Review of: "An intrinsic endothelial dysfunction causes cerebral small vessel disease"

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This article describe research of an animal-based knock out gene model of Small Vessel Disease (SVD). It offers a focused animal model of a single biological system that my offer a biological systems explanation of a single system that may contribute to the development of SVD in normotensive rats causing increases in white matter hyperintensities. It offers a new explanation of an underlying mechanism in support of increasing evidence of underlying vulnerability to SVD-related brain damage, not just extrinsic factors. The authors incorporate a novel normotensive transgenic rat model where the phospholipase flippase *Atp11b* is deleted. It outlines relationships between multiple phenotypes and biomarkers in this animal model allowing for study of the changes typical of those in human sporadic SVD occurring without hypertension. This deletion precipitates a secondary maturation block in oligodendroglia and myelin disruption around the small vessels. The primary theme is an example of a biological system that contributes to intrinsic endothelial dysfunction underlying the vulnerability of sporadic SVD, and suggests possible alternative therapeutic targets to prevent SVD and reduce the burden of stroke and dementia.

The SHRSP has a deletion mutation in *Atp11b*, which predicts a truncated ATP11B protein, but leads to its total loss by western blot with an N-terminal antibody. Using this model, they observed several changes in rate physiology and behavior. This occurred in a normotensive rat model. The *Atp11bKO* rat is normotensive and all cellular change within and without the vasculature were seen in a manner independent from exposure to HTN.

They validated endothelial dysfunction is culture cell lines of EC for which *Atp11b*KO-ECs show signatures of dysfunction despite the absence of hypertension. They identified several common markers of EC dysfunction including inflammatory receptors ICAM etc. as well as volatile messenger systems nitric oxide ENOS based systems in embryonic precursor cells. They examined this in many small fetal blood vessels as well as alternate small vessel based organ systems primarily the retina and categorized many cellular molecular changes including receptors and proteins consistent with EC dysfunction.

The *Atp11b*KO rat has white matter changes similar to those in human sporadic SVD including changes in myelin and premyleniated cell types, a smaller number of mature cell types and variable expression of key myelin proteins including those necessary for signally cell growth and proliferation. The *Atp11b*KO rat has MR changes similar to human SVD longitudinal MR scanning using T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR) at 3-4 months and 9-10 months as well as microbleeds.

The *Atp11b*KO rat has behavioral changes similar to SVD KO rats have problems with mobility, measured using the Catwalk equipment. have cognitive problems, with less interaction with novel objects in the Novel Object Recognition, in the elevated plus maze, KO rats at both ages travelled significantly less distance overall They had behavior changes suggesting an additional degree of apathy.

Methods and statistics: the cloning and CRISPIR of these rats were done with state of the art approaches. The EC cultures rat behavioral testing and MRI techniques were all well executed.

This animal study is well done and addresses an early exploration of the one system knock out model of this gene. It has not delineated other potential interactions with significant biological system and other messenger rs, which may intervene to cause the final phenotype and may affect the development of EC dysfunction at different spaces and time points. It seems the SVD is a polygenic disease with multiple inputs from different genes and biological systems. It is an intriguing system, which consolidates knowledge about EC dysfunction and examines one altered genetic input causing reduction in function of the protein ATP11B protein. It would be interesting to elaborate on this model to see if any interactions with different genes or proteins could neutralize or accelerate the effects of this protein on the various phenotypes studied.