GABA$_A$ Receptors and GABAergic Interneurons in Chronic Temporal Lobe Epilepsy

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Disclosure

I have nothing to disclose.
The GABA system is vulnerable, reorganized and compromised in temporal lobe epilepsy.
• Loss of GABA neurons?
• Reorganization of GABA neurons?
• Loss of GABA$_A$ receptor subunits?
• Reorganization of GABA$_A$ receptors?
1. Are GABA neurons lost in temporal lobe epilepsy?
Hilar neurons regulate dentate gyrus output.

Hilar neuron loss is a major feature of classical hippocampal sclerosis.

Hilar neuron loss is one of the most consistent pathological alterations in TLE.

Hilar neurons include numerous GABA neurons.

Hilar GABA neurons are vulnerable to damage while other GABA neurons in the dentate are relatively resistant.

Hilar GABA neurons have extensive axonal projections.

GABAergic terminals are abundant in TLE.

- Increased GAD in remaining axon terminals?
- Sprouting of remaining GABAergic axons and terminals?

Control

Pilocarpine – 2 months

Houser lab, unpublished.
2. Do GABAergic axons undergo reorganization in temporal lobe epilepsy?
Hilar somatostatin (GABA) neurons are vulnerable to damage.

Control Pilocarpine-treated

Houser lab, unpublished.
Hilar somatostatin neurons innervate the outer molecular layer.

Houser lab, unpublished.
Hilar somatostatin (GABA) neurons are depleted after status epilepticus.

Houser lab, unpublished.
Time course of somatostatin changes

Houser lab, unpublished.
Axons of remaining GABA neurons exhibit reorganization or sprouting.

- Houser and Esclapez, Epilepsy Res. 26:207-218, 1996. (Review)
- Bausch, Epilepsy Behav. 7:390-400, 2005. (Review)
3. Is there a decrease of GABA receptor subunits in temporal lobe epilepsy?
• Differences among subunits - ↑ & ↓
• Differences among regions
• Differences among cell types
GABA<sub>A</sub> RECEPTOR SUBUNITs

Slide from R.W. Olsen.

70% Identity

30% Identity
PHASIC INHIBITION

- Relatively low GABA affinity
- Mainly synaptic locations
- Potentiated by benzos

TONIC INHIBITION

- High GABA affinity
- Nonsynaptic locations
- Modulated by neurosteroids

δ subunit is most highly expressed in the dentate gyrus.

$\delta$ subunit labeling is decreased in granule cells of pilocarpine-treated mice.

δ subunit decreases progressively.

What are the functional effects of δ subunit loss in dentate granule cells?

- Decrease in tonic inhibition?
- Decrease in effects of modulators such as neurosteroids?
Tonic inhibition is maintained in dentate granule cells during the chronic period.

Modulation of tonic inhibition is impaired.

- Reduced modulation of tonic inhibition by neurosteroids is consistent with loss of the δ subunit.

Expression of the \( \alpha_5 \) subunit is decreased in CA1 in chronic pilocarpine-treated rats.

• Scimemi et al., J. Neurosci. 25:10016-10024, 2005. (α5 ↓ CA1)


Consistent with microarray studies –

Maintained by:

- Low levels of the $\delta$ subunit?
- Receptors composed of other subunits that are associated with tonic inhibition, such as $\alpha_5$ or $\alpha\beta$?
- Different receptors – different subunit partnership?
4. Is there reorganization of GABA \(_A\) receptor subunits in temporal lobe epilepsy?
$\alpha_4$ and $\gamma_2$ subunits are increased in epileptic animals in the chronic period.

Timecourse of Changes in Subunits

Subunit Partnerships

\[ \delta \rightarrow \gamma_2 \rightarrow \alpha_4 \]
δ subunit is most concentrated at perisynaptic sites in dentate granule cells.

\( \gamma^2 \) is normally highly concentrated at synaptic contacts.

In pilocarpine-treated mice, the $\gamma_2$ subunit is increased at perisynaptic sites.

In pilocarpine-treated mice, the $\gamma_2$ subunit is increased at perisynaptic sites.

Perisynaptic localization of the γ2 subunit increases at the expense of synaptic localization on granule cell dendrites.

• Following a decrease in the $\delta$ subunit, $\alpha 4$ forms an alternate partnership with the $\gamma 2$ subunit at perisynaptic locations.

• $\gamma 2$-containing receptors could contribute to tonic inhibition, but with altered pharmacology.

• Phasic inhibition at granule cell dendrites is decreased.
interneurons
δ subunit labeling is increased in interneurons of the dentate gyrus in pilocarpine-treated mice.

δ subunit expression is increased in \( \alpha_1 \)-labeled interneurons in epileptic mice.

Do GABA neurons exhibit higher levels of tonic inhibition in pilocarpine-treated mice?

20 pA
20 ms

W. Wei and I. Mody, unpublished.
δ subunit changes extend beyond the dentate gyrus to other temporal lobe regions.

Houser lab, unpublished.
Changes in δ subunit expression in the epileptic animals can increase the excitability of the dentate gyrus and other regions by altering tonic inhibition. This could occur through:

- Altered modulation and pharmacology of tonic inhibition in principal cells.
- Increased tonic inhibition of GABAergic interneurons.
For both GABA neurons and GABA$_A$ receptor subunits -

- **Loss occurs** — but is selective.
- **Reorganization occurs** — but may result in altered circuitry and function.
- **GABAergic function is compromised** — potentially leading to failure at times of increased demand, as at the onset of seizure activity.
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