Respiration, Seizures and SUDEP - Possible Prevention Approaches

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Learning Objectives

- To understand which brain neurochemicals may contribute to SUDEP and their mechanisms
- To consider possible drugs to prevent SUDEP based on these neurochemicals
- To consider possible drugs to avoid in patients who might be susceptible to SUDEP based on these neurochemicals
DBA Mouse Models of SUDEP

(Death is due to Seizure-Induced Depressed Respiration)

1. DBA mice exhibit sound-induced audiogenic seizures that are fatal (SUDEP model) without resuscitation
2. Seizure-induced sudden death in DBAs results from respiratory arrest leading to cardiac arrest
3. Serotonin (5-Hydroxytryptamine, 5-HT) is a brain chemical that is excitatory to normal respiration & is released during seizures
4. Increasing 5-HT in brain prevents SUDEP in DBA mice
5. Adenosine is a brain chemical that inhibits normal respiration & is released during seizures

---------------------PRELIMINARY DATA---------------------

6. Increasing adenosine increases sudden death in DBA mice
7. Adenosine antagonist blocks sudden death in DBA mice
DBA Mouse Video

Acoustic Stimulus
122 dB SPL
Seizure behaviors
1. Wild Running
2. Generalized Tonic-Clonic convulsion
3. Tonic Extension

Resulting in Respiratory Arrest

Sudden Death
Respiration, in a DBA/1 mouse quantified using the whole-body plethysmography (EMKA Technologies, Paris, France), before (blue area left of the arrow), during, & after (red area right of the arrow) an auditory stimulus (solid arrow) that induces seizures, including respiratory depression and death (open arrow). The starting point of the tonic seizure is indicated by a black dot. (Faingold et al., Prelim data)
A: typical ECG in DBA/1 mouse- non-seizure (anesthetized, ketamine/xylazine )
B-D: ECG changes associated with seizure-induced respiratory arrest (RA).

B: reduced ECG rate immediately after RA
C: ECG rate and pattern ~17 sec following RA onset (same mouse)
D: the ECG is nearly absent in the same mouse 295 sec post RA onset
The ECG was completely absent subsequent to this trace.}

(Faingold et al., Epilepsy & Behav. 2010)
EEG Changes in a DBA/1 Mouse Induced by Seizure (Prelim. Data)

Pre-Seizure

Seizure

Post-Seizure

EEG “shut down”
Diagram of Audiogenic Seizure & Respiratory Network

Brainstem Seizure Network

CSF + blood

Neuroactive substances

+ serotonin

RVLM

Post-ictal Depression

Brainstem Respiratory Network

Cardiac Arrest

Respiratory Arrest

DEATH

physical obstruction

RVLM = rostral ventral lateral medulla

Acoustic Stimulus
SSRIs - Fluoxetine Blocks Respiratory Arrest (doses that do not block seizures) in DBA/1 mice

Faingold et al., Epilepsy Behav. 22 (2):186-190, 2011.
5-HT antagonist (cyproheptadine) induces respiratory arrest following seizures in DBA/2 Mice that do NOT show RA (10%).

(Wilcoxon signed ranks test; ** P<0.01; # P<0.005)
Chronic (5-day) Fluoxetine (SSRI) Blocks Respiratory Arrest in DBA/1 mice

Faingold et al., *Epilepsy Behav.* 22 (2):186-190, 2011.
Fluoxetine (Fluox) Acts in the brain to block Respiratory Arrest (RA) in DBA/1 mice  (Preliminary Data)

1. Fluox injected directly in the brain blocks RA

<table>
<thead>
<tr>
<th></th>
<th>% Seizure Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic Seizure</td>
<td>Respiratory Arrest</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
</tr>
<tr>
<td>Fluox</td>
<td>50</td>
</tr>
<tr>
<td>Post-Drug</td>
<td>0</td>
</tr>
</tbody>
</table>

Focal bilateral microinjection of fluoxetine, [(3.5 nmol/side) in 0.1 μl (over 30 sec)] (but not saline) into respiratory center (rostral ventral lateral medulla, RVLM) blocked RA but did not block tonic seizures.

2. Systemic injection of 5-HT\(_7\) agonist (AS-19), which acts on the spinal cord does NOT block RA and is toxic (in high doses)
SSRI (Paroxetine) Effects on Sleep Apnea - Humans

During Total Night Sleep

- Control
- Paroxetine

During NREM# Sleep Only

- Control
- Paroxetine

* P = 0.01
** P = 0.003 (ANOVA)

@ 20 mg/day- 6 weeks, Randomized double-blind placebo controlled

# Apnea during REM sleep was NOT affected
Adenosine in Respiration & Seizures

- Adenosine receptors are localized in brainstem respiratory centers and regulate respiration (decrease).
- Adenosine is released during seizures and may contribute to post-ictal depression (PID) of respiration. Adenosine agonists (A1) prolong PID in epilepsy models.
- Abnormal levels of Adenosine A1 receptors occur in human epilepsy.
- Adenosine extracellular levels rise in epileptic patients after seizures.
- Adenosine antagonists shorten the duration of PID.
- Adenosine A1 and A2A agonists are effective anticonvulsants.
- Adenosine receptor blockers may be effective in preventing respiratory arrest during seizures.
- Adenosine significantly enhances the incidence of respiratory arrest following seizures in DBA/2 mice not exhibiting this response (preliminary studies).
- Adenosine antagonist reduces respiratory arrest following seizures in DBA/2 mice (preliminary studies).
Most Human SUDEP Occurs After Seizure (Post-Ictal State)

Post-Ictal State Aspects
- Depressed Consciousness
- Depressed Respiration
- Depressed Heart Rate/ Dysrrhythmia
- Cerebral “Shutdown”

Neuroactive Substances Involved in the Post-Ictal State
- Serotonin (5-HT)
- Adenosine
- Opioid peptides
- Nitric oxide
- Endocannabinoids

**Adenosine Model of SUDEP**

- **Adenosine breakdown**
- **Convulsant**
- **Death**

**Graph A:**
- 5-ITU, i.p. 15 min
- Seizure suppression by ADO surge
- SUDEP

**Graph B:**
- Seizure score
- SUDEP

**Graph C:**
- Survival time (min)
- SUDEP + SAL
- SUDEP + CAF

Adenosine increases respiratory arrest following seizures [Non-RA DBA/2 Mice]

* P<0.05 (Wilcoxon signed ranks test)

N = 14

(2 mg/kg)

* P<0.05 (Wilcoxon signed ranks test)
Adenosine Blood Levels DBA/1 Mice (prelim data)
5-HT & Adenosine - Opposite Effects on SUDEP

CSF + blood

Neuroactive substances
Adenosine & others
Post-ictal Depression

Seizure Network

Acoustic Stimulus

Respiratory Network

RVLM

5-HT & fluoxetine

Cardiac Arrest

Respiratory Arrest

DEATH

physical obstruction

RVLM= rostral ventral lateral medulla
SSRI Effect & Safety in Epilepsy Patients


Don't be afraid to treat depression in patients with epilepsy!

• Thomé-Souza MS, Kuczynski E, Valente KD. Epilepsy Behav. 2007 May;10(3):417-25. 2007.

Sertraline and fluoxetine: safe treatments for children and adolescents with epilepsy and depression.


Serotonin reuptake inhibitors are associated with reduced severity of ictal hypoxemia in medically refractory partial epilepsy.
Summary and Conclusions

1. Human SUDEP is often associated with seizure and respiratory depression.

2. Serotonin (5-HT) is released during seizures and normally enhances respiration especially when CO₂ is elevated.

3. DBA mice are models of SUDEP that die from respiratory arrest, which can be prevented by prompt resuscitation.

4. SSRIs enhance 5-HT action and prevent seizure-induced death in DBA mice and a 5-HT antagonist increases sudden death.

5. Clinical evidence suggests that SSRIs will reduce seizure-induced respiratory depression in certain patients.

6. Adenosine is released during seizures and reduces respiration.

7. Adenosine increase sudden death in DBA mice, and an adenosine antagonist reduces it.

8. The balance between release of neurochemicals that excite respiration (e.g., 5-HT) and agents that inhibit respiration (e.g., adenosine) may determine the degree of respiratory depression occurring during a patient’s seizure and susceptibility to SUDEP.
Future Research

ANIMALS
• Further work on selective 5-HT drugs in DBA Mice
• Work on selective adenosine drugs in DBA Mice
• Evaluate other potential SUDEP affecting neurochemicals in DBA mice (e.g., endorphins)

PATIENTS
• Prospectively evaluate SSRIs effect in epilepsy patients
• Evaluate large public health data base on SSRIs and SUDEP (Sweden?)
• Evaluate seizure-induced release of neurochemicals in blood to personalize prevention treatments
Impact on Clinical Care and Practice

• Use of SSRIs should be considered in the patient population most likely to be subject to SUDEP (NOT FDA approved)

• Care should be exercised in giving serotonin blocking drugs to epilepsy patients

• Patient blood levels of neurochemicals should be drawn after each seizure in the EMU for neurochemical analysis
Tilting at Windmills of the Mind

(Arremetiendo Contra los Molinos de Mente)

Thank You

(Don Quixote by Picasso)