Alois Alzheimer described the symptoms, the presence of tangles in the brain and extracellular deposits of a substance in the brain and blood vessels of his patient Auguste D. The disease is now associated with his name, Alzheimer’s disease (AD) (1). AD occurs generally late in life, affecting over 35 million individuals worldwide. Aging is a major risk factor, and with increasing longevity by 2050 the incidence of AD will increase by about 3 fold (2). Despite extensive research there is no treatment that alters the biological progression of the disease. However, we now understand that the brain deposits in AD are caused by progressive oligomerisation of amyloid β-peptides (Aβ) to form oligomers, protofibrils and fibrils, and that these Aβ species contribute to neurotoxicity.

The relative levels and distribution of Aβ species in the brain may influence the disease progression. This led to the ‘amyloid hypothesis’, as a possible explanation for the development of AD, in which Aβ is central to AD pathology (3). A small number (<1%) of AD cases, familial AD (early-onset), is linked to genetic mutations which are associated with increased Aβ production. The cause of the majority of AD cases, sporadic (late-onset), may be due to faulty clearance of Aβ from brain. In this new concept, dementia in AD is associated with a cerebrovascular disorder, which leads to accumulation of Aβ on blood vessels (cerebral amyloid angiopathy, CAA) and in the brain parenchyma, extracellular deposits, and intraneuronal lesions - neurofibrillar tangles (4).

The clearance of the Aβ production from the brain to the blood is rigorously regulated across the blood-brain barrier (BBB). BBB is a sophisticated system, made up of endothelial cells, pericytes, and neuronal and astrocytic endfeet. This system highly regulates the import and export of nutrients, metabolites and immune cells as well as of xenobiotics. The BBB plays critical roles in the maintenance of central nervous system (CNS) homeostasis. Dysfunction of the BBB occurs in a number of CNS diseases, including AD. Tight junctions between endothelial cells in brain capillaries are the most important structural elements of the BBB. BBB regulates the entry of plasma-derived Aβ into the CNS and clears brain-derived Aβ through the receptor for advanced glycation end products (RAGE) and low-density lipoprotein receptor-related protein (LRP), respectively (5).

RAGE, a multiligand receptor in the immunoglobulin superfamily, binds a number of ligands including Aβ. RAGE expression is determined by the levels of its ligands. When pathogenic Aβ species accumulate in AD brain, RAGE expression increases in affected cerebral vessels, neurons or microglia, or in transgenic models of β-amyloidosis and in the human brain. This mechanism provides the potential for exacerbating cellular dysfunction due to RAGE-Aβ interactions. Soluble Aβ binds RAGE in the nanomolar range, and mediates its pathophysiologic cellular responses. RAGE/Aβ interaction is implicated in the development of Alzheimer’s neurovascular disorder by mediating transcytosis of circulating
Aβ across the BBB, inflammatory responses in endothelium, brain endothelial NF-κB-dependent apoptosis and suppression of cerebral blood flow (6). In addition, RAGE mediates Aβ-induced migration of monocytes across the human brain endothelial cell monolayers.

LRP expression in brain capillary endothelium is reduced during normal aging in rodents, non-human primates, and in AD. Since LRP is the main receptor for Aβ transport across the BBB in the direction of brain to blood, it’s down regulation in brain endothelium in AD and in patients with the Dutch-type of cerebrovascular β-amyloidosis will reduce Aβ clearance and promote Aβ cerebrovascular and brain focal accumulations. Binding of Aβ to LRP at the abluminal side of the BBB in vivo initiates a rapid Aβ clearance via transcytosis across the BBB into blood in mice and rats (7). Human Aβ injected into different brain regions was found intact in murine plasma, confirming its vascular clearance. This demonstrates rapid transcytosis of intact monomeric Aβ across the BBB, from brain into blood. This in turn may lead to Aβ accumulation in brain and its gradual oligomerisation and greater levels of neurotoxic Aβ oligomers. Thus, continuous removal of Aβ species from the brain by transport across the BBB and/or metabolism is essential to prevent their potentially neurotoxic accumulations in brain.

In conclusion, BBB dysfunction contributes to AD through a number of mechanisms that could be initiated in the presence or absence of Aβ pathology. In AD, RAGE levels at the BBB are increased and LRP levels at the BBB and the capacity binding of peripheral Aβ are reduced, favoring Aβ accumulation in the brain. Thus, therapies focused on upregulation of the cell surface LRP levels or reducing RAGE activity, represent promising approaches to control brain Aβ levels and the associated pathology by targeting transport processes at the BBB.

References: