ET-1-mediated reduction of cerebral blood flow in Alzheimer’s disease: therapeutic potential of zibotentan

https://neurodegenerationresearch.eu/survey/et-1-mediated-reduction-of-cerebral-blood-flow-in-alzheimers-disease-therapeutic-potential-of-zibotentan/

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Country

United Kingdom

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ET-1-mediated reduction of cerebral blood flow in Alzheimer's disease: therapeutic potential of zibotentan

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MRC

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The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Cerebral blood flow (CBF) is reduced in Alzheimer’s disease (AD) before the onset of dementia. More severe reduction predicts more rapid cognitive decline. In mouse models the reduction in

CBF greatly exceeds the decline in neuronal metabolic activity. The distribution differs from that of structural vessel disease and is probably mediated by functional vascular abnormalities. AD is thought to be initiated by the intracerebral accumulation of amyloid beta (Abeta). We have shown that Abeta42 upregulates neuronal endothelin-converting enzyme (ECE)-2 and angiotensin-converting enzyme (ACE). ACE catalyses production of angiotensin II (Ang II) and ECE that of endothelin-1 (ET-1), both potent vasoconstrictors. ET-1 concentration is significantly elevated in AD cortex. In addition, Abeta40 increases ECE-1 activity in endothelial cells, and both ECE-1 activity and ET-1 level are elevated in blood vessels from AD brains; this is likely to contribute to impairment of functional hyperaemia in AD. Cerebral vasoconstriction reduces CBF, impairs the delivery of oxygen and nutrients and slows the removal of waste products (including Abeta). Brain ischaemia also increases Abeta production. We and others reported the use of Ang II blockers (ARBs) to be associated with a reduced incidence of AD. No comparable human data are available for ET-1 receptor blockers. In a rat model of AD, injection of ET-1 exacerbated Abeta accumulation and neurodegeneration and impaired memory test performance. We suggest that Abeta40- and Abeta42-mediated increases in ET-1 and/or ACE are at least partly responsible for reduced CBF in AD. ET-1 mediates its cerebrovascular effects through ET-A receptors. We propose to compare the effects of zibotentan, a specific ET-A blocker, and losartan, an ARB, on CBF, autoregulation, functional hyperaemia and other vasoregulatory pathways, in a rat model of Abeta-mediated cerebral vasoconstriction, with a view to zibotentan usage in AD.

Lay Summary
Further information available at:

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Investments > €500k

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Alzheimer's disease & other dementias

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2016

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