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Investigations of non-classical axis of renin angiotensin system in Alzheimer's Disease

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Introduction: The classical axis of RAS (ACE-1/Ang II/AT1R) has been highlighted as exerting damage effects on the brain in both animal and human studies. Hyperactivity of this axis contributed to the pathogenesis of Alzheimer's disease (AD). However, the involvement of the non-classical axis of RAS (ACE-2/Ang (1-7)/MasR) in the etiology and progression of AD remain to be clarified. Therefore, investigating components of the non-classical axis of RAS is important for understanding the role of this system in the pathogenesis of AD.

Methods: Human Post-Mortem brain tissue used in this study was obtained from the South West Dementia Brain Bank, University of Bristol, with local Research Ethics Committee approval. The AD cases (n=72) and the age-matched controls (n= 47) were selected. In this cohort, we measured Ang (1-7) levels in the mid-frontal cortex (Brodmann area 9) using in-house direct ELISA. A commercially available ELISA kit was used to measure MAS1 levels. Data on Ang II and ACE-2 activity had been previously obtained for all cases.

Results: In this study, Ang (1-7) levels were unchanged in AD group compared to age-matched controls. However, Ang II/Ang (1-7) ratio (as a proxy indicator of ACE-2 activity) was significantly increased in AD group, indicating a reduction of ACE-2 activity in AD. For the first time, we showed that the MAS1 levels were significantly reduced in AD. This reduction in MAS1 levels was correlated with reduction in ACE-2 activity.

Conclusions: Together, our findings suggested that dysregulation of ACE-2/Ang(1-7)/MasR) axis might be implicated in the pathogenesis of AD. Thus, maintaining the activity of the non-classical axis of RAS may be essential for targeting therapeutic strategies of AD.

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