Peripheral post-ischemic vascular repair is impaired in a murine model of Alzheimer's disease

Titre	Peripheral post-ischemic vascular repair is impaired in a murine model of Alzheimer's disease
Type de publication	Article de revue
Auteur	Merkulova-Rainon, Tatyana [1], Mantsounga, Chris S [2], Broquères-You, Dong [3], Pinto, Cristina [4], Vilar, José [5], Cifuentes, Diana [6], Bonnin, Philippe [7], Kubis, Nathalie [8], Henrion, Daniel [9], Silvestre, Jean-Sébastien [10], Lévy, Bernard I [11]
Editeur	Springer Verlag
Type	Article scientifique dans une revue à comité de lecture
Année	2018
Langue	Anglais
Date	Août 2018
Numéro	3
Pagination	557-569
Volume	21
Titre de la revue	Angiogenesis
ISSN	1573-7209
Mots-clés	Alzheimer’s disease Vascular dysfunction Hind limb ischemia Vascular repair Angiogenesis [12]
Résumé en anglais	The pathophysiology of sporadic Alzheimer's disease (AD) remains uncertain. Along with brain amyloid-β (Aβ) deposits and neurofibrillary tangles, cerebrovascular dysfunction is increasingly recognized as fundamental to the pathogenesis of AD. Using an experimental model of limb ischemia in transgenic APPPS1 mice, a model of AD (AD mice), we showed that microvascular impairment also extends to the peripheral vasculature in AD. At D70 following femoral ligation, we evidenced a significant decrease in cutaneous blood flow (- 29%, $P < 0.001$), collateral recruitment (- 24%, $P < 0.001$), capillary density (- 22%; $P < 0.01$) and arteriole density (- 28%; $P < 0.05$) in hind limbs of AD mice compared to control WT littermates. The reactivity of large arteries was not affected in AD mice, as confirmed by unaltered size, and vasoactive responses to pharmacological stimuli of the femoral artery. We identified blood as the only source of Aβ in the hind limb; thus, circulating Aβ is likely responsible for the impairment of peripheral vasculature repair mechanisms. The levels of the majority of pro-angiogenic mediators were not significantly modified in AD mice compared to WT mice, except for TGF-β1 and PlGF-2, both of which are involved in vessel stabilization and decreased in AD mice ($P = 0.025$ and 0.019, respectively). Importantly, endothelin-1 levels were significantly increased, while those of nitric oxide were decreased in the hind limb of AD mice ($P < 0.05$). Our results suggest that vascular dysfunction is a systemic disorder in AD mice. Assessment of peripheral vascular function may therefore provide additional tools for early diagnosis and management of AD.

URL de la notice	http://okina.univ-angers.fr/publications/ua17587 [13]
DOI	10.1007/s10456-018-9608-7 [14]
Lien vers le document	https://link.springer.com/article/10.1007%2Fs10456-018-9608-7 [15]
Autre titre	Angiogenesis
Identifiant (ID) PubMed	29516292 [16]
Grant List	ANR-12-MALZ-0006 / / Agence Nationale de la Recherche / ANR-13-BSV1-0015-01 / / Agence Nationale de la Recherche / FDT20140930795 / / Fondation pour la Recherche Médicale /

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