Therapeutic targets and biomarkers of epilepsy comorbidities: lessons from animal models

December 10, 2013

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Disclosure

NIH/NINDS: Research grant R01 NS065783.

UCLA Children’s Discovery and Innovation Institute/Today's and Tomorrow's Children Fund: Research grant.

American Epilepsy Society | Annual Meeting
Learning Objectives

- Identify therapeutic targets for epilepsy-associated depression and attention deficit / hyperactivity disorder (ADHD).
- Identify biomarkers and therapeutic targets for epilepsy-associated autism stemming from maternal infection.

<table>
<thead>
<tr>
<th>Epilepsy comorbidity</th>
<th>Patients with epilepsy</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depressive Disorder</td>
<td>30-50%</td>
<td>5-17%</td>
</tr>
<tr>
<td>ADHD</td>
<td>25%</td>
<td>3-5%</td>
</tr>
<tr>
<td>Autism</td>
<td>30%</td>
<td>0.1-1%</td>
</tr>
</tbody>
</table>
## Disclosure (pt. II)

Role of monoamine transmitters in mechanisms of epilepsy, depression and ADHD

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Norepinephrine</th>
<th>Serotonin</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>Yes!</td>
<td>ДА!</td>
<td>YOU BET!</td>
</tr>
<tr>
<td>Depression</td>
<td>Aber ja!</td>
<td>Absolutely!</td>
<td>Totally!</td>
</tr>
<tr>
<td>ADHD</td>
<td>Sure!</td>
<td>M-m-m.. Yep!</td>
<td>!ץ!</td>
</tr>
</tbody>
</table>
Inhibitory influence of frontal cortex on locus coeruleus neurons

Susan J. Sara and Anne Hervé-Minvielle

POTENT EXCITATORY INFLUENCE OF PREFRONTAL CORTEX ACTIVITY ON NORADRENERGIC LOCUS COERULEUS NEURONS

E. Jodo,† C. Chiang‡ and G. Aston-Jones*
Depression and epilepsy: Epidemiologic and neurobiologic perspectives that may explain their high comorbid occurrence

Andres M. Kanner, Steven C. Schachter, John J. Barry, Dale C. Hersdorffer, Marco Mula, Michael Trimble, Bruce Hermann, Alan E. Ettinger, David Dunn, Rochelle Caplan, Philippe Ryvlin, Frank Gilliam

Can neurobiological pathogenic mechanisms of depression facilitate the development of seizure disorders?

Andres M. Kanner
Depressive behavior in rats with epilepsy

Mazarati et al., Brain 2008;131:2071-83
Pineda et al., Epilepsy & Behavior, 2014, In Press
Mood regulation by ascending monoaminergic pathways

5-HT: Raphe nucleus-prefrontal cortex
NE: Locus coeruleus-prefrontal cortex

**Diminished serotonergic tone in depression**

- 5-HT is suppressed in all “depressed”
- NE is suppressed in some “depressed”
- NE is suppressed in all “struggling”
- 5-HT is normal in all “struggling”

Mazarati et al., Brain 2008;131:2071-83
Pineda et al., Epilepsy & Behavior, 2014, *In Press*

Review Article

Attention Deficit Disorder and Epilepsy

Romaine Schubert, MD

Topical Review Article

Attention-Deficit Disorders and Epilepsy in Childhood: Incidence, Causative Relations and Treatment Possibilities

Rami Kaufmann, MD, Hadassa Goldberg-Stern, MD, and Avinoam Shuper, MD
Lateralized Reaction Time Task
Measures impulsivity and attention
(food reward after temporally and spatially correct response to the light signal)

**Figure:**
- **Impulsivity**:
  - Bars for Naive and All conditions with asterisk indicating significance.
- **Attention deficit**:
  - Scatter plot showing percent correct choices vs. percent impulsive responses.
  - Labels for Naive, Post-SE "non-impulsive," and Epilepsy "impulsive" conditions.

**References**:
- Lustig et al., Neurosci Biobehav Rev 2012; In Press
- Pineda et al., Epilepsy & Behavior, 2014, In Press
NE is suppressed in all “impulsive”
These animals are “struggling” in the forced swimming test

5-HT is suppressed in all “non-impulsive”
These animals are “immobile” in the forced swimming test

Pineda et al., Epilepsy & Behavior, 2014, In Press
Is triple-morbidity possible?

12-50% depression frequently masks ADHD

Some rats show both NE and 5-HT deficits

Some hyper-impulsive rats are also depressed

Pineda et al., Epilepsy & Behavior, 2014, In Press
Venlafaxine in the Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder


Robert L. Findling, M.D.,1,2 Laurence L. Greenhill, M.D.,3 Nora K. McNamara, M.D.,1 Christine A. Demeter, M.A.,1 Lisa A. Kotler, M.D.,3 Mary Ann O’Riordan, M.S.,2 Carolyn Myers, Ph.D.,2 Michael D. Reed, Pharm. D.2
Review

Epilepsy and autism: Is there a special relationship?

Anne T. Berg a,⁎, Sigita Plioplys b

Epilepsy in autism: features and correlates

Patrick F. Bolton, Iris Carcani-Rathwell, Jane Hutton, Sue Goode, Patricia Howlin and Michael Rutter
Infection during pregnancy as a risk factor for autism in the offspring

“...maternal influenza was associated with a twofold increased risk of autism; prolonged episodes of fever caused a threefold increased risk of autism.”

“...maternal viral infection in the 1st trimester and bacterial infection in the 2nd trimester were associated with ASDs in the offspring, with hazard ratios 2.98 and 1.42.”
Sociability test

Pregnant mouse

Viral (Poly I:C) or Gram-negative (LPS) infection

Offspring

Autism

Epilepsy

Malkova et al., Brain Behavior and Immunity, 2012; 26: 607-16
Yin et al., Brain Res, 2013; 1519:78-86
Kirschman et al., Metab Brain Dis, 2011; 26:91-93
Increased plasma levels in pregnancy/infection
IL-6 - risk for autism
IL-6+IL-1β - risk for autism+epilepsy
in the offspring

Pregnant mice
Poly IC + antibody

Offspring

Autism
Epilepsy

Saline
Poly I:C

pg/ml of plasma

0
10
20
30
40
50
60
70

IL-6
IL-1β
TNFα
IL-3
IL-9
IL-8
IL-10
IL-12

Maternal Immune Activation

Infection

Siltuximab*
Canakinumab†

* - Anti-IL6 monoclonal antibody
(Clinical trials for NHL, Multiple Myeloma, Castleman's Disease)

† - Anti-IL-1β monoclonal antibody
(Clinical trials for COPD, CAD, gout)

Smith et al., J Neurosci 2007; 27: 10695-702
Impact on Clinical Care and Practice

• Epilepsy-associated depression is linked to 5-HT deficiency; SSRI are prompted.
• Epilepsy-associated ADHD is linked to NE deficiency; NRI should be considered.
• Triple-morbidity between epilepsy, depression and ADHD is possible. Diagnosis of ADHD may be complicated. SNRI may be particularly effective.

• Do not underestimate environmental causes of autism and comorbid epilepsy.
• Detrimental effects of maternal infection on the offspring may be predicted using a simple blood test during pregnancy (IL-6- autism; IL-6+IL-1β- epilepsy).
• Active prevention of autism and epilepsy caused by maternal infection may be achieved by treating viral infections during pregnancy with IL-6 (and IL-1β) MAB.