Energy in the balance

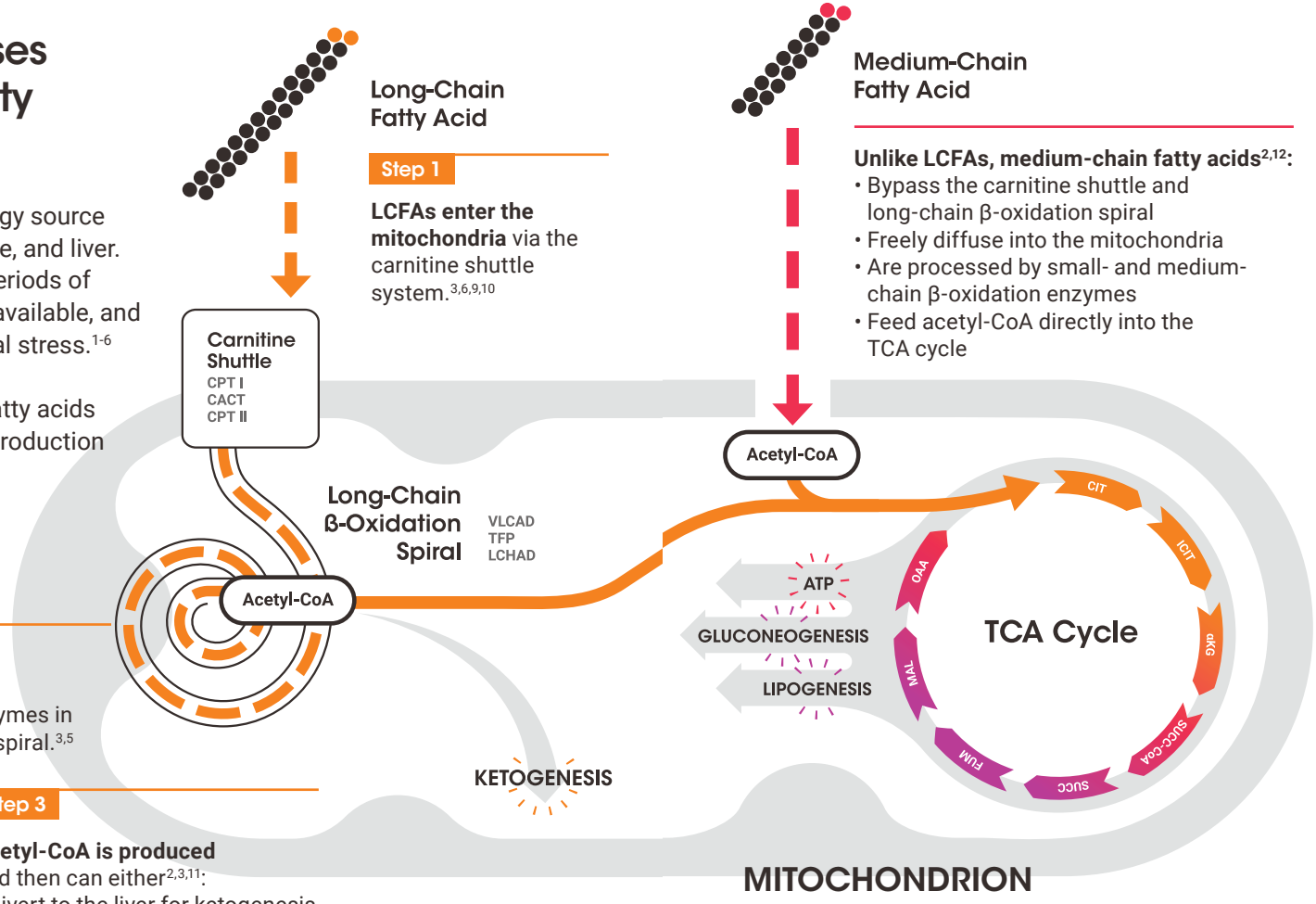
Understanding the Mechanism of Disease in LC-FAOD*

*Long-chain fatty acid oxidation disorders.

Multiple processes drive healthy fatty acid oxidation

Fatty acids are a major energy source for the heart, skeletal muscle, and liver. This energy is vital during periods of fasting, when glucose is unavailable, and during times of physiological stress.[1-6]

Metabolism of long-chain fatty acids (LCFAs) to support energy production centers around oxidation of acetyl-CoA to CO_2 in the mitochondrial tricarboxylic acid (TCA) cycle.[2,7,8]



Step 2

LCFAs are metabolized by long-chain–specific enzymes in the long-chain β-oxidation spiral.[3,5]

Step 3

Acetyl-CoA is produced and then can either[2,3,11]:
- Divert to the liver for ketogenesis
- Enter the TCA cycle to generate ATP through oxidative phosphorylation

ENERGY HOMEOSTASIS RELIES ON THE BALANCE OF ANAPLEROSIS AND CATAPLEROSIS

In proper TCA cycle function, inflow (anaplerosis) is balanced by outflow (cataplerosis). In anaplerosis, intermediates are constantly replenished to maintain TCA function and drive ATP production. With cataplerosis, other intermediates are removed to drive gluconeogenesis and lipogenesis. This balance is critical to maintaining energy homeostasis.[2,7,8]

Acetyl-CoA=acetyl coenzyme A; αKG=alpha-ketoglutarate; ATP=adenosine triphosphate; CACT=carnitine-acylcarnitine translocase; CIT=citrate; CPT=carnitine palmitoyltransferase; FUM=fumarate; ICIT=isocitrate; LCHAD=long-chain 3-hydroxyacyl-CoA dehydrogenase; MAL=malate; OAA=oxaloacetate; SUCC=succinate; SUCC-CoA=succinyl-CoA; TCA=tricarboxylic acid; TFP=mitochondrial trifunctional protein; VLCAD=very long-chain acyl-CoA dehydrogenase.

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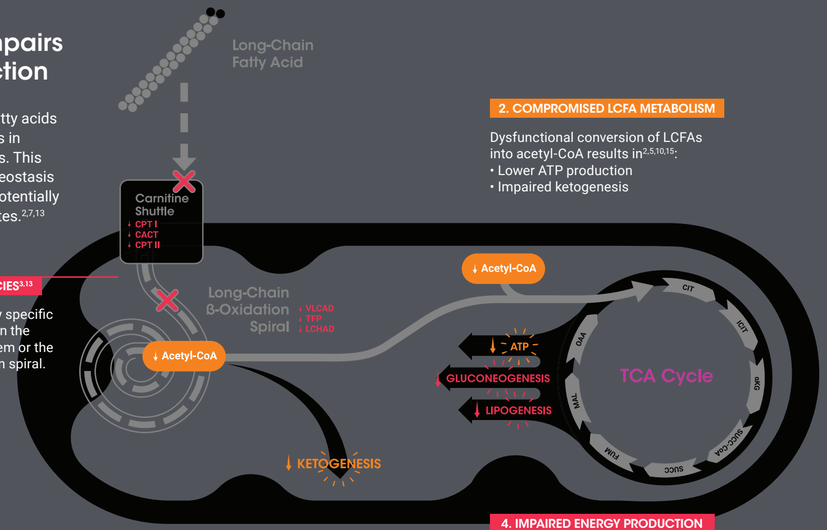
Impacts of LC-FAOD are both acute and chronic

Long-chain fatty acid oxidation disorders (LC-FAOD) are a group of rare, life-threatening autosomal recessive disorders.[13,14] They present across a broad spectrum and require lifetime management. Patients may experience acute metabolic crises resulting from rhabdomyolysis, cardiomyopathy, or hypoglycemia, in addition to chronic symptoms of fatigue, muscle pain, and weakness.[2,15-19]

Patients with TFP and LCHAD deficiencies may also have progressive manifestations of peripheral neuropathy and pigmentary retinopathy.[2,20]

Unbalanced metabolism impairs energy production

In LC-FAOD, oxidation of fatty acids is disrupted by deficiencies in key mitochondrial enzymes. This compromises energy homeostasis and triggers a buildup of potentially toxic fatty acid intermediates.[2,7,13]



1. ENZYME DEFICIENCIES[3,13]

LC-FAOD is caused by specific enzyme deficiencies in the carnitine shuttle system or the long-chain β-oxidation spiral.

- ↓ CPT I
- ↓ CACT
- ↓ CPT II
- ↓ VLCAD
- ↓ TFP
- ↓ LCHAD

2. COMPROMISED LCFA METABOLISM

Dysfunctional conversion of LCFAs into acetyl-CoA results in[2,5,10,15]:

- Lower ATP production
- Impaired ketogenesis

3. TCA CYCLE IMBALANCE

Enzyme deficiencies can disrupt the anaplerosis-cataplerosis balance, leading to[2,8,19]:

- Accumulation of toxic metabolites
- Lack of replenishing substrates in the TCA intermediate pools

4. IMPAIRED ENERGY PRODUCTION

Incomplete TCA cycle processing may impair[2,5,7,15,21]:

- Gluconeogenesis
- Lipogenesis

Acetyl-CoA=acetyl coenzyme A; αKG=alpha-ketoglutarate; ATP=adenosine triphosphate; CACT=carnitine-acylcarnitine translocase; CIT=citrate; CPT=carnitine palmitoyltransferase; FUM=fumarate; ICIT=isocitrate; LCHAD=long-chain 3-hydroxyacyl-CoA dehydrogenase; MAL=malate; OAA=oxaloacetate; SUCC=succinate; SUCC-CoA=succinyl-CoA; TCA=tricarboxylic acid; TFP=mitochondrial trifunctional protein; VLCAD=very long-chain acyl-CoA dehydrogenase.

Unmet needs in LC-FAOD

There remains an unmet clinical need in LC-FAOD. Many patients still experience lifestyle limitations, as well as significant morbidities and life-threatening complications.[13,15,21,22]

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References: 1. Berg JM, Tymoczko JL, Stryer L. *Biochemistry*. 5th ed. New York, NY: WH Freeman Publishing; 2002:Section 30.2. **2.** Knottnerus SJG, Bleeker JC, Wüst RCI, et al. *Rev Endocr Metab Disord*. 2018;19(1):93-106. **3.** Wanders RJ, Ruiter JP, IJlst L, Waterham HR, Houten SM. *J Inherit Metab Dis*. 2010;33(5):479-494. **4.** Rinaldo P, Matern D, Bennett MJ. *Annu Rev Physiol*. 2002;64:477-502. **5.** Houten SM, Wanders RJ. *J Inherit Metab Dis*. 2010;33(5):469-477. **6.** Kiens B, Roepstorff C. *Acta Physiologica Scand*. 2003;178(4):391-396. **7.** Owen OE, Kalhan SC, Hanson RW. *J Biol Chem*. 2002;277(34):30409-30412. **8.** Brunengraber H, Roe CR. *J Inherit Metab Dis*. 2006;29(2-3):327-331. **9.** Sharpe AJ, McKenzie M. *Cells.* 2018;7(6):46. **10.** Longo N, di San Filippo CA, Pasquali M. *Am J Med Genet C Semin Med Genet*. 2006;142C(2):77-85. **11.** Hagenbuchner J, Scholl-Buergi S, Karall D, Ausserlechner MJ. *Sci Rep*. 2018;8(1):3254. **12.** Schönfeld P, Wojtczak L. *J Lipid Res*. 2016;57(6):943-954. **13.** Vockley J, Burton B, Berry GT, et al. *Mol Genet Metab*. 2017;120(4):370-377. **14.** Klose DA, Kolker S, Heinrich B, et al. *Pediatrics*. 2002;110(6):1204-1211. **15.** Wajner M, Amaral AU. *Biosci Rep*. 2015;36(1):e00281. **16.** Vishwanath VA. *Ann Neurosci.* 2016;23(1):51-55. **17.** Kang E, Kim YM, Kang M, et al. *BMC Pediatr*. 2018;18(1):103. **18.** Vockley J, Burton B, Berry GT, et al. *J Inherit Metab Dis*. 2019;42(1):169-177. **19.** Janeiro P, Jotta R, Ramos R, et al. *Eur J Pediatr*. 2019;178(3):387-394. **20.** Fletcher A, Pennesi M, Harding C, et al. *Mol Genet Metab*. 2012;106(1):18-24. **21.** Gillingham MB, Heitner SB, Martin J, et al. *J Inherit Metab Dis*. 2017;40(6):831-843. **22.** Roe C, Brunengraber H. *Mol Genet Metab*. 2015;116(4):260-268.

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