UC San Diego
SCHOOL OF MEDICINE

Rady Children's Hospital San Diego

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Danish Epilepsy Society Meeting, Copenhagen

Ketogenic Diet: Overview of Mechanisms of Action Potentially Targeting Disease Pathophysiology

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Department of Neurosciences

Department of Pediatrics

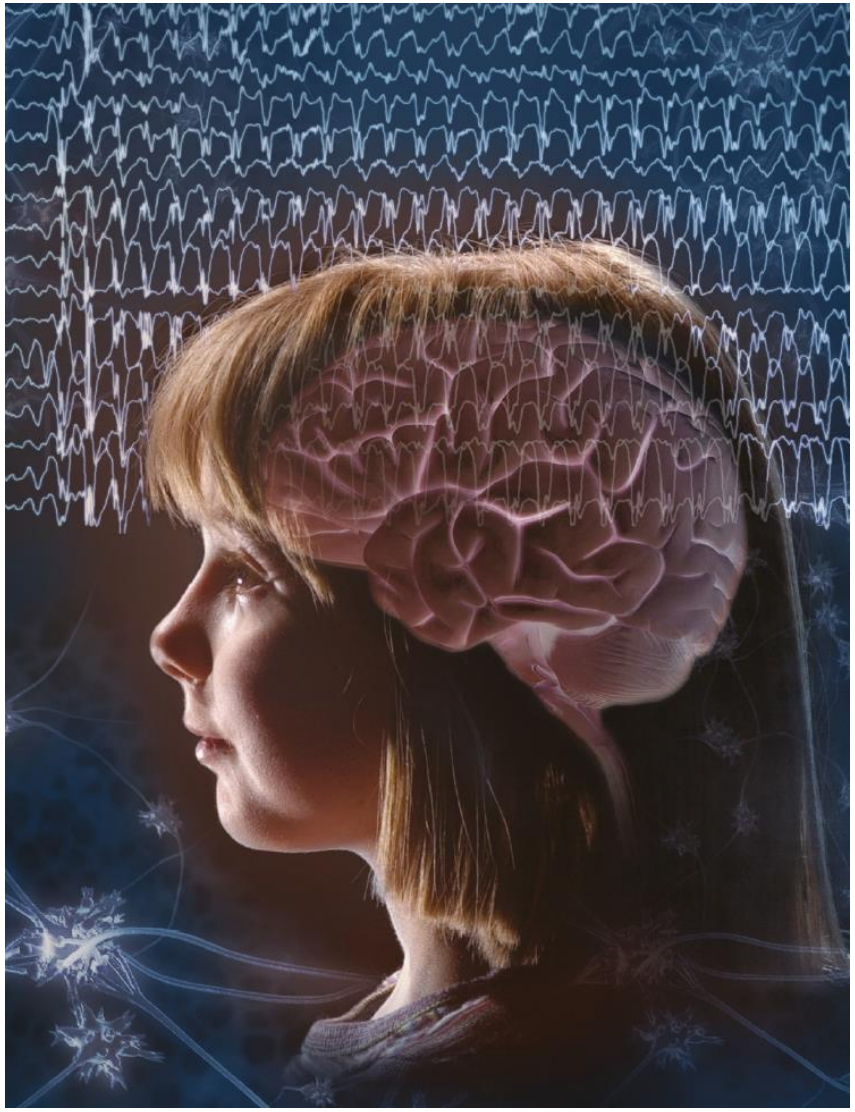
Disclosures

- ***Consultant, Speakers Bureau, Scientific Advisory Board Activity (2020-2023)***

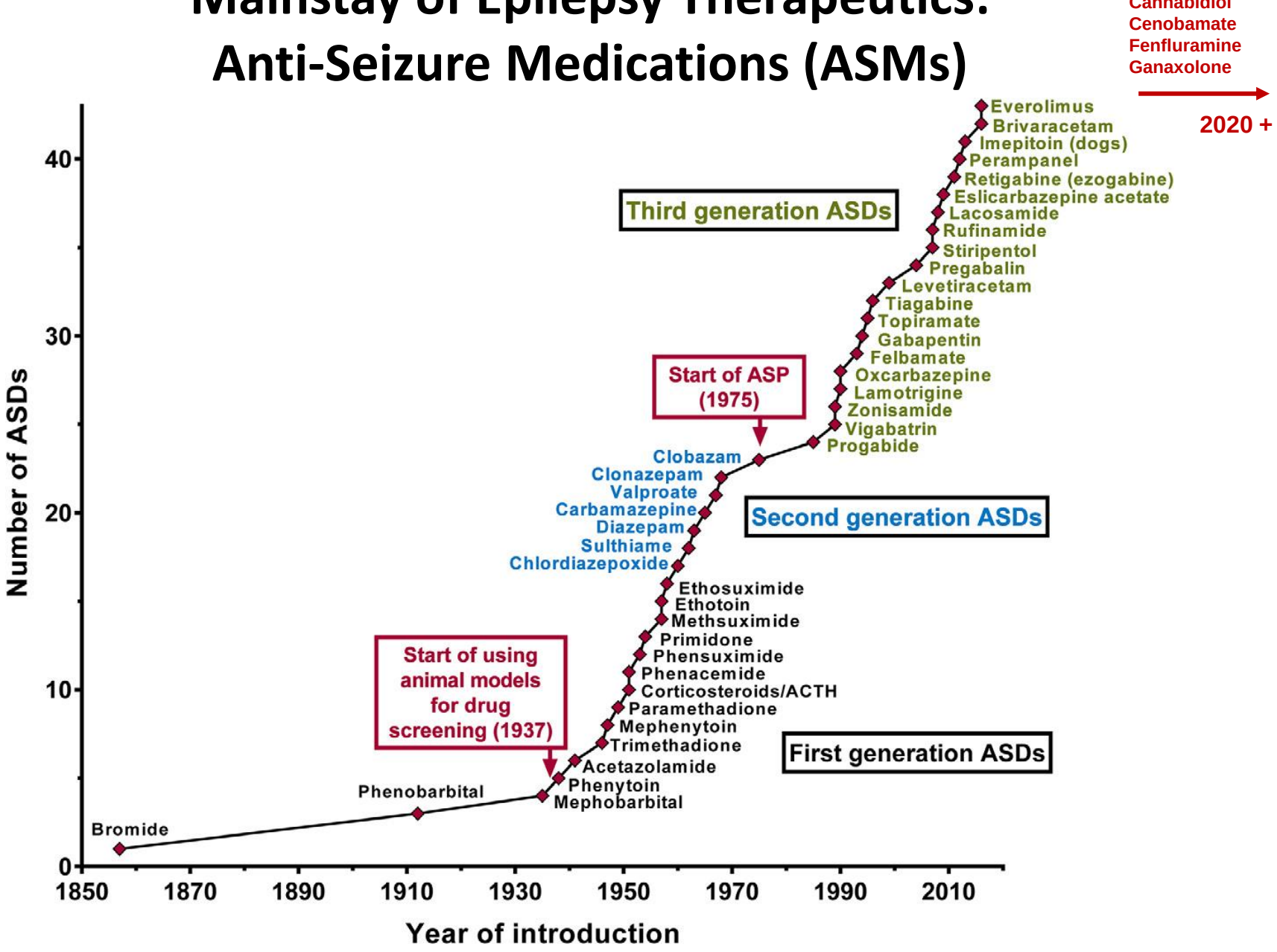
  - The Charlie Foundation (Santa Monica, CA)
  - Matthew's Friends Foundation (Surrey, United Kingdom)
  - Danone Nutricia
  - Eisai Canada/US
  - Aquestive Pharmaceuticals
  - Cerecin
  - Biocodex
  - Zogenix

Epilepsy

- Neurological disorder affecting 1% of the general population, and across the age-span
- Characterized by spontaneous recurrent seizures
- Despite dozens of medications, a third of patients do not respond
- Epilepsy can be progressive, and often impairs cognition, behavior, and general health
- There is a heightened risk of accidents, trauma, and even sudden unexpected death (SUDEP)

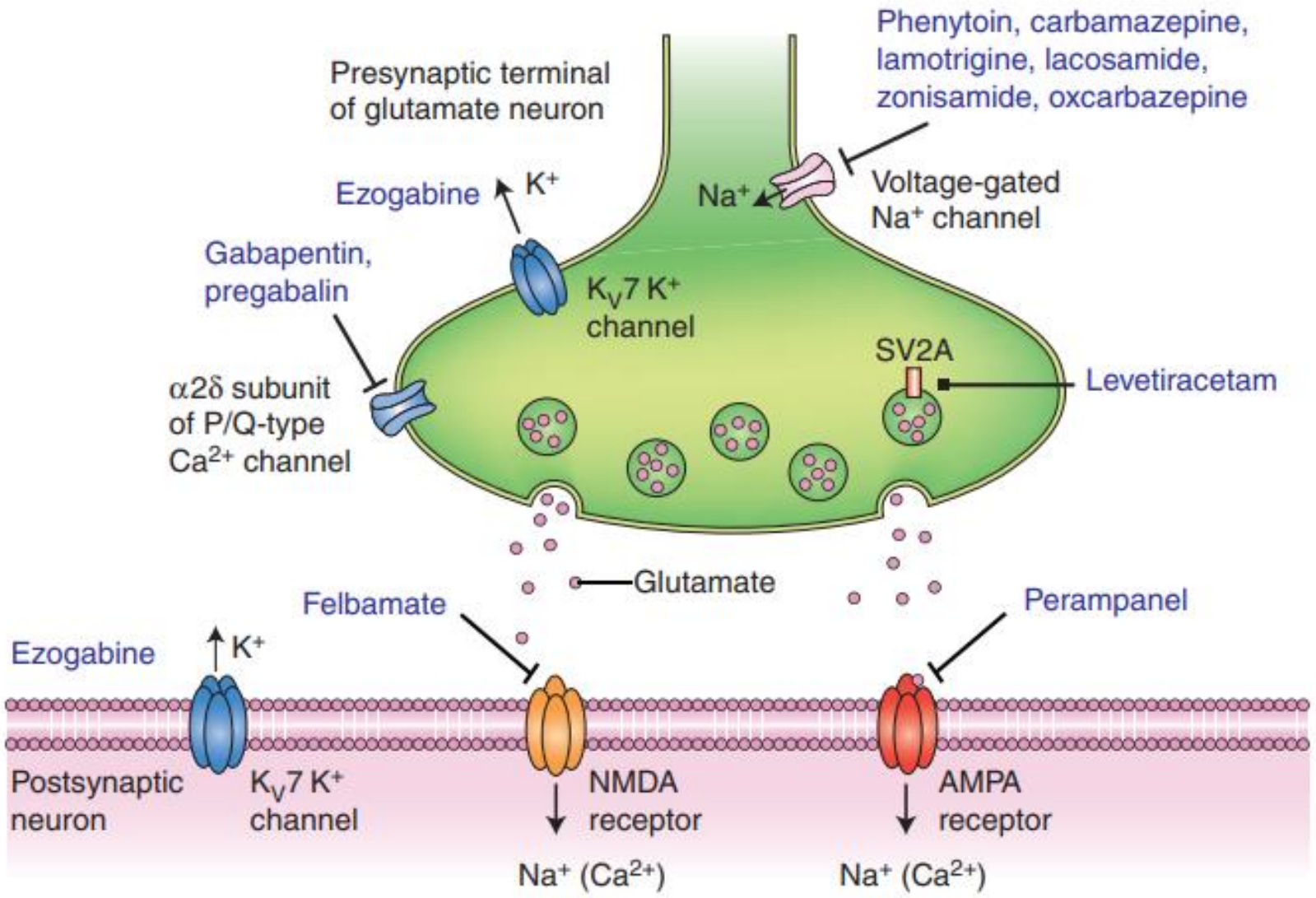


Mainstay of Epilepsy Therapeutics: Anti-Seizure Medications (ASMs)



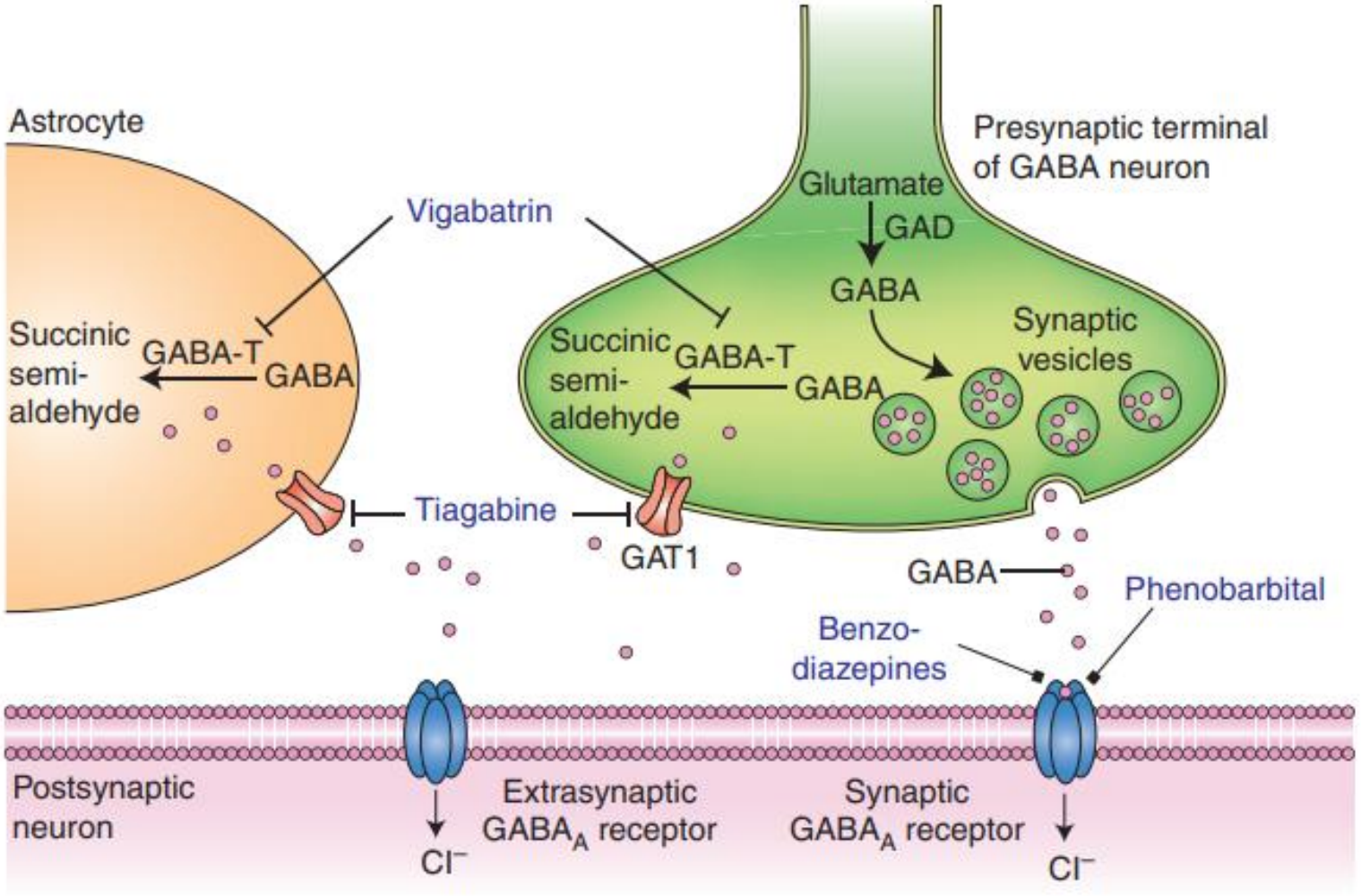
Rho & White, Epilepsia Open 2018

Central Excitatory Synapse



Rogawski, Löscher & Rho, Cold Spring Harbor Symposia 2016

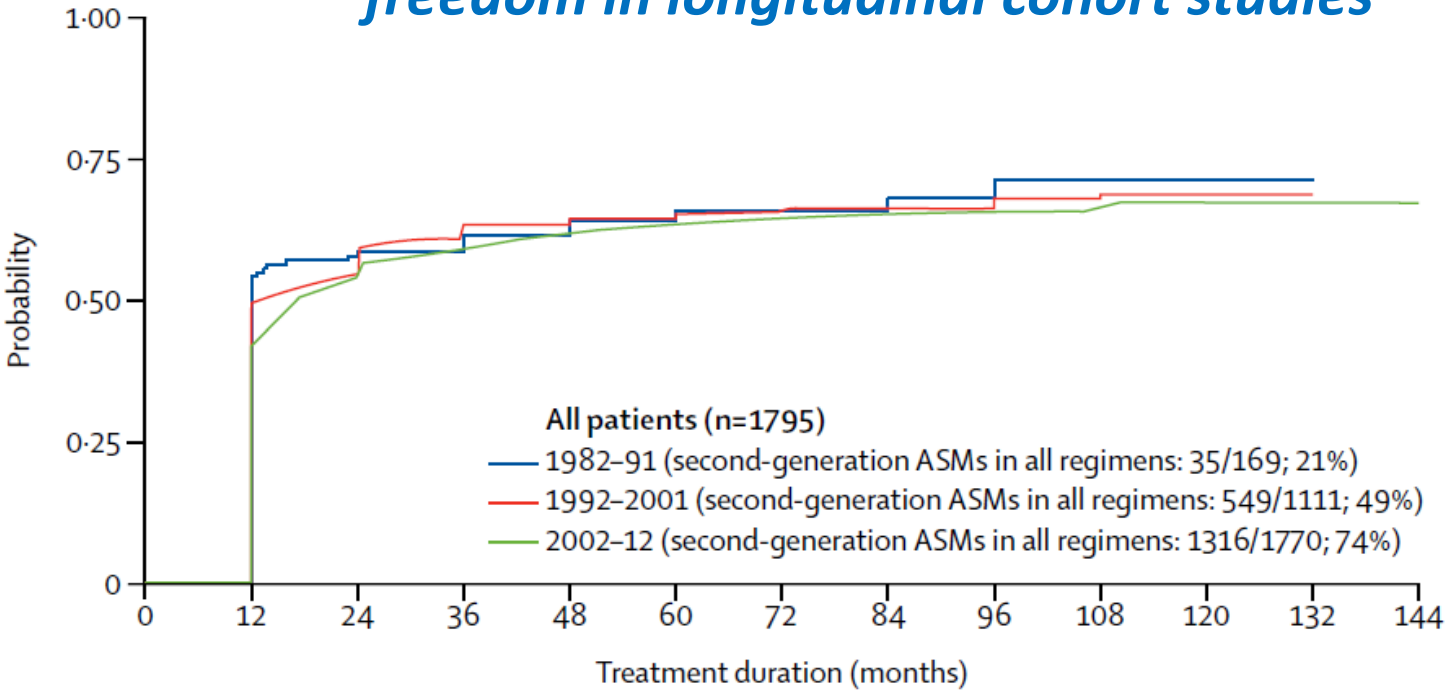
Central Inhibitory Synapse



Rogawski, Löscher & Rho, Cold Spring Harbor Symposia 2016

How Effective Are Current Anti-Seizure Medications?

Cumulative probability of one-year seizure freedom in longitudinal cohort studies



Number at risk

1982–91	142	57	43	27	21	18	16	10	3	1	1	0
1992–2001	684	301	229	197	156	123	106	74	42	21	8	0
2002–12	969	389	312	261	228	202	175	148	119	98	69	29

Chen et al, JAMA Neurol 2018

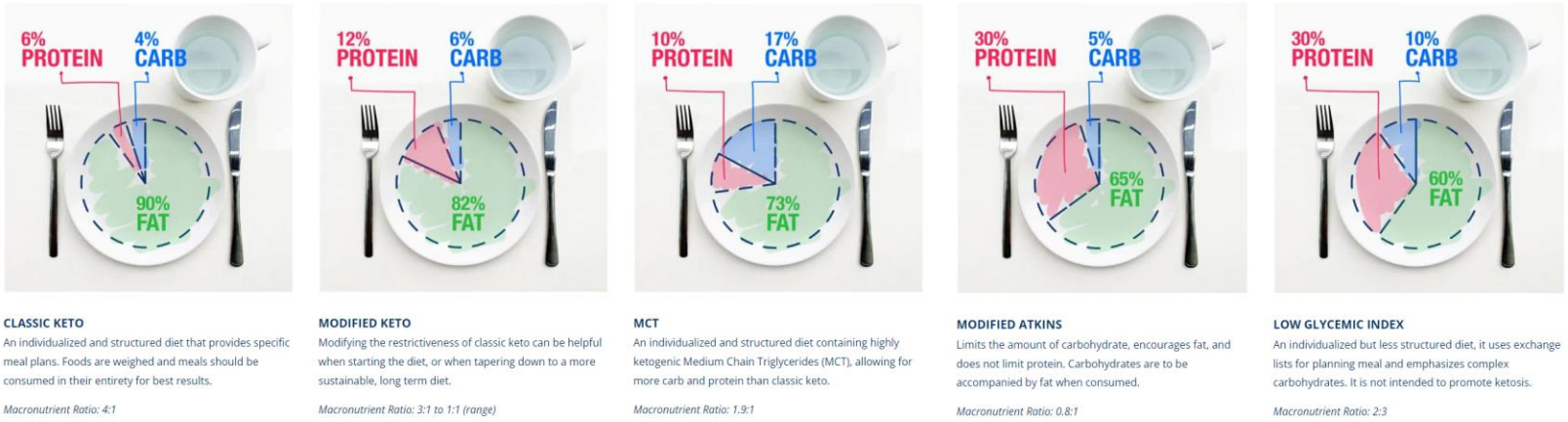
Metabolism-Based Treatments for Epilepsy

The Ketogenic Diet

High-fat, low-carbohydrate, adequate protein anti-seizure diet designed to mimic the biochemical changes associated with fasting.

- *Ketosis*
- *Glycolytic restriction*

https://charliefoundation.org/diet-plans/



Five Variations on a Theme




The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial

Elizabeth G Neal, Hannah Chaffe, Ruby H Schwartz, Margaret S Lawson, Nicole Edwards, Geogianna Fitzsimmons, Andrea Whitney, J Helen Cross

	Patients who achieved cut-off points		p value
	Diet group (n=73)	Control group (n=72)	
>90% reduction in seizures	5 (7%)	0 (0%)	0·0582
>50% reduction in seizures*	28 (38%)	4 (6%)	<0·0001
<50% reduction in seizures†	45 (62%)	68 (94%)	<0·0001

Percentages based on numbers allocated to each intervention. *Includes patients who reported >90% reduction. †Includes 71 patients with data and 42 unknown (16 did not recieve treatment, 10 discontinued treatment, 16 with no data).

Table 4: **Number of children in each group who achieved 50% and 90% seizure reduction at 3 months**

Lancet Neurol 2008

Cochrane Library

2020

Cochrane Database of Systematic Reviews

Ketogenic diets for drug-resistant epilepsy (Review)

Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN

Authors' conclusions

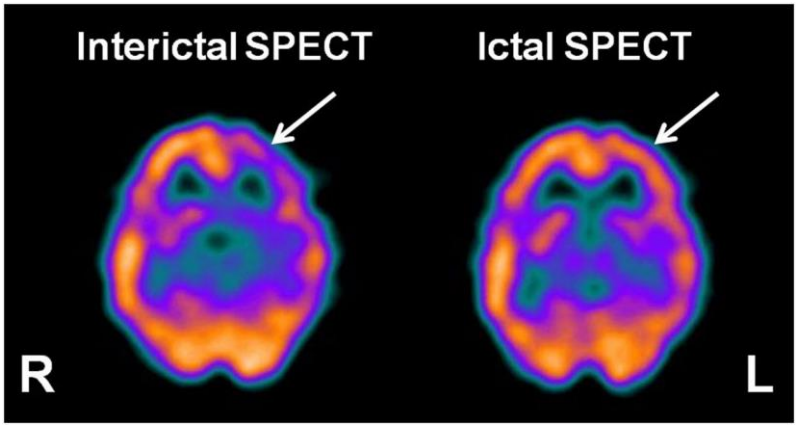
The evidence suggests that KDs could demonstrate effectiveness in children with drug-resistant epilepsy, however, the evidence for the use of KDs in adults remains uncertain. We identified a limited number of studies which all had small sample sizes. Due to the associated risk of bias and imprecision caused by small study populations, the evidence for the use of KDs was of low to very low certainty.

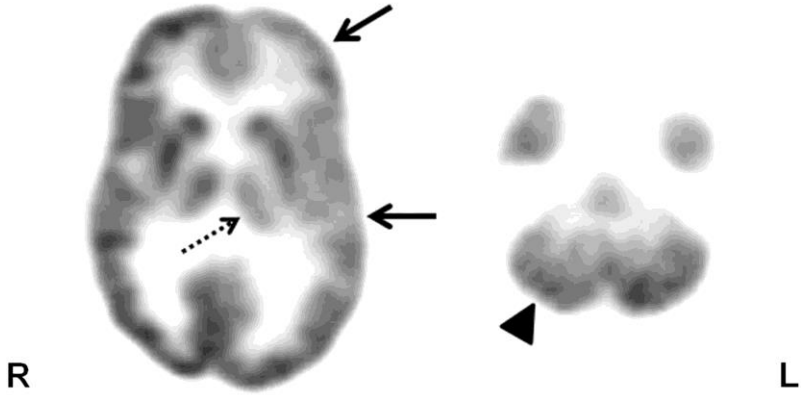
More palatable but related diets, such as the MAD, may have a similar effect on seizure control as the classical KD, but could be associated with fewer adverse effects. This assumption requires more investigation. For people who have drug-resistant epilepsy or who are unsuitable for surgical intervention, KDs remain a valid option. Further research is required, particularly for adults with drug-resistant epilepsy.

Over a dozen randomized controlled trials in epilepsy, more so than any drug we use for epilepsy !!!

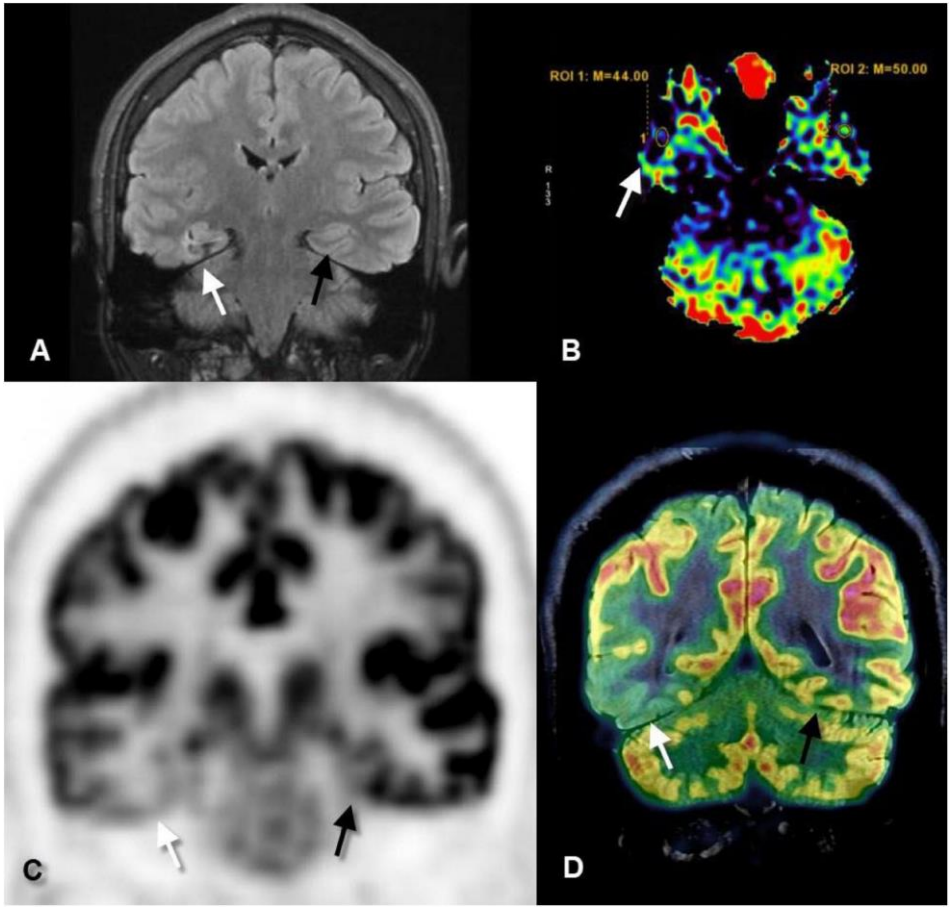
What are the linkages between aberrant cellular metabolism and neuronal excitability & hypersynchrony?

Cerebral Blood Flow, Bioenergetics & Metabolism in Epilepsy



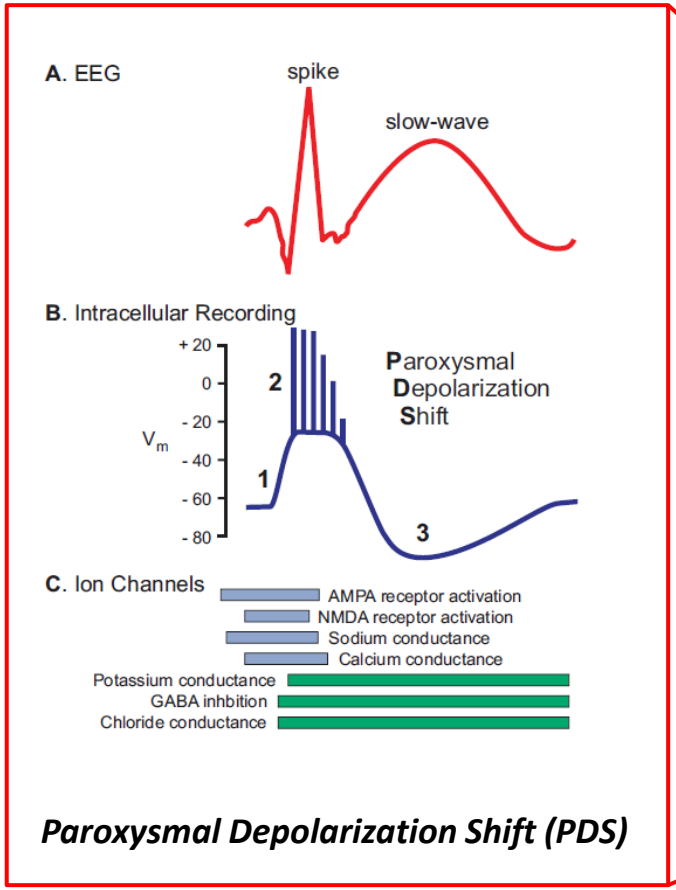


Kumar & Chugani, J Nuclear Med Technol 2017

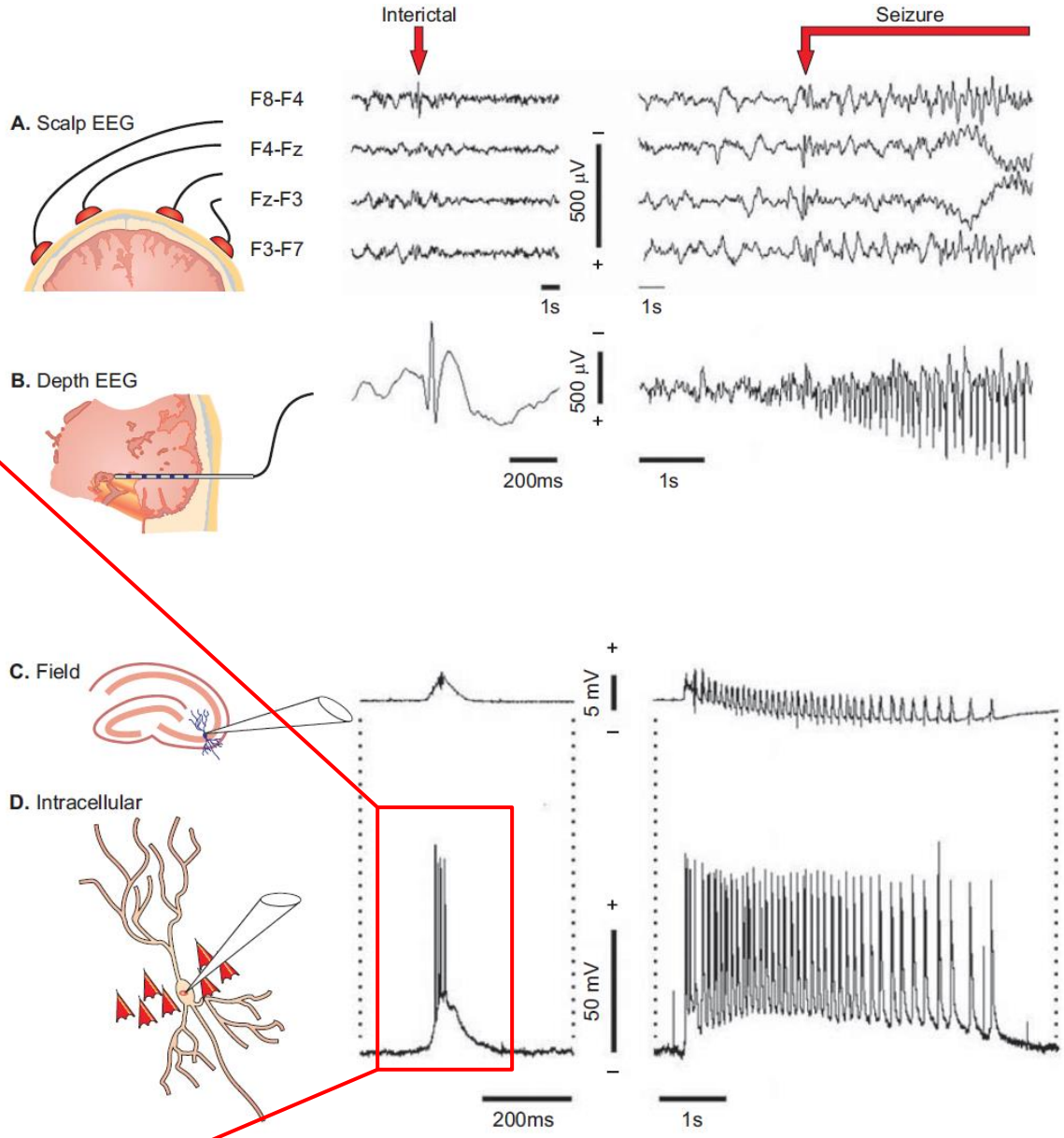


Algahtany eta al, Front Neurosci 2021

Hierarchy of Hyperexcitability and Hypersynchrony in the Epileptic Brain

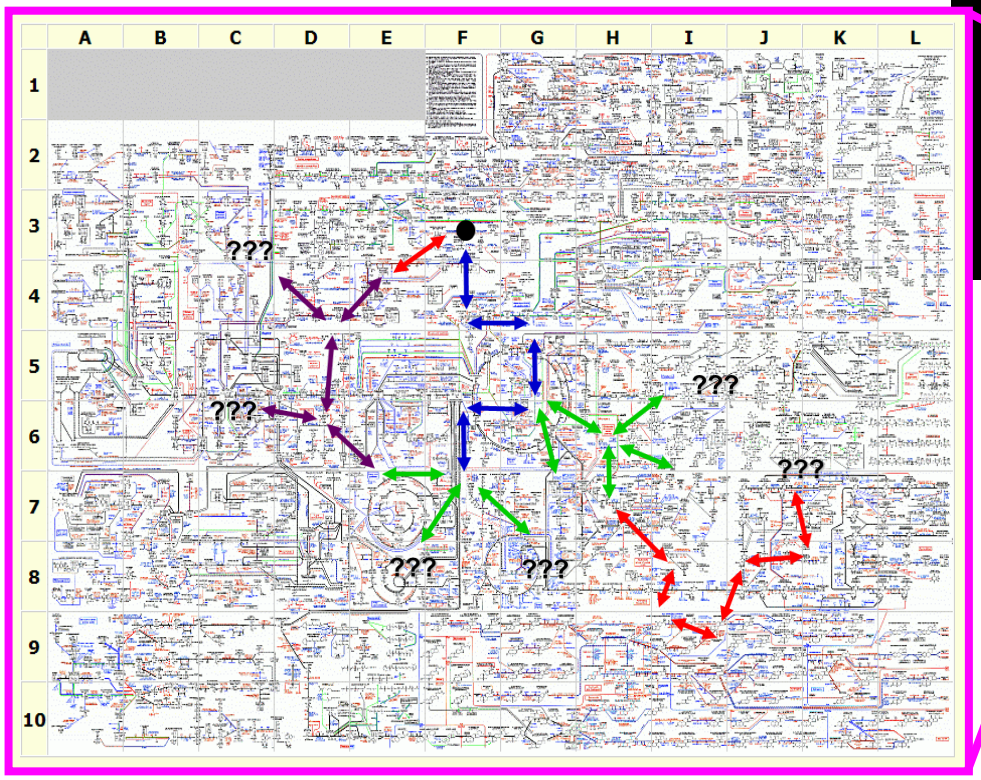


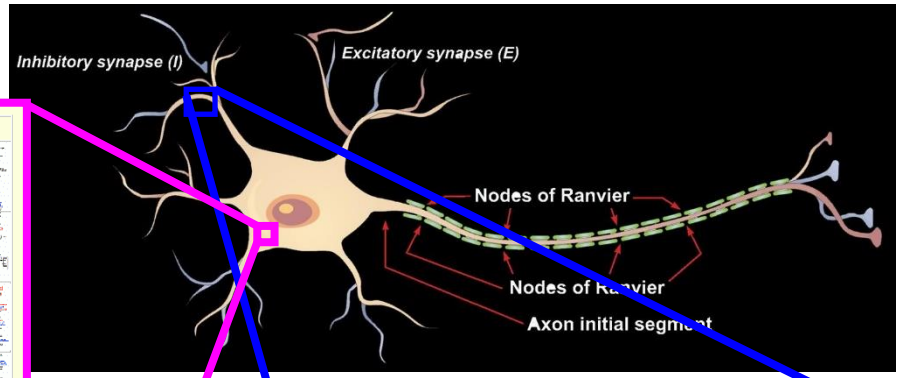
Paroxysmal Depolarization Shift (PDS)

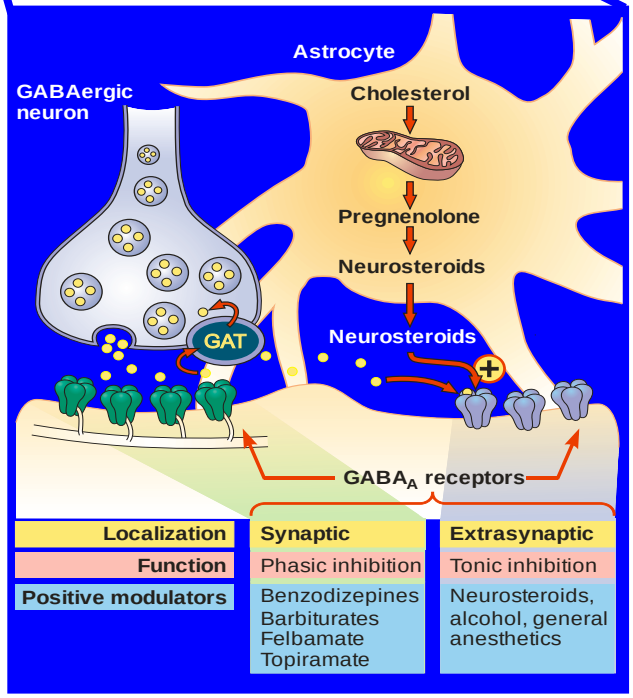


White & Rho, PCI Communications 2010

Conventional View of Drug Action on Synaptic Neurotransmission



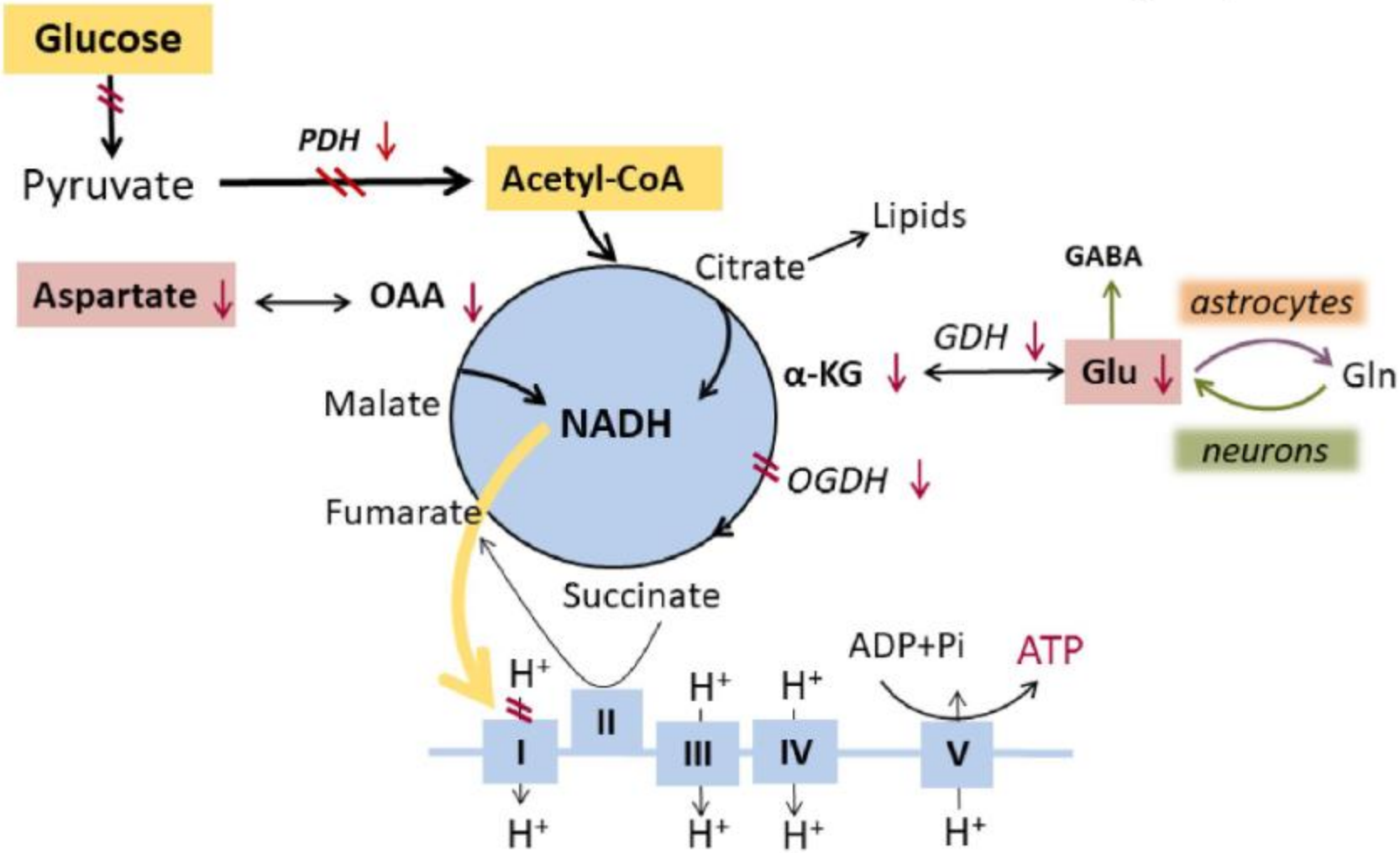




CELLULAR BIOENERGETICS & METABOLISM

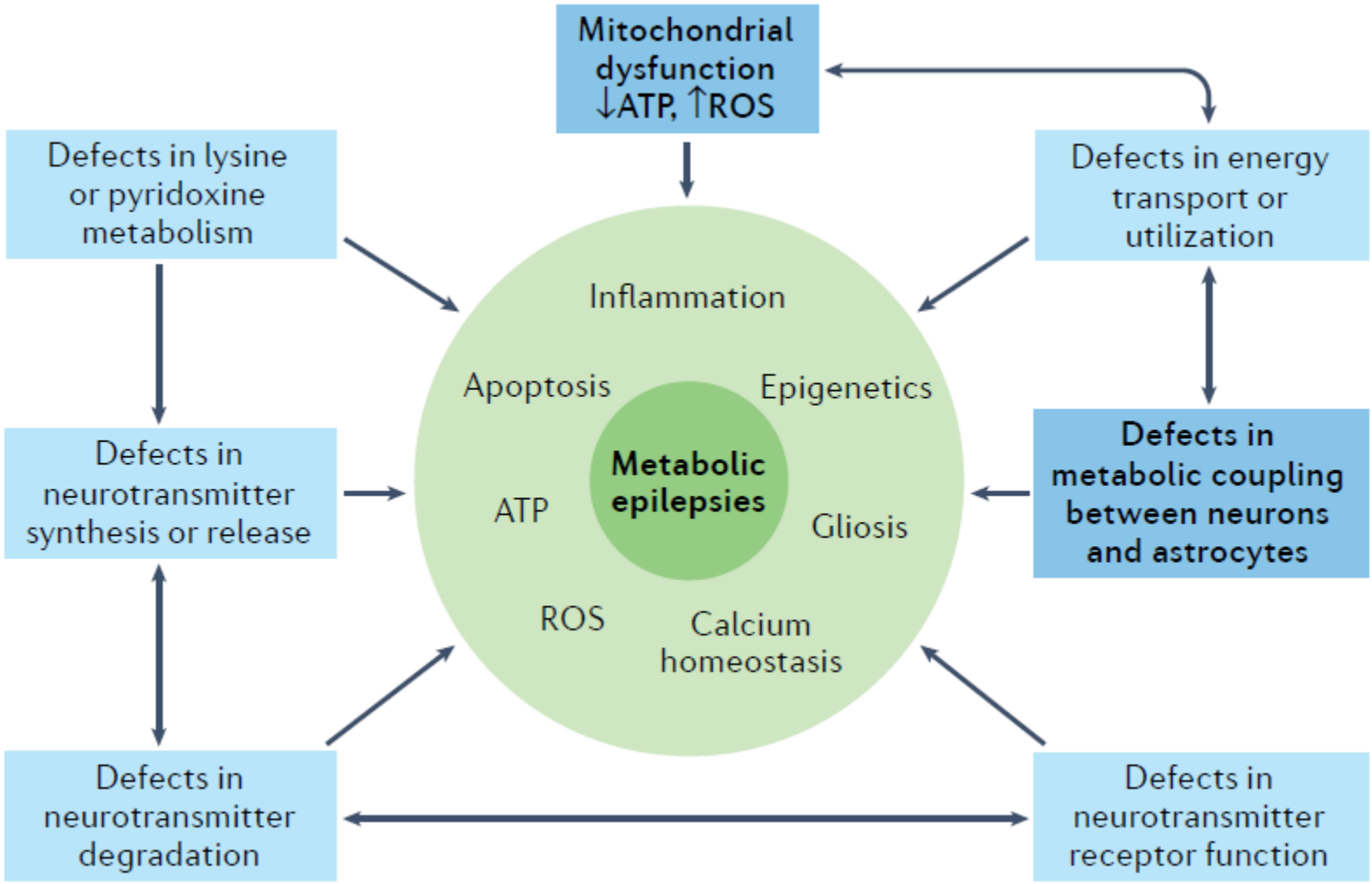
Benarroch EE. *Neurology*. 2007;68(8):612-614.

Changes in Brain Cell Energy Metabolism in Epilepsy



Han et al, Epilepsia 2021

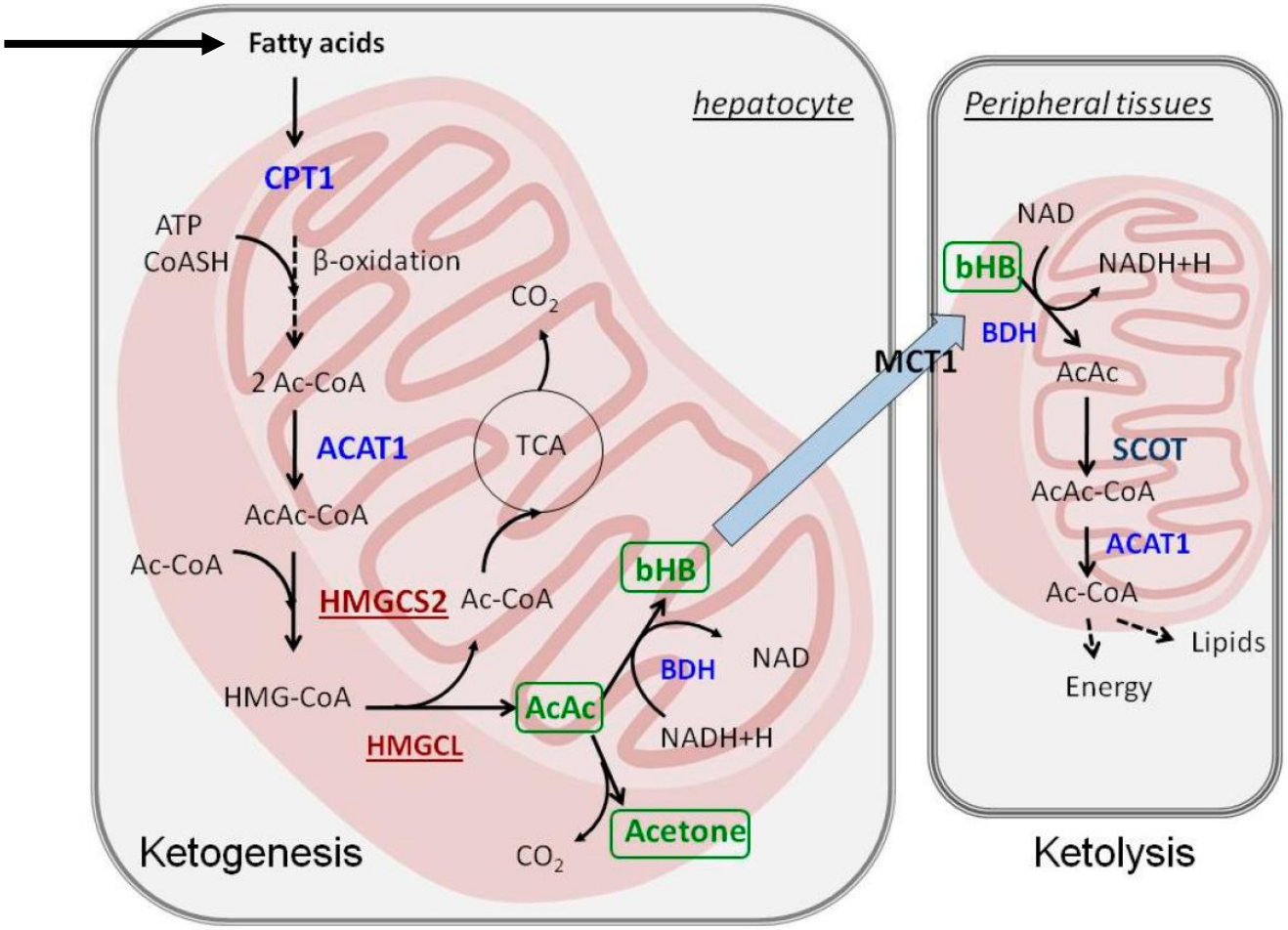
Pathogenesis of Metabolic Epilepsies



Rho & Boison, Nature Reviews Neurology 2022

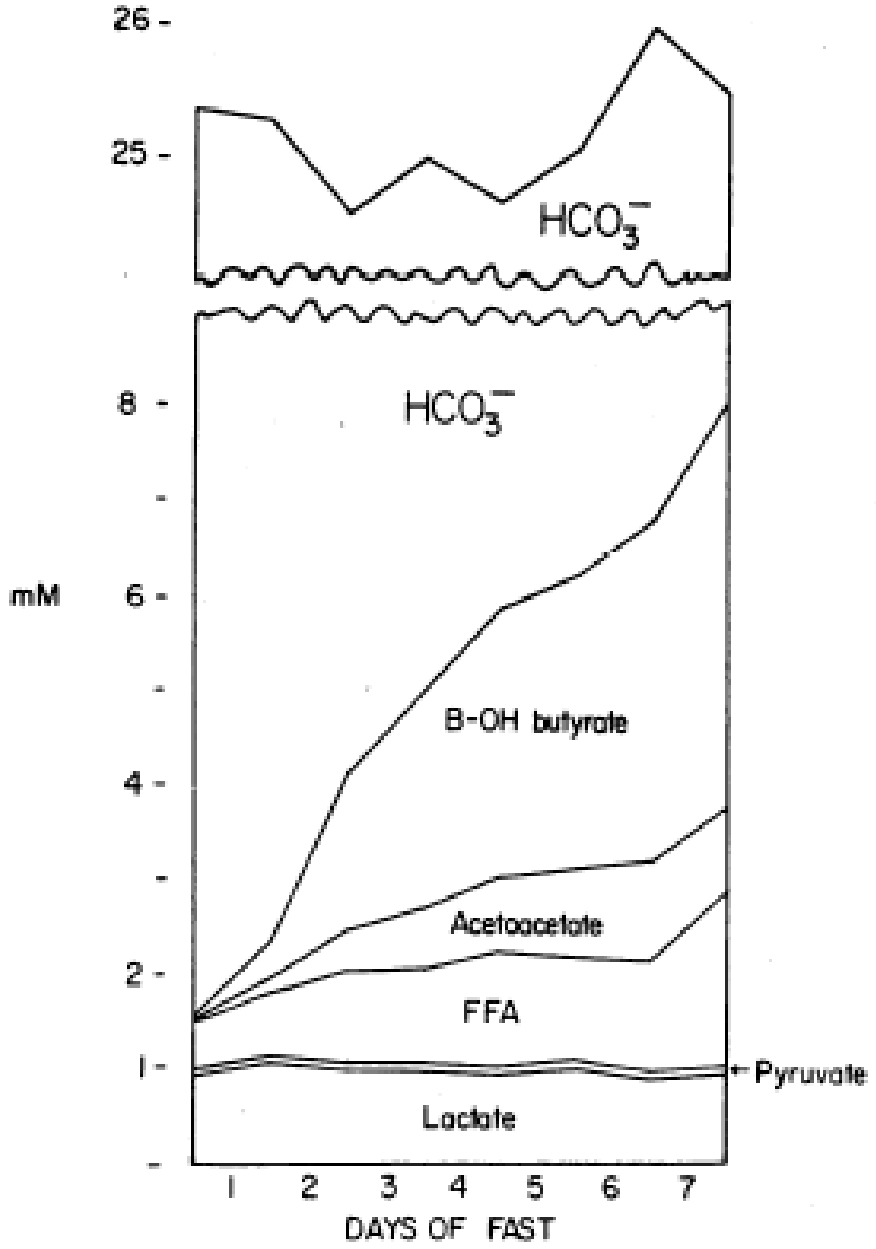
Ketogenesis and Ketolysis

Ketogenic Diet



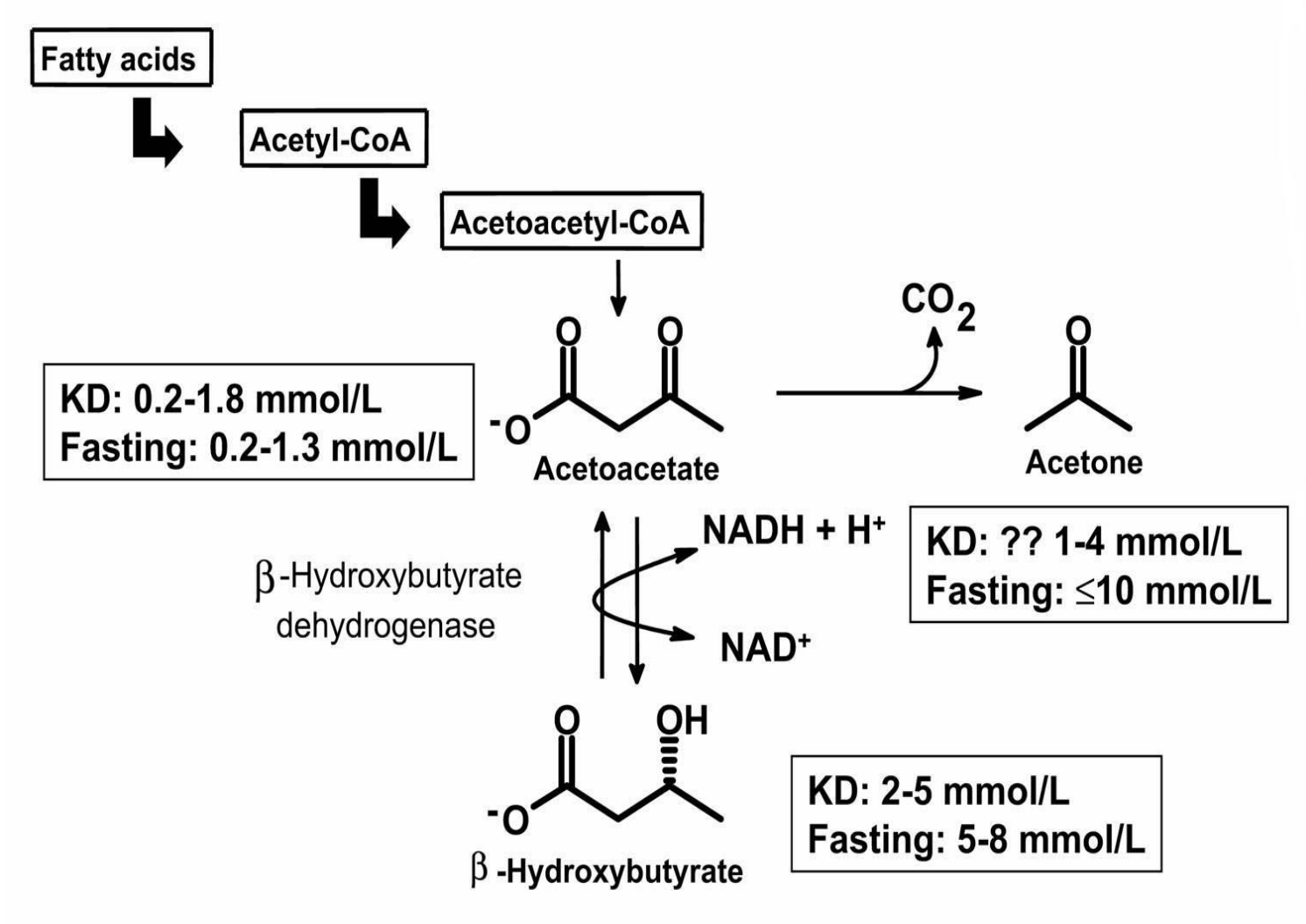
Grabacka et al, Int J Mol Sci 2016

Metabolic Changes During Fasting



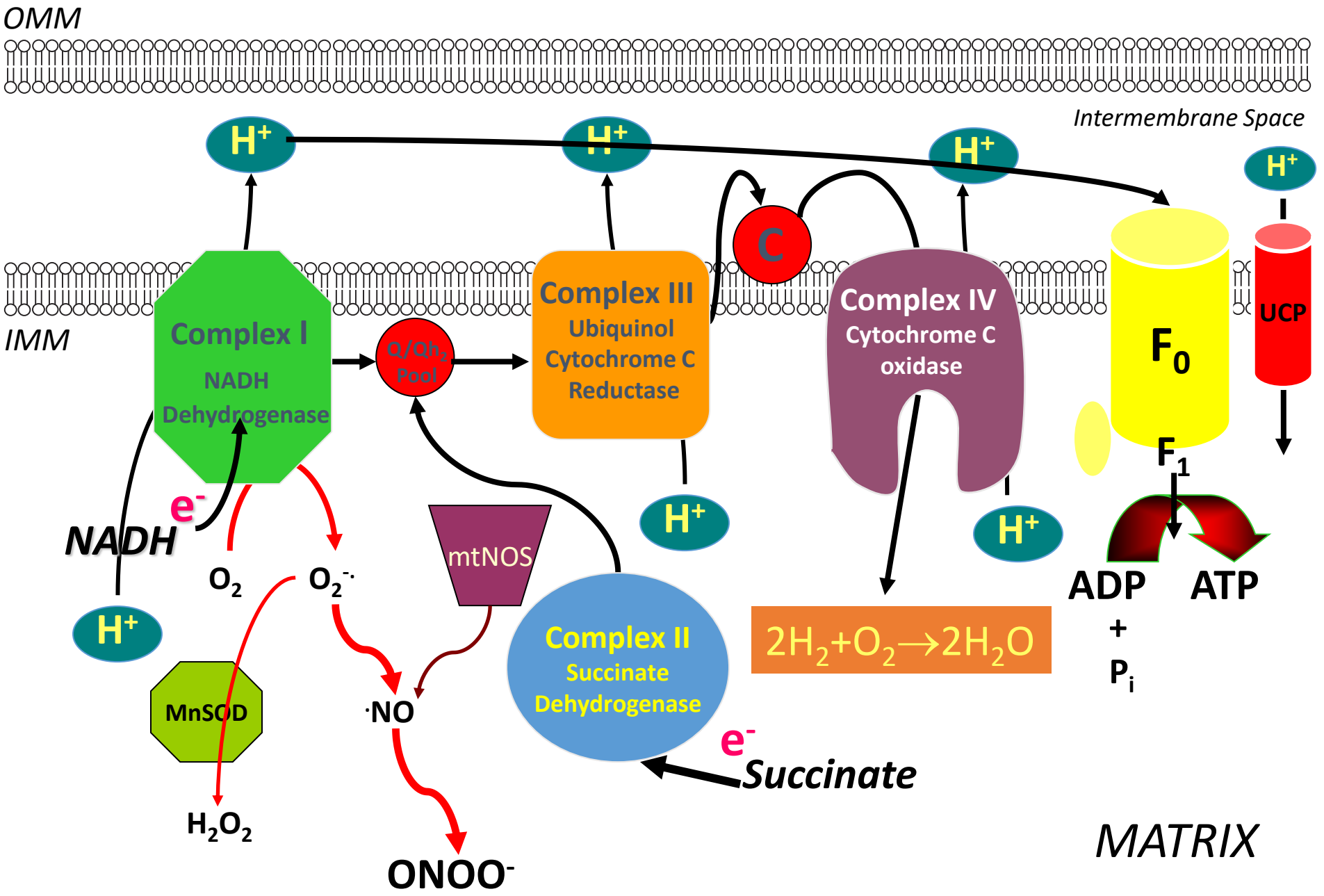
Cahill et al, J Clin Invest 1966

Clinically Relevant Ketone Body Concentrations

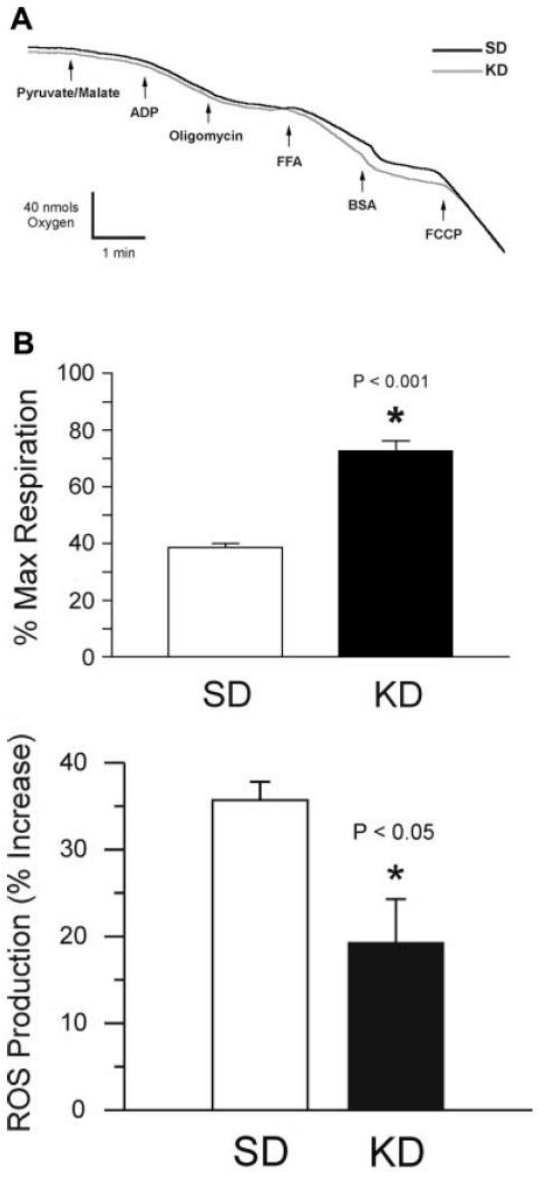


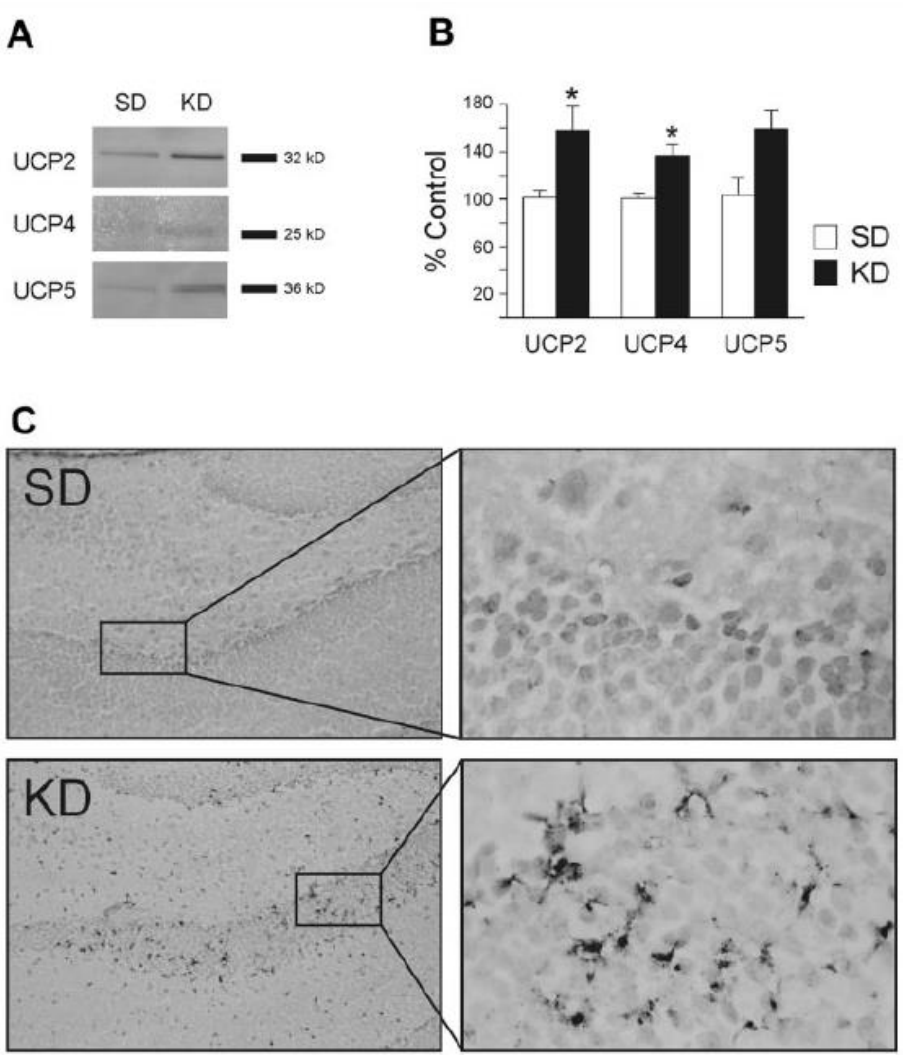
Likhodii & Burnham, Epilepsy and the Ketogenic Diet, Humana Press 2004

MITOCHONDRIAL RESPIRATORY CHAIN



KD Effects on Mitochondrial Uncoupling Proteins



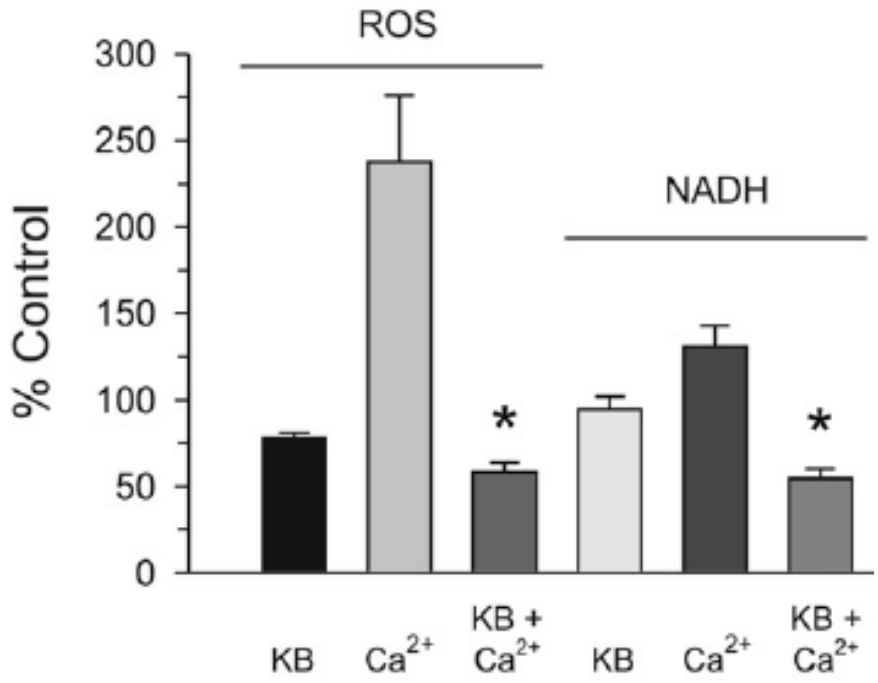


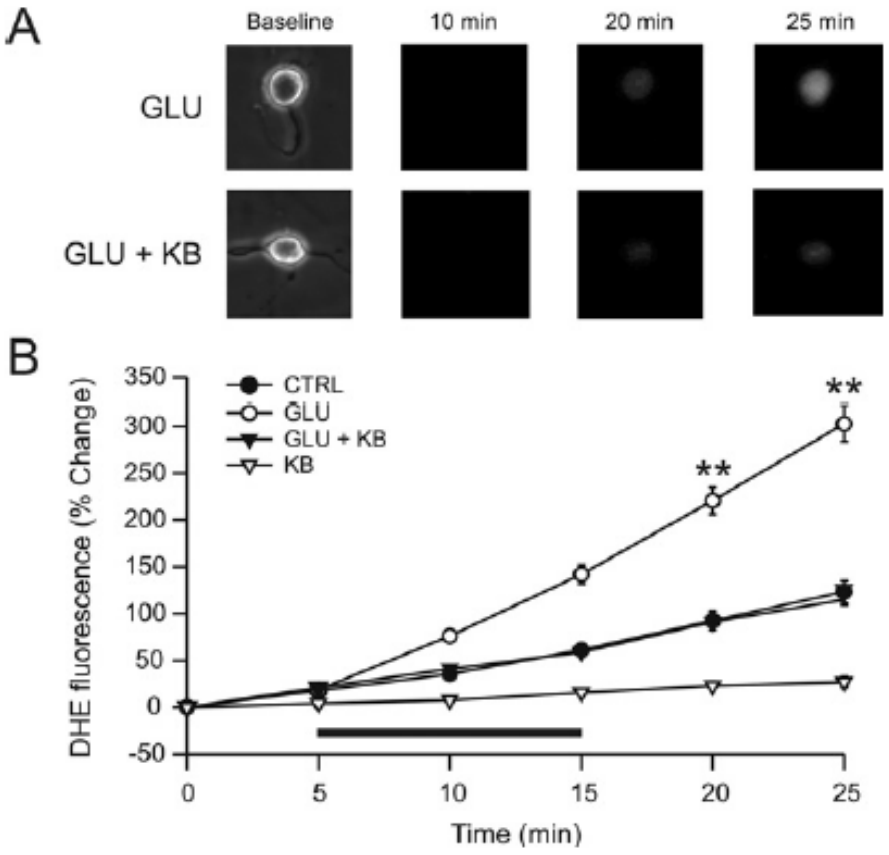
Sullivan et al, Ann Neurol, 2004

Neuroscience 145 (2007) 256–264

KETONES INHIBIT MITOCHONDRIAL PRODUCTION OF REACTIVE OXYGEN SPECIES PRODUCTION FOLLOWING GLUTAMATE EXCITOTOXICITY BY INCREASING NADH OXIDATION

M. MAALOUF,[a] P. G. SULLIVAN,[b] L. DAVIS,[b] D. Y. KIM[a] AND J. M. RHO[a]*



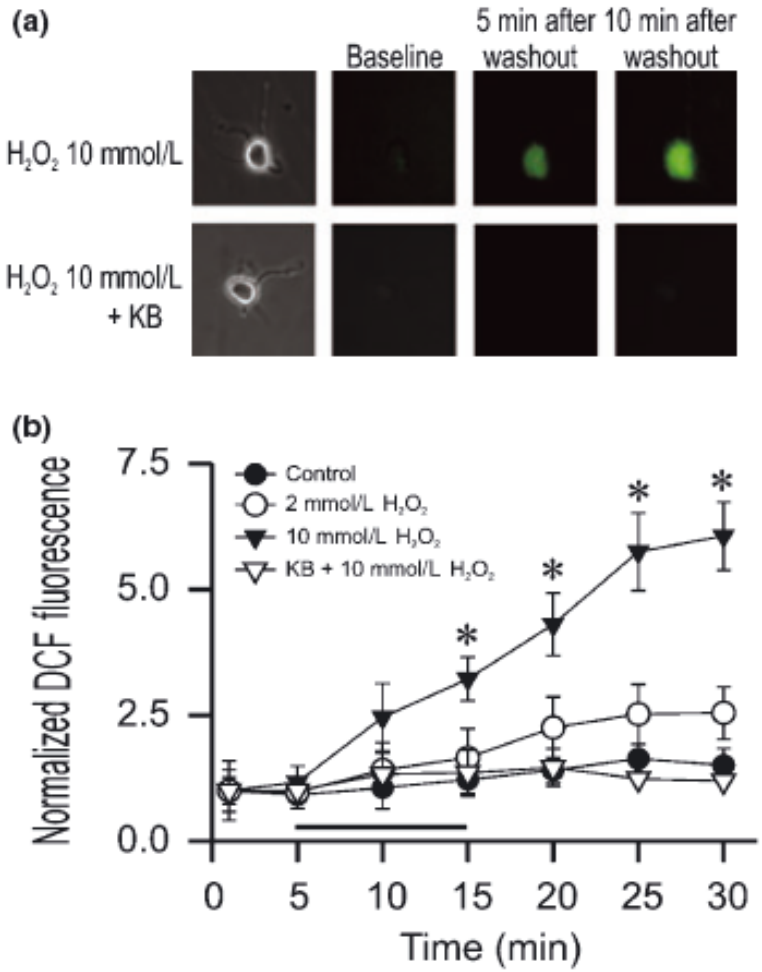


Ketone Bodies Mitigate Oxidative Stress

Journal of Neurochemistry, 2007, **101**, 1316–1326 doi:10.1111/j.1471-4159.2007.04483.x

Ketone bodies are protective against oxidative stress in neocortical neurons

Do Young Kim,* Laurie M. Davis,† Patrick G. Sullivan,† Marwan Maalouf,* Timothy A. Simeone,* Johannes van Brederode‡ and Jong M. Rho*



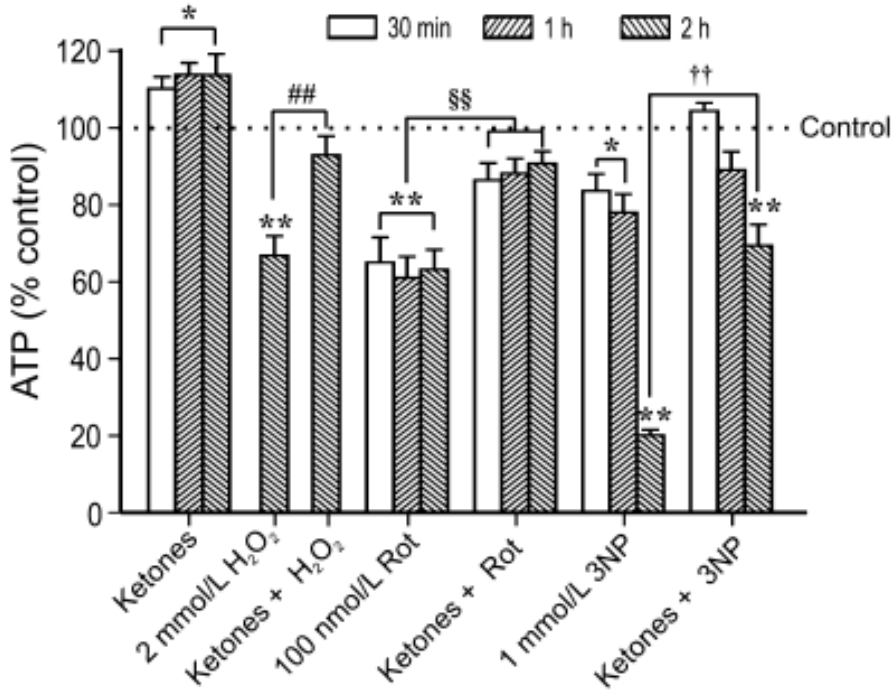
Ketone Body Effects on Mitochondria

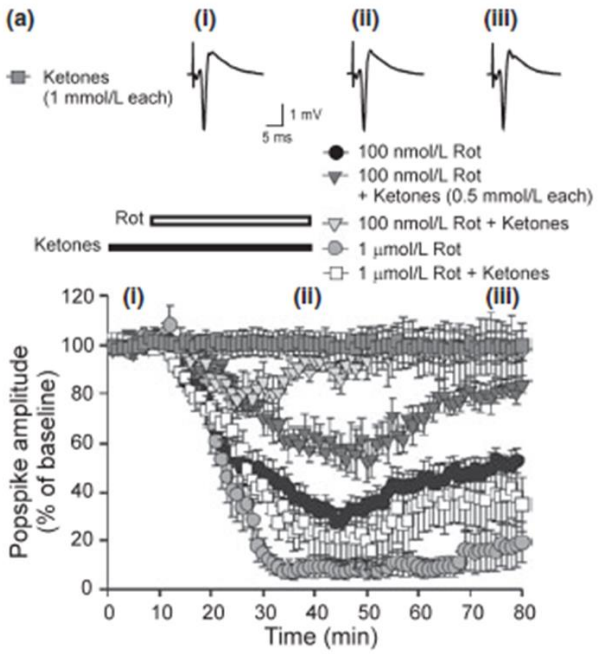
Journal of Neurochemistry JNC

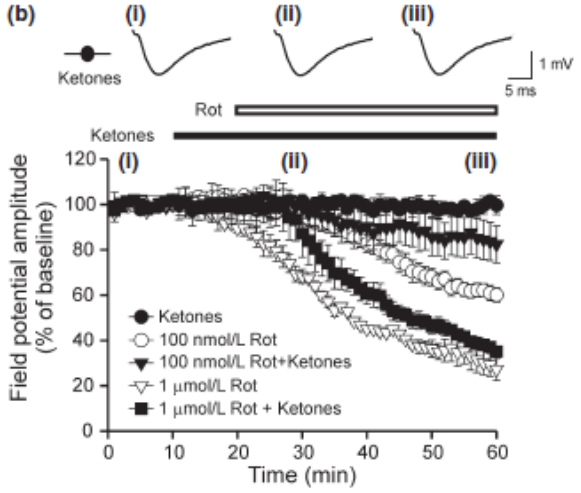
JOURNAL OF NEUROCHEMISTRY | 2010 | 114 | 130–141 doi: 10.1111/j.1471-4159.2010.06728.x

Ketones prevent synaptic dysfunction induced by mitochondrial respiratory complex inhibitors

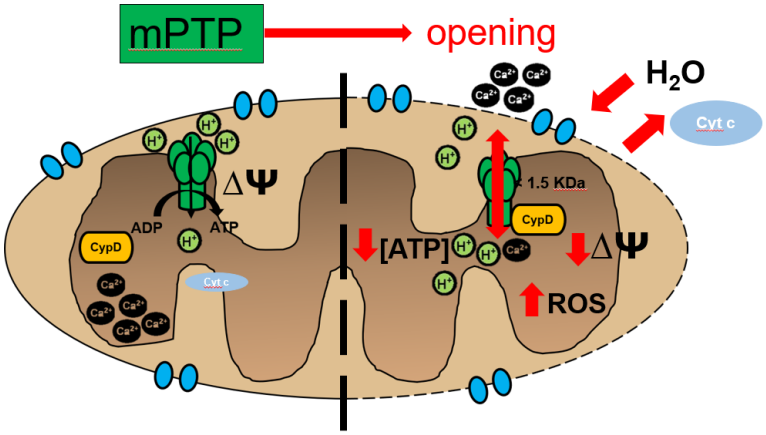
Do Young Kim,* Johana Vallejo† and Jong M. Rho*

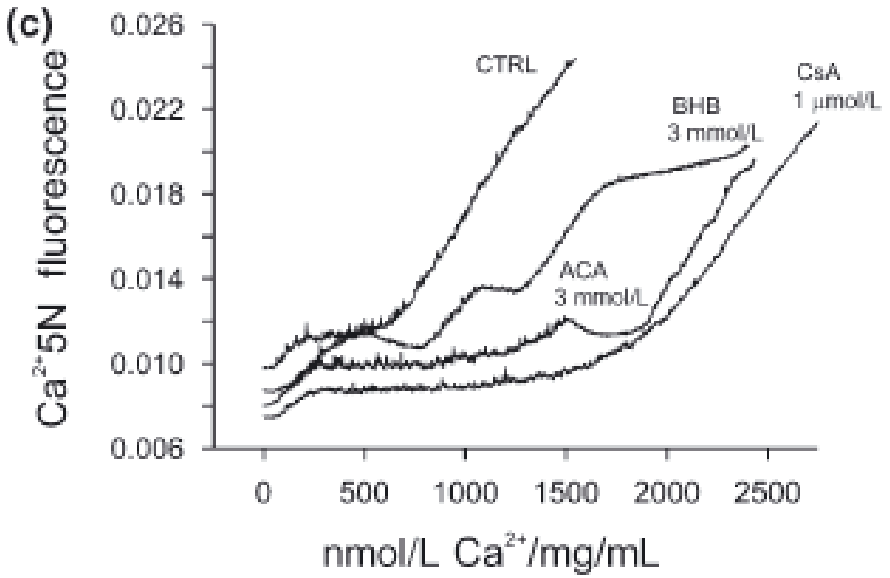


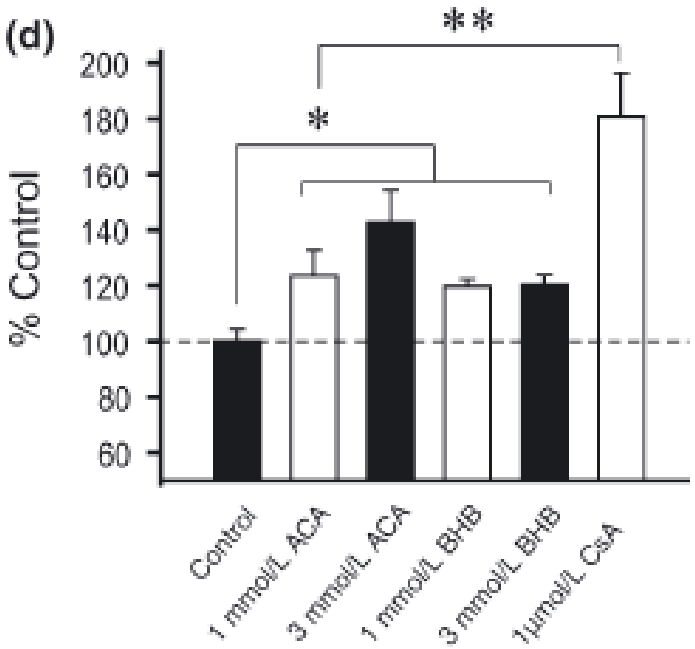




Ketone Body Effects on Mitochondrial Permeability Transition







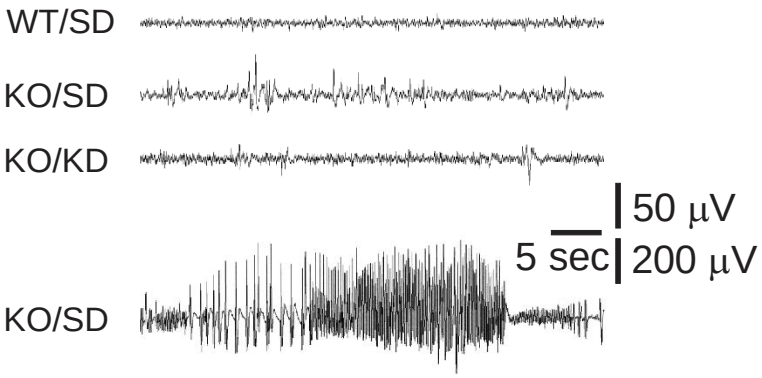
Kim et al, J Neurochem 2007

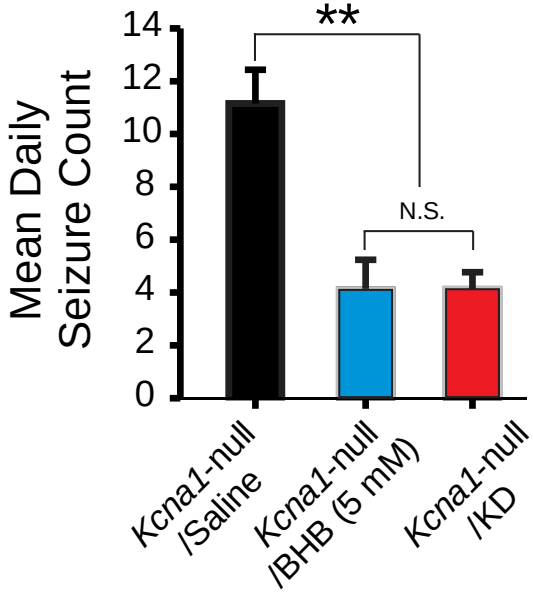
Ann Neurol 2015

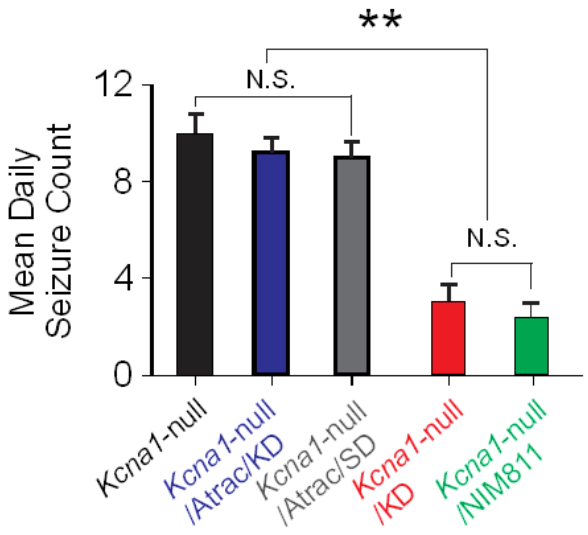
RESEARCH ARTICLE

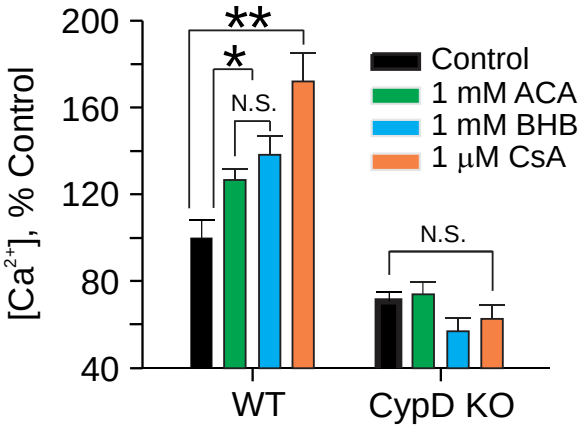
Ketone Bodies Mediate Antiseizure Effects through Mitochondrial Permeability Transition

Do Young Kim, DVM, PhD,[1] Kristina A. Simeone, PhD,[2] Timothy A. Simeone, PhD,[2] Jignesh D. Pandya, PhD,[3] Julianne C. Wilke, BS,[1] Younghee Ahn, PhD,[4] James W. Geddes, PhD,[3] Patrick G. Sullivan, PhD,[3] and Jong M. Rho, MD[4]

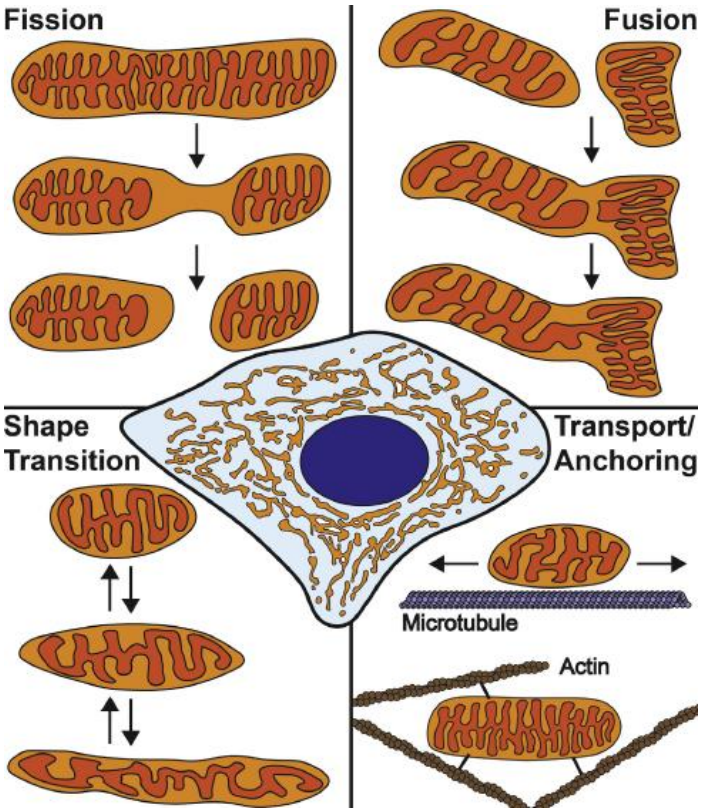




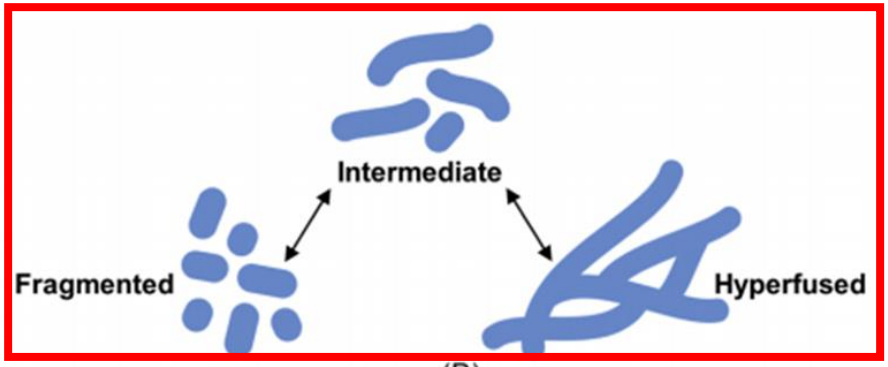




Mitochondrial Fusion & Fission Proteins Are Reciprocally Regulated



Fenton et al, Curr Opin Cell Biol 2020



(A) **Fragmented mitochondrial networks**

Regulator	▲ Fission	▼ Fusion
ERK1/2	• ↑DRP1-pS616	• ↑MFN1-pT562
O-GlcNAc	• DRP1 *O*-GlcNAc	• OPA1 *O*-GlcNAc • Milton *O*-GlcNAc
Acetylation	• ↑DRP1-AcK642 • Microtubules-Ac	• MFN1-Ac • MFN2-Ac • OPA1-Ac
MAPL	• DRP1-SUMO	• MFN1/2-Ub • AKT-Ub
Ca^{2+}	• CaMKII/ERK1/2 > ↑DRP1-pS616 • Calcineurin > ↓DRP1-p637 • S-OPA1	• Blocks MFN1 oligomerization

(B) **Hyperfused mitochondrial networks**

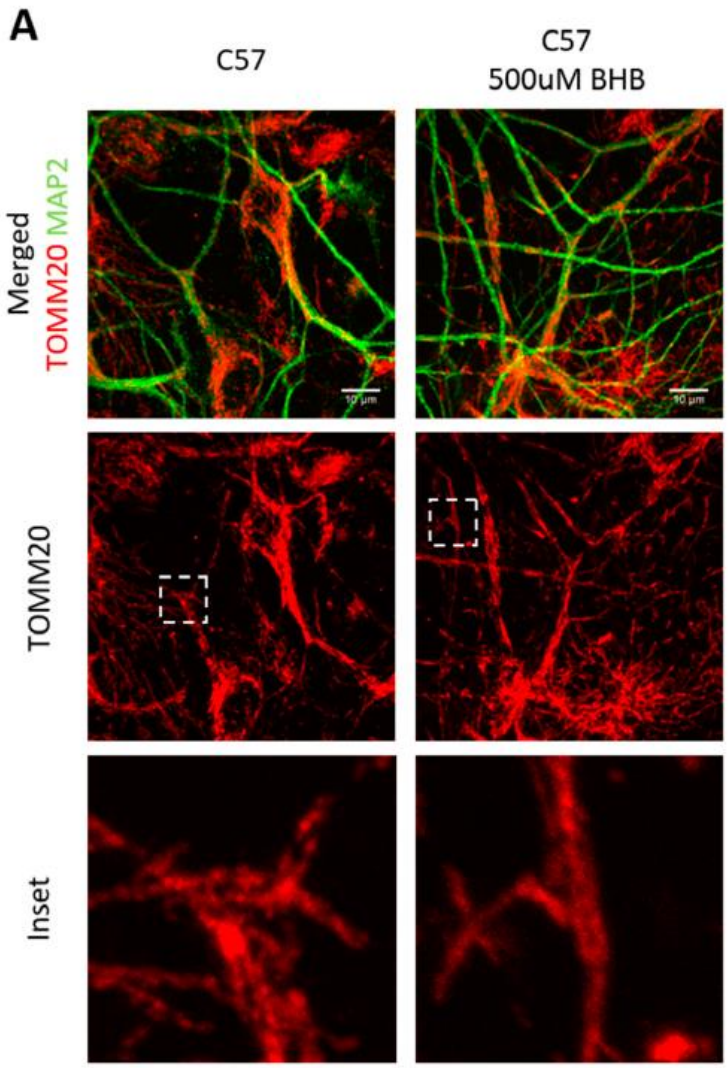
Regulator	▼ Fission	▲ Fusion
PKA	• ↑DRP1-pS637	• ↑MFN2-pS442 (?)
AKT	• GSK3β • PIM1 > ↑DRP1-pS637, ↓pS616	• OPA1 oligomers and GTPase activity
cAMP	• PKA > ↑DRP1-pS637	• Increased MFN1 expression • SIRT3 > OPA1 deAc
Redox imbalance	• NRF2 > DRP1 degradation • 20S proteasome activity	• MFN *cis* oligomers • 26S proteasome dissociation
Phosphatidic acid	• Block DRP1 GTPase activity	• Induce membrane curvature

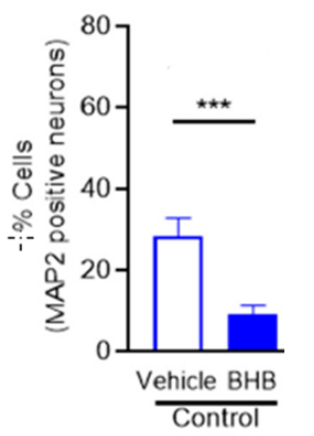
(C)

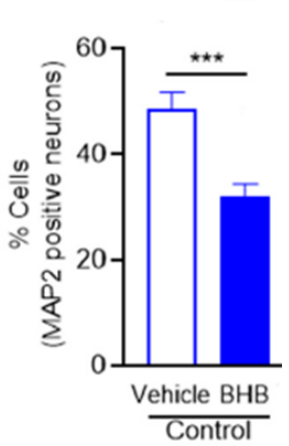
▲ Fission	Regulator	▼ Fission
↑DRP1-pS40/S44	GSK3β	PKA > ↑DRP1-pS637
▼ Fusion	Ubiquitination	▲ Fusion
MFN1/2 degradation		MFN1 oligomers
▲ Fission	Cardiolipin	▲ Fusion
OMM: Promote DRP1 GTPase activity		IMM: Promote OPA1 GTPase activity

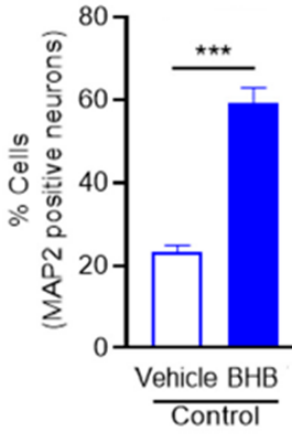
Sabouny & Shutt, Trends Biochem Sci 2020

Effects of BHB on Mitochondrial Morphology



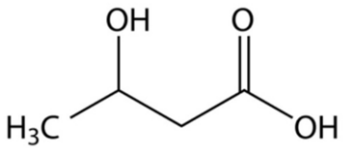


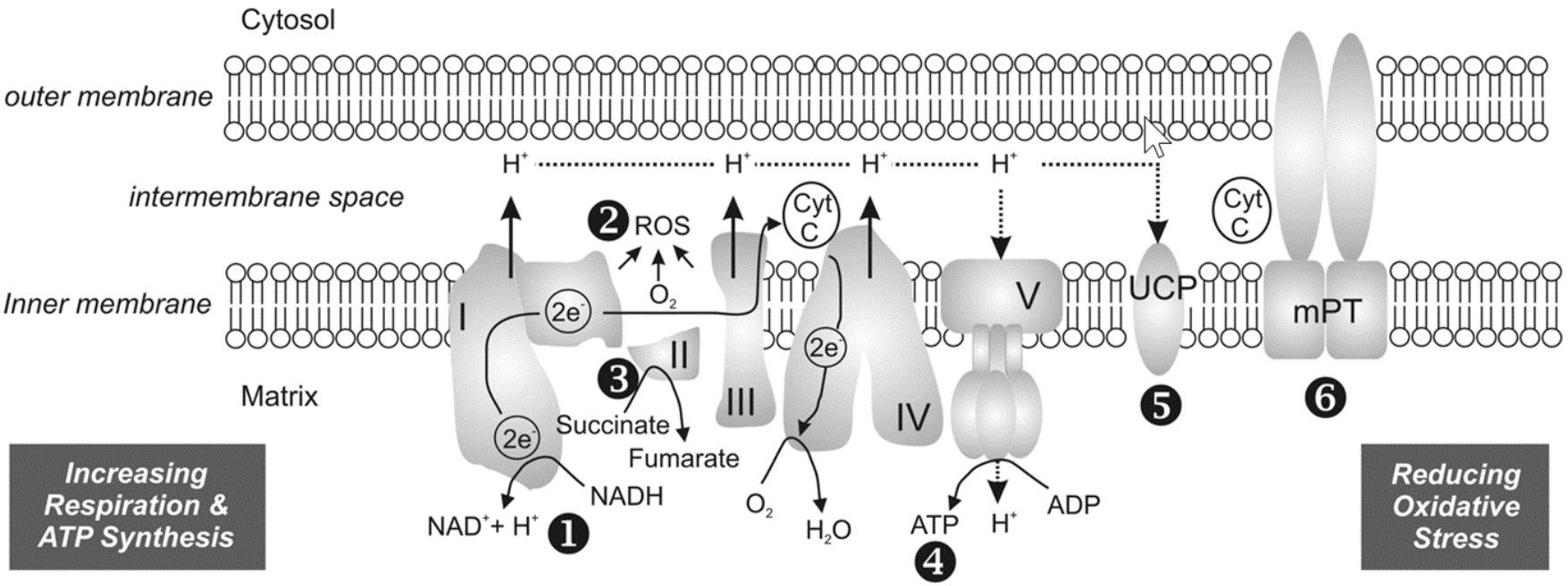




Ahn et al, Int J Mol Sci 2020

Beta-Hydroxybutyrate: Mitochondrial Effects

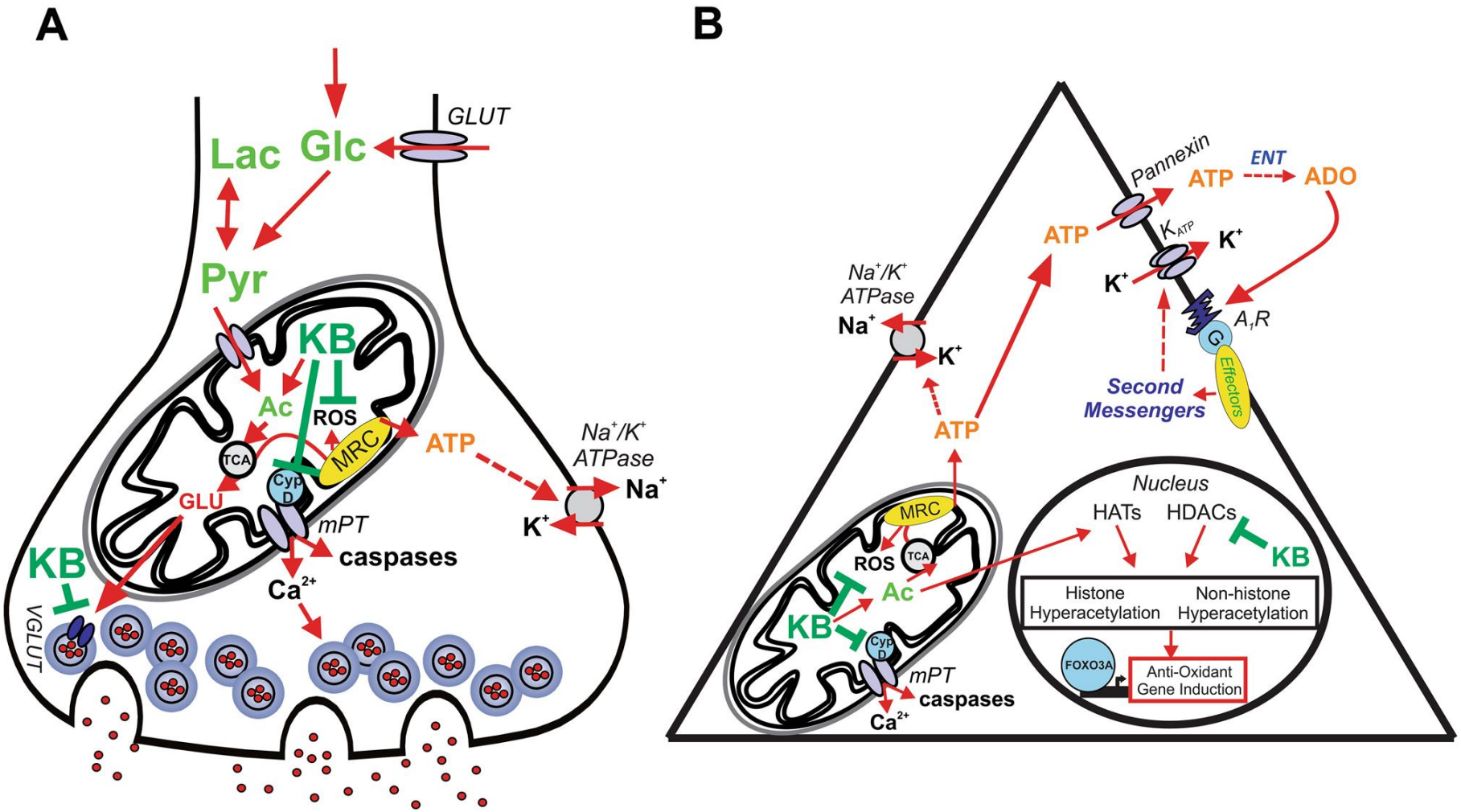




1,2. Maalouf et al, Neuroscience 2007
2,3,4. Kim et al, J Neurochem 2010
5. Sullivan et al, Ann Neurol 2004
6. Kim et al, J Neurochem 2007 and Kim et al, Ann Neurol 2015

Adapted from Masino & Rho, Adv Neurol 2012

Ketone Bodies as Anti-Seizure Agents: A Mechanistic Summary



Simeone et al, Neurochem Res 2017

Ketone Body Efficacy in Models of Seizures & Hyperexcitability

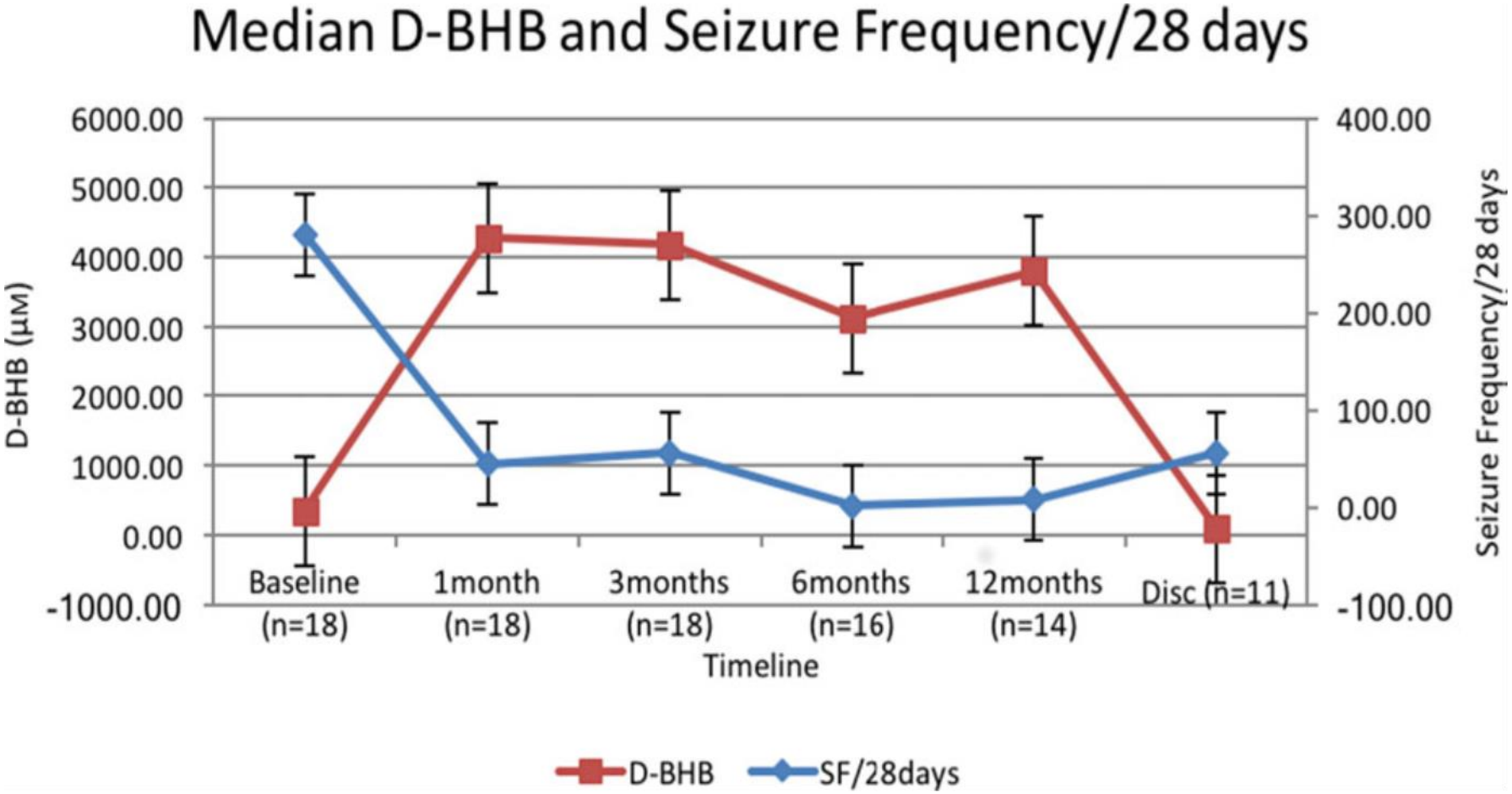
In vivo	Acetone	AcAc	BHB
Induced Seizures			
Thujone	+	+	-
Audiogenic	+	+ (BD-AcAc2, AS mice)	-
MES	+	N.D.	N.D.
PTZ	+	+ (BD-AcAc2)	N.D.
Amygdala Kindling	+	N.D.	N.D.
AY-9944	+	N.D.	N.D.
4-AP	+	+	N.D.
Li-pilo SE	+	N.D.	N.D.
Hyperbaric Oxygen	N.D.	+ (BD-AcAc2)	- (1,3-butandiol)
Kainate	N.D.	+ (BD-AcAc2, AS mice)	N.D.
Repeated flurothyl	N.D.	N.D.	+ (rat neonates)
Spontaneous Seizures			
Intrahippocamapal Kainate	N.D.	+	N.D.
betamethasone-NMDA	N.D.	N.D.	+
Kcna1-null mice	N.D.	N.D.	+

In vitro	Acetone	AcAc	BHB
Cellular and population excitability			
mEPSCs	N.D.	+	N.D.
Field Potentials	N.D.	-	-
Population Spikes	N.D.	-	-
LTP	N.D.	-	-
Mitochondrial mediated synaptic dysfunction			
ETC inhibitors	N.D.	+	+
ROS	N.D.	+	+
Induced Seizure-like events in slices			
4-AP	N.D.	N.D.	-
Low Mg^{2+}	N.D.	N.D.	-
PTZ	N.D.	-	-
bicuculline	N.D.	N.D.	-
High frequency stimulation	N.D.	N.D.	-
OGD	N.D.	N.D.	+
Kcna1-null mice	N.D.	+	+

Abbreviations: AcAc, acetoacetate; BHB, β-hydroxybutyrate; MES, maximal electroshock; PTZ, pentylenetetrazole; 4-AP, 4-aminopyridine; Li-pilo, lithium pilocarpine; SE, status epilepticus; HFS, high-frequency stimulation; OGD, Oxygen-glucose deprivation; N.D., not determined; +, attenuation effect; -, inactive; BD-AcAc2, R,S-1,3-butanediol acetoacetate diester; AS, Angelman syndrome; mESPC, miniature excitatory post-synaptic current; LTP, long-term potentiation; ETC, electron transport chain; ROS, reactive oxygen species.

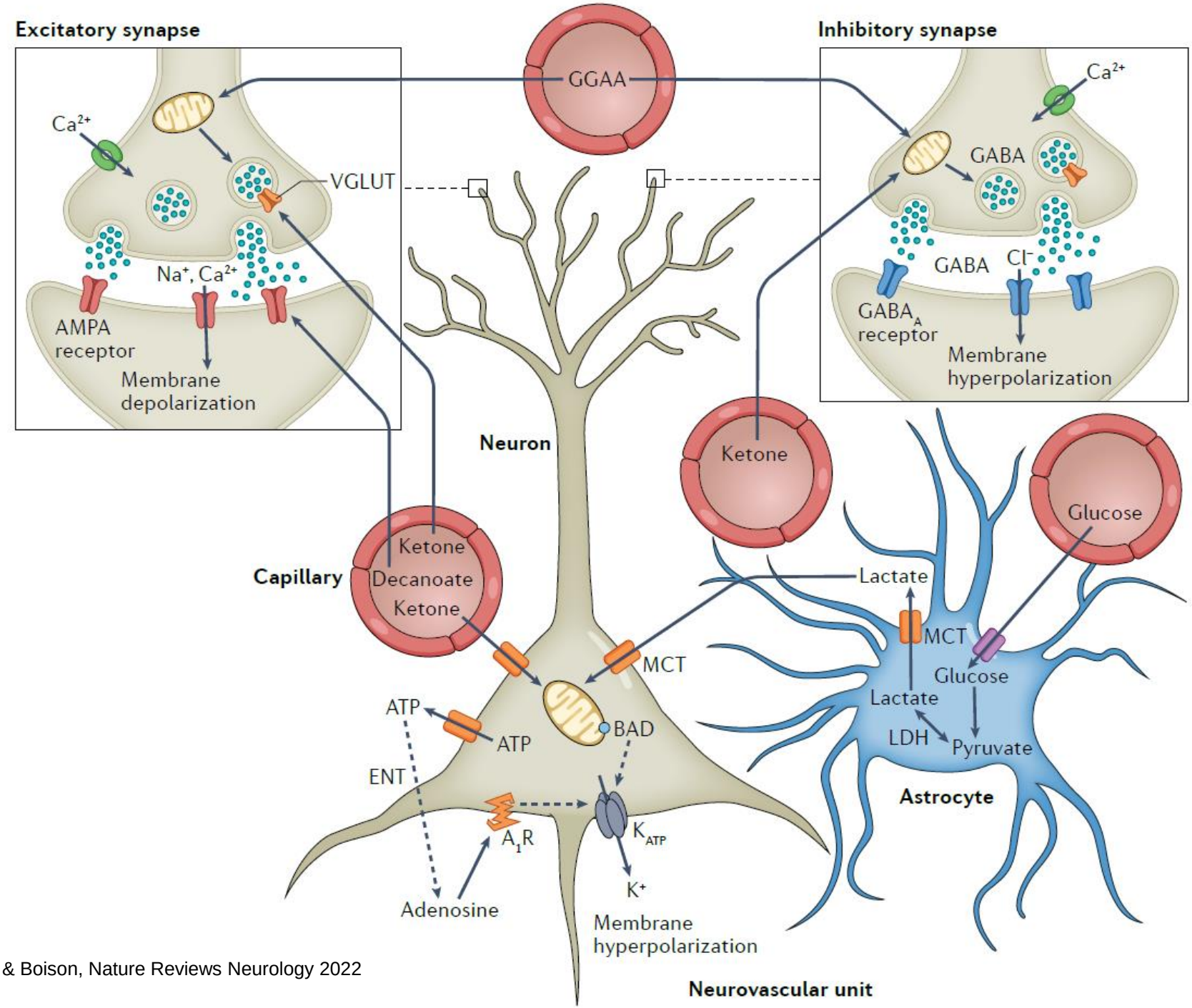
Simeone et al, Neuropharmacology 2018

Do Ketone Body Levels Correlate With Seizure Control?

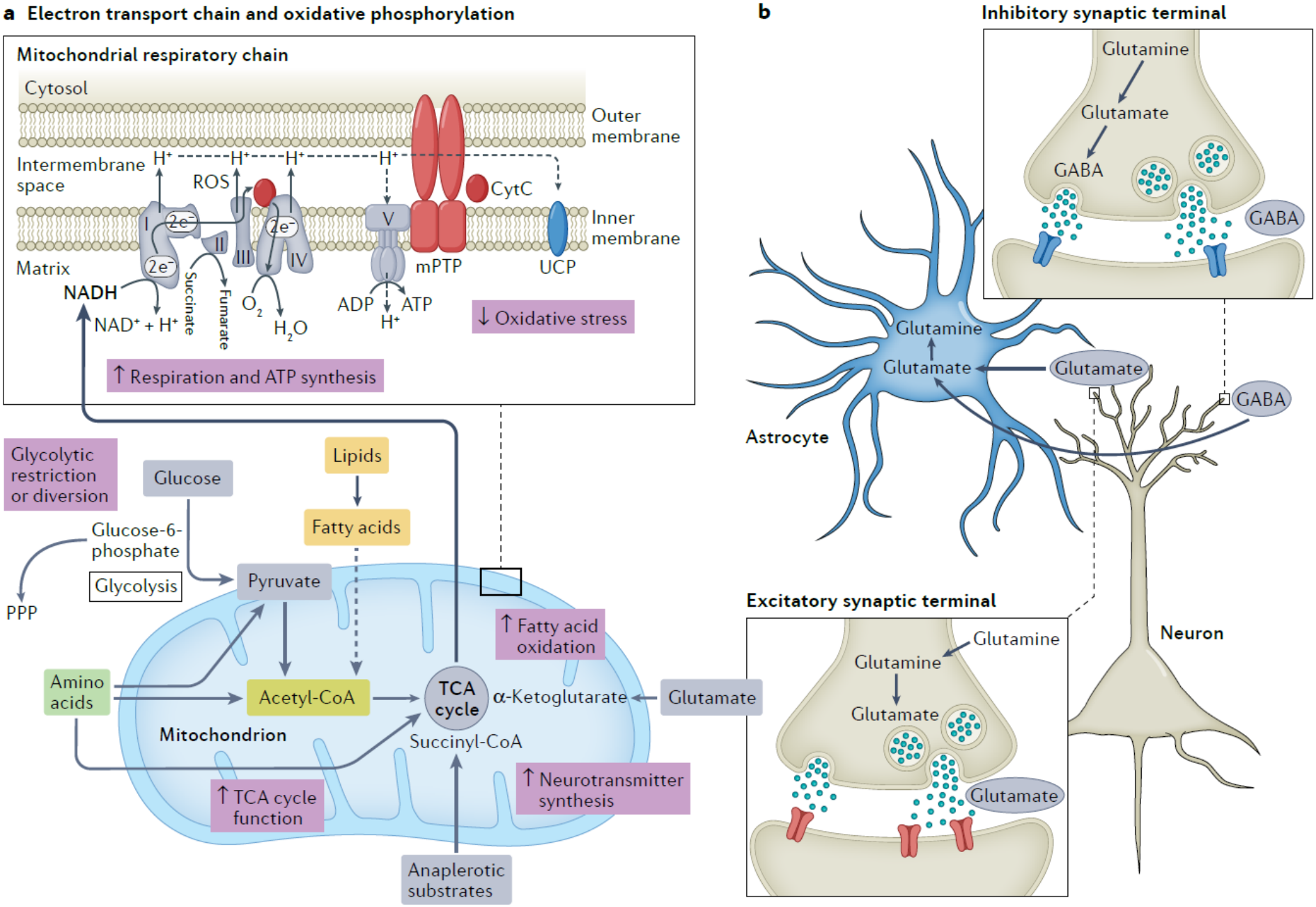


Buchhalter et al, Epilepsia Open 2017

Ketogenic Diet Mechanisms: Metabolism at the Synapse



Rho & Boison, Nature Reviews Neurology 2022



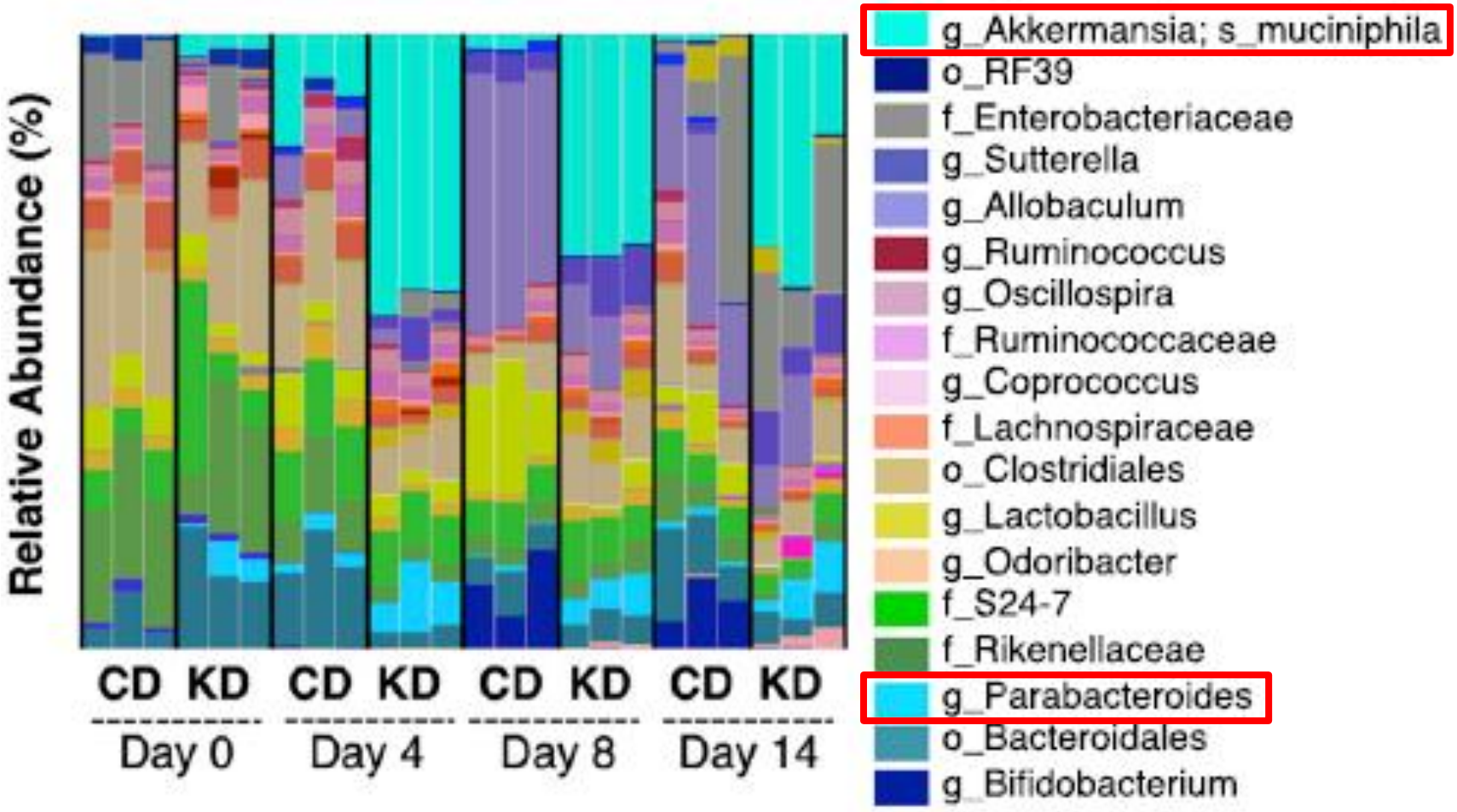
Rho & Boison, Nature Reviews Neurology 2022

The Ketogenic Diet and the Gut Microbiome

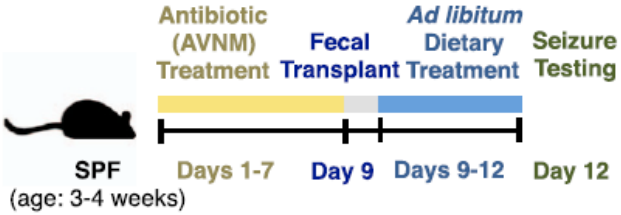
The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet

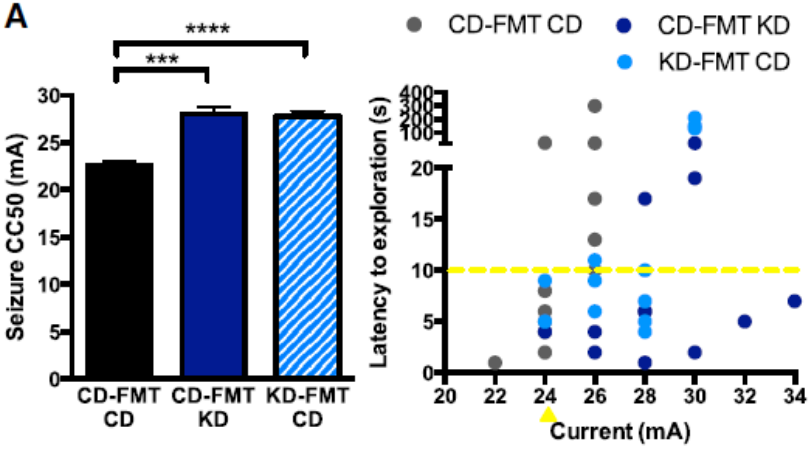
Cell 2018

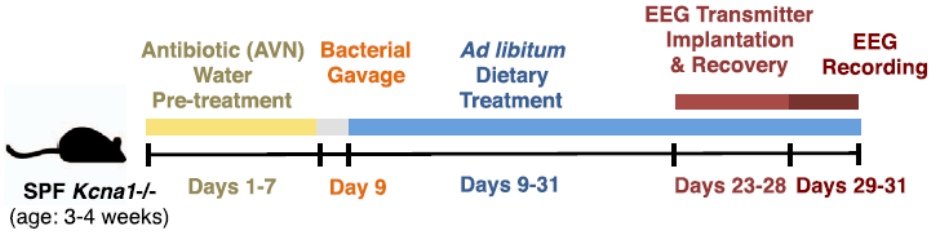
Christine A. Olson,[1] Helen E. Vuong,[1] Jessica M. Yano,[1] Qingxing Y. Liang,[1] David J. Nusbaum,[1] and Elaine Y. Hsiao[1,2,*]
[1]Department of Integrative Biology and Physiology, University of California, Los Angeles, Los Angeles, CA 90095, USA
[2]Lead Contact
*Correspondence: ehsiao@ucla.edu
https://doi.org/10.1016/j.cell.2018.04.027

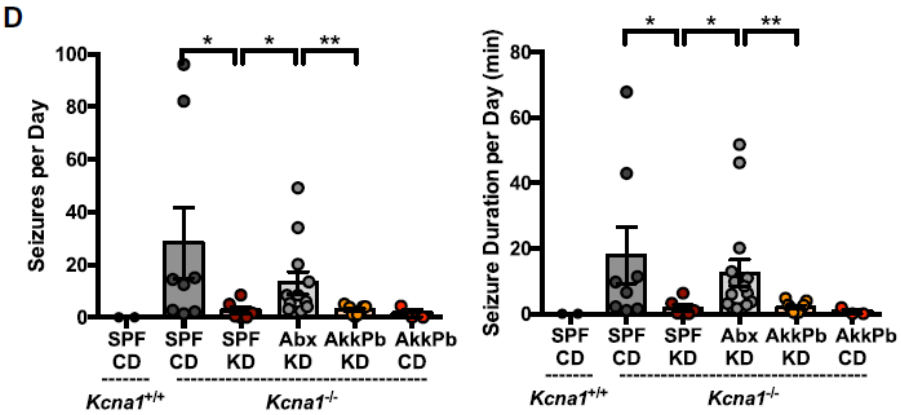


Fecal Microbiome Transplantation and Bacterial Enrichment









Olson et al, Cell 2018

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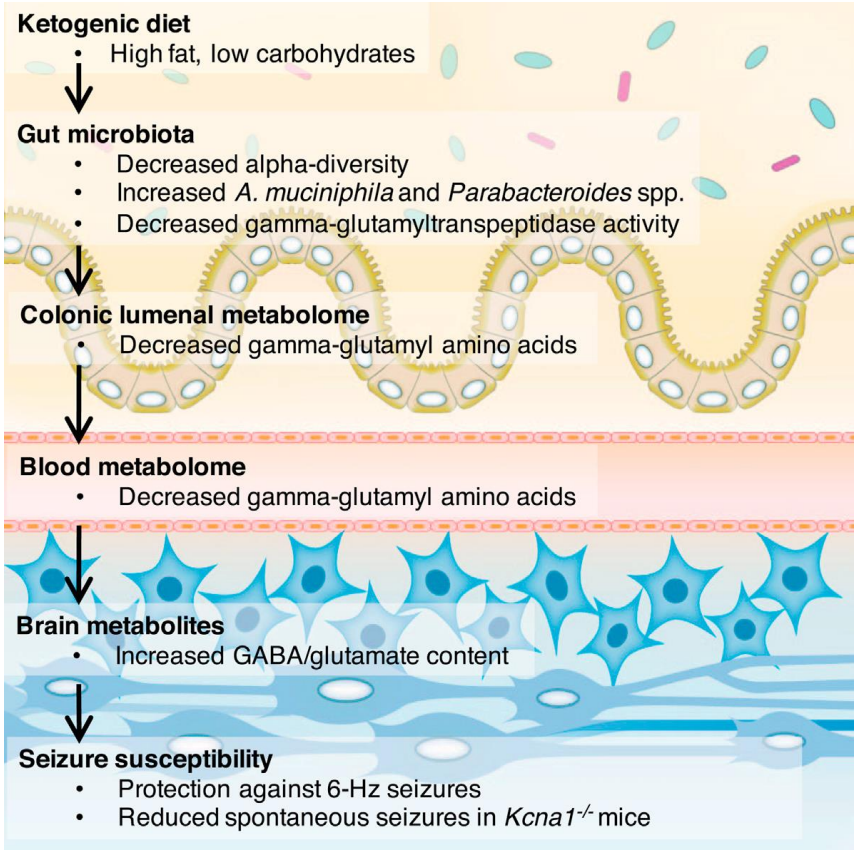

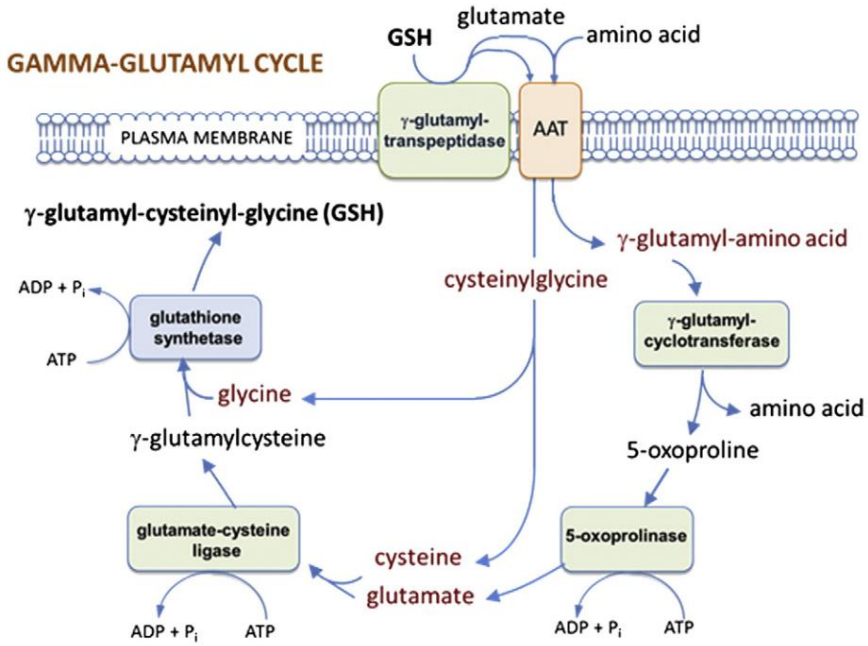

https://flipper.diff.org/app/pathways/info/8031

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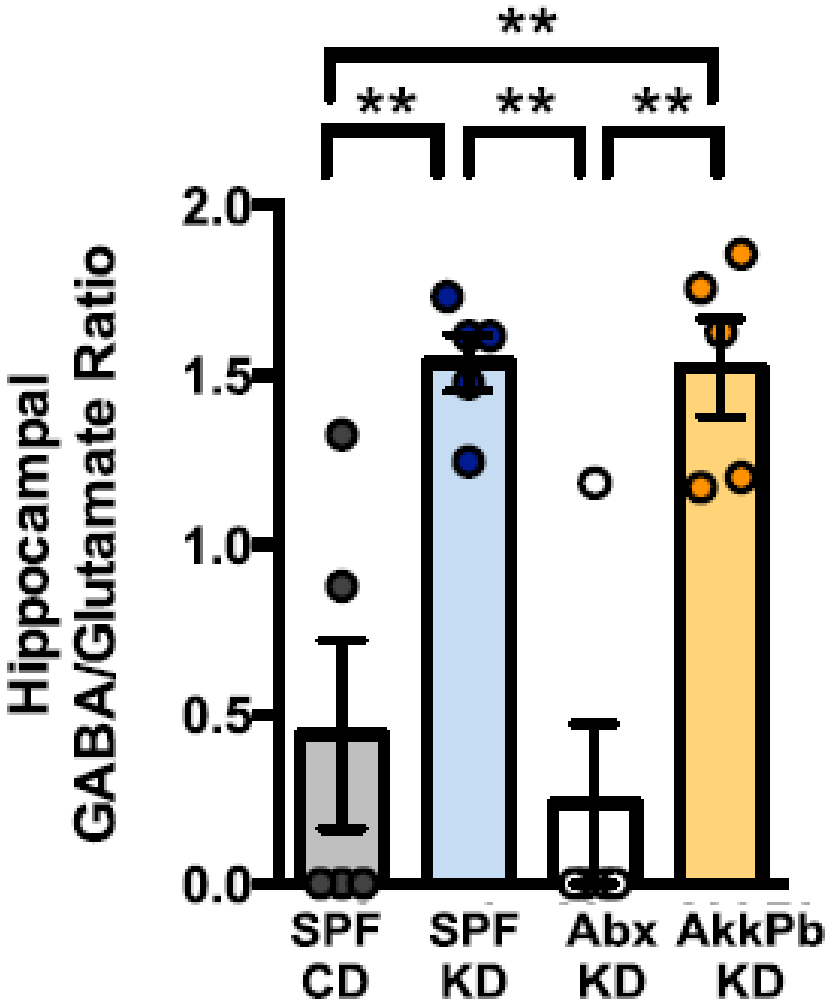
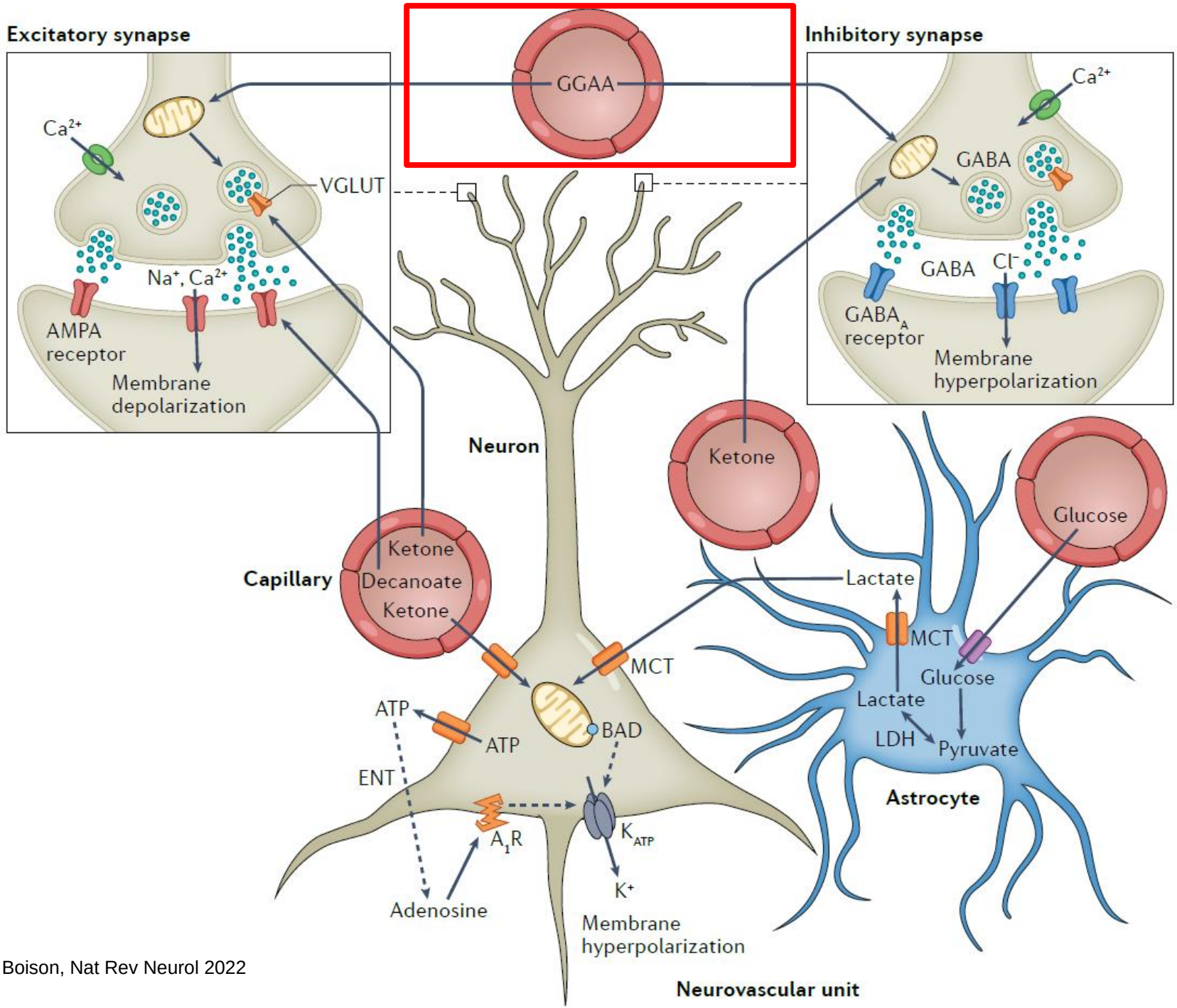
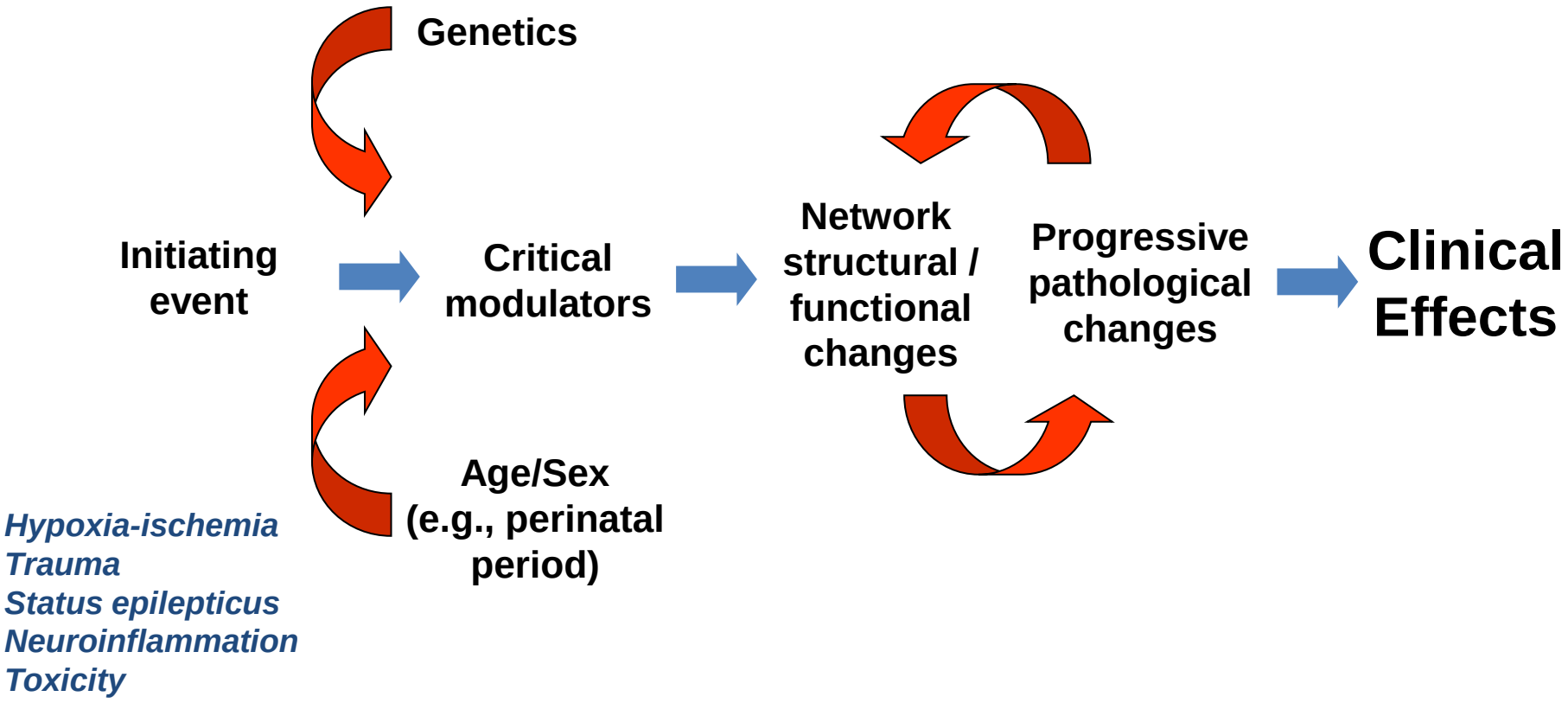


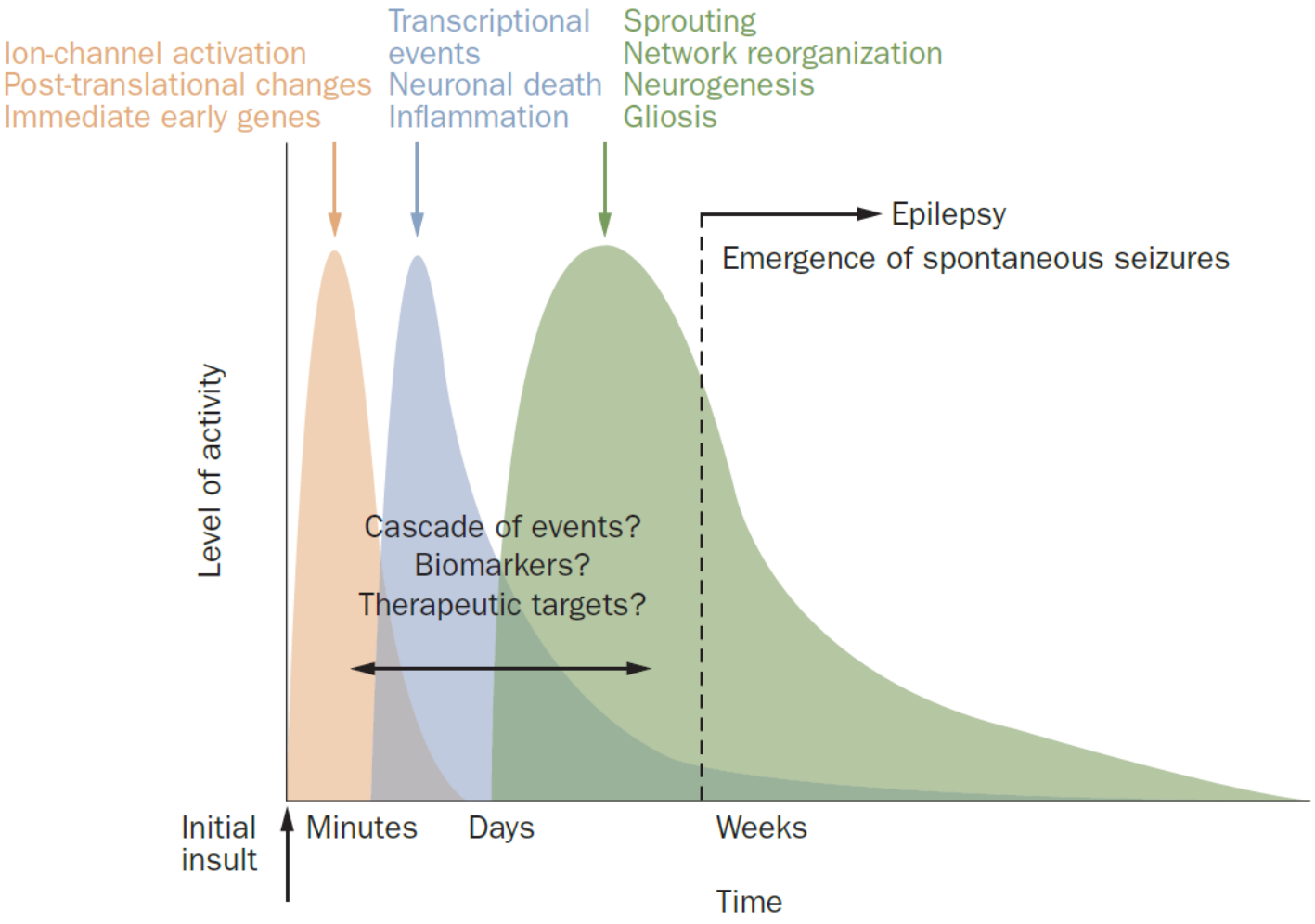


Rho & Boison, Nat Rev Neurol 2022

Neuroprotection & Disease Modification

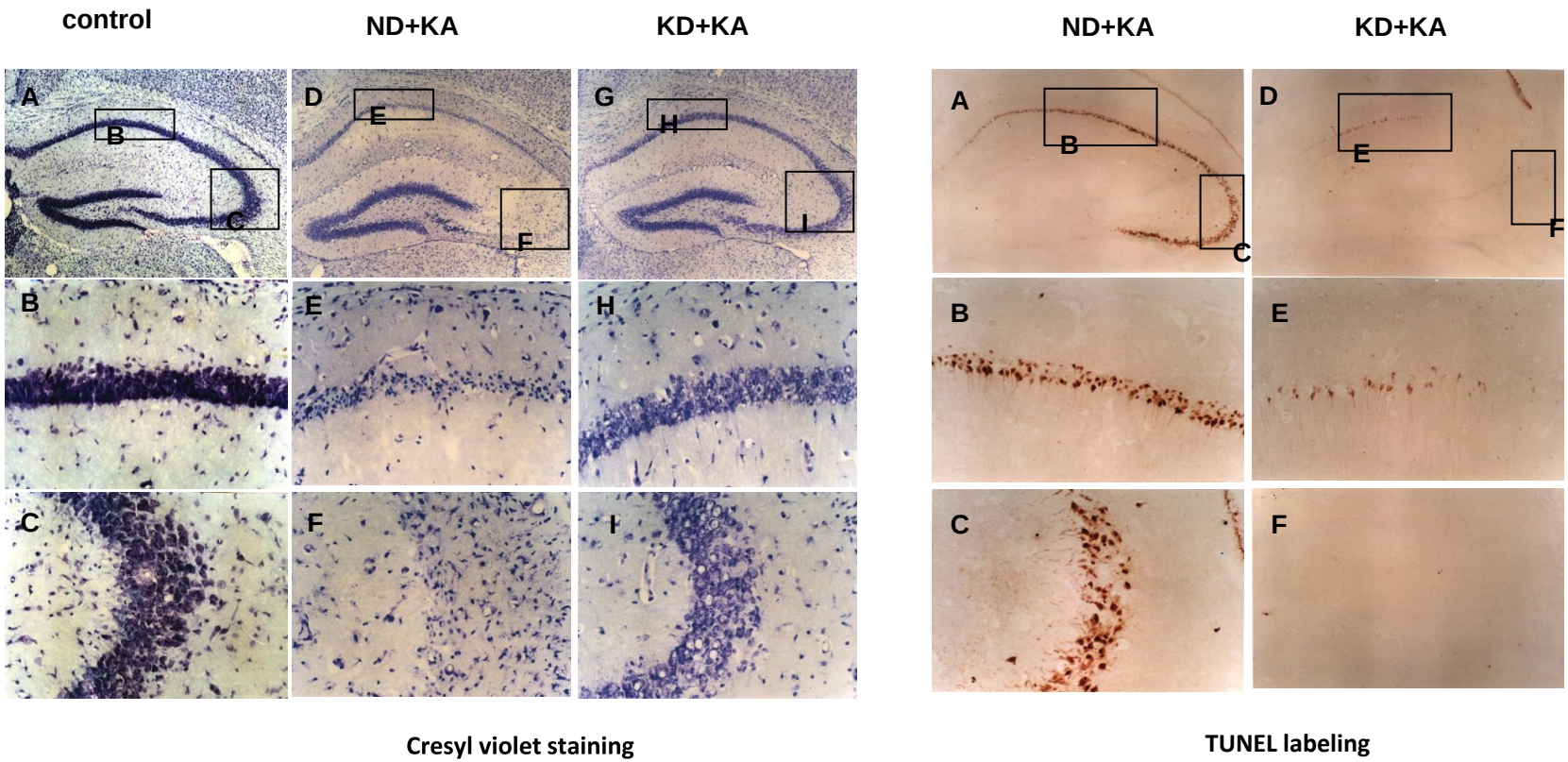


Epileptogenesis



Rakhade & Jensen, Nat Rev Neurol 2009

Ketogenic Diet Protects Against Kainic Acid-Induced Cell Death



Cresyl violet staining

TUNEL labeling

Noh et al., Epilepsy Res 2003

Received: 14 January 2021 | Revised: 14 June 2021 | Accepted: 14 June 2021

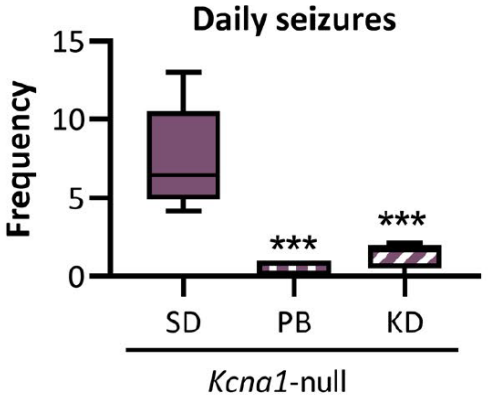
DOI: 10.1111/epi.16983

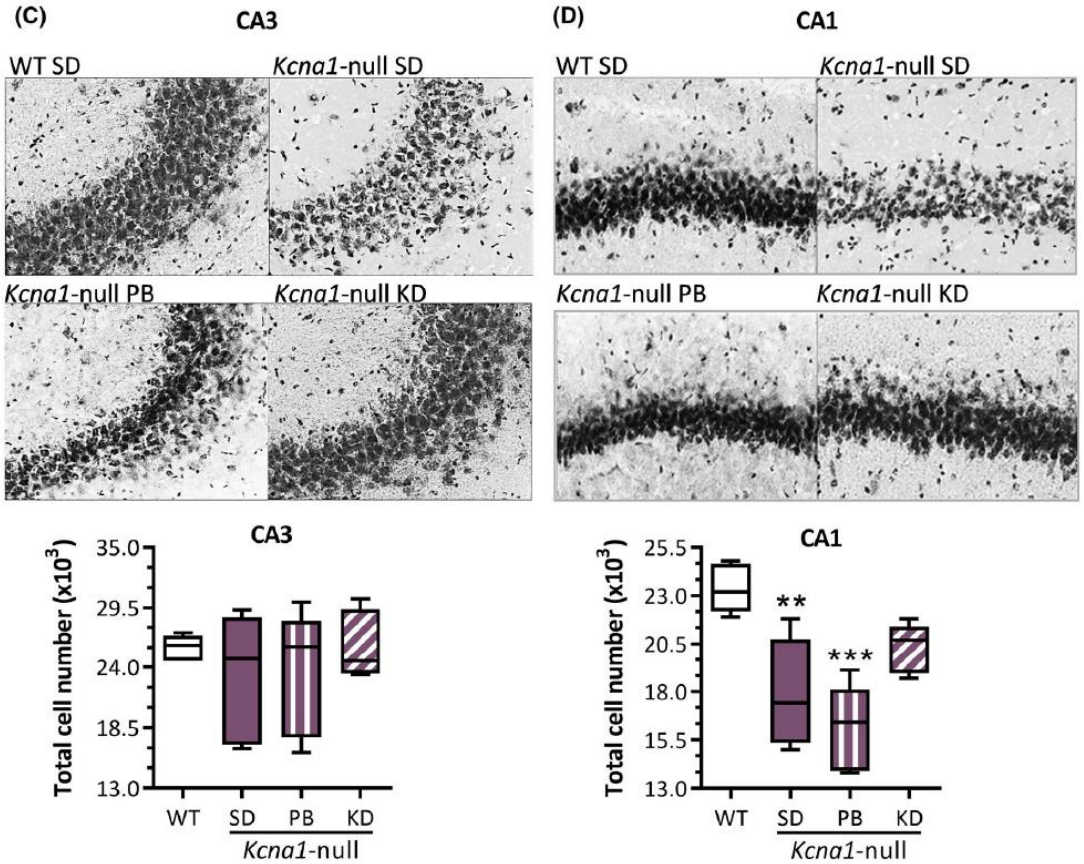
Epilepsia®

BRIEF COMMUNICATION

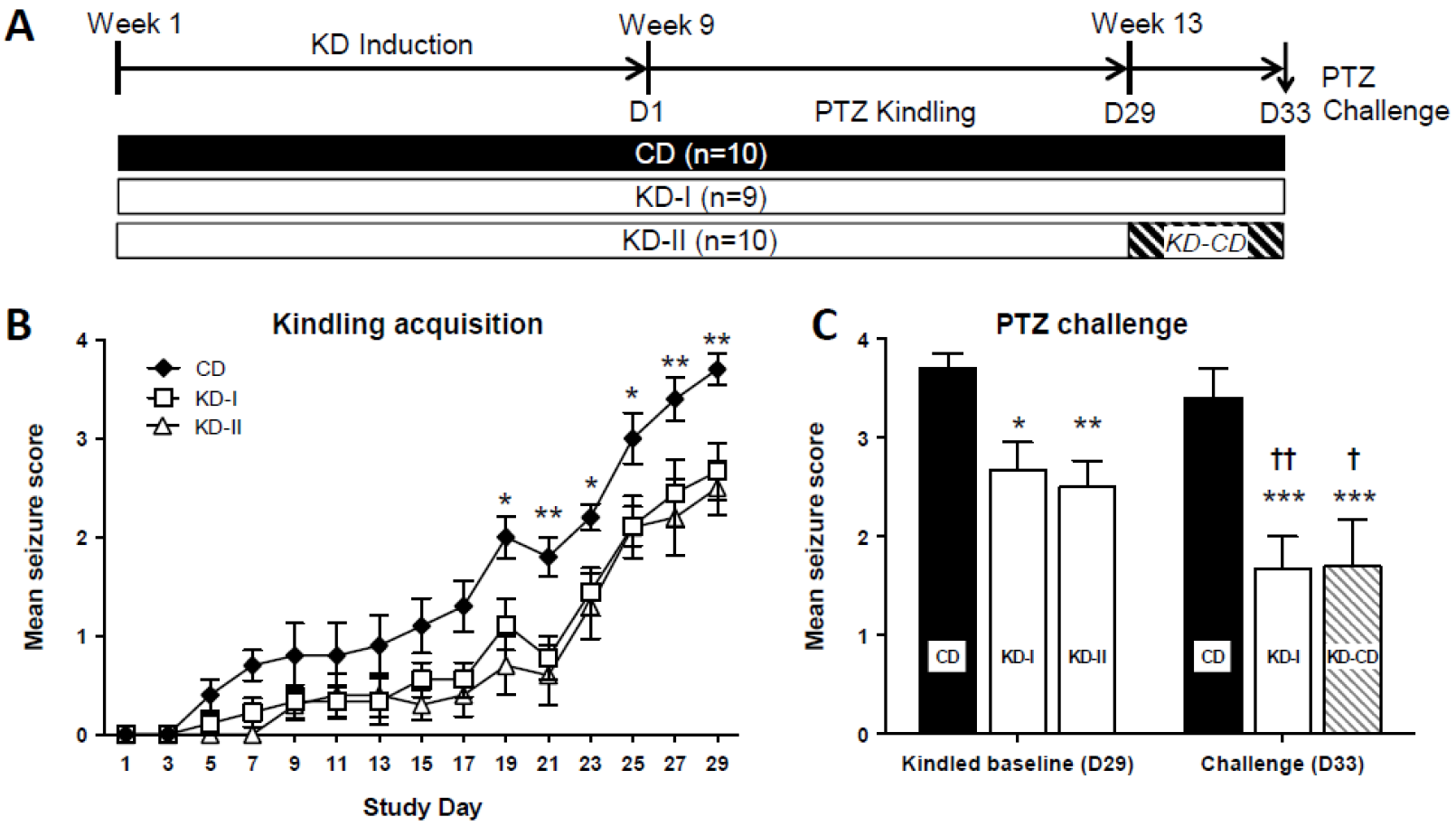
Ketogenic diet–mediated seizure reduction preserves CA1 cell numbers in epileptic *Kcna1*-null mice: An unbiased stereological assessment

Kristina A. Simeone[1] | Julianne C. Wilke[2,3] | Stephanie A. Matthews[1] | Timothy A. Simeone[1] | Jong M. Rho[2,3,4]



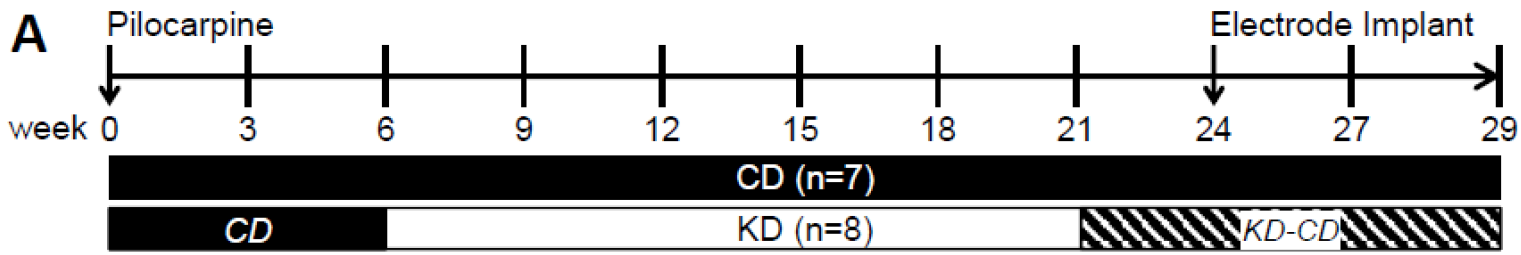


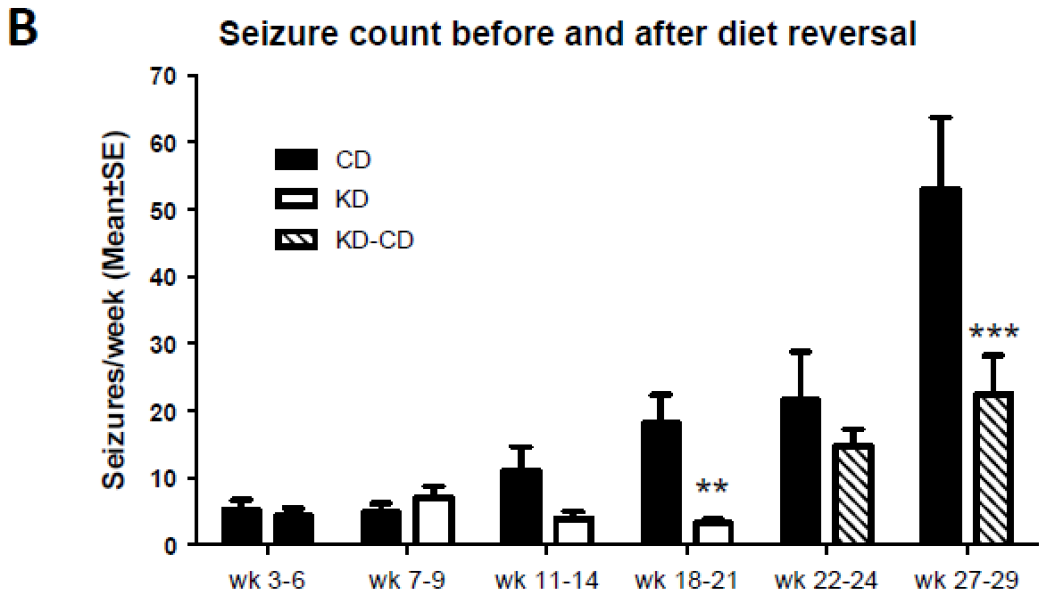
Disease Modification: KD Prevents Kindling Epileptogenesis



Lusardi et al, Neuropharmacology 2015

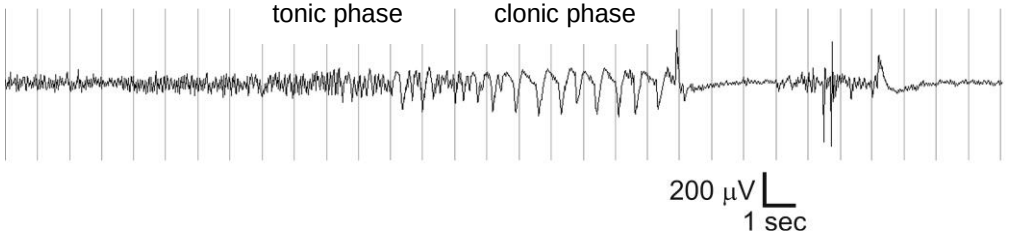
Disease Modification: KD Prevents Pilocarpine-Induced Epileptogenesis

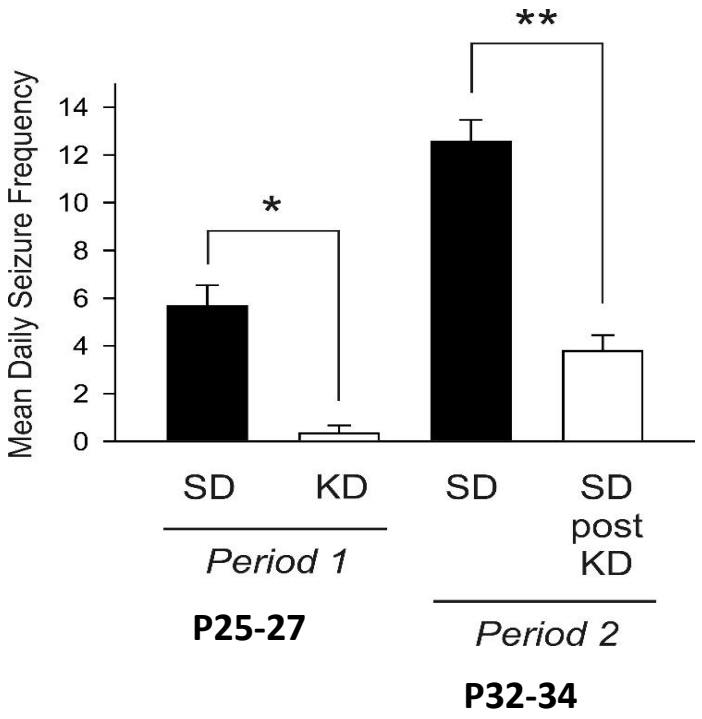




Lusardi et al, Neuropharmacology 2015

Ketogenic Diet Blocks Epileptogenesis in *Kcna1*-null Mice

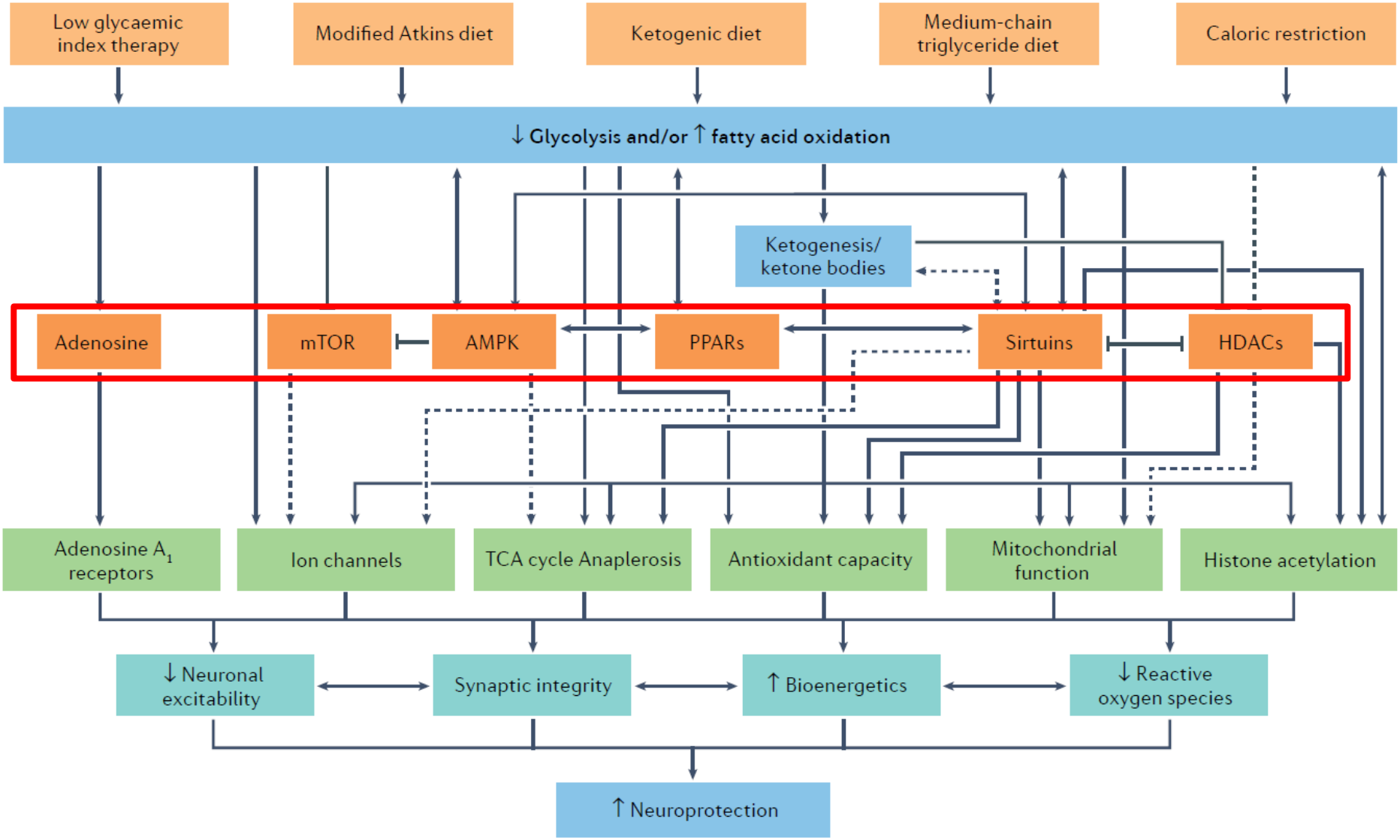




Unpublished data

*, P<0.05: **, P<0.01

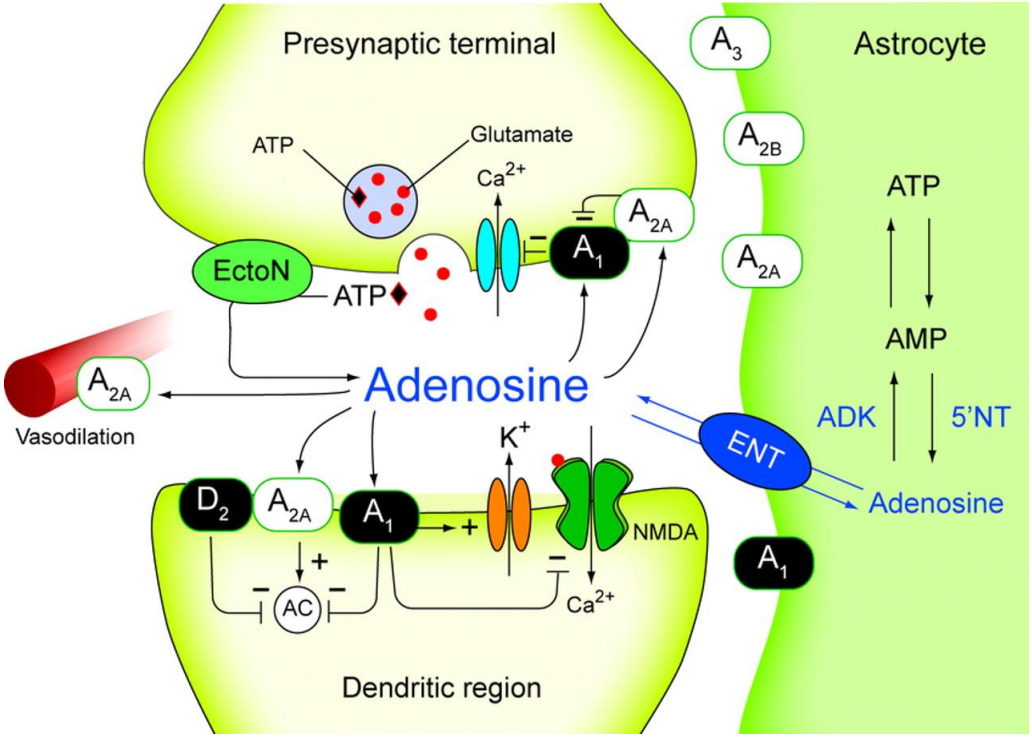
The Ketogenic Diet and Neuroprotection



Rho & Boison, Nat Rev Neurol 2022

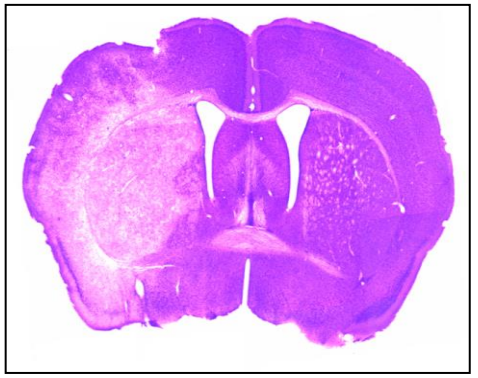
Adenosine and Neuroprotection

Stroke prevention by adenosine-releasing stem cells

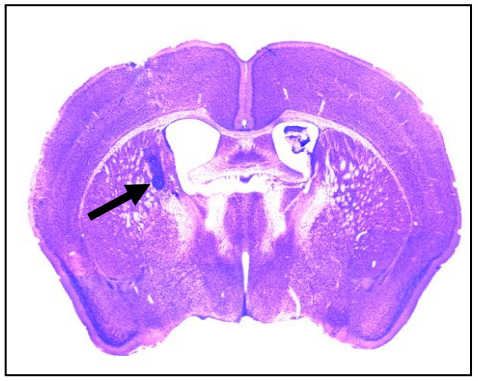


Bennaroch, Neurology 2008

Stroke - MCAO control



Stroke prevention after cell graft



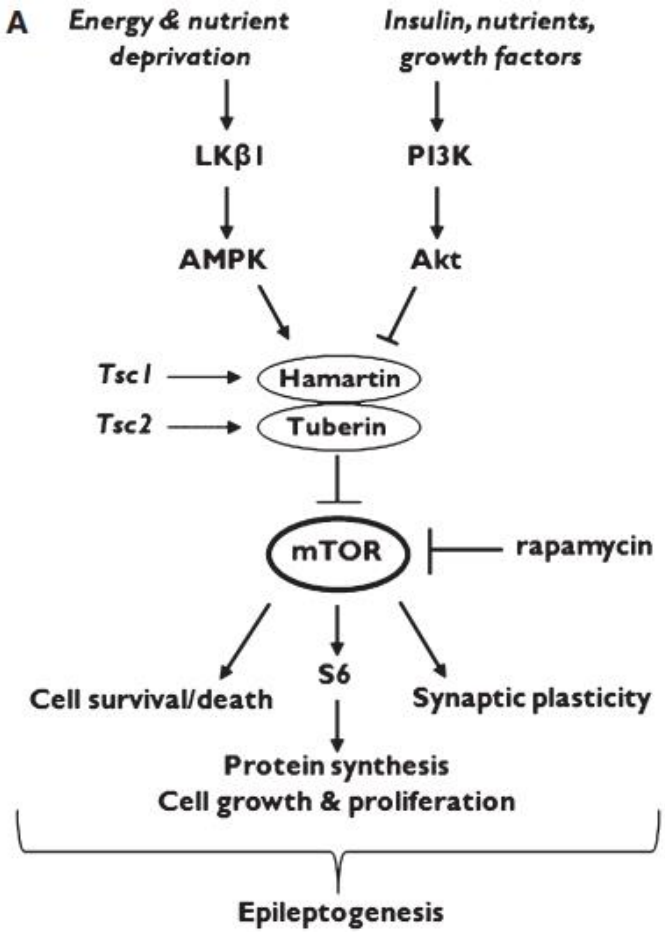
Pignataro et al, J Cereb Blood Flow Metab 2007

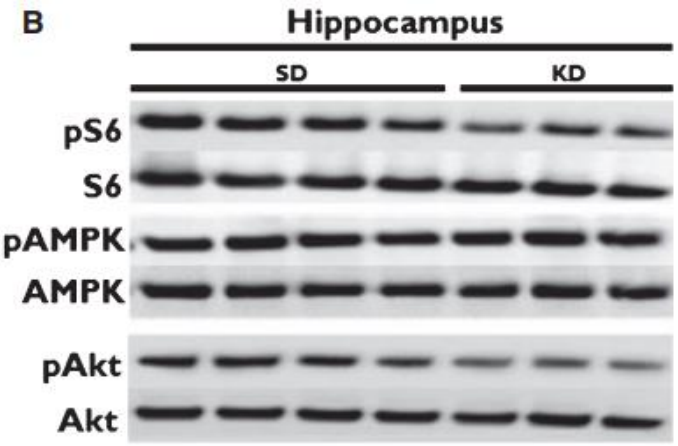
Epilepsia, 52(3):e7–e11, 2011
doi: 10.1111/j.1528-1167.2011.02981.x

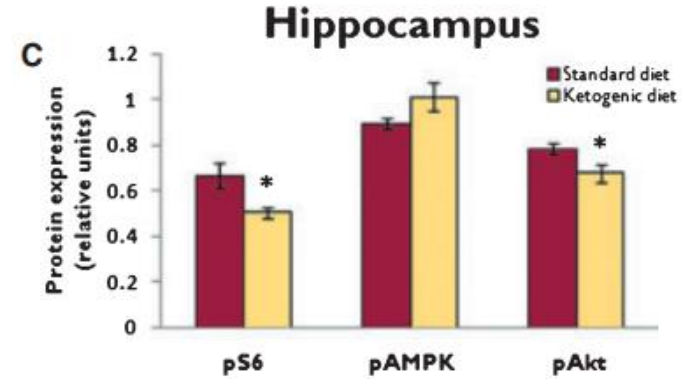
BRIEF COMMUNICATION

The ketogenic diet inhibits the mammalian target of rapamycin (mTOR) pathway

Sharon S. McDaniel, Nicholas R. Rensing, Liu Lin Thio, Kelvin A. Yamada, and Michael Wong







Experimental Neurology 287 (2017) 54–64

Contents lists available at ScienceDirect

Experimental Neurology

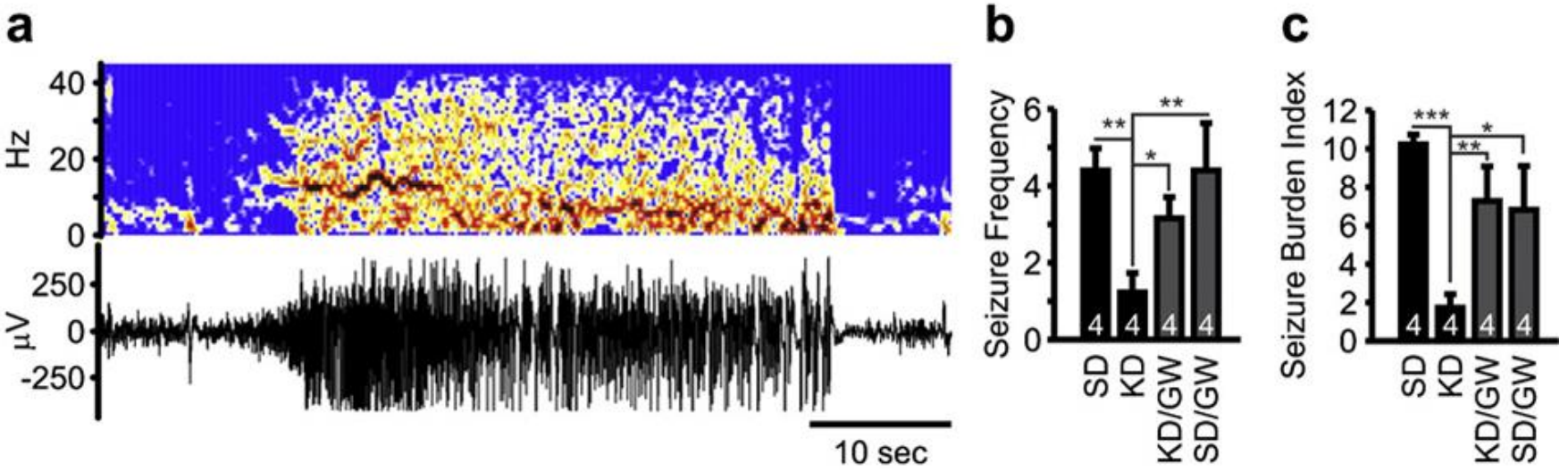
journal homepage: www.elsevier.com/locate/yexnr

Research Paper

Regulation of brain PPARgamma2 contributes to ketogenic diet anti-seizure efficacy

Timothy A. Simeone Ph.D *, Stephanie A. Matthews M.S, Kaeli K. Samson M.S, Kristina A. Simeone Ph.D

Creighton University, School of Medicine, Department of Pharmacology, Omaha, NE 68174, USA



nutrients 2020

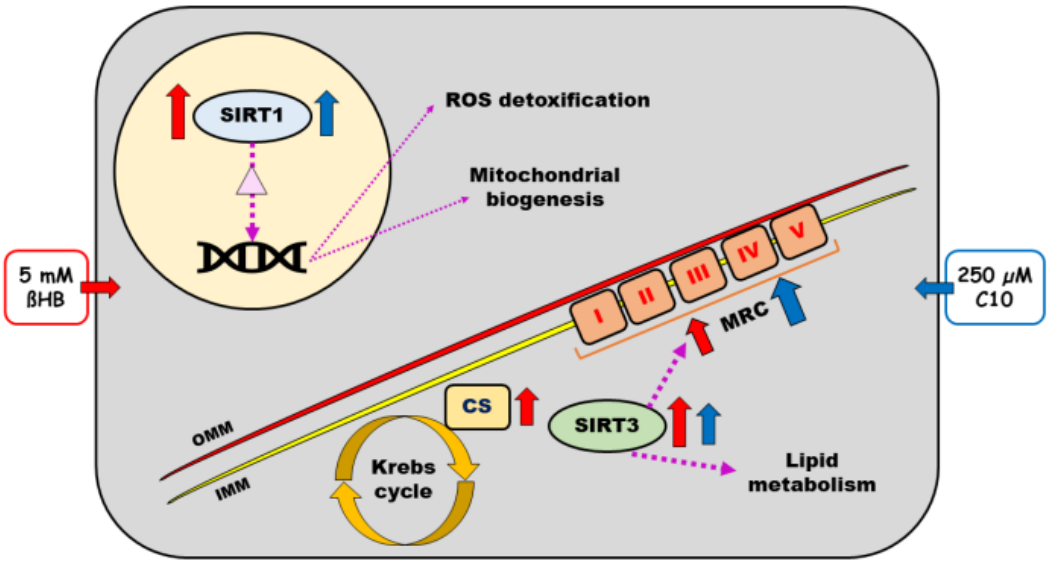
MDPI

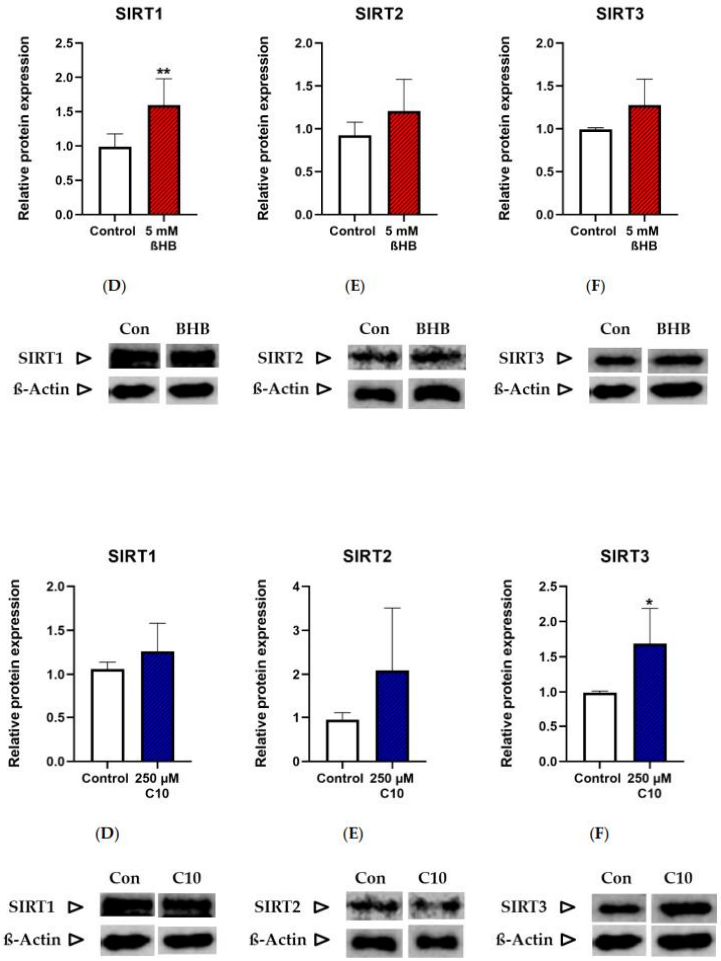
Article

Mechanism of Action of Ketogenic Diet Treatment: Impact of Decanoic Acid and Beta—Hydroxybutyrate on Sirtuins and Energy Metabolism in Hippocampal Murine Neurons

Partha Dabke and Anibh M. Das *

Clinic for Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, 30625 Hannover, Germany; dabke.partha@mh-hannover.de

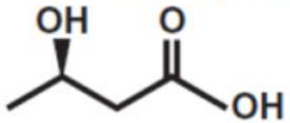




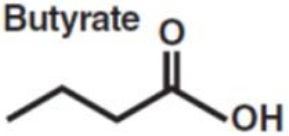
Suppression of Oxidative Stress by β-Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor

Tadahiro Shimazu,[1,2] Matthew D. Hirschey,[1,2] John Newman,[1,2] Wenjuan He,[1,2] Kotaro Shirakawa,[1,2] Natacha Le Moan,[3] Carrie A. Grueter,[4,5] Hyungwook Lim,[1,2] Laura R. Saunders,[1,2] Robert D. Stevens,[6] Christopher B. Newgard,[6] Robert V. Farese Jr.,[2,4,5] Rafael de Cabo,[7] Scott Ulrich,[8] Katerina Akassoglou,[3] Eric Verdin[1,2]*

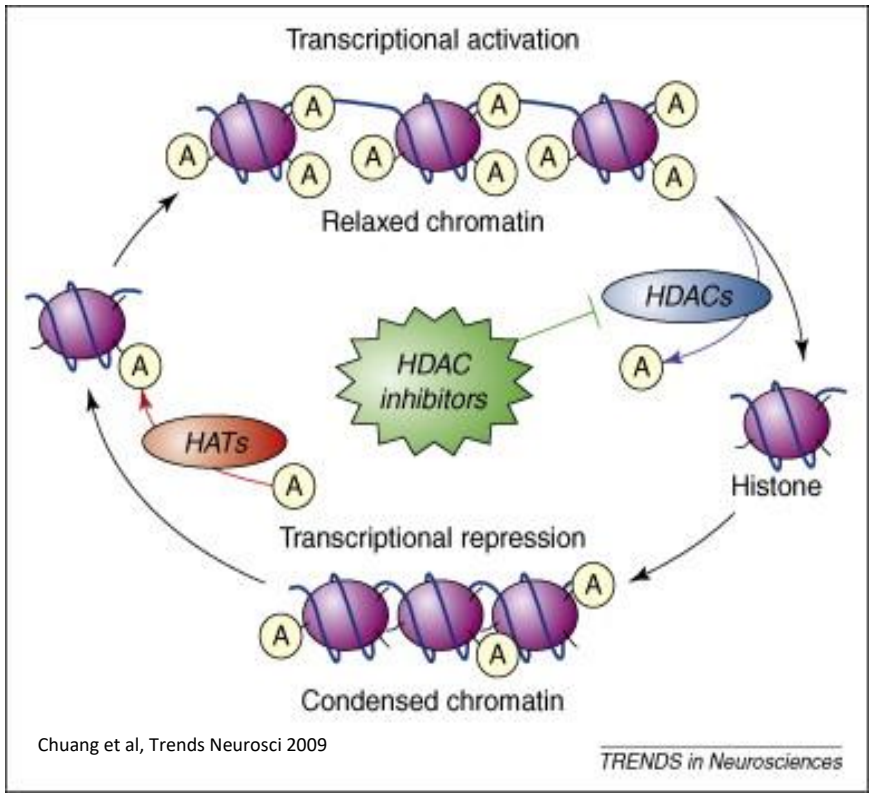
β-Hydroxybutyrate



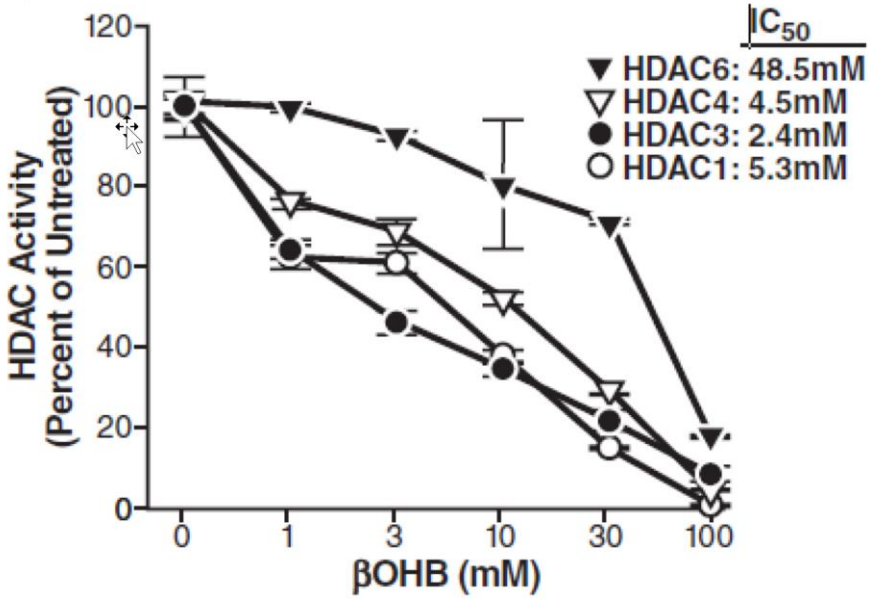
Butyrate



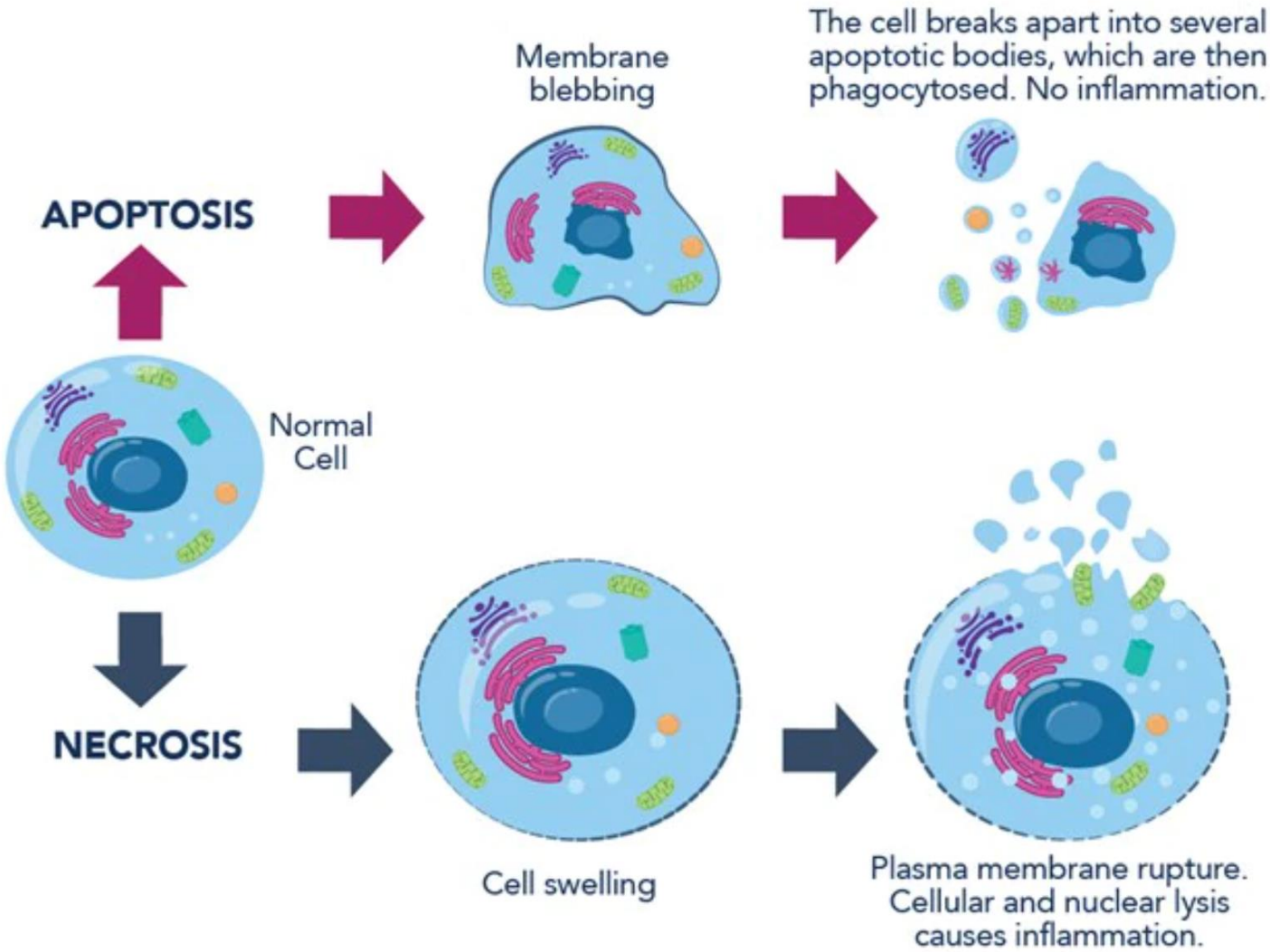
Science, 2013



Chuang et al, Trends Neurosci 2009



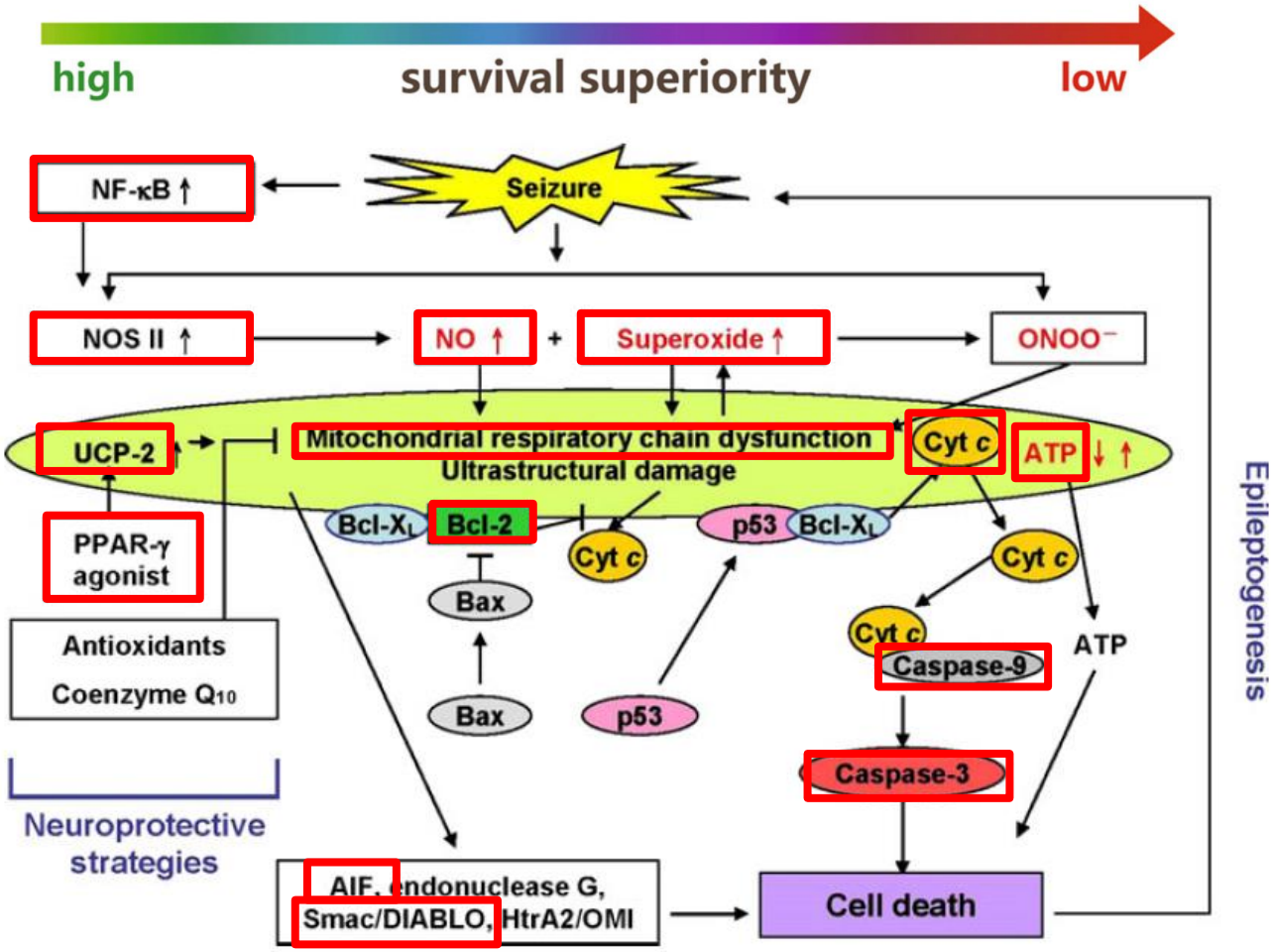
Cell Death: Apoptosis vs. Necrosis



www.ptglab.com

Ketogenic Diet Effects on Cell Death Mechanisms

Chen et al, Sig Trans Targeted Ther 2018



Chen et al, J Bioenerg Biomembr 2010

frontiers in
PHARMACOLOGY

REVIEW ARTICLE
published: 09 April 2012
doi: 10.3389/fphar.2012.00059

The ketogenic diet as a treatment paradigm for diverse neurological disorders

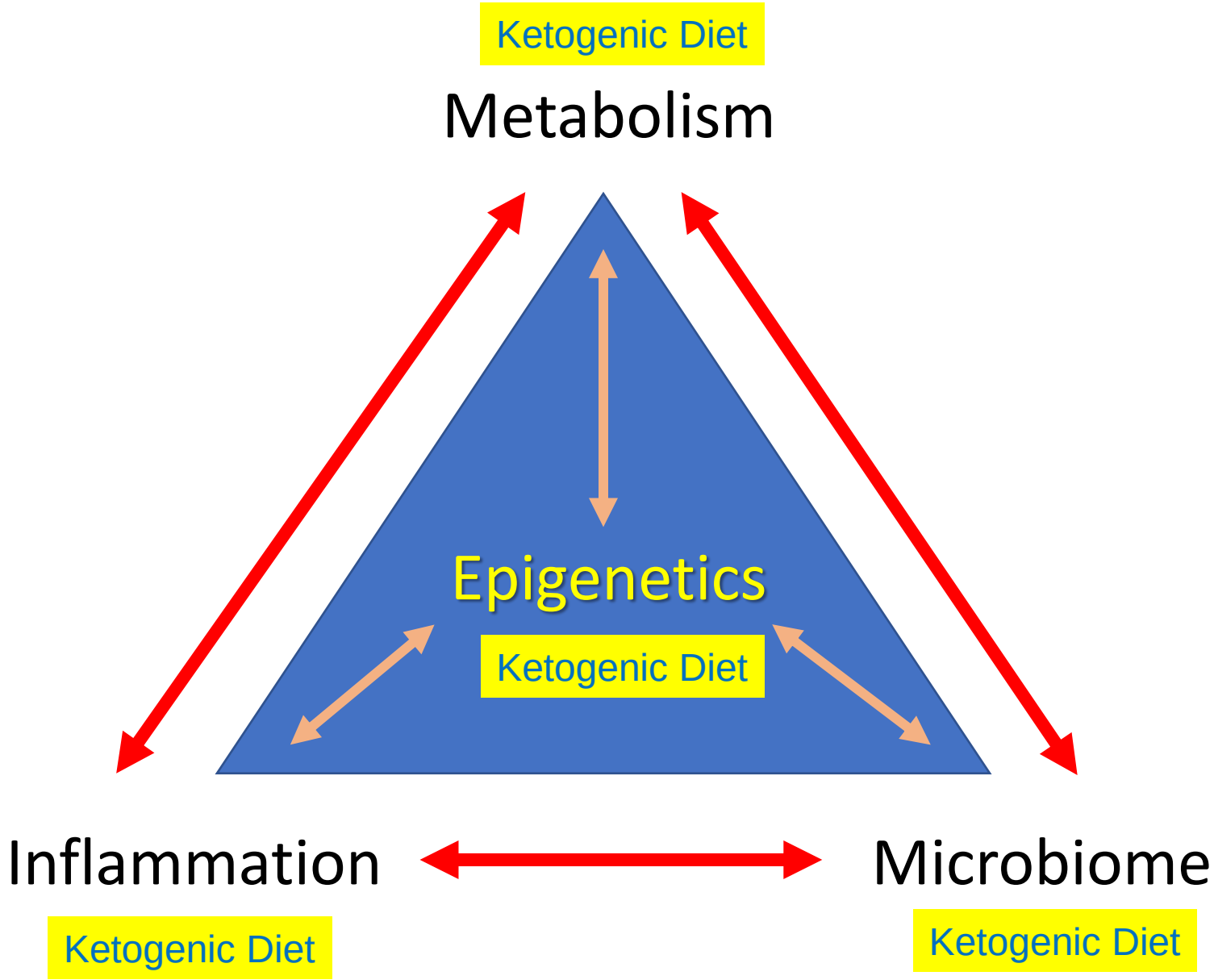
*Carl E. Stafstrom[1,2] and Jong M. Rho[3,4]**

[1] Department of Neurology, University of Wisconsin, Madison, WI, USA
[2] Department of Pediatrics, University of Wisconsin, Madison, WI, USA
[3] Department of Pediatrics, University of Calgary Faculty of Medicine, Calgary, AB, Canada
[4] Department of Clinical Neurosciences, University of Calgary Faculty of Medicine, Calgary, AB, Canada

The Ketogenic Diet: Beyond Epilepsy

- Amyotrophic Lateral Sclerosis
- Alzheimer's Disease
- Anorexia
- Autism Spectrum Disorder
- Bipolar Affective Disorder
- Brain Tumors
- Cognitive Disorders
- Depression
- Diabetes
- Glut1 Deficiency Syndrome
- Glycogenosis Type V
- Huntington Disease
- Hypertension
- Metabolic Syndrome
- Migraine
- Mitochondrial Cytopathies
  - PDH, SSADH, ETC Deficiencies
- Multiple Sclerosis
- Narcolepsy
- Obesity
- Pain Syndromes
- Parkinson's Disease
- Paroxysmal Dyskinesias
- Polycystic Ovary Syndrome
- Post-Hypoxic Myoclonus
- Schizophrenia
- Sleep Disorders
- Stroke
- Traumatic Brain and Spinal Cord Injury

Modified from Kossoff et al, J Child Neurol 2009


Ketogenic Diet
Metabolism
Epigenetics
Ketogenic Diet
Inflammation
Ketogenic Diet
Microbiome
Ketogenic Diet

Summary

- There is growing evidence that metabolic dysregulation is both a cause and consequence of epileptic seizures
- Metabolism-based treatments exert a multitude of molecular and cellular actions
- Many of the putative mechanisms of action of diet-related substrates & enzymes are relevant to neuroprotection (and potentially, disease-modification)
- The science underlying dietary therapies for epilepsy is becoming increasingly validated.

Acknowledgements

Rho Lab (Univ. Calgary and UCSD)

- Cezar Gavrilovici, PhD
- Younghee Ahn, PhD
- Jaehyouk Choi, PhD
- Bianca Villa, PhD
- Shuhe Wang
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