegeneration after effects.

Several ways have been proposed to clear out β-amyloid peptide through blood-brain barrier including: especially receptor-mediated β-amyloid peptide reverse transport *via* blood-brain barrier [126], enzyme mediated β-amyloid peptide degradation and β-amyloid peptide bindable molecule mediated β-amyloid peptide clearance. Receptor mediated transport of β-amyloid peptide *via* blood-brain barrier is mainly responsible for both efflux and influx of

amyloid peptide. Lipoprotein receptor-related protein mediates efflux of β-amyloid peptide from brain into blood [12,35]. The interaction between lipoprotein receptor-related protein and amyloid mediates β-amyloid peptide blood-brain barrier vessels binding, endocytosis and transcytosis through blood-brain barrier into circulatory system [66]. Additionally p-glycoprotein has been proposed to be involved in amyloid clearance *via* blood-brain barrier [87]. Currently, some results suggest that the neonatal Fc receptor at the blood-brain barrier plays a crucial role in IgG-assisted β-amyloid removal from the aging brain [36]. Receptor for advanced glycation-end-products mediates influx of amyloid from serum into brain tissue [33,35]. Downregulation of receptor for advanced glycation-end-products can inhibit influx of amyloid peptide [33]. Gp 330/megalin has been noted to transport blood β-amyloid peptide in a complex with apolipoprotein J into brain tissue through blood-brain barrier [192]. Lipoprotein receptor-related protein and receptor for advanced glycation-end-products play opposing roles in β-amyloid peptide transport through blood-brain barrier [35]. One important strategy would be to discover new drugs, which regulate the function or expression of amyloid transport receptors *via* blood-brain barrier vessels. The decreased regulation of receptor for advanced glycation-end-products and increased regulation of lipoprotein receptor-related protein in blood-brain barrier might readjust the transport equilibrium for amyloid by promoting its net efflux from brain into plasma. Statins, which increased lipoprotein receptor-related protein in blood-brain barrier, might facilitate the clearance of amyloid from brain tissue [34]. It is worth noting that receptor for advanced glycation-end-products blockades using receptor for advanced glycation-end-products specific IgG [108] can also increase the expression of lipoprotein receptor-related protein [34].

Gene treatment

Gene treatments are completely new forms of therapy in which genes are transferred into the damaged cells [64]. Current results suggest that damaged genes in ischaemic brain injury might be harmful to different kinds of brain cells. Thus gene treatment may serve to rescue those cells from potential cells death. In this respect, recent developments have presented medical effects of gene treatment in experimental global and focal ischaemic models [114]. Using gene therapy against apoptosis may reduce apoptotic cells following ischaemic brain injury [23,190]. Beneficial results were noticed by inhibiting apoptosis and enhancing glial cell survival following ischaemic neurodegeneration [183]. Moreover, midkine and heat shock protein gene transfer showed neuroprotection in ischaemic brain [8,171]. As such, gene treatment offers new interesting and powerful therapies in the future for ischaemic stroke and AD patients reducing amyloid plaque burden *via ex vivo* gene delivery of an amyloid degrading protease [64]. As example neprilysin gene transfer reduces human amyloid pathology in transgenic mice [79,100].

Other treatments

Scientific data suggest that ischaemic neuronal cells undergo necrosis and apoptosis, necroptosis and autophagic programmed cell death, which finally leads to neurodegeneration with dementia. The important factors in apoptosis are tumor necrosis factor-receptor-1 and CD95, which in ischaemic brain are overexpressed. Thus, influence on tumor necrosis factor-receptor-1 and CD95 by antibody treatment will induce neuroprotection in brain ischaemia. On the basis of this idea *i.v.* therapy with antibodies against tumor necrosis factor-α and/or CD95L significantly reduced the infarct volume in experimental brain ischaemia [11,110] and mortality [101]. These results suggest that blocking tumor necrosis factor and CD95L activity with antibodies, we can prevent primary and secondary responses to ischaemia and probably to AD.

Conclusions

Considerable progress has been made in the last decade by handful scientists in resolving the etiology and the development of new perspective therapies for AD. Efforts to intensification of therapy research are justified at both humanistic and economic levels [27,157]. Extensive investigation designed to discovery new ways to delay onset and progression of AD and on new therapies recently is ongoing worldwide [103]. Since all degenerative diseases share commonalities that lead to neurons death, these treatments proposals not only apply to ischaemic model of AD [120,122,125,132,138,141,142] but to AD transgenic models [94,166]. Scientists are evaluating other

potentially promising approaches studying e.g. the active and passive immunization treatments and trying combinations of therapies and investigating relationships between ischaemic and Alzheimer's dementia therapies. Among treatments for AD in both experimental and clinical trials are many strategies to block toxic β-amyloid peptide 1-42 and to rescue the vulnerable neuronal cells from death. Other proposals aim to prevent the co-pathogenic effects of different proteins e.g. amyloid and tau protein [6,83]. New insights into selective neurons vulnerability and the link between brain ischaemia and AD may provide novel entry points for effective therapy. By controlling blood-to-brain and brain-to-blood β-amyloid peptide movement [35,120,126] the blood-brain barrier may self-limit amyloid dependent capillary injuries and decrease the risk of neurons death and β-amyloid plaques formation [132,137,140]. It can be concluded that immunotherapy and other treatments based on β-amyloid peptide removal from brain may be beneficial in limiting the degree of secondary degeneration caused by amyloid properties [6]. Enhancement of β-amyloid peptide degradation enzymes *via* gene therapy, transcriptional activation or even pharmacological activation of the β-amyloid peptide degrading enzymes represents a new therapeutic proposal for the treatment of AD [48]. Based on the peripheral sink theory, it is possible to decrease brain β-amyloid peptide burden without the need for antibodies and therapeutic agents to move *via* the blood-brain barrier [41,42]. These findings indicated that treatment against β-amyloid peptide might still be a viable option for the treatment of AD, if potentially harmful proinflammatory effects can be avoided. These data also suggest that stopping leakage of β-amyloid peptide from blood into brain [43] and increasing its reverse movement from brain tissue into blood [12,126] can help individuals with AD [34,42,73,85, 172].

Recently it has been difficult in translating experimental treatments into effective clinical cure. The issue is that investigators do not consider important variables in dealing with human cases as opposed to rodent models. Actually the standard in developing drugs has been to focus on a single target. However, the underlying degenerative pathways in neurological disorders involve an intertwining of many mechanisms and treating one will not necessarily change the outcome of the disorder. The current focus is shifting to a multi-functional approach in which a single drug has multiple neurobiochemical targets and can therefore cure the disorder or consequences of pathology more fully [188]. In the future treatment proposals will likely address events, which are upstream of a more broadly construed pathological cascade, which includes but is not limited to the production and deposition of β-amyloid peptide.

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