Alzheimer’s Disease—Failure of Drainage of Fluid from the Brain

An Expert Interview with Roxana Carare
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Roxana Carare is a Professor in Clinical Neuroanatomy in the Faculty of Medicine, University of Southampton. Roxana graduated in General Medicine in 1994, completed her basic surgical training by 1996 and embarked on an academic career in Anatomy in 1998. She developed a strong international profile in research and is recognized for discovering the lymphatic drainage pathways of the brain that become clogged up with aggregated proteins, leading to Alzheimer’s disease. She is a recipient of a Dementia Leaders Award from Alzheimer’s Society UK, active member of the International Vascular Behavioral and Cognitive Disorders Society (VasCog), Cerebral Amyloid Angiopathy Society and Romanian Alzheimer’s Society, serves on the Editorial Board of Neuropathology and Applied Neurobiology, and reviewer for specialist neuropathology and neurology journals, as well as major international funding agencies.

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Q. How is soluble amyloid-beta cleared from the brain in healthy individuals?
Amyloid-beta (Aβ) is produced in all brains, as it is key to the maintenance of brain health. Normally Aβ is broken down by enzymes and eliminated across the walls of the blood vessels into the blood, or is removed by intramural periarterial drainage (IPAD), described by the Carare group. Enzymes and transporters of Aβ into the blood fail with increasing age and with other risk factors for Alzheimer’s disease, so the burden of removing Aβ via IPAD from aging brains is increased. IPAD takes place along tiny channels (vascular basement membranes, composed of extracellular matrix) in the walls of arteries that supply blood to the brain.

Q. How does this process change in Alzheimer’s disease?
The direction of IPAD is opposite to that of blood flow and relies on the contraction of smooth muscle cells to function properly. With aging, high blood pressure and high cholesterol in midlife, diabetes and obesity, the arteries become stiffer and smooth muscle cells do not contract properly (Figure 1). This leads to a poor perfusion of the brain with blood, as well as reduced clearance of Aβ from the brain. A failure of efficient drainage of Aβ and other proteins from the aging brain results in their deposition in the walls of blood vessels as sticky plaques, giving rise to cerebral amyloid angiopathy, a key feature of Alzheimer’s disease (Figure 2).

Q. What lifestyle factors might affect protein clearance?
Prevention or early treatment of metabolic diseases such as diabetes, high cholesterol, high blood pressure, low vitamin B and maintaining a healthy heart should also maintain healthy blood vessels in the brain, preventing Alzheimer’s disease.
Q. What therapeutic strategies may help the clearance of Aβ from the brain?

There are already promising experimental studies demonstrating that compounds that increase the activity of the smooth muscle cells of blood vessels are able to reverse the features of Alzheimer's disease. Such compounds (for example cilostazol, a selective phosphodiesterase type 3 inhibitor in clinical trials in Japan and Edinburgh, UK) are able to slow the progression from mild cognitive impairment to full blown Alzheimer's disease.16,17