Epigenetic–Neuroimmune and HPA Axis Interactions during Early PTZ-Induced Epileptogenesis Associated with Depressive-like Phenotypes

Poster

Neurobiología de enfermedades - Neurobiology of disease

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Depression is one of the most prevalent comorbidities in epilepsy, yet the mechanisms linking early epileptogenesis to affective dysfunction remain poorly understood. We investigated whether PTZ-induced epileptogenesis promotes depressive-like phenotypes and whether these behavioral outcomes associate with neuroimmune activation, epigenetic remodeling, and hypothalamic–pituitary–adrenal (HPA) axis dysregulation. Adult male Sprague-Dawley rats underwent PTZ kindling or vehicle treatment; behavioral profiling used Z-score–integrated indices derived from the Forced Swim Test and Splash Test to identify a passive coping phenotype. Molecular analyses were conducted in the posterior and anterior pituitary, including microglial activation (IBA1+ morphology and immune gene expression), epigenetic regulators (Dnmt1, Dnmt3a, Mecp2, Tet2), global methylation marks (5-mC, 5-hmC), and HPA-related genes (Crhr1, Nr3c1). A distinct subset of PTZ-treated animals (38.5%) exhibited a passive coping phenotype, absent in controls. This subgroup showed enhanced microglial activation and upregulation of inflammatory markers in the posterior pituitary, accompanied by increased Dnmt3a expression and elevated 5-mC levels, indicative of heightened de novo methylation activity. In the anterior pituitary, PTZ exposure induced decreased Crhr1 and increased Nr3c1 expression, alongside upregulation of Dnmt1, Dnmt3a, and proinflammatory genes. 5-hmC levels remained stable across all conditions. These findings indicate that depressive-like

phenotypes emerging during early epileptogenesis reflect the convergence of neuroimmune activation, epigenetic remodeling, and stress-axis dysregulation positioning the pituitary as a key integrative node in brain–periphery communication.

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