Animal model of impaired autoregulation for study of age related vascular cognitive impairment

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Research Abstract

? DESCRIPTION (provided by applicant): Vascular cognitive impairment (VCI) in elderly is a medical crisis in the United States. VCI is closely associated with hypertension. 67 millions of adults in the United States (33.3% of the population) have hypertension and over 40% of hypertensive patients develop VCI. The Medicare costs for the treatment of hypertension exceeds $47 billion/year and 159 billion/year for dementia. Aged people, especially those with hypertension that is associated with a higher incidence of developing vascular cognitive impairments (VCI) commonly have impaired myogenic response and autoregulation of cerebral blood flow (CBF). However, the mechanism of how these cerebral vascular impairments contribute to the development of VCI is still obscure, part of the reason has been the lack of genetic animal models exhibiting an impaired myogenic response. We first discovered that FHH rats have impaired myogenic response of middle cerebral artery (MCA) and fail to autoregulate in the cerebral circulation, and this impairment is restored by substitution of 2.4 Mbp of chromosome 1 of Brown Norway (BN) rats containing 15 genes including Add3. In the preliminary studies, we found that the expression of Add3 is reduced in FHH relative to FHH.1BN rats and the rescued vascular reactivity of MCA in FHH.1BN rats was back to be impaired after knocking down of Add3 using DsiRNA. We also have preliminary results in the whole animal level to support this view using our newly generated Add3 transgenic and knockout (KO) rat models. As expected, KO of Add3 impairs, and knockin of wildtype (WT) Add3 enhances the myogenic response in freshly isolated MCA in vitro and autoregulation of CBF in vivo. Moreover, we observed vascular remodeling, blood-brain barrier (BBB) leakage, neurodegeneration, learning and memory cognitive impairments those are all characters' of VCI after induction of hypertension in FHH rats. Thus, we hypothesize that Add3 plays an important role in the regulation of impaired myogenic response and autoregulation of CBF, and contributes to the development of age and hypertension related VCI in FHH rats. In this proposal, we will use our newly created Add3 transgenic FHH rats (FHH.Add3TG) vs. FHH rats to examine the myogenic response and autoregulation of CBF, as well as the development of VCI as they age and after the induction of hypertension. These studies should provide novel insights into the role of Add3 in the regulation of the myogenic response and its contribution to age-related small vessel disease, especially in hypertensive individuals, and supply the scientific community with the first genetic animal model in which the myogenic response is impaired to study mechanisms involved in VCI as age. The results will be critical for the development of new treatments to postpone the onset of age and hypertension related vascular diseases.

Further information available at:

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