Metal Transporter ZIP14 (slc39a14) in Mice Increases Manganese Deposition and Produces Neurotoxic Signatures and Altered Motor Activity

Cousins, R.J., Aydemir, T.B. (FSHN - University of Florida), Febo, M. (Psychiatry - University of Florida) and Marcei, T.H. (BMB - University of Florida)

Introduction

Mice with a global deletion of the *Zip14* gene deletion display and an altered gait and upon analysis have excessive manganese accumulation in the brain. ZIP14 is a metal transporter normally associated with zinc transport and biochemical roles of zinc functions in cells. Experiments were undertaken to study zinc and manganese metabolism and signatures of neurotoxicity in these mice. Others had recently linked mutations in the human *ZIP14* gene to early- onset dystonia/parkinsonism.

Experimental

Brains of both wild-type (WT) and *Zip14* KO mice in Fluorinert oil (FC-43) were used for imaging. A 17.6 tesla magnetic resonance spectrometer interfaced with a Paravision 6.0 console and a 20-mm inner diameter birdcage coil of the ARMIS facility was used. Facilities of ARMIS were also used for open field spontaneous activity testing of mice of both geneotypes.

Metabolic studies with the radioisotopes ^{65}Zn and ^{54}Mn and other studies were conducted at the Cousins lab at FSHN.

Results and Discussion

Manganese accumulation was 4x to 5x higher in brains of the KO mice. Less ^{54}Mn administered by subcutaneous injection was accumulated of the KO mice suggesting impaired elimination due to ZIP14 deletion. Intensity of MR images from brains of the KO mice was indicative of major manganese accumulation as was impaired motor function. The KO mice had up-regulated signatures of brain injury.

Conclusions

Normal ZIP14 function is necessary for normal manganese elimination and prevention of manganese-related neurotoxicity.

Acknowledgements

A portion of this work was performed at the National High Magnetic Field Laboratory, which is supported by National Science Foundation Cooperative Agreement No. DMR-1157490 and the State of Florida.

In addition, the research is supported by NIH Grant DK 94244 (to RJC).

References

Aydemir, TB, Kim, MH, Kim, J, Colon-Perez, L, Bana, G, Mareci, TH, Febo, M, Cousins, RJ. Metal Transporter *Zip14 (Slc39a14)* Deletion in Mice Increases Manganese Deposition and Produces Neurotoxic Signatures and Diminished Motor Activity. ***Journal of Neuroscience*** 37: 5996-6006 (2017).