A PATHOGENETIC HYPOTHESIS OF UNVERRICHT–LUNDBORG DISEASE ONSET AND PROGRESSION

Buzzi Andrea[b], Franceschetti Silvana[a], Sancini Giulio[a], Zucchini Silvia[b], Paradiso Beatrice[b], Magnaghi Giuseppina[a], Frassoni Carolina[a], Chikhladze Maia[a], Avanzini Giuliano[a], Simonato Michele[b]

[a]Neurological Institute "C. Besta", Milan, Italy
[b]University of Ferrara, Italy

Unverricht–Lundborg disease (EPM1), the most common progressive myoclonic epilepsy, is associated with a defect of cystatin B (CSTB), a protease inhibitor. We used CSTB knockout mice to test the hypothesis that EPM1 onset is related to a latent hyperexcitability and that progression depends on higher susceptibility to seizure-induced cell damage. Hippocampal slices prepared from CSTB-deficient mice were hyperexcitable, as they responded to afferent stimuli in CA1 with multiple population spikes and kainate perfusion provoked the appearance of epileptic-like activity earlier than in WT mice. This hyperexcitability may depend on loss of inhibition, because the density of GABA-immunoreactive cells was reduced in the hippocampus of CSTB knockouts. In vivo, CSTB-deficient mice treated with kainate displayed increased susceptibility to seizures, with shorter latency to seizure onset and increased seizure severity compared with WT littermates. Furthermore, a greater degree of neuronal damage was observed in CSTB-deficient than in WT mice after seizures of identical grade, indicating increased susceptibility to seizure-induced cell death.