Endometriosi alle porte del nuovo decennio

Stili di vita: l'approccio alimentare

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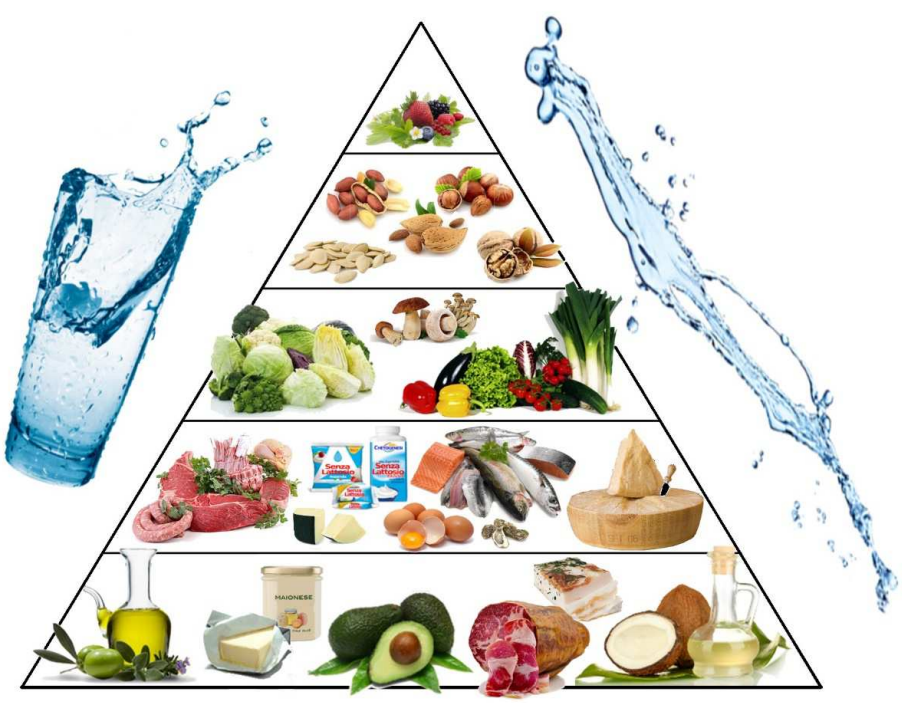
Trieste, 13/12/2019

The Ketogenic Food Pyramid



Omnivore vs Vegan

Ketogenic Diet

Blood levels	*Normal diet*	*Ketogenic diet*	*Diabetic ketoacidosis*
Glucose (mg/dl)	80-120	65-80	>300
Insulin (μU/l)	6-23	6.6-9.4	≅ 0
Glucagon	Low	High	High
KB produc. (gr/day)	Low	115-180	400
KB conc. (mmol/dl)	0.1	4-10	>20
pH	7.4	7.4	<7.3

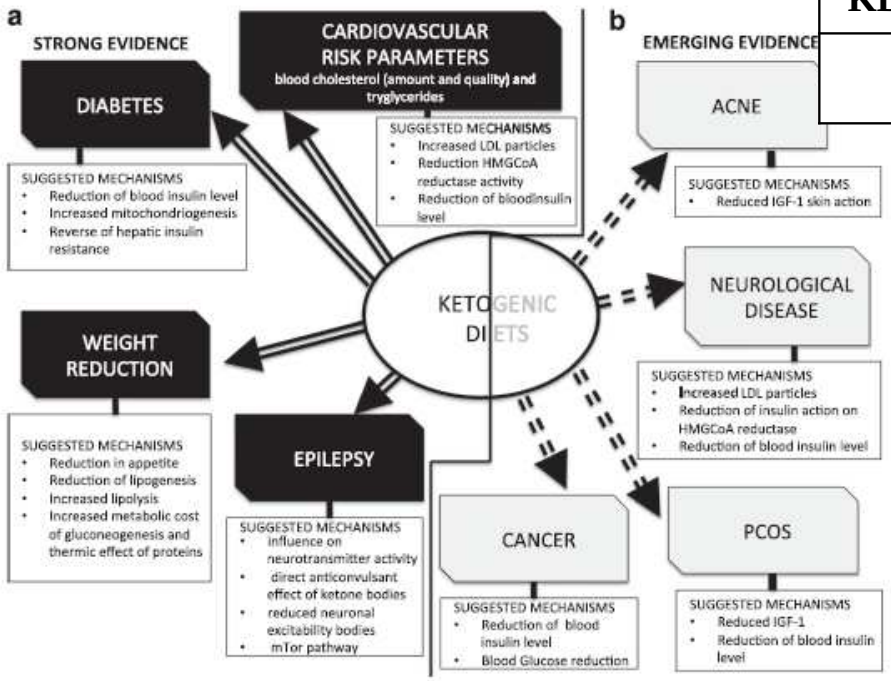
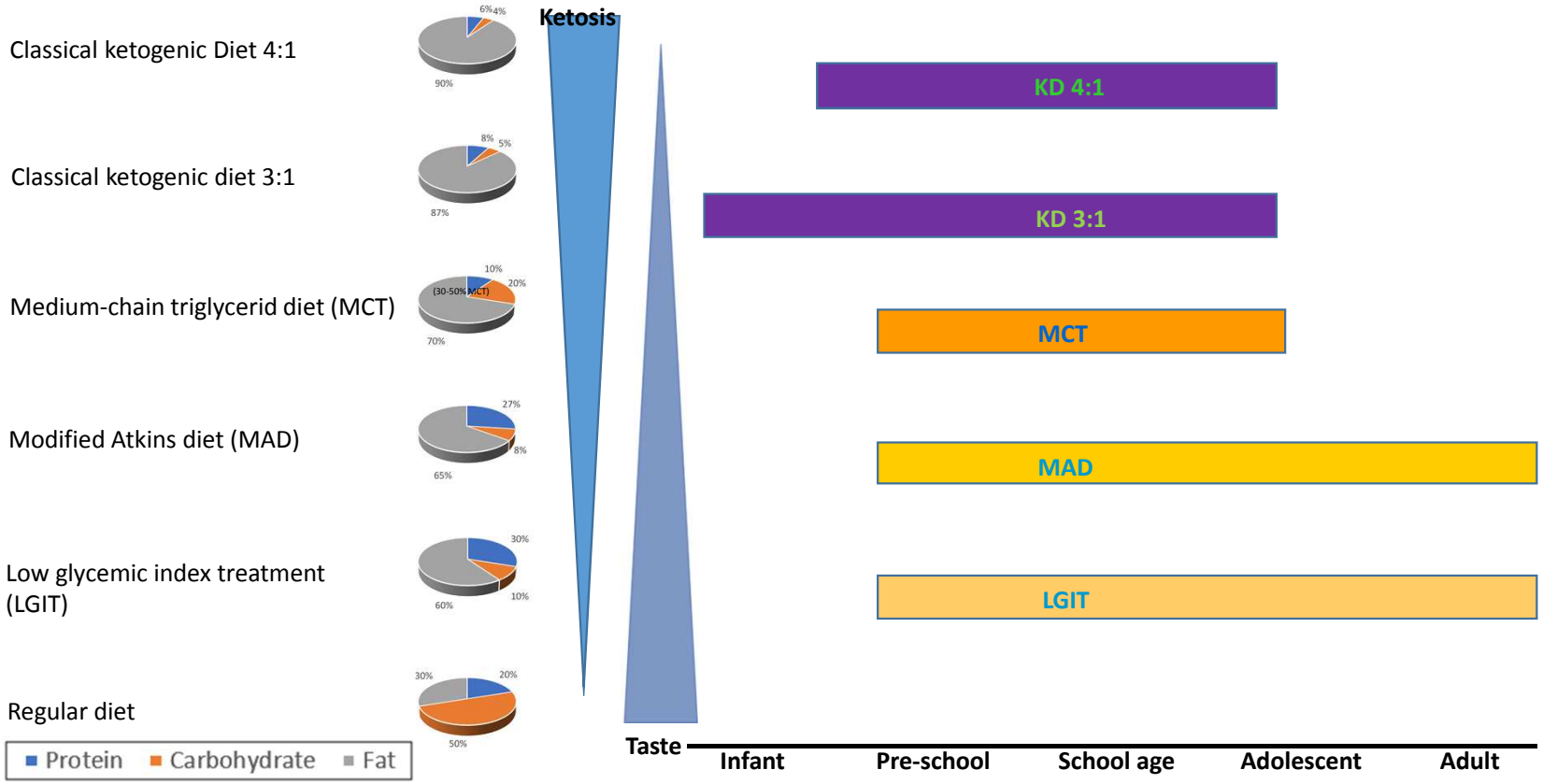
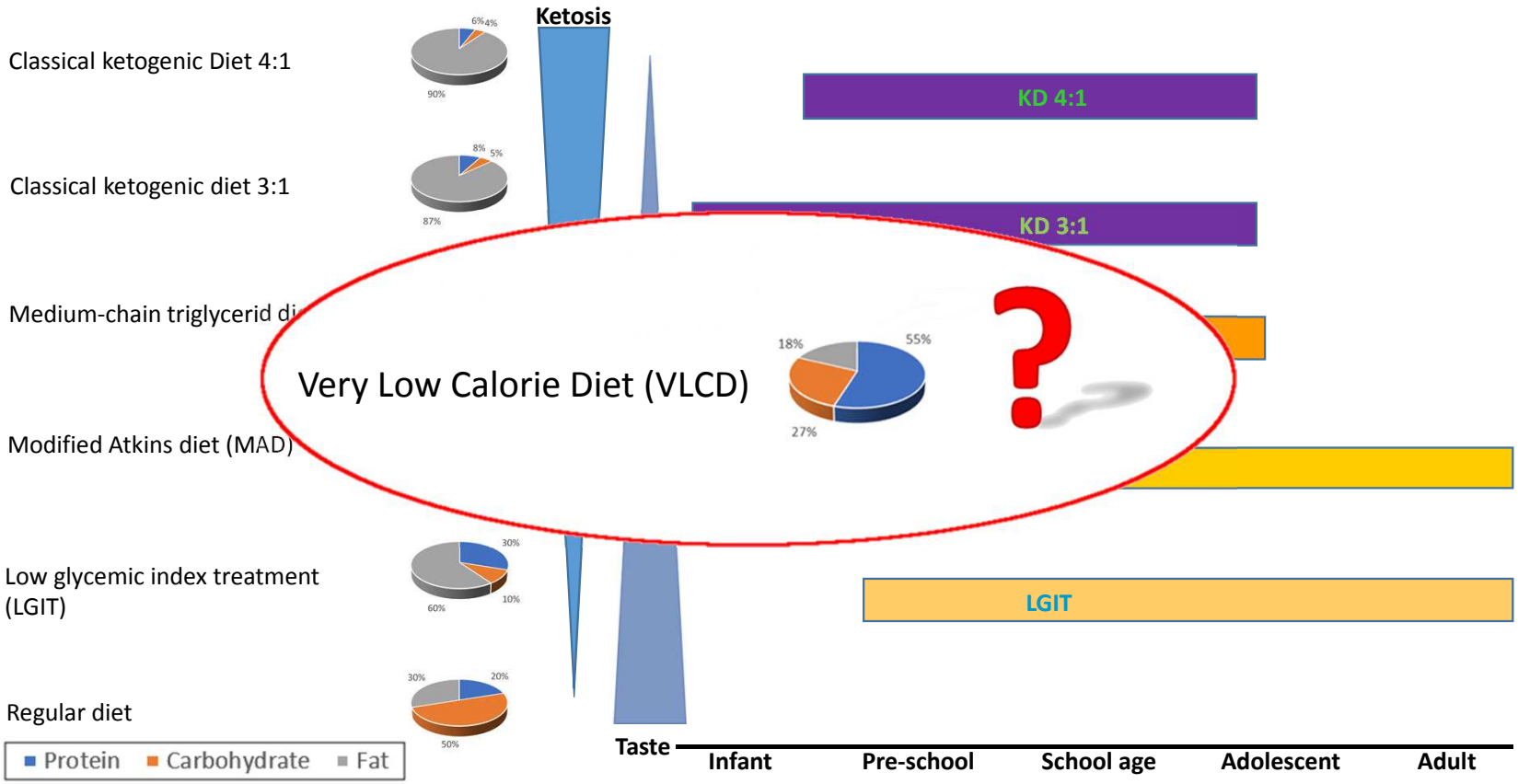


Figure 1. Suggested mechanisms for the therapeutic action of ketogenic diets in pathologies for which there exists strong (**a**) and emerging (**b**) evidence.


Classical ketogenic Diet 4:1
6%
4%
90%
Classical ketogenic diet 3:1
8%
5%
87%
Medium-chain triglycerid diet (MCT)
10%
20%
(30-50% MCT)
70%
Modified Atkins diet (MAD)
27%
8%
65%
Low glycemic index treatment (LGIT)
30%
10%
60%
Regular diet
30%
20%
50%
Protein
Carbohydrate
Fat
Ketosis
Taste
KD 4:1
KD 3:1
MCT
MAD
LGIT
Infant
Pre-school
School age
Adolescent
Adult

Other Ketogenic diets?

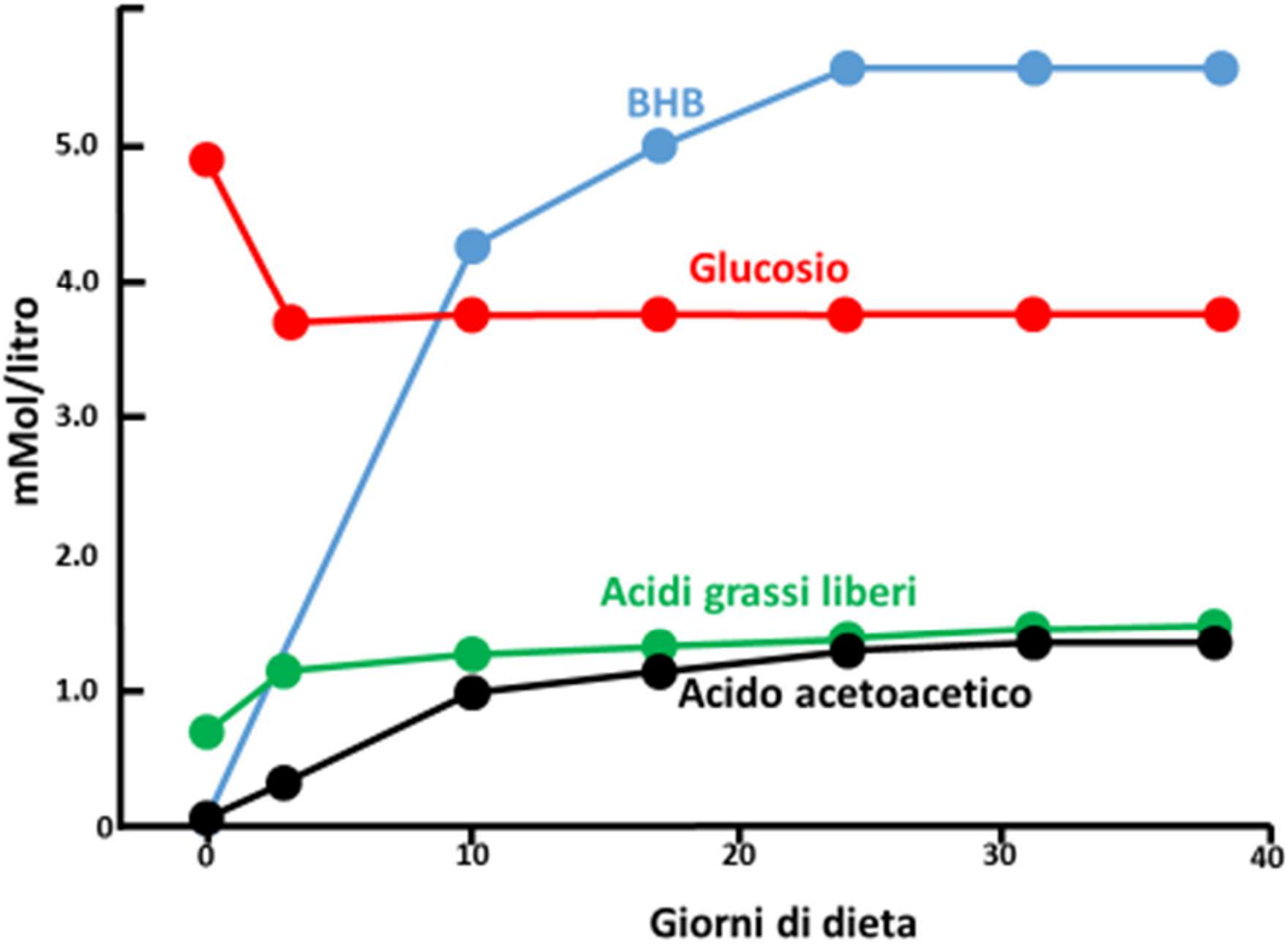


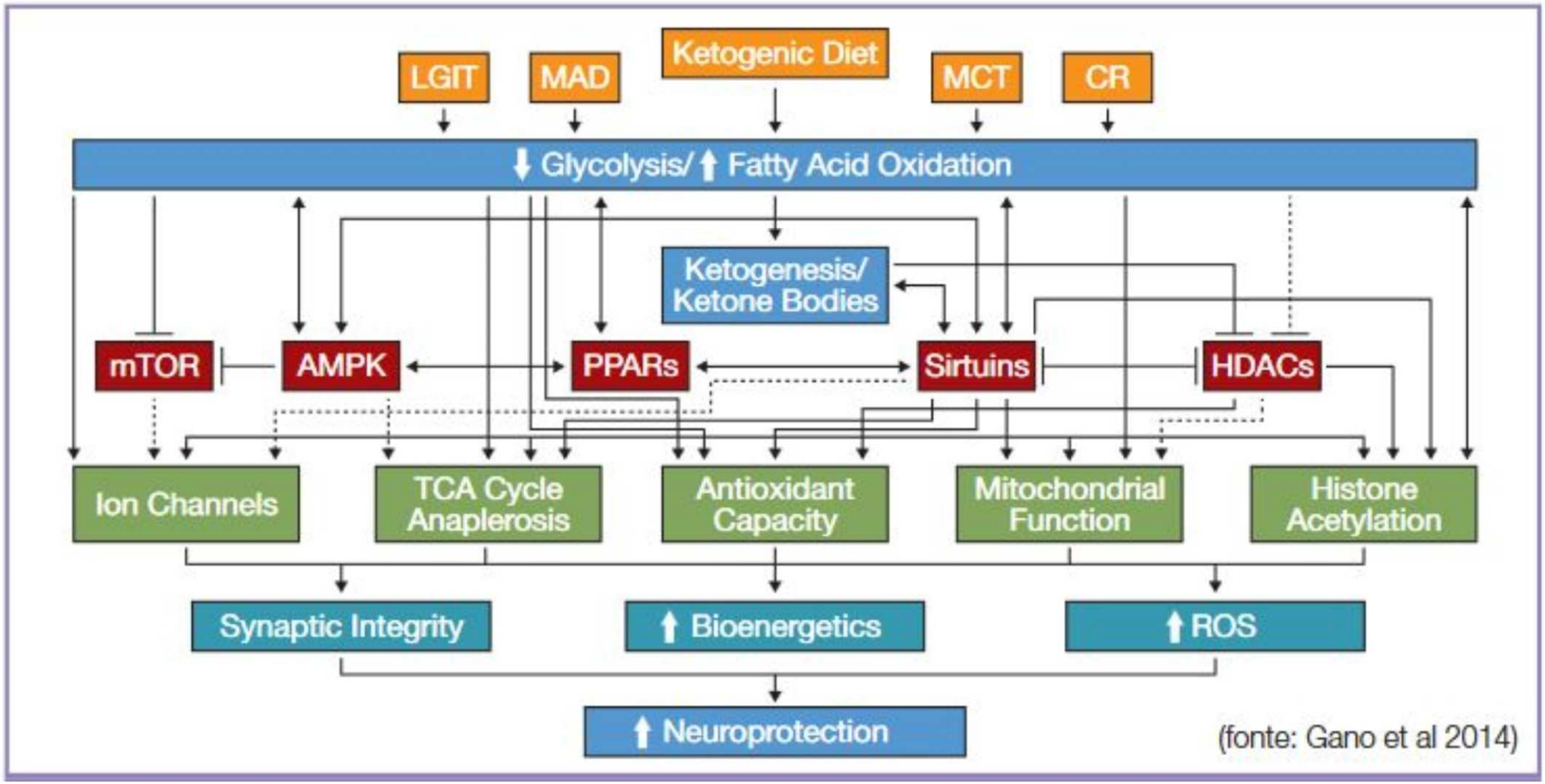
Very low calorie diets (VLCDs)

- 400 (600 in Europe) – 800 Kcal/day
- Low carbohydrate: Ketogenic (**VLCKD**)
- Hihg carbohydrate: non-Ketogenic (**VLCnKD**)

VLCKD

- The vantages of KD + prolonged fasting
- Limits: duration


BHB
Glucosio
Acidi grassi liberi
Acido acetoacetico
mMol/litro
5.0
4.0
3.0
2.0
1.0
0
0
10
20
30
40
Giorni di dieta

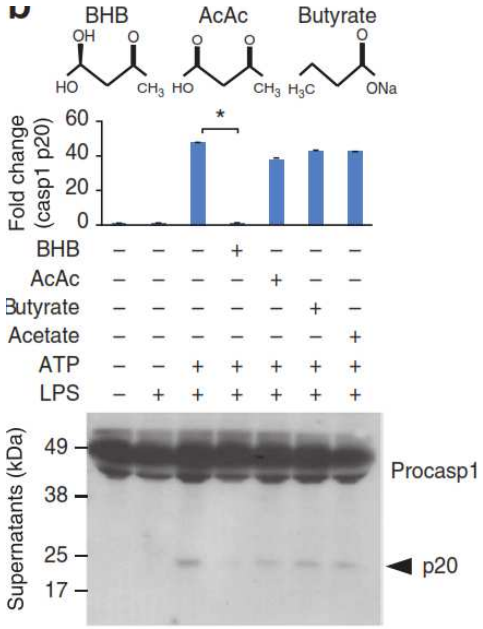


(fonte: Gano et al 2014)

nature medicine

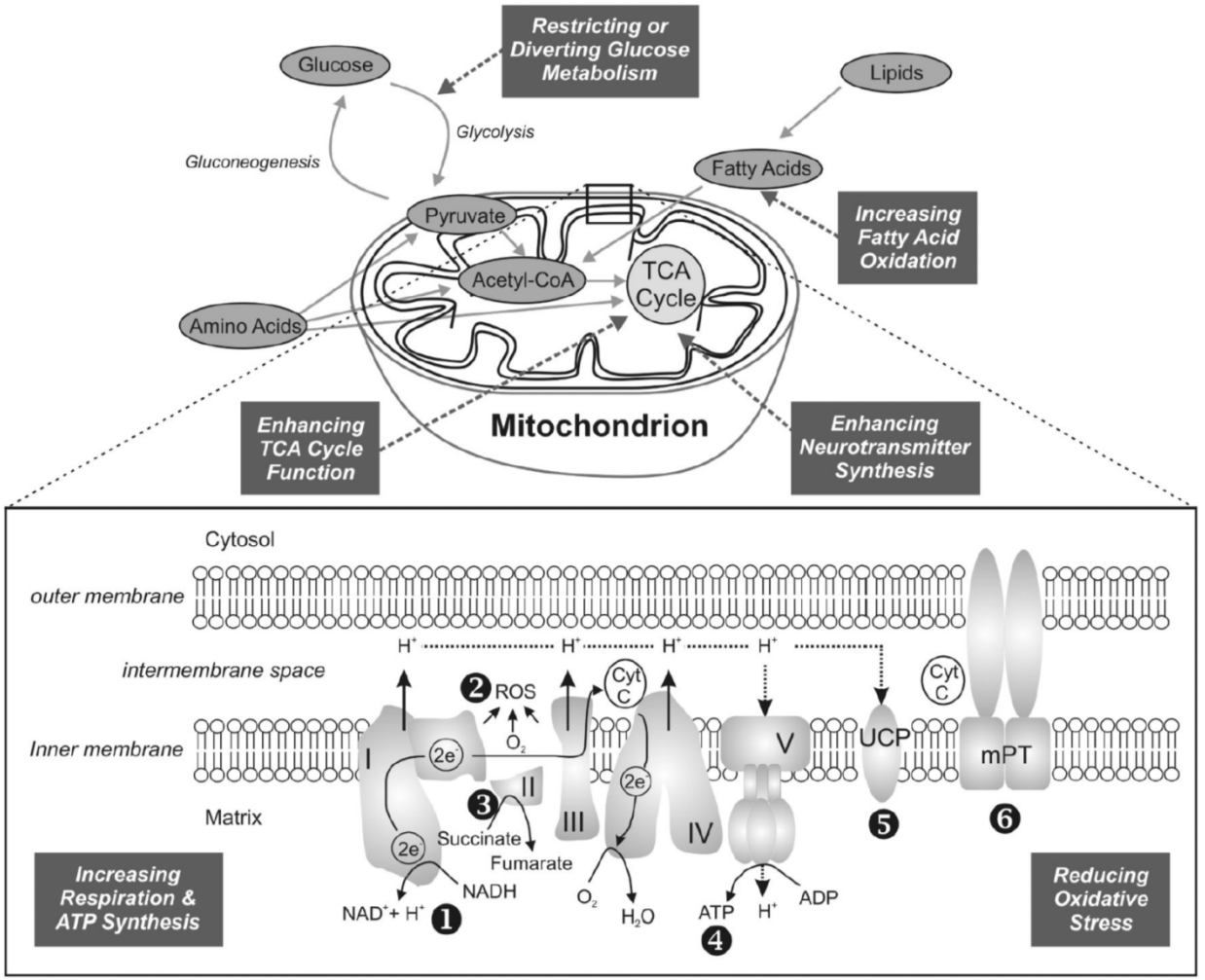
The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease

Yun-Hee Youm[1,11], Kim Y Nguyen[1,11], Ryan W Grant[2], Emily L Goldberg[1], Monica Bodogai[3], Dongin Kim[4], Dominic D'Agostino[5], Noah Planavsky[6], Christopher Lupfer[7], Thirumala D Kanneganti[7], Seokwon Kang[8], Tamas L Horvath[1], Tarek M Fahmy[4], Peter A Crawford[9], Arya Biragyn[3], Emad Alnemri[8] & Vishwa Deep Dixit[1,10]



Jasper's Basic Mechanisms of the Epilepsies

KD and Mitochondria



Electron Transport & Oxidative Phosphorylation

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]

Objective: Ketone bodies (KB) are products of fatty acid oxidation and serve as essential fuels during fasting or treatment with the high-fat antiseizure ketogenic diet (KD). Despite growing evidence that KB exert broad neuroprotective effects, their role in seizure control has not been firmly demonstrated. The major goal of this study was to demonstrate the direct antiseizure effects of KB and to identify an underlying target mechanism.
Methods: We studied the effects of both the KD and KB in spontaneously epileptic *Kcna1*-null mice using a combination of behavioral, planar multielectrode, and standard cellular electrophysiological techniques. Thresholds for mitochondrial permeability transition (mPT) were determined in acutely isolated brain mitochondria.
Results: KB alone were sufficient to: (1) exert antiseizure effects in *Kcna1*-null mice, (2) restore intrinsic impairment of hippocampal long-term potentiation and spatial learning–memory defects in *Kcna1*-null mutants, and (3) raise the threshold for calcium-induced mPT in acutely prepared mitochondria from hippocampi of *Kcna1*-null animals. Targeted deletion of the cyclophilin D subunit of the mPT complex abrogated the effects of KB on mPT, and in vivo pharmacological inhibition and activation of mPT were found to mirror and reverse, respectively, the antiseizure effects of the KD in *Kcna1*-null mice.
Interpretation: The present data reveal the first direct link between mPT and seizure control, and provide a potential mechanistic explanation for the KD. Given that mPT is increasingly being implicated in diverse neurological disorders, our results suggest that metabolism-based treatments and/or metabolic substrates might represent a worthy paradigm for therapeutic development.

ANN NEUROL 2015;00:000–000

Science. 2013 January 11; 339(6116): 211–214. doi:10.1126/science.1227166.

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], and **Eric Verdin**[1,2,*]

Epigenetics regulation
&
Oxidative stress reduction

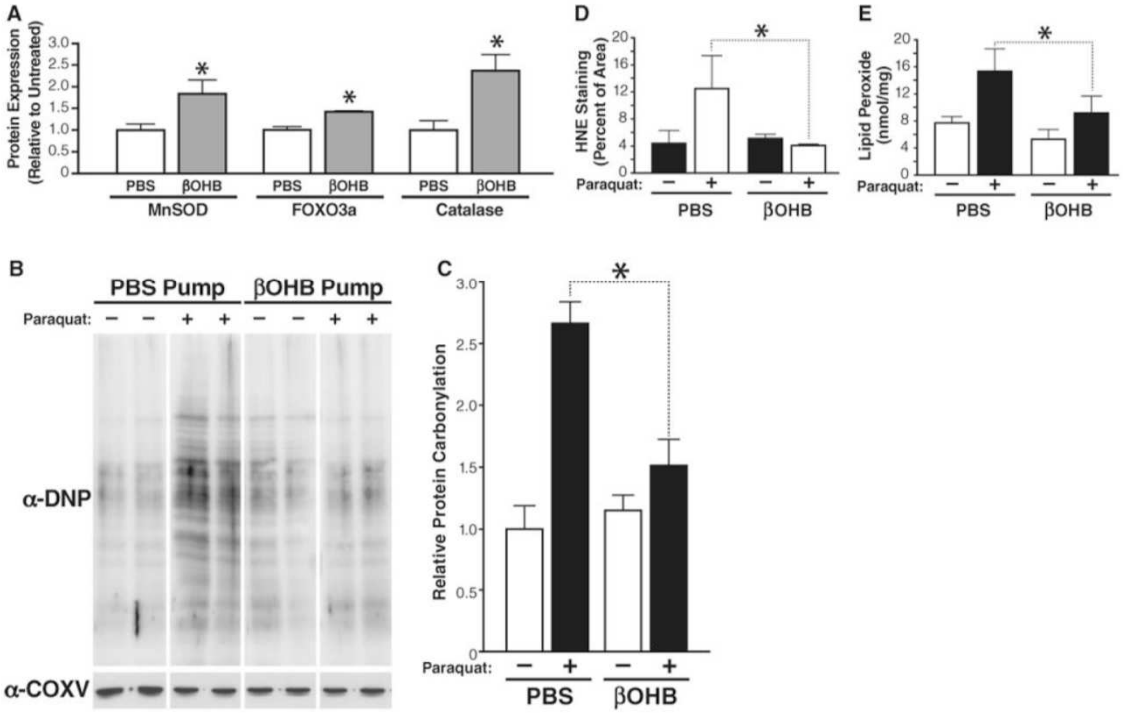


Fig. 4.

Protective effect of βOHB treatment against oxidative stress. (**A**) Amounts of catalase, MnSOD, or FOXO3A measured by protein immunoblotting in kidney tissue from 16-week-old mice implanted with an osmotic pump delivering PBS or βOHB (as in Fig. 2; $n = 3$); mean ± SE, $^*P < 0.05$ by *t* test between PBS and βOHB conditions. (**B**) Protein carbonylation in kidney samples from mice implanted with an osmotic pump delivering PBS or βOHB (as in Fig. 2; $n = 3$) and treated with paraquat (50 mg/kg) or vehicle for 2 hours. Car-bonylation was measured by immunoblotting with anti-DNP. All samples were run on a single gel; after imaging, lanes were rearranged for presentation. (**C**) Quantification of protein carbonylation in (B). Mean ± SE, $^*P < 0.05$ by *t* test between PBS and βOHB conditions. (**D**) Sections of kidney obtained from the same mice as in (B) were stained with anti-4-HNE and quantified (see fig. S16 for primary picture). Mean ± SE, $^*P < 0.05$ by *t* test between PBS and βOHB conditions. (**E**). Lipid peroxides were quantified in mice kidneys (LPO assay kit, Cayman, Ann Arbor, MI). Mean ± SE, $^*P < 0.05$ by *t* test between PBS and βOHB conditions.

npj | Biofilms and Microbiomes

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ARTICLE OPEN

The ketogenic diet influences taxonomic and functional composition of the gut microbiota in children with severe epilepsy

Marie Lindefeldt[1], Alexander Eng[2], Hamid Darban[3], Annelie Bjerkner[4], Cecilia K Zetterström[5], Tobias Allander[4], Björn Andersson[3], Elhanan Borenstein[2,6,7,8,9], Maria Dahlin[1] and Stefanie Prast-Nielsen[10]

The gut microbiota has been linked to various neurological disorders via the gut–brain axis. Diet influences the composition of the gut microbiota. The ketogenic diet (KD) is a high-fat, adequate-protein, low-carbohydrate diet established for treatment of therapy-resistant epilepsy in children. Its efficacy in reducing seizures has been confirmed, but the mechanisms remain elusive. The diet has also shown positive effects in a wide range of other diseases, including Alzheimer's, depression, autism, cancer, and type 2 diabetes. We collected fecal samples from 12 children with therapy-resistant epilepsy before starting KD and after 3 months on the diet. Parents did not start KD and served as diet controls. Applying shotgun metagenomic DNA sequencing, both taxonomic and functional profiles were established. Here we report that alpha diversity is not changed significantly during the diet, but differences in both taxonomic and functional composition are detected. Relative abundance of bifidobacteria as well as *E. rectale* and *Dialister* is significantly diminished during the intervention. An increase in relative abundance of *E. coli* is observed on KD. Functional analysis revealed changes in 29 SEED subsystems including the reduction of seven pathways involved in carbohydrate metabolism. Decomposition of these shifts indicates that bifidobacteria and *Escherichia* are important contributors to the observed functional shifts. As relative abundance of health-promoting, fiber-consuming bacteria becomes less abundant during KD, we raise concern about the effects of the diet on the gut microbiota and overall health. Further studies need to investigate whether these changes are necessary for the therapeutic effect of KD.

npj Biofilms and Microbiomes (2019)5:5 ; https://doi.org/10.1038/s41522-018-0073-2

KD in GLUT1 and Pyruvate dehydrogenase deficit

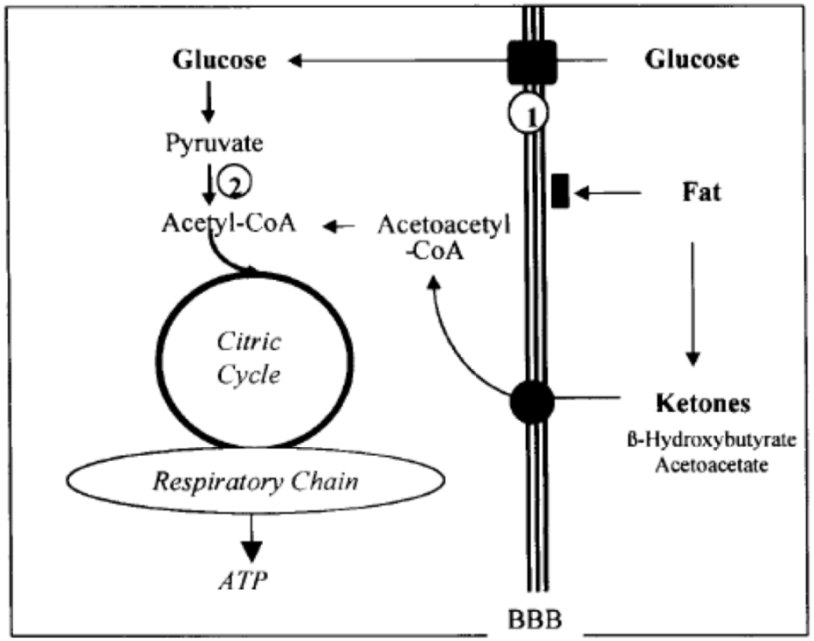
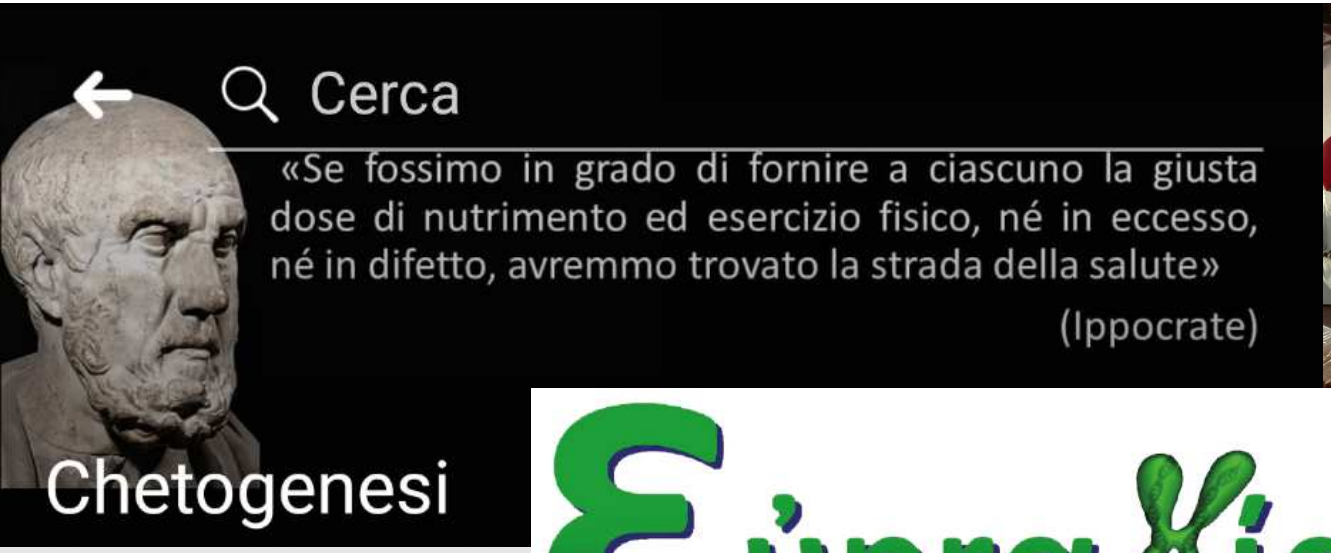


Figure 1 Ketosis and brain energy metabolism. Glucose enters the brain via the facilitated glucose transporter GLUT1 (■); ketones penetrate the blood–brain barrier (BBB) via the MCT1-transporter (●). Both substrates enter the citric acid cycle as acetyl-CoA for energy production. ① GLUT1 DS is caused by a defect in GLUT1-mediated glucose transport into brain. ② Pyruvate dehydrogenase deficiency impairs acetyl-CoA production. In both conditions, ketones bypass the transport/enzyme defect as acetoacetyl-CoA and provide acetyl-CoA.

Alone at home?



Εὐπραξία

Membri 18.000

Ketogenesis and Endometriosis

Adipocyte alterations in endometriosis: reduced numbers of stem cells and microRNA induced alterations in adipocyte metabolic gene expression

Masoumeh Majidi Zolbin, Ramanaiah Mamillapalli*, Sepide E. Nematian, Laura Goetz and Hugh S. Taylor

Abstract

Background: Endometriosis is an estrogen dependent, inflammatory disorder occurring in 5–10% of reproductive-aged women. Women with endometriosis have a lower body mass index (BMI) and decreased body fat compared to those without the disease, yet few studies have focused on the metabolic abnormalities in adipose tissue in women with endometriosis. Previously, we identified microRNAs that are differentially expressed in endometriosis and altered in the serum of women with the disease. Here we explore the effect of endometriosis on fat tissue and identified a role for endometriosis-related microRNAs in fat metabolism and a reduction in adipocyte stem cell number.

Methods: Primary adipocyte cells cultured from 20 patients with and without endometriosis were transfected with mimics and inhibitors of microRNAs 342-3p or Let 7b-5p to model the status of these microRNAs in endometriosis. RNA was extracted for gene expression analysis by qRT-PCR. PCNA expression was used as a marker of adipocyte proliferation. Endometriosis was induced experimentally in 9-week old female C57BL/6 mice and after 10 months fat tissue was harvested from both the subcutaneous (inguinal) and visceral (mesenteric) tissue. Adipose-derived mesenchymal stem cells in fat tissue were characterized in both endometriosis and non-endometriosis mice by FACS analysis.

Results: Gene expression analysis showed that endometriosis altered the expression of *Cebpa*, *Cebpb*, *Ppar-γ*, *leptin*, *adiponectin*, *IL-6*, and *HSL*, which are involved in driving brown adipocyte differentiation, appetite, insulin sensitivity and fat metabolism. Each gene was regulated by an alteration in microRNA expression known to occur in endometriosis. Analysis of the stem cell content of adipose tissue in a mouse model of endometriosis demonstrated a reduced number of adipocyte stem cells.

Conclusions: We demonstrate that microRNAs Let-7b and miR-342-3p affected metabolic gene expression significantly in adipocytes of women with endometriosis. Similarly, there is a reduction in the adipose stem cell population in a mouse model of endometriosis. Taken together these data suggest that endometriosis alters BMI in part through an effect on adipocytes and fat metabolism.

Keywords: Endometriosis, microRNAs, MiR, Fat tissue, Adipocytes, Let-7, miR-342, Stem cells

Maturitas 103 (2017) 45–53

Contents lists available at ScienceDirect

Maturitas

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

Review

Estrogen–gut microbiome axis: Physiological and clinical implications

James M. Baker[a,b,1], Layla Al-Nakkash[c], Melissa M. Herbst-Kralovetz[a,d,*]

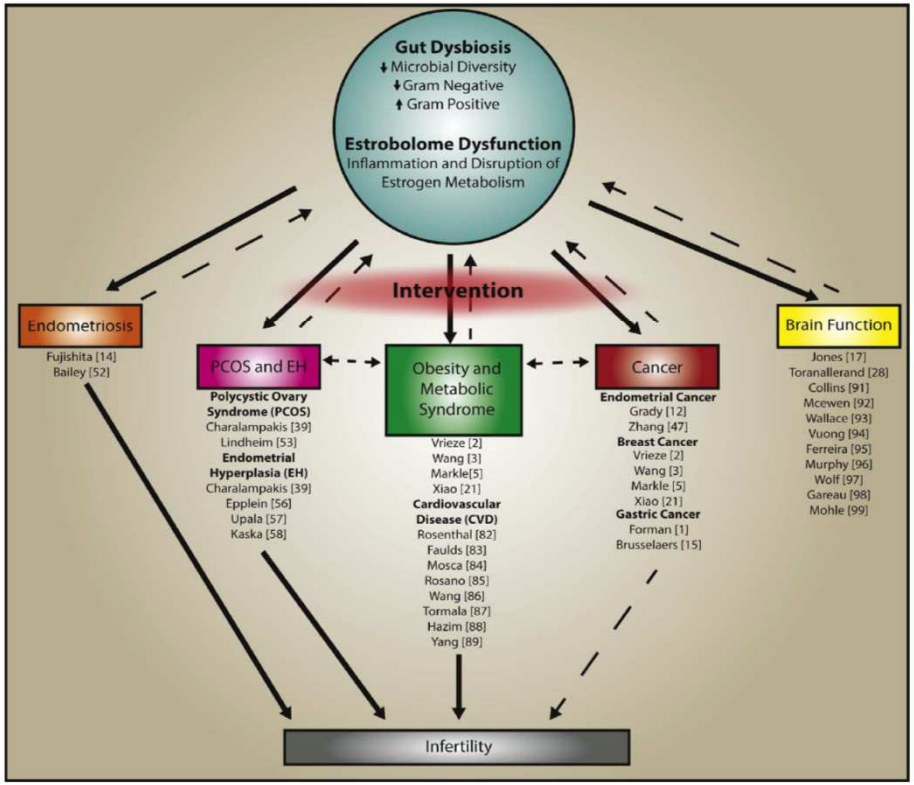


Fig. 1. Estrogen-gut microbiome interactions exhibit physiological and clinical implications. Dysbiosis and a reduction of gut microbiota diversity impacts the estrobolome, which may lead to a wide range of disease states, illustrated. Reduction in gut microbiome diversity as result of dysbiosis and inflammation reduces the β-glucuronidase activity. This reduced β-glucuronidase activity results in decreased deconjugation of estrogen and phytoestrogen into their circulating and active forms. The subsequent decrease in circulating estrogens alters estrogen receptor activations which may lead to the hypoestrogenic pathologies: obesity, metabolic syndrome, CVD and cognitive decline. Hyperestrogenic pathologies can also be driven by the estrobolome through the increased abundance of β-glucuronidase-producing bacteria, which leads to elevates levels of circulating estrogens to drive diseases such as endometriosis and cancer. Obesity/metabolic syndrome can impact other disease states such including PCOS, EH and ultimately fertility. Intervention: Bariatric surgery, metformin and FMT provide therapeutic interventions that can mitigate the associated disease state through modulation of the gut microbiota composition. Solid arrows indicate the established interaction between estrobolome and disease states; dashed arrows indicate putative feedback mechanisms or interactions.

Digestive and Liver Disease 50 (2018) 213–219

Contents lists available at ScienceDirect

Digestive and Liver Disease

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

Review Article

Irritable bowel syndrome and endometriosis: New insights for old diseases

Davide Viganò[a,b], Federica Zara[a,b], Paolo Usai[a,b,*]

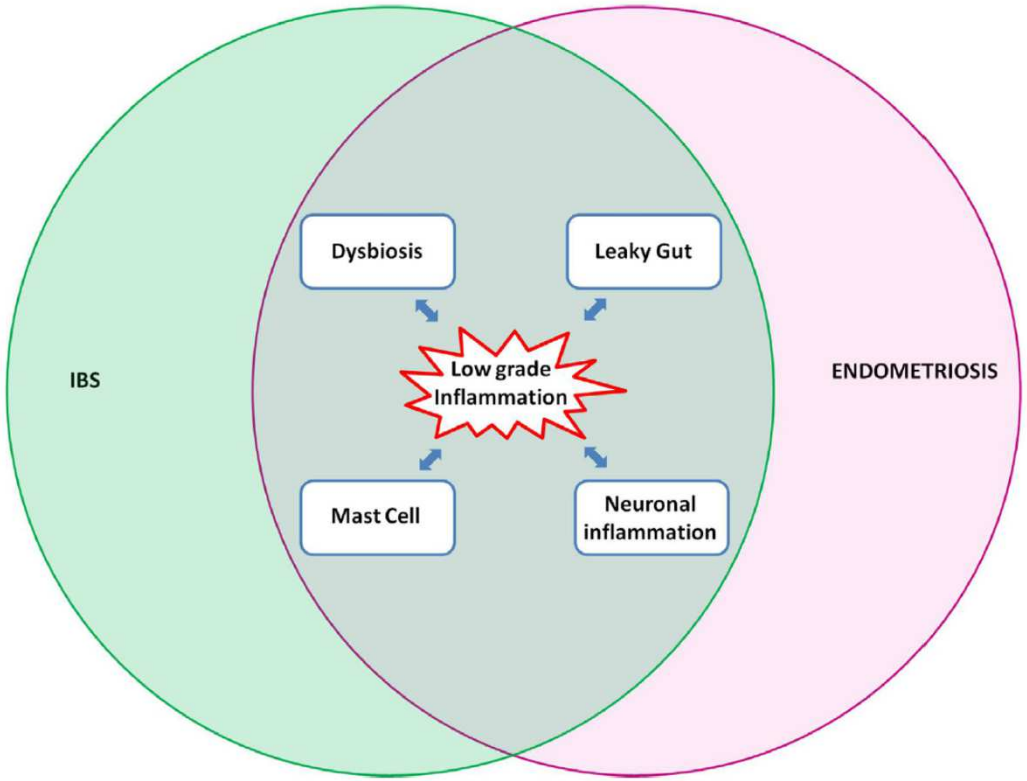
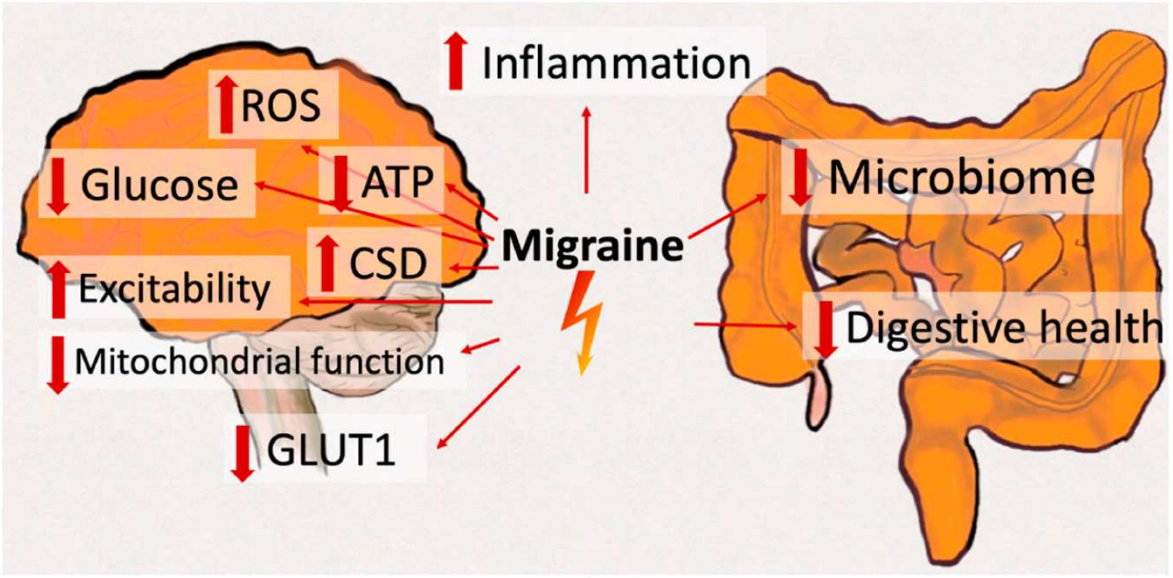
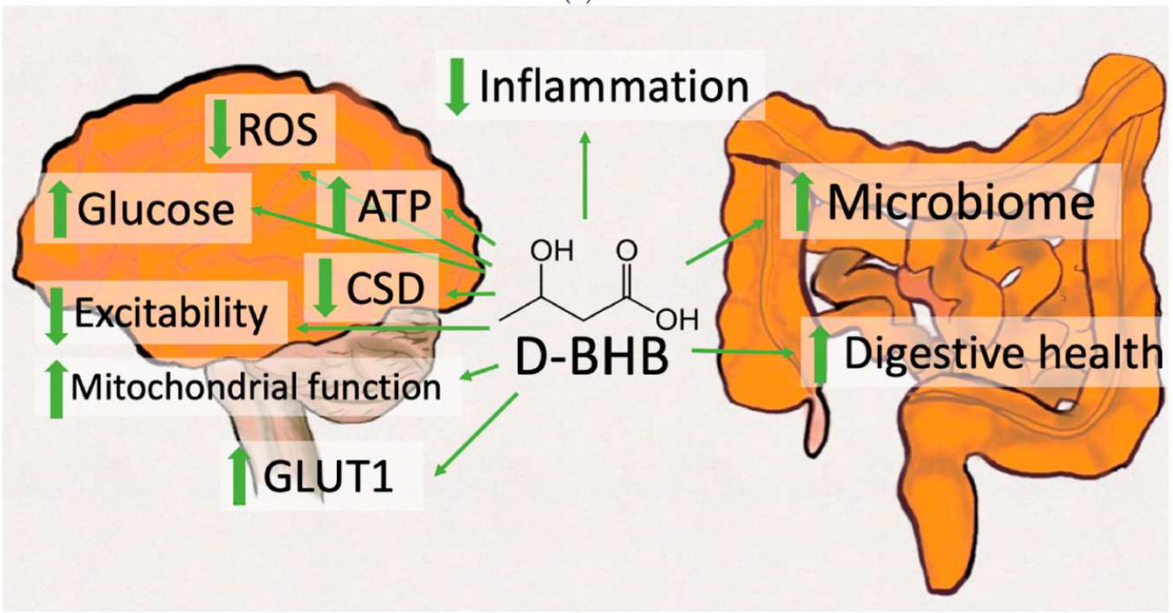


Fig. 1. Common pathophysiological features between irritable bowel syndrome (IBS) and endometriosis.
In IBS and endometriosis a state of low-grade chronic inflammation has been detected contributing to maintain the pathological condition. Furthermore, these diseases share common key factors related to this chronic low-grade inflammatory state: the activation of mast cell line, neuronal inflammation, dysbiosis and an impaired intestinal permeability.



(a)



(b)

Nutrients **2019**, *11*, 811; doi:10.3390/nu11040811

nutrients

MDPI

Review

Potential Protective Mechanisms of Ketone Bodies in Migraine Prevention

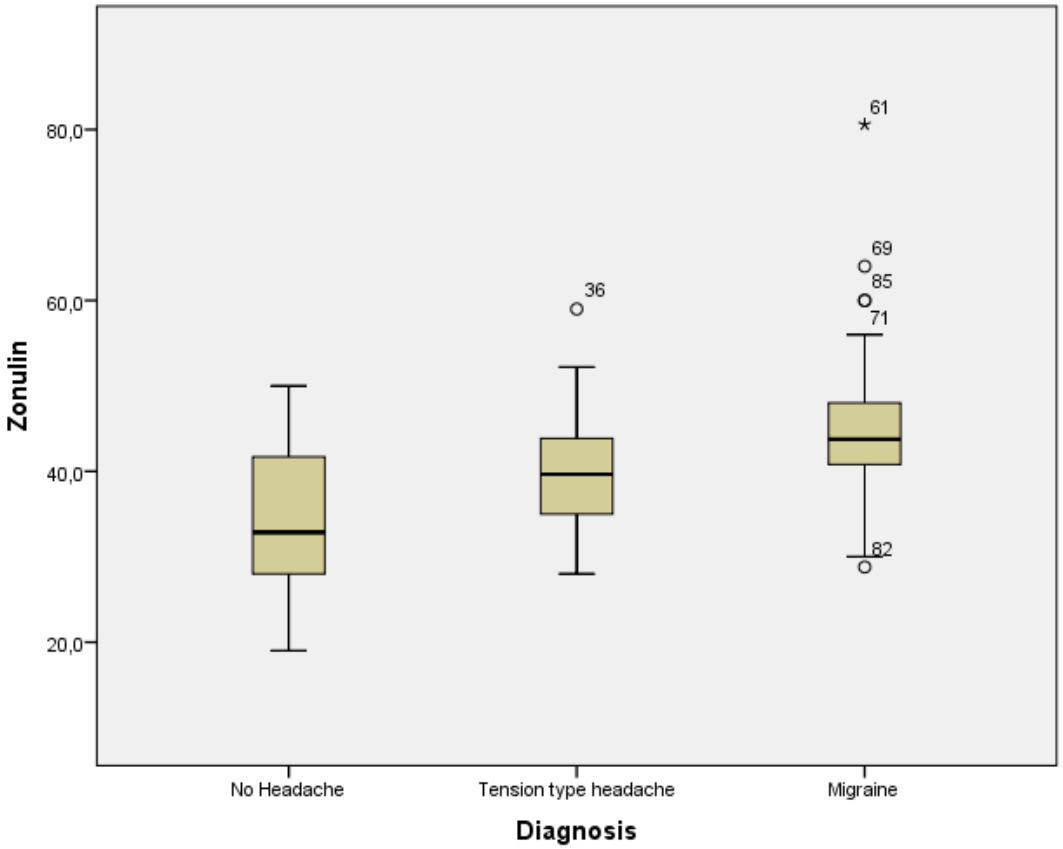
Elena C. Gross [1,*], Rainer J. Klement [2], Jean Schoenen [3], Dominic P. D'Agostino [4,5] and Dirk Fischer [1]

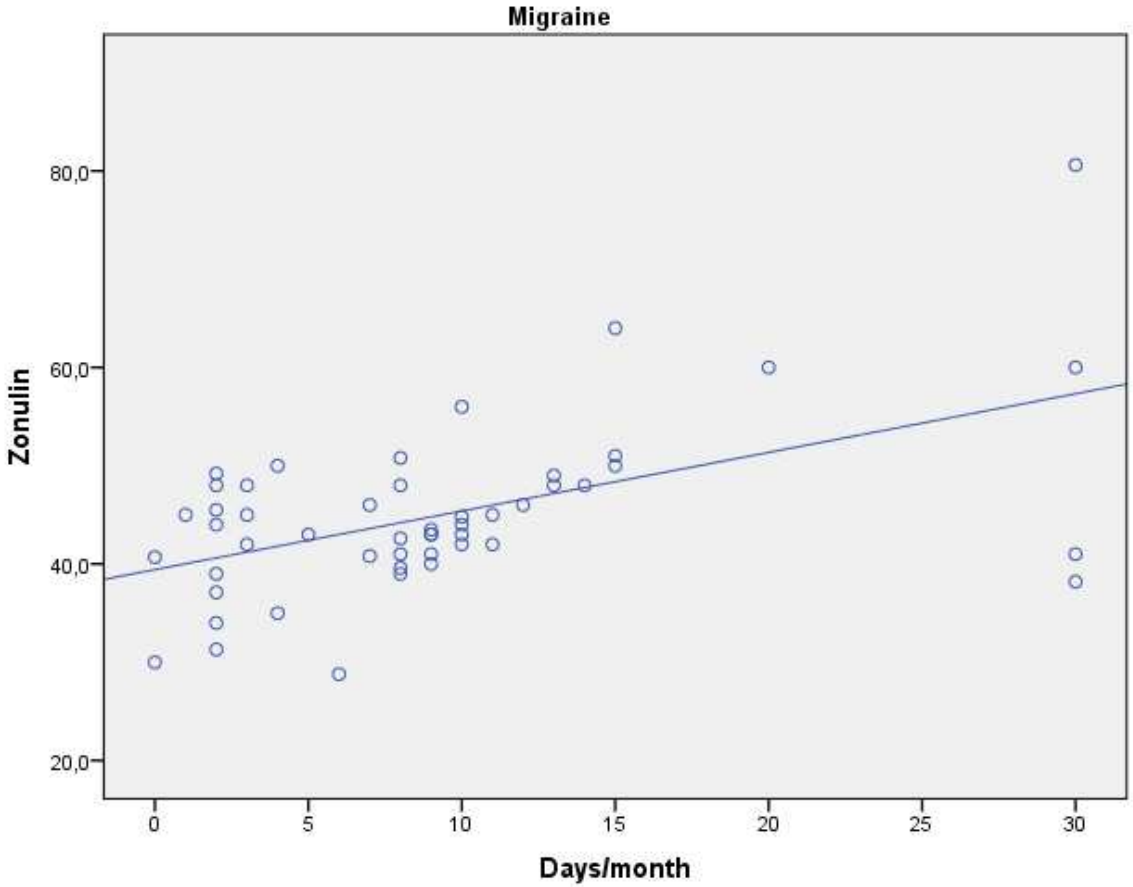
Potentially migraine relevant mechanisms of ketosis.

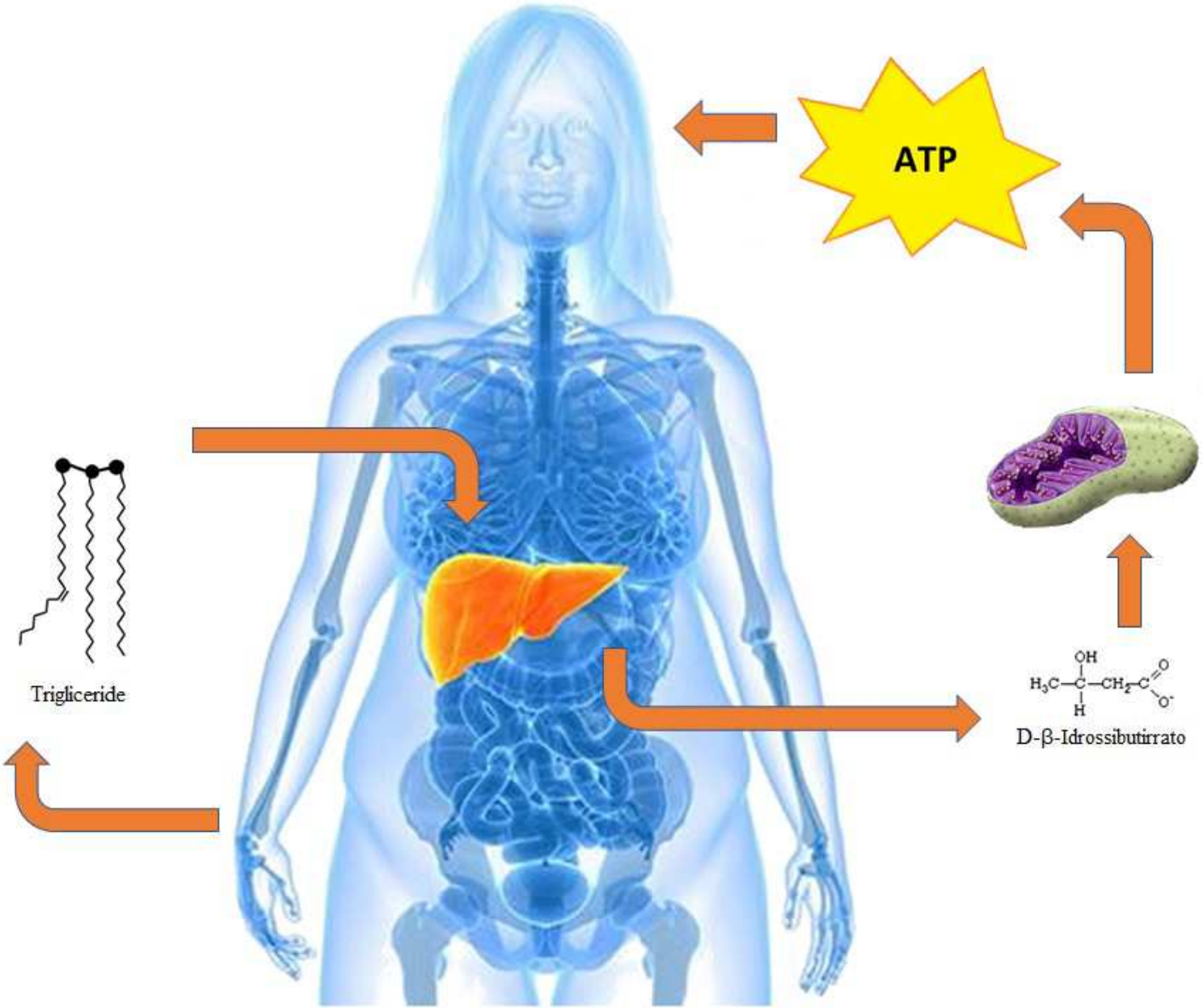
(**a**) Amongst key migraine pathophysiological mechanisms are hypometabolism, decreased glucose transport (including glucose transporter 1 (GLUT1) deficiency), reduced mitochondrial functioning, increased cerebral excitability, increased cortical spreading depressions (CSD) incidence, increased oxidative stress (reactive oxygen species (ROS)), increased inflammation, microbiome abnormalities and reduced digestive health.

(**b**) D--hydroxybutyrate (D-BHB; with or without the context of a ketogenic diet) has been shown to positively influence each of these mechanisms: increasing cerebral metabolism, increasing glucose transport (including glucose transporter 1 (GLUT1) deficiency), increasing mitochondrial functioning, reducing cerebral excitability, decreasing cortical spreading depressions (CSD) incidence, reducing oxidative stress (reactive oxygen species (ROS)), decreasing inflammation, improving the microbiome and increasing digestive health. ATP = adenosine triphosphate; CSD = cortical spreading depressions; D-BHB = D--hydroxybutyrate; GLUT1 = glucose transporter 1; ROS = reactive oxygen species.

Gut-Brain Axis?






ATP
Trigliceride
D-β-Idrossibutirrato