UPREGULATION OF BRAIN RENIN ANGIOTENSIN SYSTEM BY 27-HYDROXYCHOLESTEROL IN ALZHEIMER’S DISEASE

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Introduction: Disturbances in cholesterol metabolism have been associated with hypertension and an increased Alzheimer’s disease (AD). Given the fact that cholesterol metabolism in the brain is efficiently separated from blood cholesterol by the blood-brain barrier (BBB), it is an unsolved paradox how high cholesterol can cause an effect in the brain.

Aims: To determine the mechanism by which hypercholesterolemia is considered a major risk factor for AD.

Methods: Members of the brain renin-angiotensin system (RAS) were analyzed from the cerebrospinal fluid (CSF) of mild cognitive impairment (MCI) and AD patients. In addition, in vitro experiments were carried out with neuronal cultures treated with 27-hydroxycholesterol (27-OH).

Results: We show that ACE activity, and levels of angiotensinogen (AGT) and angiotensin I/II are increased in the CSF of patients with MCI and AD. Moreover, we present a positive correlation of ACE activity with both plasma and CSF levels of 27-OH, an oxysterol known to pass the blood-brain barrier and is taken up by the brain from the circulation. Furthermore, treatment of neuronal cultures with 27-OH resulted in increased production of AGT.

Conclusions: Our results demonstrate that upregulation of RAS in AD brains occurs not only at the enzymatic level (ACE) but also at the substrate level (AGT). These data suggest that 27-OH could be a link between hypercholesterolemia, hypertension and AD pathogenesis.