CELLULAR AND MOLECULAR NEUROBIOLOGY

GABAergic Signaling in the Aging Cerebellum and the Influence of Membrane Cholesterol Dynamics

Elena Vásquez[1], Eduardo Callegari[2], María D. Paez[2], Diego Masone[3], Estela M. Muñoz[1]

1. 1. Laboratory of Neurobiology: Chronobiology Section, IHEM-UNCuyo-CONICET, Mendoza, Argentina.3. 3. Laboratory of Biochemistry of Acrosomal Exocytosis, IHEM-UNCuyo-CONICET, Mendoza, Argentina., 4. Funding: CONICET (PUE 2017), ANPCyT (PICT2017-0499: EMM, PICT2017-1002: DM), MINCyT-SNCAD (DM), SeCTyP UNCuyo J051 (DM), NIH (2 R01 GM083913-41A1: EMM and EV; 2P20GM103443-19: EC and MDP).,

Presenting Author:
***Elena Vásquez**, elenavasquez92@gmail.com*

Membrane lipids undergo changes that directly impact lipid raft dynamics, which in turn affect downstream receptor-mediated signaling. Some of these oscillations occur during brain aging and are associated with the onset and progression of neurological disorders. Here, we analyzed the levels of major neuronal lipid classes, protein expression, and their interactions at the cell surface in young and aged rat cerebella. We focused on members of the GABAergic system: the heterodimeric GABAB receptor and KCC2, the transporter responsible for modulating the strength of ionotropic GABAAR-mediated currents. GABABR subunits and KCC2 are present in multiple isoforms in the old cerebellum, as our UHPLC-MS/MS analysis has confirmed. By applying WB and IHC, we observed that GABAB2 subunit levels decrease with aging. We further explored and compared membrane lipid profiles using TLC, and we discovered that cholesterol content increases significantly with age. By performing Co-IP, we observed that GABABR and KCC2 partially cluster within the same macromolecular protein complex in both groups, but the magnitude of the interaction fluctuates according to age. Then, we investigated how the GABABR-transporter complex responded to changes in the ratio of cholesterol to phospholipids by simulating their molecular dynamics using a neuronal membrane model. Our results suggest that cholesterol levels impact protein-protein interactions of the GABAergic system, as present in the cerebellum.