GABAergic transmission

2025/06/28 17:13

GABAergic transmission refers to activation of GABA receptors and release of GABA by endogenous or pharmacological modulators. g-Aminobutyric acid (GABA) is the most prevalent inhibitory neurotransmitter in the mammalian central nervous system.

Dysregulation of GABAergic transmission has been reported in lesional acquired epilepsy (gliomas, hippocampal sclerosis).

Blauwblomme et al., investigated its involvement in a developmental disorder, human Focal Cortical Dysplasia, focusing on chloride regulation driving GABAergic signals.

In vitro recordings of 47 human cortical acute slices from 11 pediatric patients operated from a Focal Cortical Dysplasia were performed on Multi Electrode Arrays. GABAergic receptors and chloride regulators were pharmacologically modulated. Immunostaining for chloride co-transporter KCC2 and interneurons were performed on recorded slices to correlate electrophysiology and expression patterns.

Focal Cortical Dysplasia slices retain intrinsic epileptogenicity. 36/47 slices displayed spontaneous interictal discharges, along with a pattern specific to the histological subtypes. Ictal discharges were induced in pro-epileptic conditions in 6/8 slices in the areas generating spontaneous interictal discharges, with a transition to seizure involving the emergence of preictal discharges. Interictal discharges were sustained by GABAergic signaling as a GABAA receptors blocker stopped them in 2/3 slices. Blockade of NKCC1 Cl- co-transporters further controlled interictal discharges in 9/12 cases, revealing a Cl- dysregulation affecting actions of GABA. Immunohistochemistry highlighted decreased expression and changes in KCC2 sub-cellular localization and a decrease in the number of GAD67-positive interneurons in regions generating interictal discharges.

Altered chloride cotransporters expression and changes in interneuron density in FCD may lead to paradoxical depolarization of pyramidal cells. Spontaneous interictal discharges are consequently mediated by GABAergic signals and targeting chloride regulation in neurons may be considered for the development of new antiepileptic drugs ¹⁾.

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Blauwblomme T, Dossi E, Pellegrino C, Goubert E, Gal Iglesias B, Sainte-Rose C, Rouach N, Nabbout R, Huberfeld G. GABAergic transmission underlies interictal epileptogenicity in pediatric FCD. Ann Neurol. 2018 Dec 31. doi: 10.1002/ana.25403. [Epub ahead of print] PubMed PMID: 30597612.

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Last update: 2024/06/07 02:50

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