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Neuronal excitability changes produced by alzheimer's related pathology and by its risk factors

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Alzheimer's Disease (AD) is characterized by synaptic dysfunction early in the progression of the disease. It remains unknown the specific neuronal abnormalities produced by AD related pathology (Amyloid and Tau) to the Entorhinal Cortex (EC)-hippocampus circuit, the region targeted earliest by AD. Here, we address this issue by studying mice that express mutated human Amyloid Precursor Protein (hAPP) or mutated human Tau protein (hTau) or both in the EC. This approach allowed us to investigate the two pathologies separately and together additionally we also studied mice expressing the main genetic risk factor for AD (APOE4). Mice (APOE4) were compared to those expressing APOE3. The experiments showed that expression of mutant hAPP in EC (EC-hAPP) produced a significant increase in the duration of spontaneous extracellular field potentials in the superficial layers of both Medial EC and Lateral EC. We also observed that in EC-hAPP mice, pyramidal neurons of the subiculum, which are monosynaptically excited by EC layer III/II neurons, showed miniature excitatory postsynaptic currents having reduced amplitude, suggesting that the increased excitation observed in EC induced a compensatory negative feedback in subicular projection neurons, a process known as synaptic homeostasis. Modeling of the EC-hippocampus microcircuits indicates that EC hyperexcitability and subicular synaptic downscaling of mice expressing hAPP could be explained by EC interneuron pruning. The functional changes produced in EC by the expression of mutant τ protein (P301L) manifested as resistance to GABAA antagonist-induced hypersynchrony, but it did not, by itself, produce significant spontaneous activity changes in EC-hippocampus circuits. Mice displaying both pathologies as early as 2.5 months of age had an intermediate and subtler phenotype, predominantly driven by τ-pathology. An intriguing finding was the fact that mice expressing APOE4 had a relatively similar phenotype that mice expressing hAPP. This is increased synchronous activity in LEC, but the mechanism of such hypersynchrony is mediated by changes in GABAA receptors abnormalities in the pyramidal cell, and this is observed late in the disease. Our findings demonstrate the significant role of the lateral and medial entorhinal cortices in the early stages of AD where contrasting and complex interactions of APP, τ and APOE are observed.

Biography

Herman Moreno is an Associate Professor of Neurology and Pharmacology/Physiology at SUNY Downstate Medical Center, New York, USA.

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