MANIPULATION OF RAS MEDIATES BDNF-DEPENDENT NEUROPROTECTION TO AD-LIKE PATHOLOGY

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Introduction: Altered renin-angiotensin system (RAS) has an important role in the development of vascular pathologies such as hypertension, stroke or atherosclerosis, which have been long linked to Alzheimer’s disease (AD). Anti-hypertensive therapies aimed at regulating RAS function have indeed been reported to delay cognitive decline in demented patients. The molecular mechanisms by which inhibition of RAS might be of benefit for cognition remain unclear.

Aim: We here hypothesized that RAS hyper-function in brain may limit the availability of brain-derived neurotrophic factor (BDNF) at synapses, therefore rendering neurons more vulnerable to neurotoxins and synaptic dysfunction, by up-regulating an important downstream effector of angiotensin II signaling, plasminogen-activator inhibitor-1 (PAI-1).

Methods: Several RAS-inhibiting drugs, such as captopril (angiotensin-converter enzyme inhibitor), propranolol (inhibitor of renin production) and tipilaxtinin (PAI-1 inhibitor) were used in neuronal primary cultures to study neuronal survival (MTT assay) and protein expression by western blot.

Results: All drugs under study were able to increase the production of BDNF and downstream proteins of Trk-B receptor pathway involved in the synaptic consolidation machinery. Both captopril and tipilaxtinin protected neurons against beta-amyloid toxicity, which appeared to occur in a BDNF-dependent manner since this protection was reversed when blocking BDNF signaling. These treatments promoted the clearance of beta-amyloid by inducing the expression of insulin-degrading enzyme (IDE) in neuronal primary culture from Tg2576 mice.

Conclusions: These data show a novel mechanism mediated by BDNF release exerted by anti-RAS drugs and suggest that inhibition of PAI-1 might constitute a potential target for AD treatment.