Abstract 10

Mechanism Studies of Malformation of Cortical Development by Prenatal Exposure of Combined Methylazoxymethanol and Thalidomide*

Q. Fan,[1] S. Ramakrishna,[1] N. Marchi,[1] V. Fazio,[1] K. Hallene,[1] and D. Janigro[1,2]

[1]Cerebrovascular Research Center and [2]Department of Molecular Medicine, Cleveland Clinic, Cleveland, OH

Malformations of cortical development (MCD) represent a common CNS pathology associated with epilepsy. Animal models of MCD include the prenatal exposure to toxins interfering with neuronal migration (methylazoxymetanoic acid, MAM) or vascular formation (thalidomide, THAL). We have recently evaluated the effect of the combination of such toxins. The offspring showed gross anatomical alterations including ectopic neurons, abnormal ventricular size, and edema. We evaluated the molecular correlate underlying such changes. We performed immunohistochemical studies using the neuronal cell marker NeuN and glial cell marker GFAP on brain sections of MAM-THAL-treated and control rats. Brain density was evaluated by gravimetric-densitometric assay. Western blot analysis of aquaporin-1 (AQP1), AQP4, vasculogenesis marker VEGF, and GFAP was performed. TIMM staining was used to visualize mossy fibers of the dentate gyrus. Our results showed ectopic neurons associated with focal leakage of the blood-brain barrier and islets of GFAP-positive cells in early MAM-THAL postnatal rats (P1-P4). Brain water content was significantly higher in MAM-THAL rats in early postnatal stage (P2 and P9), but significantly lower in adult stage (P29), compared with controls. AQP1 and AQP4 levels were significantly higher in MAM-THAL rats throughout the early postnatal and adult stage. VEGF and GFAP levels were downregulated in the early postnatal stage and back to normal in the adult stage. The adult MAM-THAL rats showed abnormal hippocampus and robust mossy fiber sprouting in dentate gyrus and CA3 of hippocampus even though the pathophysiological phenomenon was minimal in cortex. Treatment with MAM-THAL provokes changes in the neurovascular architecture resembling some of the features observed in animals exposed to a single toxin. However, a more dramatic effect on brain water content and significant changes in the levels of expression of channels associated with water parenchymal homeostasis were observed in MAM-THAL-treated animals.

** Finalist for Young Investigator Award.*