



Gilles Huberfeld,
Epilepsy Unit, CHU Pitié-
Salpêtrière & INSERM
U975, Brain & Spine
Institute, Paris.



Albert J. Becker,
Translational Epilepsy
Research Section,
University of Bonn Medical
Center.

Mesial temporal lobe epilepsy (mTLE) is characterized by a complex cellular and functional pathology pattern. The relationship of individual pathogenic elements remains frequently elusive and their functional consequence is often unclear. Hippocampal sclerosis with segmental neurodegeneration and concomitant astrogliosis as pathologic hallmarks is the most frequent damage pattern. Infiltrates of adaptive and innate inflammatory cells including activated microglia represent striking observations in affected tissue and have only recently gained attention with respect to potential epileptogenic relevance.^{1,2} Aberrant microglial-to-neuronal signaling contributes to impaired hippocampal excitation/inhibition balance, and therefore represents an intriguing potential pathophysiologic mechanism. Hippo-

campal biopsy specimens from patients with pharmacoresistant mTLE undergoing epilepsy surgery for seizure relief allow unique insights into these mechanisms. However, several obstacles, including sufficient tissue quality for functional analyses and the limited availability of adequate controls, challenge the use of human hippocampal biopsy tissue for research. Epilepsy is however a unique brain disease that allows functional testing of postoperative tissues together with histologic exploration.

In their awarded publication, Roseti et al.³ report on excellent complementary electrophysiologic, biochemical, and histopathologic analyses to unravel the pathogenic role of the chemokine CX3CL1 and its receptor CX3CR1 in modulating γ -aminobutyric acid (GABA)ergic function in human mTLE tissue.

The chemokine fractalkine/CX3CL1 and its G protein-coupled receptor CX3CR1 have been suggested as critical for neuronal excitability modulation. This includes modifying (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-mediated currents, and modulation of long-term synaptic plasticity and (GABA)ergic currents. CX3CR1 is present in innate and adaptive immune cells including microglia and T lymphocytes, and it was suggested to play a role in status epilepticus-induced neuronal damage and is abundant in mTLE tissue. GABA receptor A (GABA_AR) functional impairment is a prominent feature of mTLE.³ Loss of subtypes of interneurons, redistribution of their projections on pyramidal cells, rearrangements of GABA_A receptors, modification of neuronal chloride homeostasis leading to depolarizing effects of GABA, and modifications of the functionality of GABA_A receptors along sustained activation have been shown previously. In their report, Roseti et al. shed light on new mechanisms linking pathologic inflammation-related findings and GABAergic signaling.⁴

The present study was based on the finding that repetitive activation of GABA_AR produces a use-dependent decrease (rundown) of the GABA-evoked currents (I_{GABA}), which is markedly pronounced in neuronal tissue of patients with pharmacoresistant mTLE and epileptic rats. Before the publication by Roseti et al., virtually no information was available on the modulation of GABAergic neurotransmission by CX3CL1 in concert with the expression of its receptor in mTLE, and on links with inflammation. This pathogenic aspect of mTLE is highly intriguing with respect to pathophysiologic mechanisms, has far-reaching therapeutic perspectives, and is difficult to address in human mTLE biopsy tissue.

Roseti et al.³ took advantage of a highly elegant methodologic approach using a “microtransplantation” of membrane method, that is, *Xenopus* oocytes are injected with membranes from surgically resected human brain tissue.

Microtransplantation relies on the fact that the oocyte's plasma membranes efficiently incorporate the foreign membrane portions and thereby acquire functional neurotransmitter receptors and channels retaining their native properties. With this fascinating approach, the authors analyzed the effects of CX3CL1 on human GABA_ARs transplanted from tissues of patients with mTLE and both autopsies and nonepileptic surgical controls in *Xenopus* oocytes. Subsequently, the authors used (double)-immunohistochemistry on respective brain tissue samples to analyze CX3CR1 expression in activated microglia.

As major findings, the authors demonstrate that in native pyramidal neurons from cortical slices of patients with mTLE, CX3CL1 reduced I_{GABA} rundown and affected the recovery of I_{GABA} amplitude from rundown. These same effects were confirmed in oocytes injected with cortical and hippocampal mTLE membranes, whereas CX3CL1 did not influence I_{GABA} in oocytes injected with nonepileptic control tissues. Supporting a specific effect of CX3CL1 on tissues from patients with mTLE, CX3CR1 immunoreactivity was more highly expressed in mTLE sclerotic hippocampi than in control tissues. Expression was prominent in activated microglial cells.

The present data from Roseti et al.³ show that in mTLE tissue, reduced GABAergic function can be modulated by CX3CL1. The increased CX3CR1 expression in microglia and the modulation of GABAergic currents by CX3CL1 in human epileptic brain may open new therapeutic perspectives for drug-resistant epilepsies. Their report contains evidence for both the genesis and the propagation of seizures to be influenced by inflammatory processes. The combination of sophisticated electrophysiologic experiments, including membrane microtransplantation as well as histopathologic analyses represents a particular strength of this report. Microtransplantation was shown as a particularly useful approach, although it remains somewhat unresolved whether CX3CL1 could affect GABA_ARs in human slices and in oocytes in identical ways.²

One of the questions that remains from the present data is the pathogenic basis of the effects of CX3CL1 observed in

mTLE tissue. The authors discuss altered phosphorylation of GABA_A receptors as well as modified GABA_A subunit composition as potential factors. Another related question refers to the apparent paradox that the run down phenomenon, increased in human mTLE tissue, may be specifically antagonized by CX3CL1 signaling in such tissues. The relevance of these data in the depolarizing versus hyperpolarizing effects of GABA in human epileptic tissues appears interesting. The authors hypothesize that CX3CL1 can induce phosphorylation of one or more GABA_A subunits differentially expressed in TLE, leading to a "stabilization" of GABA_ARs. Future studies including functional, molecular biologic, and biochemical experiments should be useful in resolving these issues. Such a mechanism could be involved in other epilepsies as well as in other diseases involving inflammation and GABAergic signaling.

The present work by Roseti et al. lays several tracks for exciting subsequent research and provides important novel vistas for epilepsy research and, therefore, clearly deserves the prestigious Morris-Coole/*Epilepsia* Prize.

DISCLOSURE

Neither of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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