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

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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.

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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

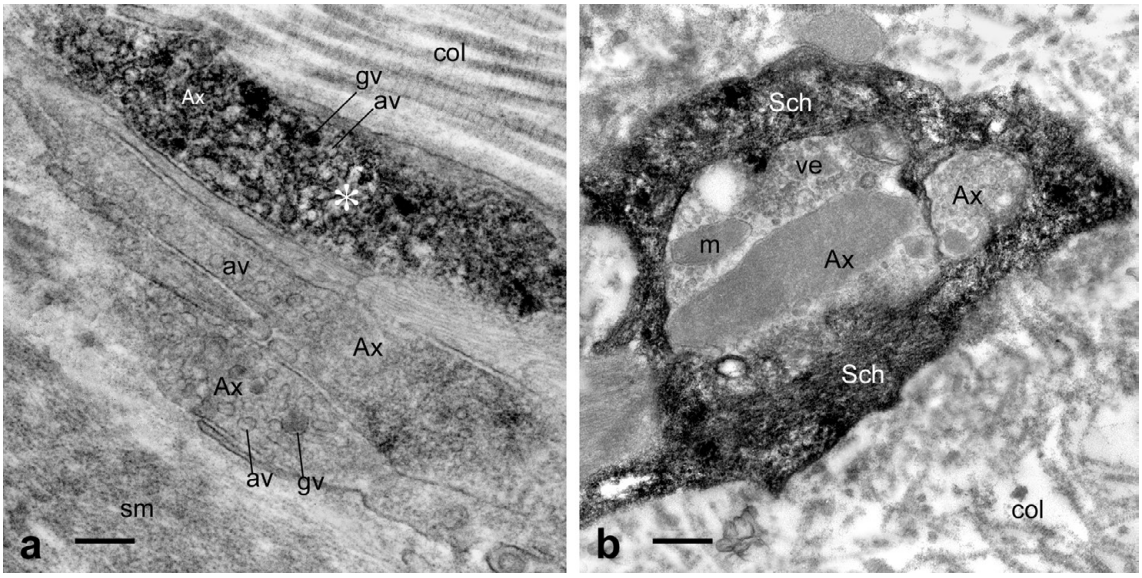

Figure 1a and 1b. *Human middle cerebral artery in a case of multiple system atrophy with autonomic failure immunolabelled for ET-1 (using ExtrAvidin method).* ***a.*** *Cerebrovascular nerve fibre/axon varicosities (Ax) close to vascular smooth muscle (sm) of the media: note that the varicosity immunoreactive for ET-1 (white asterisk) contains granular (gv) and agranular (av) vesicles; core of granular vesicles is labelled for ET-1. col-collagen. Bar: 200 nm.* ***b.*** *A Schwann cell (Sch) displaying immunoreactivity for ET-1 is embracing ET-1-negative axon varicosities (Ax). m-mitochondria. Bar: 200 nm. It is kindly acknowledged that image* ***a*** *is obtained from [21], while image* ***b*** *is from [22]*

(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_A and ET_B receptors [17]. In fact ET-1 and its ET_A and ET_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

1. Iturria-Medina Y, Sotero RC, Toussaint PJ, et al. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nat Commun 2016; 7: 11934.
2. Schneider JA, Aggarwal NT, Barnes L, et al. The neuropathology of older persons with and without dementia from community versus clinic cohorts. J Alzheimers Dis 2009 18: 691-701.
3. Ralevic V, Burnstock G. Neural-endothelial interactions in the control of vascular tone. 1993; R.G. Landes Company, Austin, Texas.

4. Loesch A, Burnstock G. Immunocytochemistry of vasoactive agents and nitric oxide synthase in vascular endothelial cells with emphasis on the cerebral blood vessels. Cell Vision: The Journal of Analytical Morphology 1996 3: 346-357.
5. Edvinsson L. Neurogenic mechanisms in the cerebrovascular bed. Autonomic nerves, amine receptors and their effects on cerebral blood flow. Acta Physiol Scand 1975; 427: 1–35.
6. Edvinsson L. Innervation of the cerebral circulation. Ann NY Acad Sci 1987; 519: 334–348.
7. Burnstock G. Neurogenic control of cerebral circulation. Cephalagia 1985; Suppl 2: 25-33.
8. Burnstock G. Local mechanisms of blood flow controlled by perivascular nerves and endothelium. J Hypertens 1990; 8: S95-S106.
9. Burnstock G. Changes in expression of autonomic nerves in aging and disease. J Auton Nerv Syst 1990; 30: S25-S34.
10. Vanhoutte PM. Say NO to ET. J Auton Nerv Syst 2000; 81: 271-277.
11. Vanhoutte PM, Shimokawa H, Feletou M, et al. Endothelial dysfunction and vascular disease – a 30th anniversary update. Acta Physiol 2016.
12. Burnstock G, Ralevic V. Purinergic signalling and blood vessels in health and disease. Pharmacol Rev 2014; 66: 102-192.
13. Bleys RL, Cowen T, Groen GJ, et al. Perivascular nerves of the human basal cerebral arteries: II. Changes in aging and Alzheimer's disease. J Cereb Blood Flow Metab 1996; 16: 1048-1057.
14. Bleys RL, Cowen T, Groen GJ, et al. Perivascular nerves of the human basal cerebral arteries: I. Topographical distribution. J Cereb Blood Flow Metab 1996; 16: 1034-1047.
15. Weller RO, Nocoll JAR. Cerebral amyloid angiopathy: Pathogenesis and effects on the ageing and Alzheimer brain. Neurol Res 2003; 25: 611-616.
16. Loesch A, Milner P, Burnstock G. Endothelin in perivascular nerves. An electron-immunocytochemical study of rat basilar artery. Neuroreport 1998; 9: 3903-3906.
17. Loesch A, Gajkowska B, Dashwood MR, et al. Endothelin-1 and endothelin receptors in the basilar artery of the capybara. J Mol Histol 2005; 36: 25-34.
18. Milner P, Loesch A, Burnstock G. Neural endothelin in hypertension: Increased immunoreactivity in ganglia and nerves to cerebral arteries of the spontaneously hypertensive rat. J Vasc Res 2000; 37: 39-49.
19. Milner P, Loesch A, Burnstock G. Endothelin immunoreactivity and mRNA expression in sensory and sympathetic neurones following selective denervation. Int J Dev Neurosci 2000; 18: 722-734.
20. Loesch A, Burnstock G. Endothelin in human cerebrovascular nerves. Clin Sci 2002; 103: 404S-407S.
21. Mickey I, Kilford L, Kingsbury A, et al. Endothelin in the middle cerebral artery: A case of multiple system atrophy. Histochem J 2002; 34: 469-777.
22. Loesch A, Kilfordt L, Kingsbury A. Endothelin in Schwann cells of middle cerebral artery in a case of multiple system atrophy with autonomic failure. Biomed Res, India 2004; 15: 157-159.
23. Dashwood MR, Loesch A. Endothelin-1 as a neuropeptide: neurotransmitter or neurovascular effects? J Cell Commun Signal 2010; 4: 51–62.
24. Domer FR, Alexander B, Milner P, et al. Effect of changes in rate of vascular perfusion on release of substances into the effluent from the brain of the rabbit. Brain Res 1993; 630: 88-94.
25. Loesch A, Domer FR, Alexander B, et al. Electron-immunocytochemistry of peptides in endothelial cells of rabbit cerebral vessels following perfusion with a perfluorocarbon emulsion. Brain Res 1993; 611: 333-337.
26. Loesch A. Localisation of endothelin-1 and its receptors in vascular tissue as seen at the electron microscopic level. Curr Vasc Pharmacol 2005; 3: 381-392.

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