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Review

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

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ABSTRACT

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%), frontotemporal dementia (approx. 5%), 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, atheriosclerotic 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

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reduced efflux of metabolic waste products in the brain, or result in dysregulated oxygen or glucose supply or last not least in a dsyfunctional clearance of different compounds at the BBB.

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 (Breteler, 2000; Dede et al., 2007; Deschaintre 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 (Rocchi 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; McIlroy 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 peroxidaton 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). Inded, 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 hyperphosporylation (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 .

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