ENERGY METABOLISM AND SEIZURES

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Faculty Disclosure

• None.
Educational Need/Practice Gap

Gap = Difference between current practice and optimal practice relevant to the educational need.

At least 1/3 of patients have seizures that do not respond to conventional medications, devices, or surgery.

Need = The issue/problem that underlies the practice gap

Currently, epilepsy is treated mainly with therapies that target ion channels or synaptic transmission.
Objectives

Upon completion of this educational activity, you will be able to:

- Explain how seizures are regulated by metabolism
- Name several metabolic treatments for epilepsy
- Describe how glycolytic inhibition affects neuronal excitability
Expected Outcome

• What is the desired change/result in practice resulting from this educational intervention?

Consider metabolic approaches as alternative therapeutic strategies for drug-resistant epilepsy.
OUTLINE

• I. Excitation/inhibition imbalance in epilepsy: paradigm shift

• II. Overview of metabolism and neuronal excitability

• III. Inhibition of glycolysis as potential mechanism for seizure suppression:
  2-Deoxyglucose (2DG)
Seizures and Epilepsy

IMBALANCE OF 
EXCITATION vs INHIBITION

SEIZURE
Standard paradigm: ion channels and synapses

- ↑ Na channel activity
- ↑ Excitatory synapse function
  - ↑ glutamate
  - ↑ network connectivity

and/or

- ↓K channel activity
- ↓ Inhibitory synapse function
  - ↓ GABA

NORMAL DISCHARGES

EPILEPTIC DISCHARGES
Restoring the E/I balance

E I

Carbamazepine
Phenytoin
Topiramate
Perampanel
Felbamate

Retigabine
Benzodiazepines
Phenobarbital
Vigabatrin
Excitation/inhibition balance

• Emerging roles of metabolism and its regulation in excitability, seizure generation, and epileptogenesis
Metabolic control of excitability and epilepsy

• Brain has an extremely high metabolic rate

• Energy needed for resting potential maintenance, action potential generation, synaptic potentials, pumps (Na-K ATPase)

• Derives majority of energy/ATP from aerobic oxidation of glucose

• Seizures very energy-consuming; energy failure promotes epileptogenesis
Dependence of neural activity on energy from glucose

- **Under normal conditions:** Brain uses glucose as obligate energy source.

- **Under conditions of low glucose availability:** Brain can use ketones from fat breakdown as its energy source.
The Ketogenic Diet

- High fat, low carbohydrate, adequate protein

KD:
4:1 ratio of fat to carb + protein by weight

90% calories from fat

- Causes metabolic shift/adaptation from carbs to fat as primary energy source
The Ketogenic Diet

• Effective in wide variety of intractable epilepsy
• Numerous uncontrolled studies, case series:
  – ~ half patients get >50% seizure reduction
• Double blind, controlled study:

Lancet Neurol 7:500, 2008
The Ketogenic Diet

How Does the Ketogenic Diet Work?

Search for mechanism:
- Role of ketones
- Role of carbohydrate restriction
The Ketogenic Diet

The Ketogenic Diet

• Search for mechanism:
  – Animal models
    • KD effective in several models:
      kindling, PTZ, KA
    • Ketosis necessary but not sufficient
    • Direct ketone application:
      no effect on membrane ionic currents or E/I synaptic currents

  Thio et al., Neurology 54:325, 2000
**Observation:**
Ingestion of small amounts of carbohydrate reverses seizure control in patients on the ketogenic diet

Huttenlocher, Ped Res 10:536, 1976
**Observation:**
Ingestion of small amounts of carbohydrate reverses seizure control in patients on the ketogenic diet.

**Hypothesis:**
Carbohydrate restriction by inhibition of glycolysis might protect against seizures.
Metabolic Pathways and Sites of Potential Seizure Suppression

Stafstrom et al., Epilepsia 49 S8:97-100, 2008
Glycolytic inhibition as potential mechanism for seizure suppression
Bypassing glycolysis has **acute** anticonvulsant effect (CA3; 7.5 mM K⁺)

Stafstrom et al., Ann Neurol 65:435, 2009
Metabolic Pathways and Sites of Potential Seizure Suppression

Stafstrom et al., Epilepsia 49 S8:97-100, 2008
2-DEOXY-D-GLUCOSE (2DG)

- Glucose analog
- Crosses blood-brain barrier
- Decades of use as a PET tracer $^{18}$F-2DG
- Approved for Phase 2 clinical trials as adjuvant chemotherapy for cancer
- Inhibits glycolysis by blocking phosphoglucone isomerase (PGI)
Metabolism of 2DG and effect on glycolysis:

```
  glucose                      glucose-6-P
  |        2DG        |
  |                  |
  v        GPI      v
fructose-6-P  2DG

  glucose-6-P                   fructose-6-P
  |                                |     pyruvate
  |                                |     fructose-1,6-P
  |                                |
  |                                |     NAD
  |                                |     NADH
  v                                v
TCA cycle
```

glycolysis inhibitor
Acute anticonvulsant effects in vitro
2DG reduces interictal and ictal bursts in CA3 in 7.5 mM $[K^+]_o$. 

Stafstrom et al., Ann Neurol 65:435, 2009
2-DG does not alter intrinsic membrane excitability in CA1 pyramidal cells

A

[Graph showing current (pA) vs. number of APs for Ctrl and 2-DG treatments after 1 min and 10 min]

B

[Graphs showing input resistance and AP threshold for Ctrl and 2-DG treatments after 1 min and 10 min]
2-DG blocks neuronal firing in CA3 and CA1 pyramidal cells

**A**

- CA3
- -66 mV
- 0.5 s
- 20 mV

**B**

- CA1
- -66 mV
- 5 s
- 20 mV
- 7.5 mM [K⁺]₀

aCSF

10 mM 2-DG

2 min

20 mV
2-DG abolishes network bursting in both CA1 and CA3

A

0 Mg$^{2+}$ + 50 μM 4-AP

CA3

CA1

10 mM 2-DG

B

10 mM 2-DG

Amplitude (mV)

Frequency (Hz)

Time (min)
Acute anticonvulsant effects in vivo
2DG has ACUTE *in vivo* anticonvulsant action.

- **6 hz seizures**
- **audiogenic seizures**
- **kainic acid status epilepticus**

**Graphs:**
- NIH ASP
- NIH ASP

**References:**
- Stafstrom et al., Ann Neurol 65:435, 2009
- Gasior et al., Epilepsia 51:1385, 2010
Kindling

- Electrical stimulation of neural pathway leads to permanent epileptic state (epileptogenesis)
- Stimuli are initially subconvulsive
- Increase current until an afterdischarge occurs
- Subsequent daily stimuli result in increasingly longer ADs, culminating in clinical seizures (focal dyscognitive with secondary generalization)

Measure: ** AD threshold
** # ADs to seizure classes
2DG Anticonvulsant effect in vivo: increases kindling afterdischarge (AD) threshold

$p < 0.001$, ANOVA

Garriga-Canut et al., Nat Neurosci 9:1382, 2006
Antiepileptic action *in vivo*:

- reduces rate of kindling progression by ~ 2-fold

- implications for intractability, memory dysfunction, cognitive deficits
Model for prevention of kindling progression by 2DG

Garriga-Canut et al., Nat Neurosci. 2006;9:1382-7

2DG Inhibits glycolysis
Repression of BDNF/trkB gene expression via CtBP/REST
↑ seizure threshold
NRSF required for 2DG effect but not for ketogenic diet effect

Hu et al., Epilepsia 52:1609, 2011
“Disease-modifying” actions of 2DG when administered AFTER seizures
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Minimal effective dose (MED)

* $p = 0.01$ vs controls

37.5 mg/kg i.p. (MED)

$p = 0.002$, ANOVA

* $p < 0.001$
2DG safety profile

• General health of animals – good, including weight gain
• Cardiotoxicity reported
• Behavioral/cognitive testing
  – Exploratory activity (open field)
  – Fear conditioning
  – Spatial learning & memory (water maze)
2DG does not alter water maze learning

Ockuly et al., Epilepsy Res 101:246, 2012
SUMMARY 1

- **2DG has acute anticonvulsant effects *in vitro*** by several methods of seizure induction:
  - high K+
  - bicuculline
  - DHPG
  - 4-AP/zero Mg

- **2DG has acute anticonvulsant effects *in vivo*** against:
  - kindling
  - 6 Hz
  - audiogenic/Fring’s
  - KA seizure latency
SUMMARY 2

• 2DG has _chronic antiepileptic_ effects _in vivo_ against progression of kindled seizures and adverse cognitive consequences often associated with seizures

• 2DG has a favorable preliminary toxicity profile
SUMMARY 2

- 2DG has *chronic antiepileptic* effects *in vivo* against progression of kindled seizures and adverse cognitive consequences often associated with seizures.

- 2DG has a favorable preliminary toxicity profile.

Inhibition of glycolysis (e.g., 2DG) is a novel therapeutic approach to epilepsy.

Rethinking of E/I paradigm.
↑Excitability, seizures

- Synapse formation
- Ion channels
- Glia homeostasis
- Metabolic factors
- Networks/circuits
- Neurotransmitters/receptors
- Molecular signaling
• Metabolic approaches hold much promise for:
  • control of neuronal excitability
  • suppression of seizure generation
  • modification of epileptogenesis
Unresolved questions

• Mechanisms of acute and chronic effects
• Age-dependence
• Clinical trials
Collaborators

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