Non-neuronal modulation of epileptic activities: glial cells and inflammatory processes

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Challenge for epilepsy treatment: searching new targets for drug development

- Treatment of resistant seizures
- Disease-modifying drugs

Pitkanen and Lukasiuk, Epilepsy & Behavior, 2008
The astrocytic activation spectrum

Loscher & Schmidt, Nat Rev Neurol, 2012

Halassa et al, 2007

Gliotransmission in health and disease


From neurons to glia

Microglia

Astrocyte

Homeostatic arm

Pathologic arm

Ca^{2+} oscillations

NMDAR function

TRENDS in Molecular Medicine

TRENDS in Neurosciences
Astrocytes-Neurons interactions & epileptic activities

Astrocytes have smart communicative functions
“Tripartite synapse” (Allen Nature 2009)

Information transmission: Ca^{++} waves
(Newman Science 1997 - Haydon 2001)
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<th>Mechanism</th>
<th>Contributors</th>
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Adapted from A. Pitkanen, Epilepsia

Inciting event

Disease or Syndrome Modification

Antiepileptogenesis

Reversal of pathology

Prevention

Seizure modification

Cure

Seizure frequency

Seizure duration

Seizure type

Seizure progression

Finding master regulators?
Combine treatments?
Prevention? Resolution?

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Open questions for optimizing pharmacological interventions:

- expression of inflammation-linked targets
- changes in glia activation /phenotype/priming/physiology
- experimental models: differences vs commonalities
- target validation in human specimens

Target expression and intervention points for antiepileptogenesis

Pitkanen et al, Epilepsia, 2013
Conclusions

Glial cells undergo phenotypic and functional alterations in epilepsy leading to changes in neuronal function (gliotransmission, tripartite synapse). Glial cells play a role in seizure mechanisms in epilepsy models (release of neuromodulatory/inflammatory molecules, modifications of brain vessels properties). They offer the potential for developing novel strategies to treat epilepsy.

Next steps

1. Their role in seizure initiation vs. spread vs. termination
2. Their functional changes during ictogenesis and epileptogenesis by differentiating homeostatic from deleterious effects
3. Their role in pharmacoresistance and in comorbidities
4. Strategic therapeutic interventions to modify their function to boost beneficial clinical outcomes

Searching biomarkers of:

- glia activation
- brain inflammation
- BBB opening

(imaging, soluble mediators in CSF/blood)

- Butler et al, J Neuroimaging, 2010
- Duffy et al, Neuroimage, 2012
- Ravizza et al, Epilepsia, 2012
Anti-ictogenic & anticonvulsive effects

**IL-1/TLR signaling**

1. Seizures induced by kainic acid (lesional) or bicuculline and FS (non lesional)  
   *(Vezzani et al, 1999; 2000; Dube’ et al, 2005; 2011; Ravizza et al, 2006)*

2. Status epilepticus in rats is reduced by anakinra *(De Simoni et al, 2000; Marchi et al, 2009)*

3. Electrical kindling: delayed + no seizure generalization  
   *(Ravizza et al, 2008; Auvin et al, 2010; 2011)*

4. Chronic seizures in mice (mTLE model) *(Maroso et al, 2009; 2010)*

5. SWD in GAERS & WAG/Rij rats (absence seizures) *(Akin et al, 2011; Kovács et al, 2011)*

50-70% decrease in seizure recurrence, delayed seizure onset, reduced generalization

*Resolution of inflammation in areas involved in seizure activity*

Harness these targets for pharmacological intervention

**TNF-α, IL-6, COX-2 & complement system** *(reviewed in Kukarni & Dhir, 2009; Vezzani et al, 2011; Aronica et al, 2012)*
Perivascular glia, inflammatory mediators & brain microvasculature: New targets for intervention?

- Neovascularization in CNS
- Increase in BBB permeability
- Induce adhesion molecules
- Induce MTP involved in pharmacoresistance (e.g. P-gp)

Abbott et al, 2006
Unmet needs

Searching biomarkers of:
  - glia activation
  - brain inflammation
  - BBB opening

Box 1. Potential biomarkers of brain inflammation in epilepsy.

- Brain imaging (cell types or macromolecules)
  - PET (microglia/macrophages, endothelial cell adhesion molecules)
  - Magnetic resonance spectroscopy (astrocytes)
  - Molecular MRI (endothelial dysfunction; VCAM)
  - Contrast-enhanced MRI (endothelial dysfunction; increased permeability)

- Soluble inflammatory mediators in cerebrospinal fluid/blood
  - Citokines/chemokines/danger signals
  - Cell adhesion molecules
  - Auto-antibodies

- Leukocytes
  - Cell sorting profile
  - In vitro responsiveness to proinflammatory challenges
  - Pro- or anti-inflammatory gene polymorphisms

See main text for details.

*Danger signals are endogenous molecules released from cells exposed to stressful events. For example, high-mobility group box 1 is a danger signal released from glia and neurons in epileptic tissue [34]; increased high mobility group box 1 blood levels have been measured in neurological disorders [72].

+A modest association between the IL-1β gene and epileptic disorders has been reported [73,74].
Perivascular glia, inflammatory mediators & brain microvasculature: New targets for intervention?

- Neovascularization in CNS
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Loscher and Potschka, Nature Rev Neurosci, 2005
Harnessing microglia to control CNS inflammation?

Adapted from Shechter & Schwartz, J Pathol, 2013
Anti-inflammatory drugs as disease-modifying drugs

mTLE
MCD
RE

Symptomatic
Genetic (scarse info)