A brief comment on cerebrovascular innervation: Relevance to brain disease.

Andrzej Loesch
Division of Medicine, Royal Free Campus, School of Life and Medical Sciences, University College London, Rowland Hill Street, London NW3 2P, UK.

Abstract
In the context of the recently published fascinating study of brain function and vascular abnormalities in Alzheimer's disease by Iturria-Medina, the current editorial discusses the possibility of contribution of autonomic cerebrovascular nerves to cerebral disease.

Keywords: Alzheimer's disease, Circulating microRNA, Mild cognitive impairment, Biomarker.

The Main Text: Commentaries

The importance of making substantial progress in the understanding of the causes and the treatment of sufferers with Alzheimer's and/or dementia, including vascular dementia, is obvious. It can be pointed out that discrimination between these diseases is not always straightforward, as brains may show mixed features of the diseases e.g. plaques and tangles plus microinfarcts or Lewy bodies can appear in more cognitively impaired cases than those whose brains contained only comparable levels of the plaques and tangles characteristic of Alzheimer's [1].

The most recently published study in *Nature Communications* by Iturria-Medina et al. [2] is particularly outstanding and important. It employed a plethora of sophisticated approaches to expose the multifactorial mechanisms underlying late-onset Alzheimer's disease (LOAD); these included multiple imaging techniques to measure amyloid concentration, glucose metabolism, cerebral blood flow (using Arterial Spin Labeling), functional activity and brain atrophy in a number (78) of regions of the brain, virtually covering all grey matter. To cut it short, these complicated studies, which analyzed more than 7,700 brain images from 1,171 people in various stages of Alzheimer's progression, revealed (among other changes) high levels of abnormality for specific proteins associated with the integrity of vascular system; they also suggest an early alteration of the peripheral vascular system during LOAD progression. It is highly recommended that anyone interested in the potential association between the onset of Alzheimer's disease and cerebrovascular dysfunction should read the details of the above-mentioned study [1].

This editorial intends to briefly outline the basic histological facts of the cerebrovascular wall, assuming that its morpho-functional integrity (homeostasis) reflects on the physiological blood supplied to the brain tissue. In a way, both cerebral and peripheral arterial walls are characterized by three more or less distinctive layers of tissues, which individually can be affected by pathology, hence reflecting on local blood flow and supply, namely: (i) intima – made of layer of endothelial cells (EC) lining inside blood vessel hence contacting blood; (ii) media – made by vascular smooth muscle (VSM) and connective tissue; and (iii) adventitia – a layer covering the media and made of connective tissue carrying perivascular nerves. It is now well established that intima, media and adventitia coexist in harmony in physiological conditions, where vasoactive agents from the intimal endothelium and adventitial perivascular nerves provide the control of local vascular tone (of the medial VSM) via respective receptors [3]. These dual neural-endothelial physiological interactions involving perivascular nerves and the endothelium [3] seem particularly important for blood flow in cerebrovascular bed [4].

Cerebral arteries and their branches penetrating brain tissue are usually well supplied with perivascular (cerebrovascular) nerves, suggesting that the innervation of these vessels is essential for the vessels' function. It is well established that the key cerebral vessels are richly innervated by sympathetic, parasympathetic and sensory nerves [5-9] able to release a variety of transmitters, co-transmitters and/or neuromodulators to act on related receptors on VSMs of the media causing it to contract or relax; similar effects are produced by vasoactive agents released from vascular endothelium [3,10,11]. In recent years, sympathetic nerves attracted considerable attention in relation to purinergic signaling involving adenosine 5'-triphosphate (ATP) as a cotransmitter with noradrenaline.
(NA) and modulator neuropeptide Y (NPY) in various areas of the autonomic nervous system [12].

Studies of cerebrovascular innervation of the human basal cerebral arteries have already disclosed changes to the innervation, principally of the sympathetic component in Alzheimer's disease and ageing [13,14] and therefore they demonstrate sensitivity/vulnerability of the cerebrovascular nerves in these conditions. It can be mentioned that cerebral amyloid angiopathy in Alzheimer's disease may potentially affect the cerebrovascular nerves resulting in impaired vascular responsiveness to vasoactive agents [15].

Despite our considerable knowledge concerning cerebrovascular innervation including the sources of the nerves (autonomic ganglia), their distribution and pharmacological properties, there still are some surprises. One of the interesting and enigmatic features of cerebrovascular innervation, that might be relevant to the control of blood supply to the brain in health and pathology, is the finding a subpopulation of cerebrovascular nerves displaying immunoreactivity for ET-1 in animal and human cerebral vessels [16-21]. Cerebrovascular nerves also show the presence of endothelin ET\textsubscript{A} and ET\textsubscript{B} receptors [17]. In fact ET-1 and its ET\textsubscript{A} and ET\textsubscript{B} receptors can also be localized to cerebrovascular Schwann cells [17]. Here, Figure 1a demonstrates an example of ET-1-positive cerebrovascular nerve varicosity, while Figure 1b shows an ET-1-positive Schwann cell interacting with ET-1-negative cerebrovascular nerves in human middle cerebral artery [21,22]. The role of the ET-1-positive cerebrovascular nerves is unknown, but it has been shown that these nerves may originate from sensory and sympathetic components of trigeminal and superior cervical ganglia, respectively [19]. Therefore it is likely that neural ET-1 indeed acts as a neurotransmitter [23] in addition to the peptide vasoactive and proliferative effects. It has also been shown that the changes in the rate of cerebrovascular perfusion affect the release of ET-1 to vascular lumen [24] with simultaneous changes in endothelial immunoreactivity to ET-1 [25]. All these facts imply the existence of ET-1-associated mechanisms in cerebrovascular wall [26].

In summary, when considering contribution of cerebral blood vessels in pathologies such as e.g. Alzheimer's disease, where cerebrovascular dysfunction can be one of the important contributors [1], it seems reasonable to suggest that the cerebrovascular nerves, of at least key cerebral vessels supplying blood to the brain, may play a role in cognitive outcome. However, the roles of some cerebrovascular nerves are yet to be defined as for example those nerves utilizing ET-1. Regardless, still it might be a complex task to differentiate between consequences and causes of pathological changes in cerebral vascular bed and brain tissue.

References


Correspondence to:
Andrzej Loesch,
Centre for Rheumatology and Connective Tissue Diseases,
Division of Medicine, Royal Free Campus,
School of Life and Medical Sciences,
University College London,
Rowland Hill Street,
London NW3 2P,
UK.
Tel: +44 (020) 7794 0500 ext. 33247
E-mail: a.loesch@ucl.ac.uk