OPEN PEER REVIEW REPORT 2

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Title: Vascular Dysfunction in Alzheimer's Disease – a Biomarker of Disease Progression and a Potential Therapeutic Target
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COMMENTS TO AUTHORS

The authors have written an agile and interesting review on the potential etiopathologic role of vascular damage in Alzheimer's disease. In order to strengthen their paper and provide a more complete picture of the topic, the authors should also mention:

1. The role of the glymphatic system in Alzheimer's brain as it is functionally integrated with the vascular system partaking in the circulation of tissue fluids and in the transport of proteins, including Amyloid-beta peptides.
2. The fact that human astrocytes cultured in vitro overproduce amyloid-beta42, nitric oxide, and VEGF-A when exogenous Amyloid-betas excite the signaling of their calcium-sensing receptor (CaSR)
3. The fact that in the hypoxic penumbra zone of experimental stroke, an acute situation, amyloid-betas are locally overproduced and increase neurons' losses, which somehow parallels the instead chronic condition of Alzheimer's: in both conditions Amyloid-beta peptides are overproduced via an interaction with the CaSR.
4. The fact that some authors report a VEGF-A overproduction in Alzheimer's which can exert neurotoxic effects and in the hippocampus can induce an early paradoxical and transient increase of the BOLD signal under specific circumstances--a potential early marker of this neuropathology.