Review

Chronic mild cerebrovascular dysfunction as a cause for Alzheimer's disease?

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A B S T R A C T

Alzheimer's disease (AD) is a progressive chronic disorder and is characterized by β-amyloid plaques and angiopathy, tau pathology, neuronal cell death, and inflammatory responses. The reasons for this disease are not known. This review proposes the hypothesis that a chronic mild longlasting cerebrovascular dysfunction could initiate a cascade of events leading to AD. It is suggested that (vascular) risk factors (e.g. hypercholesterolemia, type 2 diabetes, hyperhomocysteinemia) causes either damage of the cerebrovascular system including silent strokes or causes dysregulation of beta-amyloid clearance at the blood-brain barrier resulting in increased brain beta-amyloid. A cascade of subsequent downstream events may lead to disturbed metabolic changes, and neuroinflammation and tau pathology. The role of NGF on the cell death of cholinergic neurons is discussed. Additional risk factors (e.g. acidosis, metals) contribute to plaque development.

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1. Alzheimers disease and other forms of dementia

Sporadic Alzheimer's disease (AD) is a progressive chronic neurodegenerative disorder (at least 95% of all cases are non-genetic), and is characterized by severe beta-amyloid deposition (senile plaques and vascular angiopathy), tau-pathology, cell death of cholinergic neurons, microglial activation and inflammation. AD is the most aggressive form of dementia and is distinguished from other forms of dementia. The differentiation of vascular dementia (VaD) from AD has been based on evidence of a cerebrovascular disorder (Roth, 1955). However, pure cases of VaD without neurodegenerative changes are very rare and autopsy of cases clinically diagnosed as VaD showed that they had pathological signs for AD (Sadowski et al., 2004). In addition, mild cognitive impairment (MCI) has been defined as the earliest form of dementia, which partly converts into AD (approx. 15% to 30% per year). Two additional forms of degenerative non-reversible forms of dementia have been described, Lewy Body dementia and frontotemporal dementia, which can be distinguished from AD and VaD. In addition, other non-specific forms of dementia are seen during, for example, HIV, Parkinson's disease, or alcohol-related diseases. Among all forms of dementia, AD is the most frequent pathological finding (approx. 60%), followed by VaD (approx. 15%), Lewy body dementia (approx. 15%), and other degenerative forms of dementia (Gearing et al., 1995; Heinemann and Zerr, 2007). In addition, the term vascular cognitive impairment (VCI) is used to describe individuals with significant cognitive impairments produced by cerebrovascular disease (CVD) (Barone et al., 2009).

2. Cerebrovascular abnormalities in AD

Possibly the most important changes arguing for a vascular hypothesis in AD are the cerebral bloodflow (CBF) measurements in MCI and the fluorodeoxyglucose positron emission tomography (FDG-PET) studies measuring glucose uptake. FDG-PET has shown decreased glucose metabolism in the medial temporal and parietal lobes of those with the APOE4 gene many decades prior to the typical age of AD onset, and that AD can be prognosed in cognitively intact persons showing reduced glucose uptake (Mosconi et al., 2010). In addition, arterial spin labeling (Alsop et al., 2010), SPECT (Varma et al., 2002) or H(2)15O positron emission tomography (Ishii et al., 2000) provided a reflection of CBF activity in cognitively intact people who later converted to AD.

A number of cerebrovascular abnormalities have been described in AD brains: decreased microvascular density, basement membrane thickening, endothelial and pericyte damage, diminished glucose transport across the blood-brain barrier (BBB), vessels that express inflammatory markers, perivascular fibrosis, capillaries with fewer branches, atrophic vessels, changes in vessel diameter, accumulation of e.g. collagen, atherosclerotic plaques, cerebral amyloid angiopathy, microglial activation in degenerating endothelial cells or thrombotic lesions (Farkas and Luiten, 2001). It is very difficult to say if these changes are an initial cause for development of AD or if these changes occur in late stages of the disease. Anyhow, there is clear evidence that these cerebrovascular abnormalities result in dysfunctional influx of toxic compounds into the brain or result in enhanced storage or
accompanied by cognitive impairment and can be counteracted by the
and perivascular detachment (Weir and Molloy, 2000; Kim et al.,
Hyperhomocysteinemia induces endothelial damage, mitochondrial
example, caspase-8 and subsequent apoptosis, it stimulates monocyte
intracellular effects of homocysteine are very divergent: it induces, for
endothelial nitric oxide synthetase (Faraci, 2003) and glucose transporter
teinemia induced by methionin administration enhanced lipid
oxidative stress (Baydas et al., 2005). These dysfunctions are
mild cerebrovascular dysregulation caused by continuous exposure to
hypothesized that neurodegeneration in AD may arise from a chronic
mild cerebrovascular dysregulation caused by continuous exposure to
the risk factors over years (Humpel and Marksteiner, 2005), which
Evidence comes from epidemiological studies that these risk factors are
old age, atherosclerosis, stroke, diabetes, homocysteine, hypertension,
hyperlipidemia, head injury, transient silent strokes, high serum
viscosity, thrombogenic factors, cardiac disease, the apolipoprotein E4 allele, smoking, alcohol consumption, high cholesterol, fat food, reduced vitamin B12 uptake, high blood pressure, high fibrinogen levels, hormonal dysregulation, depression, and others. It is evident that several of these risk factors are vascular risk factors.

3. Risk factors for AD and vaD

It is well known that less than 2.5% of all AD cases have a genetic origin, but the majority of AD is a sporadic form and the major risk factor is age (~60 years). The causes for this sporadic AD are yet unknown, but several risk factors may trigger this disease. There is increasing evidence that vascular risk factors contribute to the pathogenesis of AD (Kudo et al., 2000; de la Torre and Mussivand, 1993; De la Torre and Stefano, 2000; De la Torre, 2002; Iadecola, 2004; Zlokovic, 2005; Humpel and Marksteiner, 2005). In fact, a cerebrovascular hypoperfusion caused by decreased cerebral blood flow, lowered metabolic rates of glucose and oxygen could be one of the initial events in AD (Breiter, 2000; Dede et al., 2007; Deschaindre et al., 2009; Farkas and Luiten, 2001; Iadecola, 2004). AD and vaD may share common risk factors, which indicate that their pathogenic mechanism could be related (De la Torre, 2002). It is hypothesized that neurodegeneration in AD may arise from a chronic mild cerebrovascular dysregulation caused by continuous exposure to the risk factors over years (Humpel and Marksteiner, 2005), which precedes hypoperfusion (De la Torre and Stefano, 2000; Iadecola, 2004).

Evidence comes from epidemiological studies that these risk factors are (Rochi et al., 2009; De la Torre, 2002; Zlokovic, 2005; Engelberg, 2004): old age, atherosclerosis, stroke, diabetes, homocysteine, hypertension, hyperlipidemia, head injury, transient silent strokes, high serum viscosity, thrombogenic factors, cardiac disease, the apolipoprotein E4 allele, smoking, alcohol consumption, high cholesterol, fat food, reduced vitamin B12 uptake, high blood pressure, high fibrinogen levels, hormonal dysregulation, depression, and others. It is evident that several of these risk factors are vascular risk factors.

3.1. Hyperhomocysteinemia

It is well established that elevated plasma levels of the amino acid homocysteine increase the risk for atherosclerosis, stroke, myocardial infarction, and AD (Gallucci et al., 2004; Faraci, 2003; Flicker et al., 2004; Skurk and Walsh, 2004; Ravaglia et al., 2005; Troen, 2005). It has been reported that plasma homocysteine levels >15 μM increase the risk for vaD and AD (Clarke et al., 1998; Mcloray et al., 2002; Seshadri et al., 2002; Luchsinger et al., 2004). In humans the effective concentration results from total levels of homocysteine and its oxidation product disulfide homocysteine (Lipton et al., 1997). Hyperhomocysteinemia induces endothelial damage, mitochondrial disintegration, swelling of pericytes, basement membrane thickening and perivascular detachment (Weir and Molloy, 2000; Kim et al., 2002; Troen, 2005). Pathologies are also seen in vaD and AD. The intracellular effects of homocysteine are very divergent: it induces, for example, caspase-8 and subsequent apoptosis, it stimulates monocyte chemoattractant protein-1/interleukin-8 and subsequent inflammation, and it enhances oxidative stress (via activation of different oxidases), inhibits endothelial nitric oxide synthetase, and generates peroxynitrite with subsequent cell death (Faraci, 2003; Lee et al., 2004; Skurk and Walsh, 2004). Furthermore, homocysteine decreases capillary endothelial nitric oxide synthetase (Faraci, 2003) and glucose transporter and transiently changes different cell adhesion molecules (Lee et al., 2004). Homocysteine directly induces cell death of cerebrocortical neurons involving NMDA (Lipton et al., 1997). Chronic hyperhomocysteinemia induced by methionin administration enhanced lipid peroxidation and decreased glutathione, suggesting the involvement of oxidative stress (Baydas et al., 2005). These dysfunctions are accompanied by cognitive impairment and can be counteracted by the antioxidant melatonin (Baydas et al., 2005).

3.2. Hypercholesterolemia

Cholesterol is increasingly recognized to play a major role in the pathogenesis of AD (Raffai and Weisgraber, 2003; Wellington, 2004; Wolozin, 2004). This is based on four lines of investigation: (1) the lipoprotein ApoE4 coordinates the mobilization and redistribution of cholesterol in the brain and affects the age of onset, (2) intracellular cholesterol stimulates γ-secretase and amyloid-precursor-protein (APP)/β-amyloid processing, (3) cholesterol-lowering drugs (statins) reduce the prevalence of AD and (4) elevated plasma cholesterol in midlife is associated with an increased risk for AD. Interestingly, rabbits fed with a 2% cholesterol diet display an accumulation of intracellular immunolabeled β-amyloid after 4 to 8 weeks (Sparks et al., 1994) and hypercholesterolemia accelerates the amyloid pathology in a transgenic mouse model (Refolo et al., 2000; Shie et al., 2002). Cholesterol does not pass the BBB and is synthesized locally in the brain and degraded to 24-hydroxy-cholesterol, which is transported outside the brain into the bloodstream. Cholesterol regulates γ-secretase with enhanced processing of β-amyloid(1–42). It is hypothesized that a breakdown of the BBB causes influx of cholesterol, with subsequent activation of γ-secretase and enhanced β-amyloid(1–42) production. These findings are consistent with the concept that AD is a dietary-fat induced phenotype of vascular dementia and accumulation of beta-amyloid-lipoprotein complexes may be an amplifier of dietary induced inflammation (Takechi et al., 2010).

3.3. Hyperglycemia and insulin depletion

Approximately 40–50% of elderly people have an impaired glucose metabolism or type 2 diabetes and hyperglycemia is a risk for AD (Kalaria, 2009; Carlsson, 2010; Ott et al., 1999). Indeed, PET studies demonstrated a reduced glucose uptake in AD patients (Erol, 2008). Hyperglycemia has disruptive effects on the brain and markedly affects cognition and memory (Brands et al., 2004). Hyperglycemia leads to increased levels of glucose in the brain, by which excess glucose is converted into sorbitol and fructose, which influences several intracellular cascades. Elevated glucose is also associated with formation of toxic advanced glycation end (AGE) products, reactive oxygen species (ROS), or hyperhomocysteinemia. Hyperglycemia is also associated with both structural and functional alterations in the cerebral vascular system. Cerebral blood flow has been reported to be decreased in diabetes and thus increasing risk of “silent strokes.” Longitudinal studies showed an association between insulin resistance and AD (Erol, 2008). Insulin regulates the metabolism of β-amyloid and tau and dysfunctional insulin signaling has been linked to oxidative stress and mitochondrial dysfunction, resulting in disturbances of cellular glucose, acetylcholine, cholesterol and ATP levels, impaired membrane function, accumulation of β-amyloid and tau hyperphosphorylation (Erol, 2008). An interesting in vivo mouse model shows hyperphosphorylated tau after streptozotocin-induced insulin deficiency (Clodfelder-Miller et al., 2006).

3.4. Chronic alcoholism

Alcohol may be a risk factor for AD because of similarities between alcoholic dementia and AD. Epidemiologic studies have investigated the relationship between alcohol and AD, however, there is clear indication that light to moderate alcohol intake (1–3 drinks per day; <20 g alcohol per day) was significantly associated with a lower risk for AD (Anstey et al., 2009; Tyas, 2001). The neuroprotective effect of antioxidant properties of wine polyphenols may be important in preventing AD (Pinder and Sandler, 2004). Heavy drinking is a risk factor for most stroke subtypes, while regular light to moderate drinking seemed to be associated with a decreased risk for ischemic strokes (Letenneur, 2004). It cannot be excluded that heavy drinking may account for vascular damage in the brain and may contribute to the development of AD.
4. Beta-Amyloid in AD and the vascular connection

So far, the β-amyloid cascade is the most prominent hypothesis for development of AD (Selkoe, 1998; Atwood et al., 2003; Tanzi et al., 2004; Wirths et al., 2004; Marchesi, 2005; Schroeder and Koo, 2005) and is thought to be the primary event that triggers the pathological cascade in AD (Selkoe, 1998), although the findings in support of the amyloid hypothesis have become questionable and controversial (Robakis, 2010). The amyloid-precursor protein (APP) is cleaved by secretases into β-amyloid peptides (40, 42, or 43 amino acids), and these peptides aggregate under certain conditions and are deposited as β-amyloid plaques. It is hypothesized that the accumulation of β-amyloid in the brain causes the AD pathology and a dysbalance between β-amyloid production and clearance results in other hallmarks of the disease. The β-amyloid cascade hypothesis (Hardy and Selkoe, 2002; Tanzi and Bertram, 2005) favors the model that insoluble fibrillar β-amyloid triggers the neuronal degeneration. Evidence is now accumulating that soluble activated monomers, soluble oligomers (dimer, trimer, tetramer), and protofibrils could be responsible for triggering the pathology in AD (Walsh et al., 2002; Canevari et al., 2004). The exact mechanism by which β-amyloid induces cell death is not known, but the “channel hypothesis” suggests that certain fibrillar forms of the peptide cause neurodegeneration by forming ion channels that are generally large, voltage independent, and relatively poor selective (Wirths et al., 2004; Marchesi, 2005). Soluble β-amyloid levels in the cortex correlate with the degree of synaptic loss in dementia, and it becomes more and more clear that AD is primarily caused by dysfunction of nerve axons and synapses (Selkoe, 2002). In AD, axonal degeneration may depend on β-amyloid levels, but not on plaque deposition, which means that nerve damage occurs before deposition of plaques.

β-amyloid is present in the brain and in the blood and is transported through the BBB via two important receptor transport systems: the receptor for advanced glycosylation end products (RAGE) and low-density lipoprotein-related protein (LRP) (Tanzi et al., 2004; Zlokovic, 2004). The influx of β-amyloid from blood into brain is mediated via RAGE, while the efflux from brain into blood is mediated via LRP (Tanzi et al., 2004; Zlokovic, 2004). This clearance from brain to blood is of pivotal importance for the regulation of β-amyloid levels in the brain (Tanzi et al., 2004; Zlokovic, 2004) and a dysregulation of the BBB contributes to enhanced β-amyloid levels in the brain. Under specific conditions (high ApoE4, low pH, metals, and dysfunctional clearance) the β-amyloid (1–42) peptide may aggregate in the brain. A very high percentage (70%–90%) of AD patients show amyloid pathology in their vessels, which narrow the vessels and produce hypoperfusion (Smith and Greenberg, 2009; Farkas and Luiten, 2001; Cullen et al., 2006; Hardy and Cullen, 2006). This cerebral amyloid angiopathy can result in hemorrhagic and (possibly) ischemic forms of stroke (Smith and Greenberg, 2009; Armstrong, 2006; Haglund et al., 2006; Soffer, 2006; Boscolo et al., 2007). The cerebral amyloid angiopathy is common in AD and is also associated with cerebral atherosclerosis (Farkas and Luiten, 2001; de la Torre, 2002; Atttems et al., 2004) and with the development of cognitive deficits (Thal et al., 2003; Solfrizzi et al., 2004). As a consequence of cerebrovascular dysfunction the breakdown of the BBB may occur. This breakdown may have several effects on neurons, such as cell death after influx of excitotoxic amino acids (e.g. glutamate) or enhanced APP expression after cholesterol influx. In addition, an enhanced influx of blood-derived serum albumin into the brain is seen after BBB disruption and may induce neurodegeneration (Moser and Hempel, 2007).

5. Tauopathies, neurodegeneration, AD and vaD

Tau protein is a microtubule-associated protein that is highly expressed in neurons in the brain. Tau is enriched in axons, where it directly binds to microtubuli. In AD tau is hyperphosphorylated at a variety of serine and threonine residues and loses its ability to bind to microtubuli. Such abnormal hyperphosphorylated tau is a major event involved in the formation of paired helical neurofibrillary tangles in the AD brain (Mandekow and Mandekow, 1998; Spillantini and Goedert, 1998; Smith et al., 2002; Iqbal et al., 2005). An imbalance between protein kinases and phosphatases may play a role in hyperphosphorylation. Interestingly, it has become apparent that tau deposits are frequently observed in the absence of amyloid plaques, such as e.g. corticobasal degeneration, Pick disease or progressive supranuclear palsy (Spillantini and Goedert, 1998). Most tauopathies are sporadic diseases but some are familial. These findings suggest that neurofibrillary tangles develop independent of β-amyloid. Tau pathology in AD is almost entirely limited to nerve cells, while in other tauopathies both nerve cells and glial cells are affected (Spillantini and Goedert, 1998). In addition, enhanced tau is a diagnostic marker in cerebrospinal fluid for different forms of neurodegeneration (e.g. Creutzfeldt Jacobs disease).

Iqbal et al. (2005) have developed the “Metabolic/Signal Transduction Hypothesis”. It is assumed that AD and other tauopathies require a genetic predisposition (e.g. ApoE) and are triggered by a variety of environmental (risk) factors (e.g. which alter the membrane fluidity). It is suggested that an imbalance of protein kinases (e.g. cdk5, glycogen synthase kinase-3, CaM kinase II, protein kinase A) and/or phosphatases (e.g. PP-2A or PP-1) may lead to an abnormal hyperphosphorylation of tau and subsequently to formation of neurofibrillary tangles in the brain. There are indications that also vascular risk factor may play a role in tau pathology, since e.g. a decreased membrane fluidity by cholesterol could be one event leading to an imbalance in this system. In addition a decreased glucose metabolism/uptake might lead to the abnormal hyperphosphorylation of tau through a decrease in its O-GlcNAcylation (Iqbal et al., 2005). Finally, recently it has been shown that application of truncated tau to the basolateral (brain) side of the BBB causes damage of the BBB involving pro-inflammatory cytokines released from microglia (Kovac et al., 2009).

6. The neurovascular unit, cholinergic neurons and NGF

The neurovascular unit (NVU) defines the cellular interaction between brain capillary endothelial cells (forming the BBB), the astrocytic end feet, and neuronal axons (ladecola, 2004). Astrocytes are involved in neuronal energy metabolism and synapse function (ladecola, 2004) and neuronal processes are closely associated with cerebral blood vessels (ladecola, 2004). Interestingly, nerve terminals from the cholinergic neurons of the basal nucleus of Meynert interact with astrocytic end feet of the BBB via muscarinic acetylcholine receptors (Vacher and Hamel, 1995; Farkas and Luiten, 2001). Thus the NVU provides a direct link between the cerebrovascular system and cholinergic neurons in the brain. Since the NVU provides the first line of defense against deleterious effects of cerebral ischemia and other forms of injury (ladecola, 2004), the NVU may display a very sensitive (pH dependent) link to the brain. In fact, conditioned medium collected from microvessels of AD patients has been shown to kill neurons in vitro, pointing to selective neurotoxic factors derived from brain capillary endothelial cells (Grammas et al., 1999). This is in agreement with our own study, where we found that rat primary capillary endothelial cells secreted factors into the medium, which killed cholinergic neurons (Moser et al., 2004).

In AD a marked reduction of cholinergic neurons in the basal forebrain (septum and nucleus basalis of Meynert) is found in advanced stages (Whitehouse et al., 1983; Wilcock et al., 1982), which leads to the cholinergic hypothesis in AD (Francis et al., 1999; Hempel and Weis, 2002). Cholinergic cell loss directly correlates with cognitive decline and a lack of acetylcholine is a hallmark in dementia and AD. It is not known, why these cholinergic neurons die, but it seems possible that the direct interaction with the cerebrovascular system may contribute to cholinergic decline. In fact, damage of the NVU may result in
structures and cholinergic nerve fi

t, very sensitive for changes in pH and the interaction between vascular
probably by releasing iron from its binding to transferrin, ferritin, or
enhances iron-catalyzed production of reactive oxygen species,
values of 6.8 (Pirchl et al., 2006). It is well known that acidosis
neurons undergo cell death when the pH is lowered to a critical
degeneration of nerve terminals and subsequent retrograde cell death of
cholinergic neurons. However, neurodegeneration in AD also results in
dysregulation of other neurotransmitter systems in the brain, such as
serotonin, noradrenaline, or glutamate.

Among all growth factors, nerve growth factor (NGF) is the most
potent growth factor to counteract cell death of cholinergic neurons in
vitro and in vivo (Thoenen and Barde, 1980; Levi-Montalcini, 1987). In
fact NGF was thought to play a role in the development of AD, but
transgenic NGF knockout mice did not show an AD pathology. However,
NGF was considered to be a candidate for treating AD and purified
mouse NGF was infused in some AD patients (Seiger et al., 1993).
Interestingly, NGF is upregulated in brains of AD patients (Fahnestock
et al., 2001) and in cerebrospinal fluid (Hock et al., 2000), while the
high-affinity NGF receptor trkA is downregulated (Mufson et al., 2002;
Counts et al., 2004). It can be explained that enhanced cortical
(target-derived) NGF is enhanced but cannot be transported to neuronal
somata, because the axonal transport is destructed and the receptors are
not functional (Mufson et al., 1999). Recent evidence shows that the
precursor form of NGF (pro-NGF) and not mature NGF is liberated in the
brain, and its processing is regulated by plasmin, which is under control
of plasminogen activator (Bruno et al., 2008). In AD it has been
suggested that β-amyloid induced microglial activation would generate
oxidative stress (iNOS, peroxynitrite), which (1) inhibits processing of
pro-NGF to mature NGF and (2) activates matrix-metalloproteinase-9 and
induces degradation of mature NGF. This event results in drastic
reduction of the bioactivity of NGF for the cholinergic neurons and may
further induce neuronal cell death (Bruno et al., 2009).

7. Silent strokes and acidosis

Cerebrovascular disease and ischemic brain injury secondary to
cardiovascular diseases are common causes of dementia and cognitive
decline in the elderly (Erkinjuntti et al., 2004). Territorial infarct, old
age, and low educational level were identified as predictors of
cognitive disorders after stroke (Rasquin et al., 2004). Stroke may
account for as many as 50% AD cases in old age (Kalaria, 2000), and it
is known that ischemic events induce APP, β-amyloid, and tau
pathology (Kalaria, 2000). Approximately 35% of AD patients show
autopsy-proven vascular infarcts and 60% show white matter lesions.
There exists an association between stroke and AD that may be due to
an underlying systemic vascular disease process or, alternatively, due
to the additive effects of stroke and AD pathologic features, leading to
an earlier age at onset of disease (Honig et al., 2003). Several
longitudinal studies report an association between stroke and
cognitive decline (Langa et al., 2004; Linden et al., 2004; Roman,
2004; Zhou et al., 2004). Such small ischemic lesions (“silent stroke”,
cortical microinfarcts; Kovari et al., 2007), which in isolation would
not alter cognition, substantially aggravate dementia, indicating that
cerebral ischemia may interact with AD pathology. It is now widely
accepted that acidosis is an important component of the pathologic
process leading to ischemic brain damage (Siesjo, 1988, 1992).
Acidosis is a result of either an increase in tissue CO₂ or an
accumulation of acids produced by dysfunctional metabolism
(Rehncrona, 1985). Moderate ischemia may cause a fall in tissue pH
to around 6.6 without any morphological evidence of irreversible cell
damage (Rehncrona, 1985). In severe ischemia, anaerobic glycolysis
leads to accumulation of acids, for example, lactate, causing a decrease
in pH to around 6.0 (Rehncrona, 1985) with strong signs of
irreversible damage. We have recently shown that cholinergic neurons
undergo cell death when the pH is lowered to a critical
values of 6.8 (Pirchl et al., 2006). It is well known that acidosis
enhances iron-catalyzed production of reactive oxygen species,
probably by releasing iron from its binding to transferrin, ferritin, or
other proteins (Li and Siesjo, 1997). It seems likely that the NVU
is very sensitive for changes in pH and the interaction between vascular
structures and cholinergic nerve fibers should be considered as a
critical element in neurodegeneration, especially in the view of long-
standing suggestions that vessels are lost in the aging brain.

It is highly interesting to note that β-amyloid processing is markedly
affected by low pH, which could link acidosis to AD. Lactate caused a
dose-dependent increase in cellular β-amyloid immunoreactivity in
hippocampal neurons but acidosis did not affect secretion of sAPP
(Brewer, 1997). A marked Cu²⁺- induced aggregation of β-amyloid
emerged when the pH was lowered to 6.8, indicating that H⁺- induced
conformational changes unmask a metal-binding site on β-amyloid that
mediates reversible assembly of the peptide that could have relevance
for plaque deposition in AD (Atwood et al., 1998). β-amyloid (15–22)
controls aggregation of β-amyloid (1–42) at acidic pH and its proteolytic
activity at neutral pH (Matsunaga et al., 1994). Prolonged acidosis may
in fact contribute to the dysregulation of β-amyloid and subsequent
plaque deposition and cell death of cholinergic neurons. We have
recently shown that under acidic conditions (pH 6.0–6.4) cholinergic neurons degenerate in brain slices that is accompanied by
aggregated β-amyloid peptides (Marksteiner and Humpel, 2008).

8. Inflammation and the vascular connection in AD and vaD

Inflammation is an important trigger of neurodegeneration during
aging (“Inflammaging”) (Franceschi et al., 2000) and considered as a
major actor of neurodegeneration in AD. Inflammation is a potential
target for AD therapy and anti-inflammatory drugs may delay AD (Perry
et al., 1995; Moore and O’Banion, 2002). In AD oxidation of DNA,
proteins and fatty acids occurs in different brain areas. Some of the
oxidation products have been found in the neurofibrillary tangles and
senile plaques (Markesbery and Carney, 1999) and these oxidative
modifications are closely associated with an inflammatory process in
the AD brain (Butterfield et al., 2002). Indeed, cholinergic neurons of
the basal nucleus of Meynert are very sensitive for inflammatory insults
(Wenk et al., 2000, 2003). Chronic release of pro-inflammatory
cytokines, such as interleukin-1beta, tumor-necrosis-factor alpha or
transforming-growth factor-beta1, indicates a powerful role in
inflammation, pathology and neuronal dysfunction associated with
AD (Perry et al., 1995; Grammas and Ovase, 2002; Wenk et al., 2003).
These inflammatory processes include activation of microglia and
subsequent neuroinflammatory processes (Gonzalez-Scarano and
Baltuch, 1999). However, again it is not clear if inflammation is a result
of β-amyloid dysregulation (Moore and O’Banion, 2002) or if
inflammation itself is the primary cause in initiation of AD. Inflammation
of brain capillary endothelial cells may play a potent role, and it is well
known that endothelial cells strongly respond to inflammatory stimuli
(Moser et al., 2004) especially involving production of reactive oxygen
species (Iadecola, 2004).

9. Oxidative stress and mitochondrial failure in AD and vaD

A rapidly growing body of evidence indicates that increased oxidative
stress from reactive oxygen radicals is associated with increased glutamate activity (Beal, 1996; Olsson, 1993; Coyle and Puttfarken,
1993). Oxidative damage induced by free radicals targets intracellular
structures such as DNA, lipids, or proteins and these free radicals,
generated through mitochondrial metabolism, can act as causative factors
of abnormal function and cell death. These oxidative changes can arise
from the normal aging process, head trauma, silent strokes, increased
levels of heavy metals (iron, aluminum, and mercury), and possibly the
aggregation of β-amyloid (Aliev et al., 2003). Interestingly, in human
cerebral endothelial cells the endothelial barrier integrity is affected
through activation of glutamate NMDA receptors resulting in loss of the
cerebral endothelial barrier dysfunction (Sharp et al., 2003). In this
respect, glutamate is also known to promote a breakdown of the BBB (Del
Zoppo and Mabuchi, 2003). Some of the oxidation products have been
found in the neurofibrillary tangles and senile plaques and these oxidative
modifications are closely associated with an inflammatory process in the
AD brain (Butterfield et al., 2002). Mitochondria are essential for generating the ATP for neurons, and a functional impairment results in neurodegeneration. Interestingly, vascular hypoperfusion induces dysfunction of mitochondria in AD with subsequent RNA oxidation, lipid peroxidation, or mitochondrial DNA deletion (Marcus et al., 1998; Nunomura et al., 1999; Zhu et al., 2004).

10. Role of reactive astrocytes

It has been assumed that reactive astrocytes could contribute to the pathomechanisms underlying AD by favoring oxidative neuronal damage (Schubert et al., 2001). Microglial cytokines, such as e.g. interleukin-1beta may, trigger production of apolipoprotein E and reactive astrocytes could promote the transformation of beta-amyloid into toxic forms (Schubert et al., 2001). Alternatively, it is well established that beta-amyloid peptides cause striking changes in astrocytes by activating astroglial calcium signaling (Abramov et al., 2004). These calcium signals were closely associated with transient acidification and generation of reactive oxygen species (ROS) and it was assumed that oxidative stress induced in reactive astrocytes may contribute to neuronal cell death (Abramov et al., 2004). Interestingly, it has been shown that astrocytic nitric oxide triggers hyperphosphorylation in hippocampal neurons (Saez et al., 2004).

11. A common hypothesis — what is the link?

How do all these puzzle stones fit into one model? It is not clear, how AD is caused and it is not clear how the different forms of dementia fit into one model. Is vascular dementia another disease or is it an early stage of AD? Is mild cognitive impairment the earliest form of AD and of vascular dementia? Many researchers favor the β-amyloid cascade hypothesis, and think that a dysregulation of β-amyloid metabolism is the primary cause for AD. Other researchers believe that only tau may account for the disease without affecting the β-amyloid processing. Putting several evidence together, it seems possible that the aging of the cerebrovascular system may trigger the development of dementia: age is the most important risk factor and different vascular risk factors correlate with the development of dementia and with cognitive deficits.

So far there is evidence that AD could be caused by two initial events (Fig. 1): chronic mild exposure to (cardiovascular) risk factors over years causes (1) damage of the brain cerebrovascular system leading to metabolic disturbances in the brain or (2) a dysbalance of the clearance of β-amyloid from brain to blood or vice versa which may increase brain β-amyloid levels. A cascade of downstream events may lead to β-amyloid plaques and tau pathology. The risk factors may include e.g. hyperhomocysteinemia, hypercholesterolemia, type 2 diabetes or likely combinations.

Pathway 1 (vascular): It is suggested that a vascular damage results in silent strokes and acidic conditions leading to several metabolic disturbances, such as enhanced influx of toxic compounds, or decreased efflux of metabolic waste and reduced energy supply (Fig. 1). In parallel a damage of the sensitive NVU may occur. As a result of the damage of the NVU cholinergic synapses lose contact with the NVU. It seems likely that such an event may cause retrograde-induced axonal damage and subsequent cell death of cholinergic neurons (Fig. 1). Such a loss of Fig. 1. A common unifying hypothesis for Alzheimer’s disease. It is hypothesized that chronic mild exposure of different (vascular) risk factors may play a role in the development of Alzheimer’s disease. These factors are e.g. hyperhomocysteinemia, hypercholesterolemia or type 2 diabetes. This leads to damage of the neurovascular brain capillaries leading to silent strokes and acidic conditions (1) or to a dysregulation of β-amyloid at the blood-brain barrier resulting in increased β-amyloid (1–42) levels in the brain (2). The cerebrovascular dysfunction may result in a damage of the sensitive neurovascular unit (3). The subsequent retrograde-induced cell death of cholinergic neurons correlates with the lack of cortical or hippocampal acetylcholine (4). Metabolic disturbances (e.g. enhanced influx of toxic compounds, reduced efflux of metabolic waste, or reduced energy supply) may induce neuroinflammation (5) and microglial activation and reactive gliosis (6). Different risk factors (such as metals, reduced pH, reduced transport or degradation of β-amyloid) may result in aggregation of beta-amyloid and plaque deposition (7). The cerebrovascular damage and dysfunctional β-amyloid clearance result in deposition of β-amyloid (angiopathy) in brain vessels (8). It is suggested that metabolic disturbances cause an imbalance of specific protein kinases (PK) or phosphatases (PP), resulting in abnormal tau phosphorylation, which finally cause the tau pathology (9). Microglia inflammation enhances matrix metalloproteinase-9 (MMP9) and cause a dysfunction of the metabolism of nerve growth factor (NGF) with a reduced bioavailability for cholinergic neurons, supporting their cell death (10). Tau pathology may on the other hand also be caused by β-amyloid plaque deposition (11) or may contribute to neuronal cell death (12).
cholinergic neurons correlates with lack of acetylcholine in cortex and hippocampus, resulting in retrograde cell death of cholinergic neurons (Fig. 1). The resulting microglial activation causes release of proinflammatory cytokines and oxidative stress with production of radicals and finally reactive gliosis. It has been shown that this results in enhanced degeneration of NFG and thus a decrease of NFG bioavailability for cholinergic neurons further induces neurodegeneration of cholinergic neurons.

Pathway 2 (clearance): Yet unknown risk factors may damage the BBB and result in dysfunctional clearance of β-amyloid from brain to blood. Alternatively, peripheral blood-derived β-amyloid enters the brain (Fig. 1). Such a dysfunctional clearance may result in enhanced β-amyloid levels in the brain tissue (Fig. 1). Different risk factors, such as metals (copper, zink), reduced pH (<6.8), dysfunctional transport or degradation of β-amyloid induce aggregation of β-amyloid resulting in plaque deposition (Fig. 1). As a cause of either vascular damage and/or β-amyloid dysfunctional clearance, deposition of β-amyloid in vessels (angiopathy) may occur (Fig. 1).

Pathway 3 (Tau pathology). It is suggested that the metabolic disturbances cause an imbalance of specific protein kinases and phosphatases. This dysregulation causes abnormal tau phosphorylation and finally formation of paired helical filaments, the typical tau pathology. The abnormal tau pathology may further contribute to cholinergic cell death. It is not fully clear if β-amyloid plaques may directly induce tau pathology.

It seems possible that the different stages in dementia are defined as the extent of damage of the cerebrovascular system and all subsequent events in the brain. However, it cannot be excluded that the “final link” is still missing, which may favor another, or a modified, hypothesis. Recently, it has been proposed that the blood-clotting factor fibrinogen could be one of the “missing links” of vascular and AD pathologies (Cortes-Canteli et al., 2010; Wood, 2010).

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