VULNERABILITY TO SEIZURES AND ASTROCYTES: A MODEL MOUSE OF DEREGULATED POLYAMINE METABOLISM

1)Cervetto C. 2)Marcoli M. 3)Venturini A. 4)Vergani L. 5)Passalacqua M. 6)Berretta N. 7)D'amelio M. 8)Maura G. 9)Voci A. 10)Mariottini P. 11)Cervelli M.

University of Genova

Standard epilepsy models are unsatisfactory in the search for new antiepileptic drugs; new models are needed to identify the molecular mechanisms that contribute to epileptogenesis, to discover new targets for novel drugs which may interfere with the processes underlying epilepsy in susceptible individuals.

Here we report that a mouse model of chronic polyamine catabolism activation (a transgenic mouse conditionally overexpressing spermine oxidase in the neocortical neurons; Dach-SMOX mouse) exhibits increased vulnerability to kainate or pentylenetetrazol-induced epileptic seizures. We investigated the mechanisms for increased vulnerability to chemical-induced seizures with electrophysiological, immunocytochemical, biochemical and neurochemical approaches. An in vitro model of epileptic-like activity in combined hippocampus-neocortex slices recorded with a multi-electrode array device confirmed increased susceptibility to kainate-evoked cortical epileptogenic activity in Dach-SMOX mice, and indicated that it was dependent on astrocyte function. In the cerebral cortex of Dach-SMOX mice we observed reactive astrogliosis. The cerebrocortical astrocyte processes from Dach-SMOX mice overexpressed the cystine/glutamate antiporter system xc-, and expressed Ca2+-permeable GluA2-lacking AMPA receptors coupled to release of glutamate. The capability of kainate to evoke release of glutamate from the Dach-SMOX astrocyte processes depended on activation of these AMPA receptors. Antioxidant systems including the enzymatic scavengers superoxide dismutase and catalase, and non-enzymatic factors (metallothioneins), appeared stimulated as sign of oxidative stress condition in Dach-SMOX cerebral cortex.

In conclusion, our findings suggest that in Dach-SMOX mice reactive astrocyte activation, with astrocyte processes overexpressing the xc- system and expressing functional Ca2+-permeable AMPA receptors, might contribute to a secondary cascade of glutamate release, which, worsened by increased reactive oxygen species production, could increase brain vulnerability to epileptic seizures and excitotoxic/oxidative insult. This model of chronic dysregulation of glutamatergic transmission in neuron-astrocyte networks could help in the search for models of vulnerability to epileptic seizures, also possibly contributing to understand the processes underlying epilepsy in susceptible individuals.

Supported by grants from the University of Genova to M.M. and C.C. and of the University of Roma Tre to M.C. and P.M.