The Blood-Brain Barrier in Alzheimer's Disease

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ABSTRACT: The current evidence for and against abnormalities of the blood-brain barrier in "normal" aging and Alzheimer's disease is reviewed. Recent studies of cerebral amyloid angiopathy, a microangiopathy commonly observed in Alzheimer's disease and one suggested to result from blood-brain barrier derangement, are discussed with particular attention to the biochemical nature of the vascular amyloid material, and features it shares with the amyloid found in senile plaque cores and with neurofibrillary tangles. Modern techniques that will probably clarify blood-brain barrier pathophysiology are reviewed.

RÉSUMÉ: La barrière hémo-encéphalique dans la maladie d'Alzheimer. Nous revoyons les données actuelles en faveur et contre la présence d'anomalies de la barrière hémo-encéphalique dans la vieillissement normal et dans la maladie d'Alzheimer. Nous analysons des études récentes sur l'angiopathie cérébrale amyloïde, une micro-angiopathie qu'on observe fréquemment dans la maladie d'Alzheimer et qu'on pense être le résultat d'une anomalie de la barrière hémo-encéphalique. Nous portons une attention particulière dans notre discussion à la constitution biochimique de la substance amyloïde vasculaire et aux particularités communes de cette substance amyloïde et de celle qu'on retrouve dans la partie centrale des plaques séniles et des enchevêtrements neurofibrillaires. Nous faisons une revue des techniques modernes qui permettront probablement d'élucider la pathophysiologie de la barrière hémo-encéphalique.

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The blood-brain barrier (BBB) is constituted by the cerebral capillary and arteriolar (microvascular) endothelium,[1-4] a highly specialized type of endothelium that modifies and restricts the passage from blood to brain of both large molecules and smaller molecular weight nutrients.[5,6] Of the numerous theories of etiology and pathogenesis proposed for Alzheimer's disease (AD) and senile dementia of the Alzheimer type (SDAT) over the past few years, only a few have suggested that BBB injury, disruption or abnormality is a key primary event from which all other clinical and pathological hallmarks of the disease evolve.[7,8] Yet there is reason to believe that BBB abnormalities commonly occur in AD, and may contribute to the cognitive deficits as well as to other clinical syndromes in the AD population.

Integrity of the BBB, as measured by several parameters in various animal species, does not seem to become impaired as a simple function of senescence.[9,10] Similar tracer studies in humans making use of sensitive high molecular weight morphologic tracers (e.g. horseradish peroxidase) and radioisotope labelled compounds (e.g. ^{14}C-sucrose) are not feasible. Detailed morphometric assessment of the *human* BBB (based on surgical biopsy specimens) in non-demented individuals from a range covering the second to the eighth decades of life[11] has shown the following: capillary walls from the white matter, normally thicker than those in gray matter, undergo progressive thinning until, at advanced age, they are similar in thickness to their grey matter counterparts; *no* change in the endothelial mitochondrial population occurs with age, and no alteration in presumed non-specific permeability routes (e.g. endothelial pinocytotic vesicles, junctional gaps) takes place with increasing age. The finding of a loss of pericytes, however, suggests that the BBB in older individuals may less effectively compensate for transient barrier leaks, should these occur.[11] Thus BBB changes are relatively subtle when compared to other age-related morphologic and physiologic phenomena that occur in the human brain.[12]

The situation is different, however, in AD/SDAT. Both direct and indirect evidence suggests that the BBB becomes leaky in this disorder. It remains to be conclusively resolved whether such a functionally abnormal BBB is a cause or an effect of the other brain changes seen in AD. Immunocytochemical studies showing the presence of serum proteins in the neuropil (including senile neuritic plaques) of SDAT brain tissue[13] imply abnormal BBB permeability during life in these patients. Work employing other methodology, however, suggests that the BBB is intact in AD, yet damaged in multi-infarct dementia.[14] The locus ceruleus, a noradrenergic pontine tegmental nucleus that, through widespread axonal projections appears to exert an

influence on BBB permeability,[15,16] becomes depleted of neurons in SDAT[17-19] though of course this does not prove the existence of a physiological BBB abnormality.

Indirect evidence for BBB abnormalities in AD exists in the common finding of a severe degree of cerebral amyloid angiopathy (CAA) or cerebrovascular amyloidosis in the brains of patients with this type of dementia.[20] CAA is a uniquely cerebral microangiopathy characterized by the presence within brain capillary and arteriolar walls of an eosinophilic homogeneous material that shows apple green birefringence when viewed under polarized light — the material is thus a β-pleated sheet protein.[21] Ultrastructural study of the amyloid shows it to consist of a random arrangement of nonbranching nonparallel fibrils with a mean diameter on the order of 9-10 nm. The angiopathy clearly involves microvessels of the size that subserve BBB function. Attempts to identify the amyloid material in CAA by immunohistochemistry have yielded conflicting results, but most investigators have agreed on one point: the walls of microvessels affected by CAA as well as the surrounding brain show the presence of serum proteins that reflect abnormal endothelial permeability in the cortex.[22-26]

CAA occurs in the human brain in an age-related fashion,[27,28] is primarily a neocortical vascular lesion that frequently affects microvessels passing from leptomeninges into cortex, tends to spare deep central grey matter and posterior fossa structures, and can result in massive, sometimes multiple lobar cerebral hemorrhages.[20,29-31] Many examples of severe CAA are found in patients with AD — in some studies, over 90% of AD brains are affected by CAA.[8,32-34] CAA, often quite severe, *is* seen without Alzheimer changes in some brains though the amyloid material has not been chemically characterized in every such case. It is also associated with several other neurodegenerative conditions, some of them familial.[20] If, as some claim, AD is a hippocampal dementia,[35] it is curious that CAA seems to spare the hippocampal formation.[27,33,36] The exact relationship between CAA and amyloid-laden senile plaques in the neocortex is also controversial[37] (see article, this issue, by Dr. Mary Bell).

Recently, it has become possible to isolate and thus study directly cerebral microvessels affected by CAA. Preparations of amyloid-laden leptomeningeal microvessels from AD and Down's syndrome brains[38-40] and parenchymal arterioles from a case of AD[41] have now been achieved, allowing for direct biochemical assay of the wall material. All studies show the cerebrovascular amyloid to be a protein with a molecular weight of 4200 daltons and a unique amino acid composition and sequence. Antibodies to a synthetically derived peptide encompassing the first 10 amino acids in this sequence label parenchymal CAA microvessels and the amyloid cores of senile plaques.[40] CAA amyloid is also similar to peptides isolated directly from the amyloid cores of senile plaques[42,43] and from purified neurofibrillary tangles.[44] This similarity of the various forms of brain amyloid detected in AD has led to the hypothesis that AD is a form of "multiple cerebral amyloidosis"[45,46] and that a circulating amyloid precursor passes from the blood through injured cerebral microvascular endothelium, resulting in vessel wall amyloid deposition (in the form we detect as CAA), and amyloid deposition within the neuropil at the core of many senile plaques. The same theory furthermore proposes that the identical amyloid precursor (perhaps after "processing" by the endothelium) is toxic to neurons and causes the formation of intracytoplasmic neurofibrillary tangles. Another possibility is that the 'amyloidogenic' precursor toxic to neurons results in neuritic degeneration and secondary amyloid deposition within the resultant plaques. The unique propensity of the *cerebral* and not visceral microvasculature to develop amyloid angiopathy is explained by the characteristic features (and probably distinctive proteolytic enzyme complement) of micovascular endothelium within the CNS. This model fails to specify whether BBB injury is a cause or a result of CAA or what the endothelial "processing" abnormality may be, and other investigators claim that neurofibrillary tangles, senile plaque core amyloid, and CAA all originate within the brain parenchyma.[44]

Whatever is the ultimate resolution of these crucial research questions, studies on the BBB in AD/SDAT and other disorders, are likely to retain the limelight for some time. They are facilitated by the fact that the key component of the BBB, viable cerebral capillaries and arterioles, can be isolated from the brain with relative ease. This has been accomplished with several animal species and, more recently, with human brain obtained at postmortem examination.[47-49] Furthermore, cerebral capillary endothelium from several sources, including human brain,[50] can be cultured, allowing for studies based on an artificially reconstructed BBB *in vitro*.[51,52] This new technology is certain to clarify many of the confusing ideas that have arisen about the BBB, its role in normal brain function and in disease states that affect the CNS.

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