Blood–Brain Barrier Disruption Enables Astrocyte-Derived Extracellular Vesicles to Transfer Epigenetic and Inflammatory Signals to the Periphery in Epilepsy

Poster

Celular/Molecular, Neurona y glía - Cellular/Molecular, Neurons and glia

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Astrocytes undergo profound molecular and epigenetic remodeling throughout epileptogenesis; however, whether these CNS-driven changes extend their influence to peripheral compartments remains poorly understood. We investigated whether blood–brain barrier (BBB) breakdown enables astrocyte-derived extracellular vesicles (A-EVs) to enter systemic circulation and deliver epigenetic cargo, including DNMT mRNAs and GFAP, alongside inflammatory mediators such as C3aR to peripheral cells, thereby establishing a CNS-to-periphery signaling axis in epilepsy. Adult male Sprague-Dawley rats underwent the lithium–pilocarpine model and were evaluated at 7, 14, and 45 days post–status epilepticus (DPSE); plasma from patients with drug-resistant temporal lobe epilepsy (TLE) was also included. BBB integrity was assessed by Evans Blue extravasation at 45 DPSE. A-EVs were isolated by EAAT1-based immunoprecipitation and characterized via Western blot (CD63, EAAT1, calnexin, C3aR); DNMT1, DNMT3a, MeCP2, IL-6, and IL-1β were quantified by qPCR. Peripheral epigenetic impact was evaluated by measuring 5mC and 5hmC in splenic tissue sections by immunofluorescence. BBB permeability remained significantly elevated at

45 DPSE. A-EVs exhibited upregulation of DNMT1, DNMT3a, and C3aR in both rat and TLE patient samples; IL-6 and IL-1β were transiently increased, with DNMT3a and C3aR expression correlating with the extent of BBB disruption. Rat Splenic tissue sections revealed elevated 5mC and reduced 5hmC at 45 DPSE, indicating systemic propagation of astrocytic epigenetic remodeling via circulating A-EVs. These findings demonstrate that BBB disruption facilitates functional CNS-periphery communication through A-EVs transporting DNMT mRNAs, GFAP, and C3aR, capable of reshaping peripheral methylation landscapes and underscoring the translational relevance of astrocyte-derived vesicles in epilepsy.

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