Vascular Dementia and Angiotensin Signaling

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Background: Angiotensin receptor (AT1R) antagonists are widely used as anti-hypertensives, but also improve cerebrovascular health and function in a variety of neurological diseases. The mechanisms underlying this protection are unclear. Vascular cognitive impairment in dementia (VCID) is a widespread problem with few treatment options. Obese and diabetic individuals likely represent a unique group of VCID patients, therefore any therapeutic or prophylactic treatment needs to reflect inherent differences within this group. We are investigating the use of AT1R blockade as a preventative for VCID in our unique mouse model.

Methods: We have created a mouse model that is obese and diabetic and has features of both AD and VCID. These mice (dbAD) are cognitively impaired by 12 months and display extensive cerebrovascular pathology, such as aneurysms and infarcts. In this study, dbAD mice were treated with telmisartan, an AT1R antagonist and partial PPARγ activator. Treatment was begun prior to the onset of MRI-detectable vascular incidents, but well after the onset of obesity and diabetes. At the end of the study, the effect of telmisartan treatment on cognitive function and vascular pathology was determined using Morris Water Maze and T2*MRI, respectively.

Results: The telmisartan dose used in this study (0.5 mg/kg/day) did not impact blood pressure, and had minimal effect on fasting blood glucose and glucose tolerance. In addition, our initial results suggest that telmisartan treatment did not have an effect on Morris Water Maze performance. We do have evidence, however, that the instance of vascular events is decreased in telmisartan-treated mice compared with age-matched controls.

Conclusions: It is intriguing that animals treated with telmisartan display a reduced number of MRi-detectable vascular incidents, especially since there is apparently no change in cognitive function. This study is ongoing. In the future, we plan to examine the effect of telmisartan treatment on other parameters of vascular function, at both the cellular and tissue level, and to investigate AT1R blockade as a potential therapeutic for pre-existing vascular conditions in the dbAD mice.