Exploring the involvement of Na pump inhibitor marinobufagenin in the interactions between age-associated vascular and neurodegenerative processes in cognitive impairment and Alzheimers disease

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USA

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Exploring the involvement of Na pump inhibitor marinobufagenin in the interactions between age-associated vascular and neurodegenerative processes in cognitive impairment and Alzheimers disease

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1

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Research Abstract

The Dahl-S rat animal model exhibits premature central and cerebral vascular remodeling, associated with premature cognitive decline. Increased CAS in this model, indexed as pulse wave velocity (PWV), is mediated by activation of arterial wall pro-fibrotic pathways that are similar to those observed in human aging, and result in increased MBG levels (Fedorova et al. Circulation 2000 and 2002; Fedorova et al. Hypertension 2001) and increased arterial wall collagen deposition. Dahl-S rats were selected, by backcrossing, for the trait of salt-sensitivity of blood pressure. Our preliminary data demonstrated that the median life span in Dahl-S rats on a low salt diet is 12 month vs. 24 months in wild type Sprague-Dawley (S-D) rats. A major abnormality in Dahl-S rats is the development of renal and cardiovascular tissue fibrosis even on a low salt diet. Angiotensin II (ANGII) signaling participates in production of MBG which becomes increased in Dahl-S rats with advancing age. Both ANGII and MBG are implicated in pro-fibrotic signaling and CAS increase. Because of that Dahl-S is an excellent model to study arterial fibrosis resulting in increased CAS and microvascular disease. MBG is detected in plasma, urine, CSF and adrenocortical and brain tissues. With advancing age, Dahl-S rats (12 months old) on a low salt diet exhibit a marked 2-fold increase in peripheral MBG and increase in CAS, evaluated as an increased PWV and an increase in collagen abundance in the aorta, coronary and peripheral arteries vs. young (3 months old) Dahl-S rats. In addition, genes implicated in AD, are overexpressed in the hippocampus in aged Dahl-S rats. Our laboratory has developed a monoclonal 3E9 anti-MBG antibody (mAb) (Fedorova et al. J Hypertens 2008), which can successfully immunoneutralize increased pro-fibrotic and pro-hypertensive MBG in animal models of chronic renal failure (Haller et al. Am J Hypertens 2012) and hypertension, and reduce arterial and interstitial fibrosis, improve renal impairment, decrease BP and PWV in aged Dahl-S rats. Thus, an anti-MBG mAb-induced reduction of vascular fibrosis in central and cerebral vasculature may ameliorate vascular cognitive impairment. Dahl-S rats exhibit cognitive dysfunction at a young age even on a low salt intake (Ruiz-Opazo et al. Hypertension 2004; Pelisch et al. Am J Hypertens 2011). Our pilot study of young Dahl-S rats showed significant impairment of hippocampal-dependent spatial memory for a goal location on a critical transfer test (water maze test), and alteration in brain structures, as detected by MRI (see below), elevated collagen deposition in small cerebral arteries (6.01 +/ 0.63 vs. 3.58 +/0 0.62; p=0.015), and increased aortic stiffness (2.9 +/- 0.1 vs. 2.3 +/- 0.2; p=0.06) vs. age-matched wild type S-D rats. Data interpretation of brain parameters assessed by MRI in Dahl-S and S-D rats: The mean diffusivity can be interpreted as a measure of tissue integrity, or a measure of the translational motion of tissue water; lower diffusivity means more dense, less hydration, more macromolecular content restricting water molecule translational motion. In pathology, diffusivity goes up. It increases in Dahl-S vs. S-D rats (1.17 +/- 0.11 vs. 0.82 +/- 0.32, x10-3 mm2/s; p< 0.05 by t-test) which may indicate edema, decreased neuronal content, loss of supportive tissue. R2 is the relaxation rate due to tissue interfaces (to a first approximation) and may

indicate changes in tissue microstructure and subcellular boundaries. This parameter is higher in Dahl-S than in S-D rats (6.36 +/- 2.49 vs. 1.34 +/- 2.40, s-1; p< 0.01) Dahl-S rats have smaller brain (1531 +/- 67 vs.1772 +/- 77, mm3; p< 0.01) and hippocampus volumes (79.9 +/- 3.9 vs. 95.1 +/- 6.8, mm3; p< 0.01) compared to S-D rats. Cortical thickness is showing a trend to decrease (7.08 +/- 0.19 vs. 7.27 +/- 0.21), and the ventricles are relatively enlarged (ventricle volume/brain volume: 0.015 +/- 0.0029 vs. 0.008 +/- 0.0028; p< 0.01) in Dahl-S vs. S-D rats. Conclusion: Dahl-S rats represent a suitable model to study the development of cognitive impairment and dementia due to the changes in cerebral microvasculature and central arterial wall, which underlie by changes in the status of pro-inflammatory and pro-fibrotic factors. We expect that in Dahl-S rats, the age-associated tissue renin-angiotensin system activation, increase in peripheral MBG and central arterial stiffness will be paralleled by cerebral microvascular disease, small cerebral blood vessel density, reduction in cerebral blood flow and cognitive impairment, recapitulating the study in humans. Further, we expect that longitudinal changes in peripheral MBG and other arterial wall pro-fibrotic markers will link the changes in arterial fibrosis to the accelerated memory impairment in old Dahl-S rats.

Lay Summary
Further information available at:

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