Fatty acid oxidation defects

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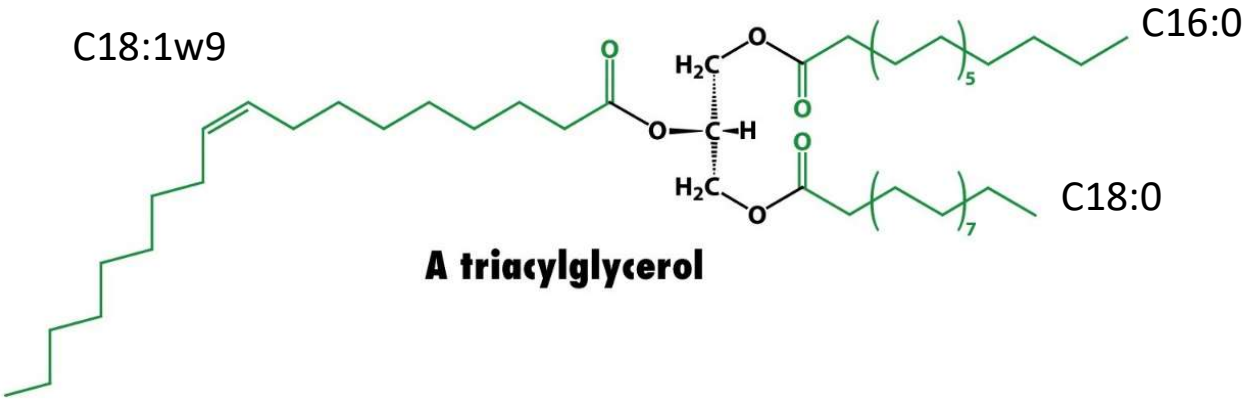
Outline

- Physiology of mitochondrial fatty acid oxidation
- Key diagnostic tests/ lab aspects
- Disorders (Presentation, Diagnosis, Treatment)
- Carnitine cycle defects
  - Carnitine transporter, CPT-I, CACT, CPT-II
- Mitochondrial beta-oxidation defects
  - Long chain (VLCAD, LCHAD, MTP), MCAD, Short chain (SCAD, SCHAD, ECHS1)
- Electron transfer flavoprotein
  - MADD, Associated Riboflavin defects
- Take Home Messages/ Summary

Physiology of mitochondrial fatty acid oxidation

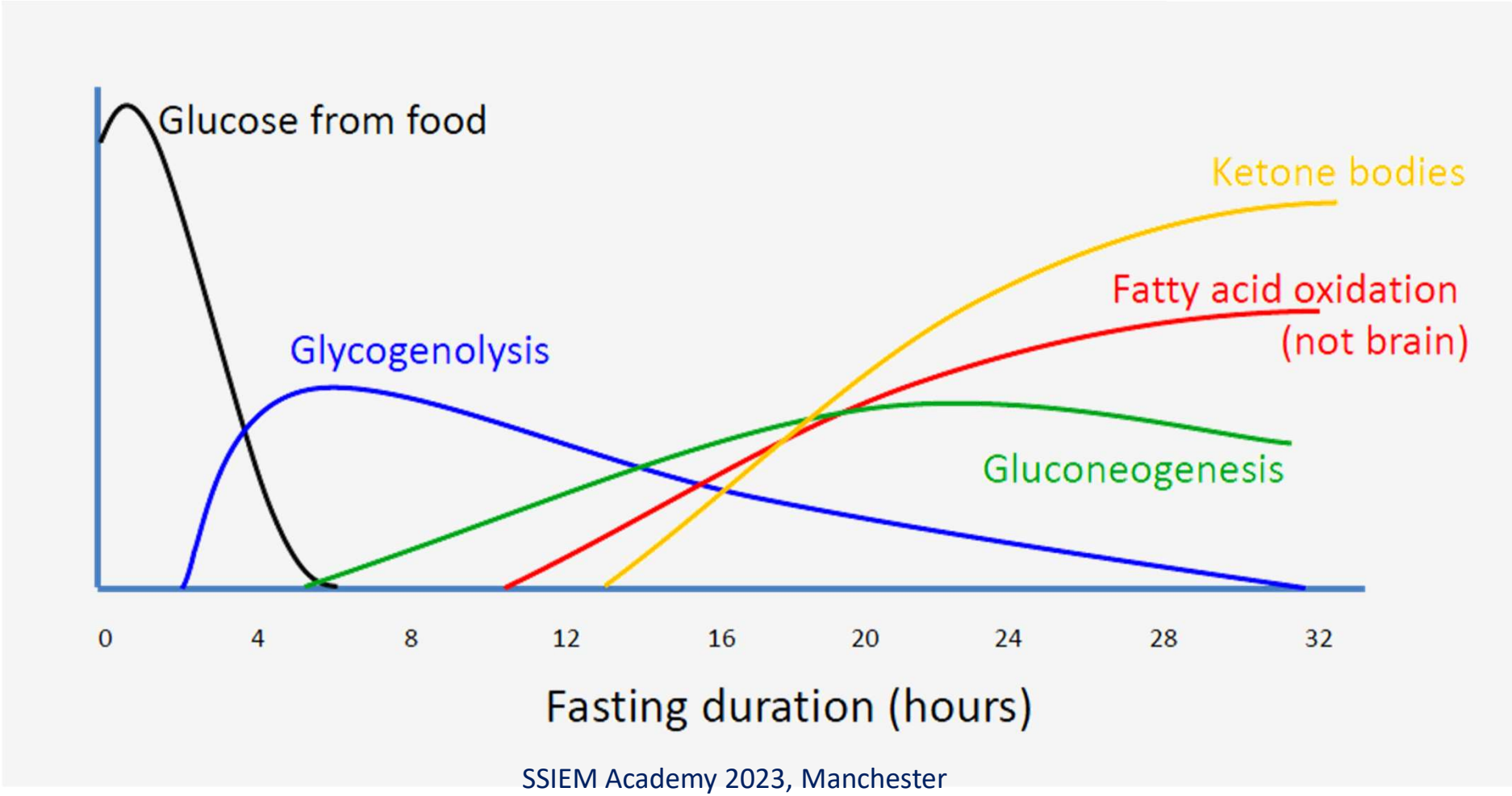
Fatty acid origin and actions



Fatty acids

- **Energy (β-oxidation)**
- **Metabolism** (desaturation, elongation, oxidation)
- **Membrane** building blocks
- **Complex lipids** (e.g. TG, CE, Phospholipids, Sphingolipids)
- **Other:**
  Intracellular signalling
  local hormone regulation
  Protein modification

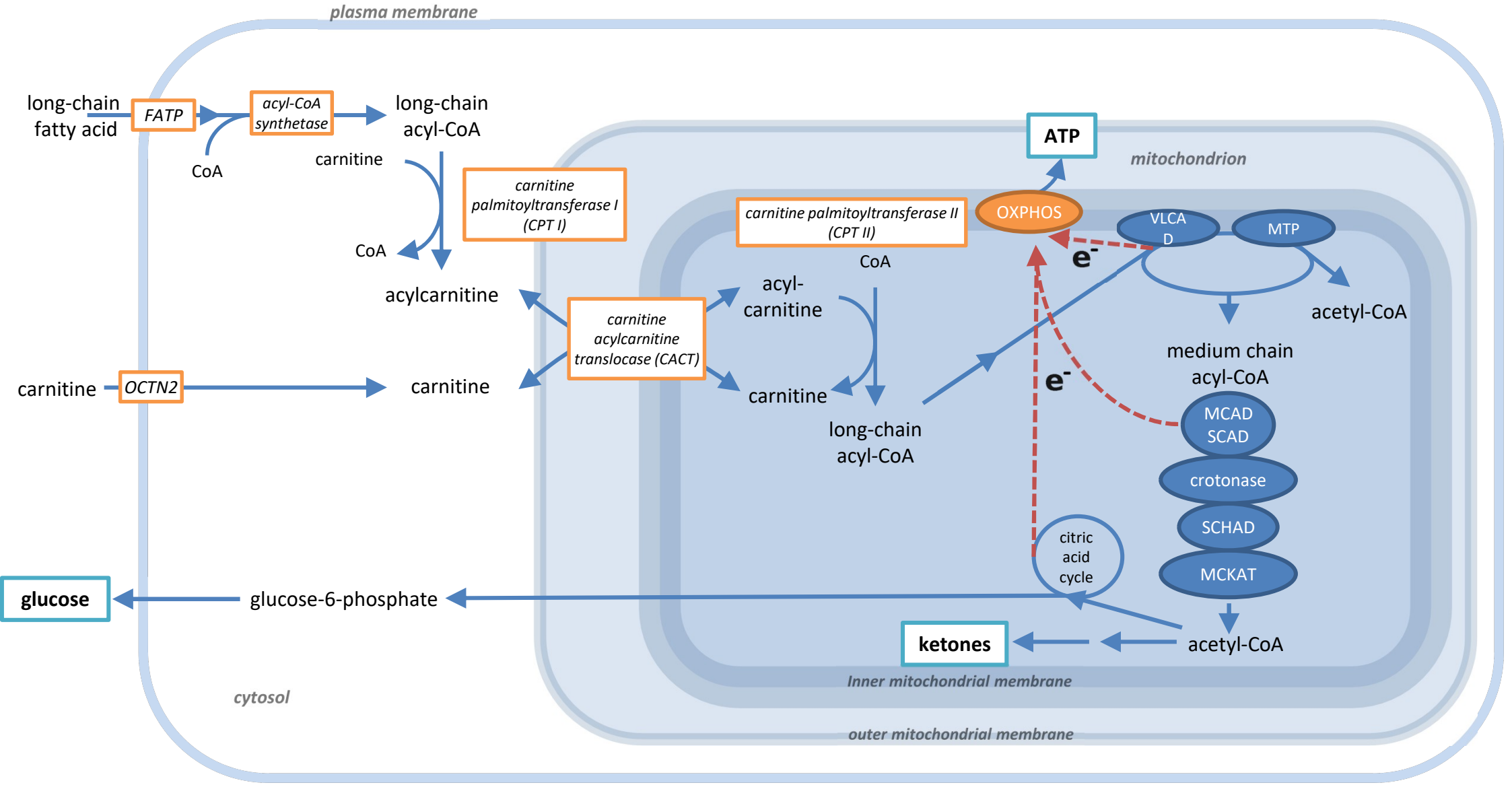
Fual utilisation during fasting



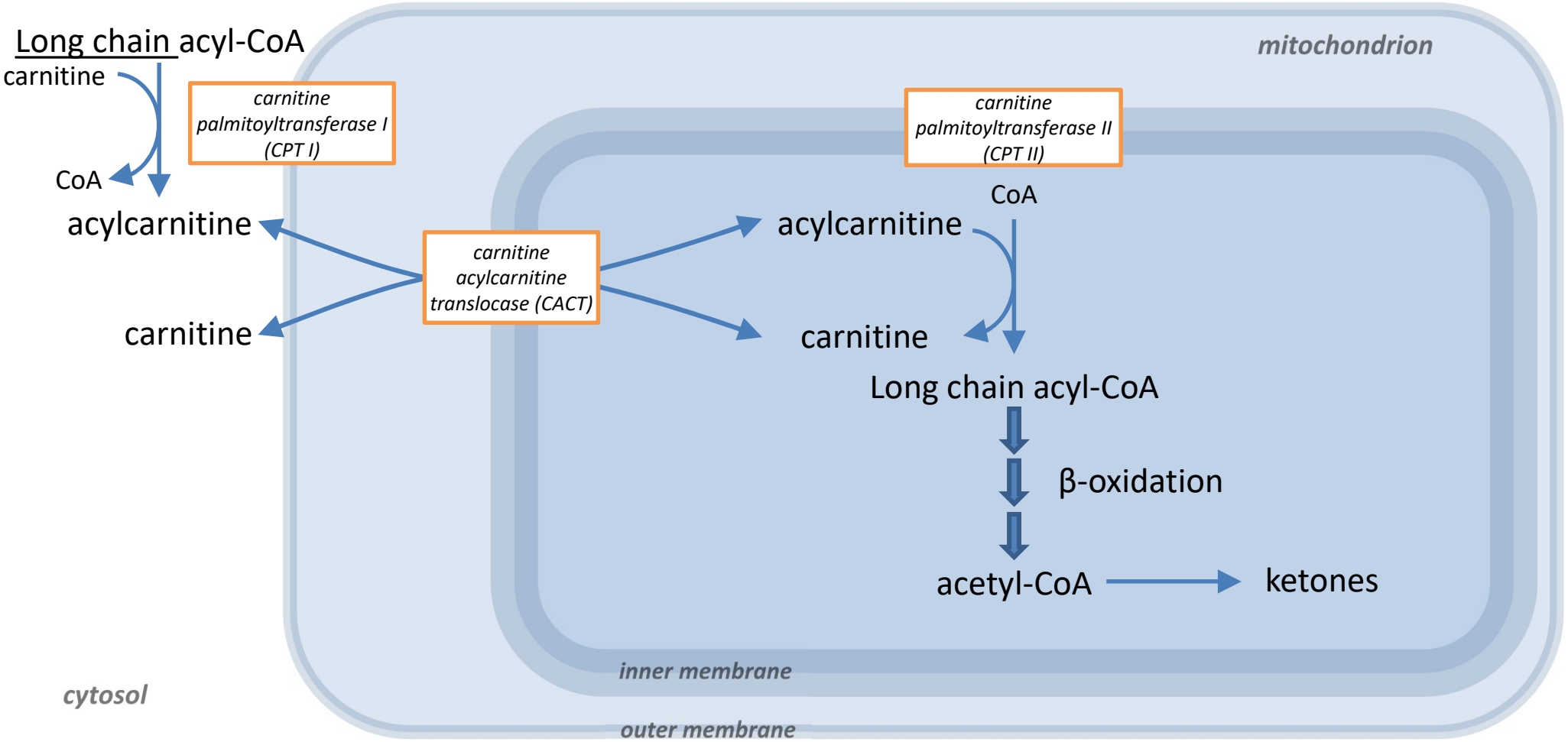
Mitochondrial fatty acid β-oxidation

- Carnitine cycle
- Mitochondrial β-oxidation

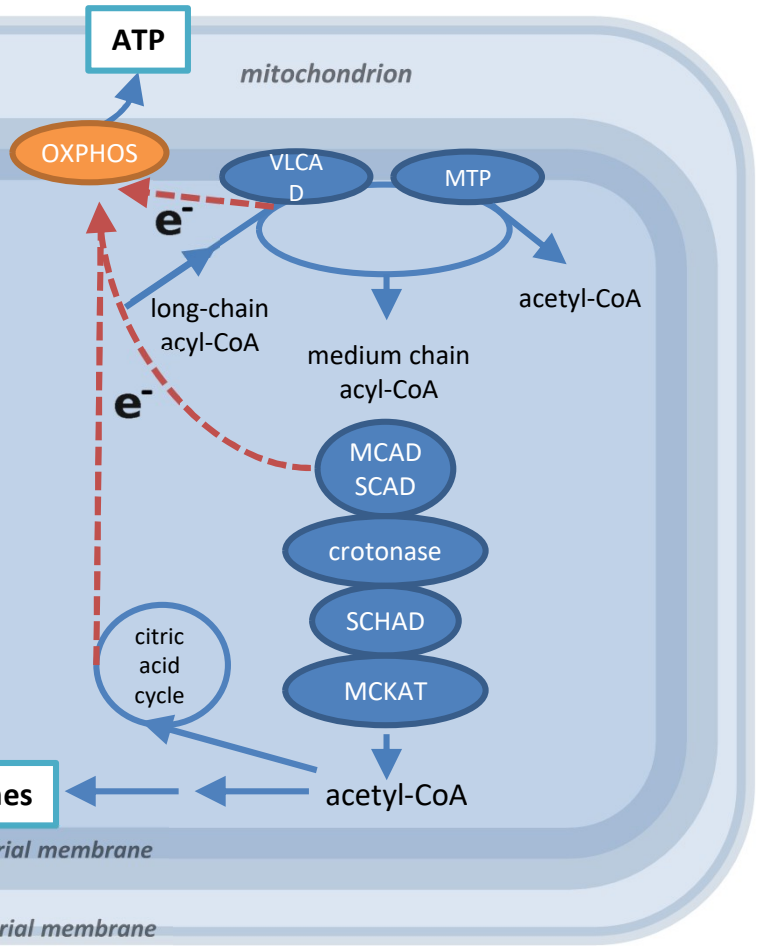
Mitochondrial fatty acid β-oxidation

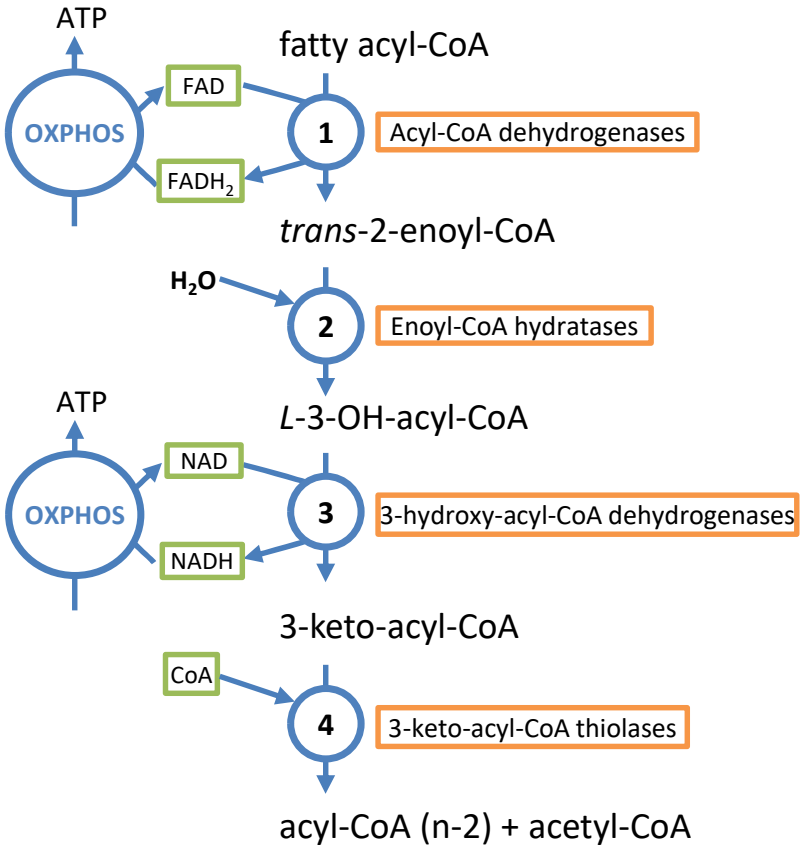


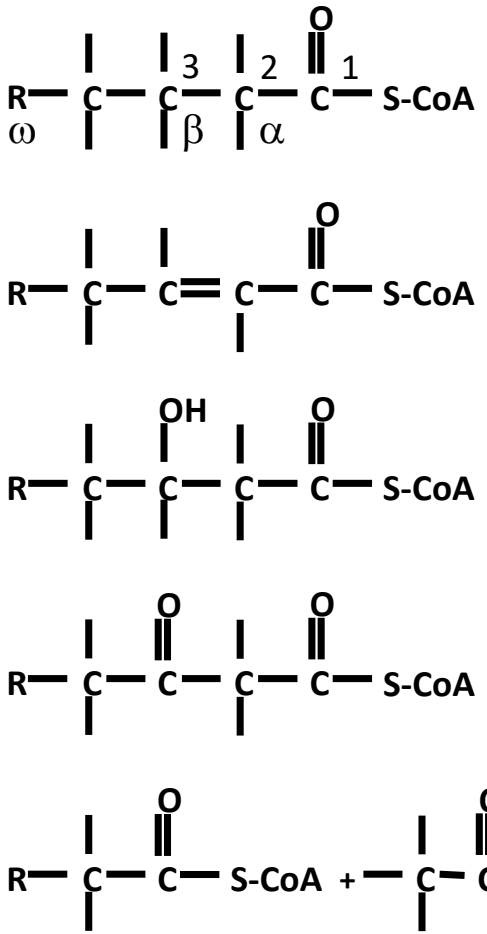
the carnitine shuttle / cycle



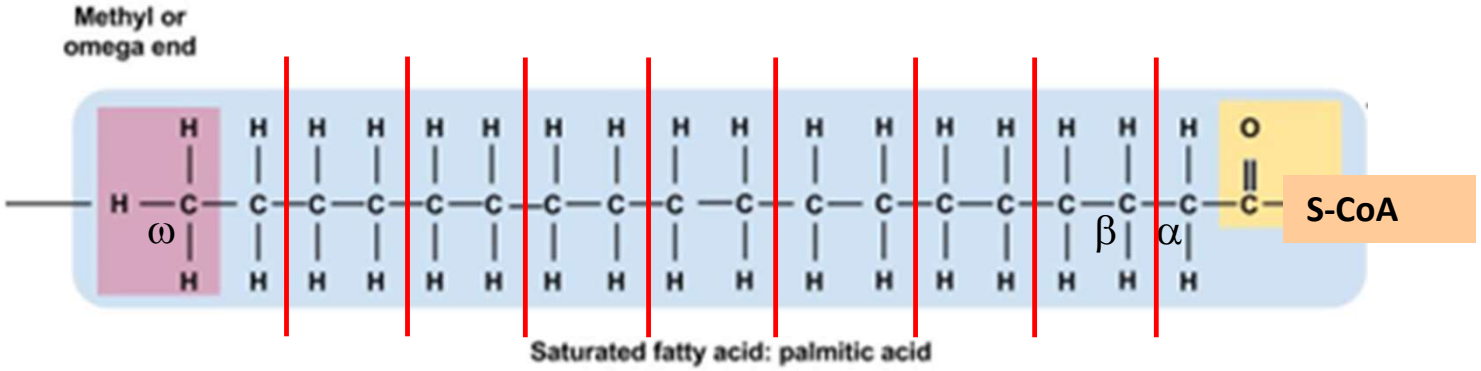
Mitochondrial β-oxidation







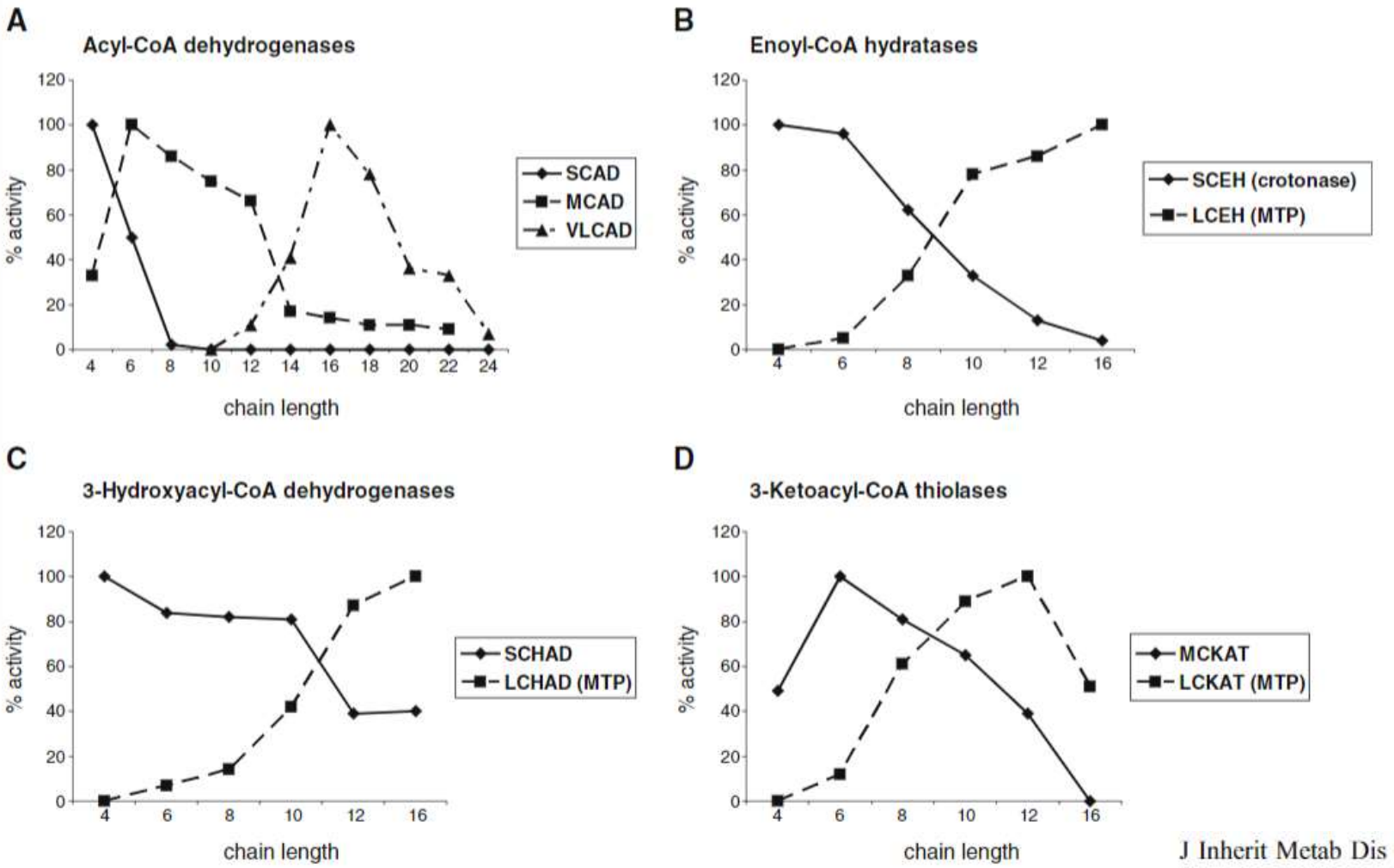
Mitochondrial β-oxidation



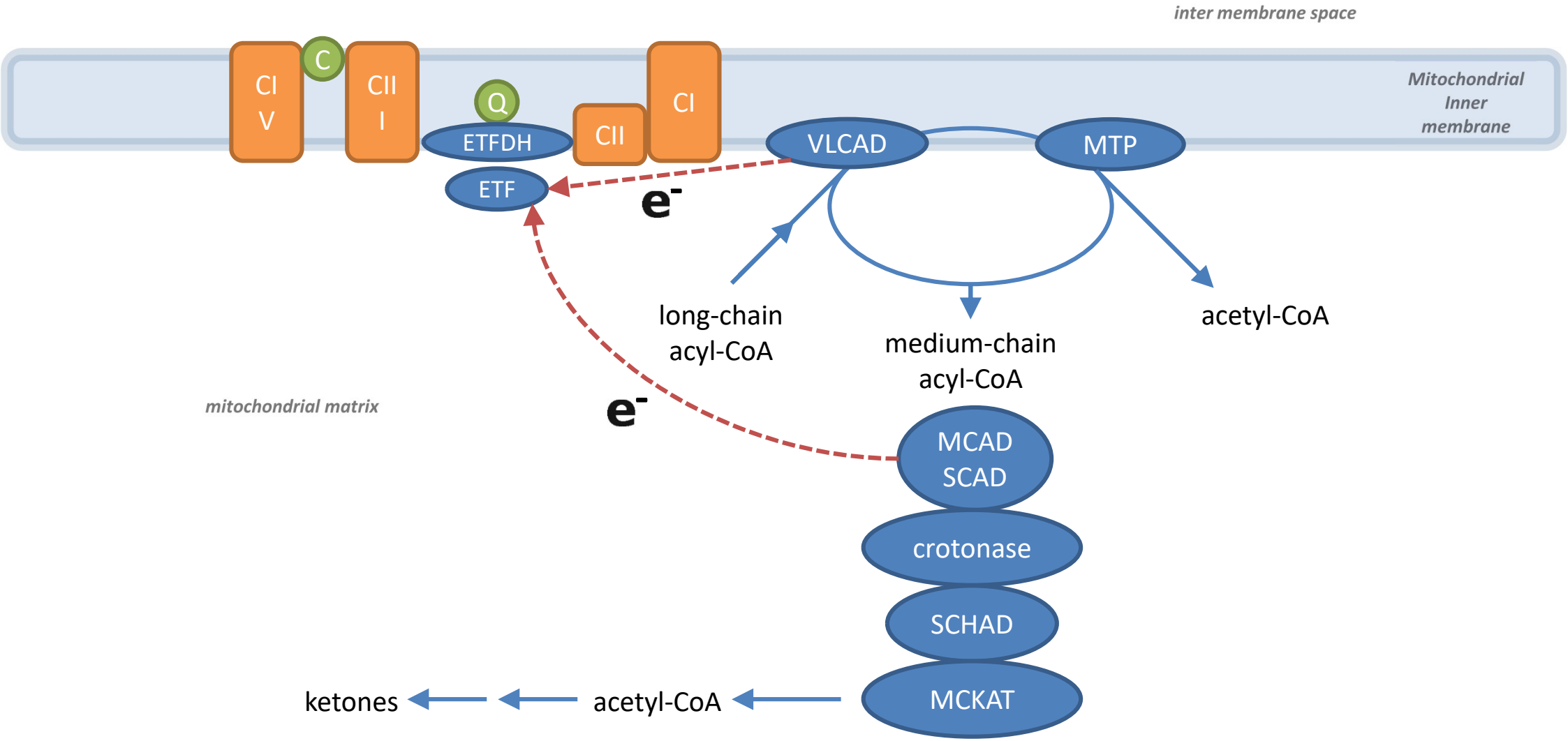
C16

7 NADH + 7 $FADH_2$+ 8 acetyl-CoA (C2)

Substrate specificity

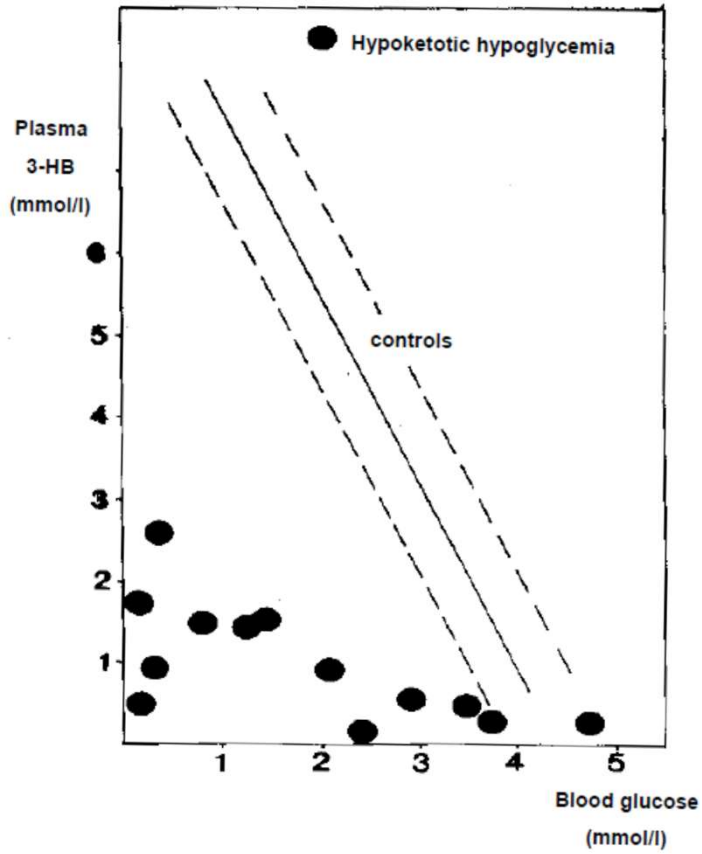


J Inherit Metab Dis (2010) 33:479–494


inter membrane space
Mitochondrial Inner membrane
CI
V
C
CII
I
Q
ETFDH
CII
CI
ETF
e-
VLCAD
MTP
long-chain acyl-CoA
medium-chain acyl-CoA
acetyl-CoA
mitochondrial matrix
e-
MCAD
SCAD
crotonase
SCHAD
MCKAT
ketones
acetyl-CoA

Key diagnostic tests / Lab aspects

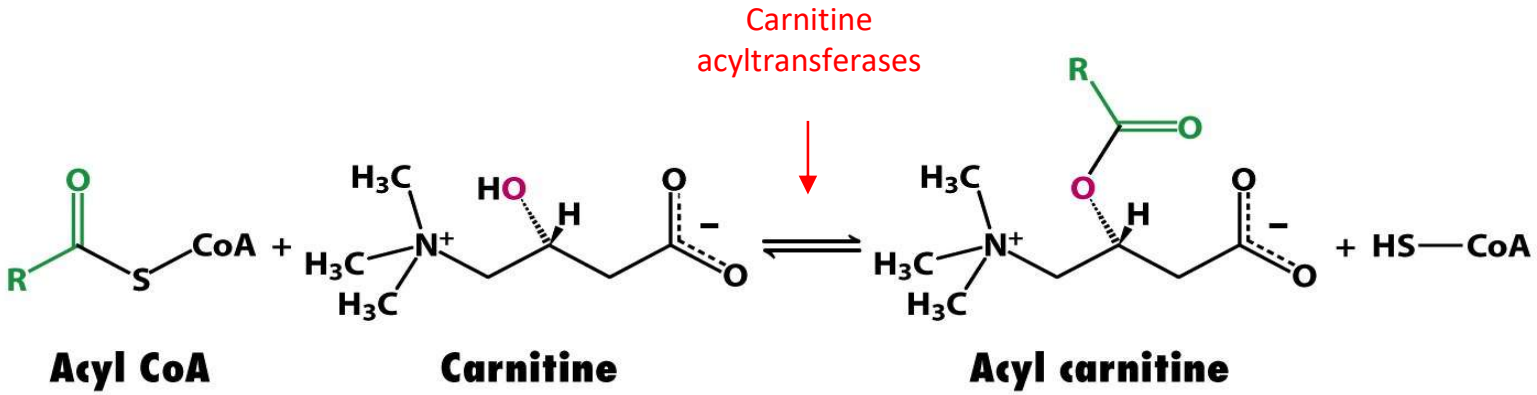
- Routine clinical chemistry tests
  - Glucose
  - Ketones
  - Free fatty acids
  - Ammonia
  - (Lactate, blood gas)
  - Organ disfunction: CK, AST/ALT
- Metabolite analyses
  - Acylcarnitine profiling
  - Urinary organic acids
- Functional enzyme testing
- Genetics



Acylcarnitine profiling using mass spectometry

- Key in diagnosis of FA oxidation disorders
- Informative in some organic acidurias

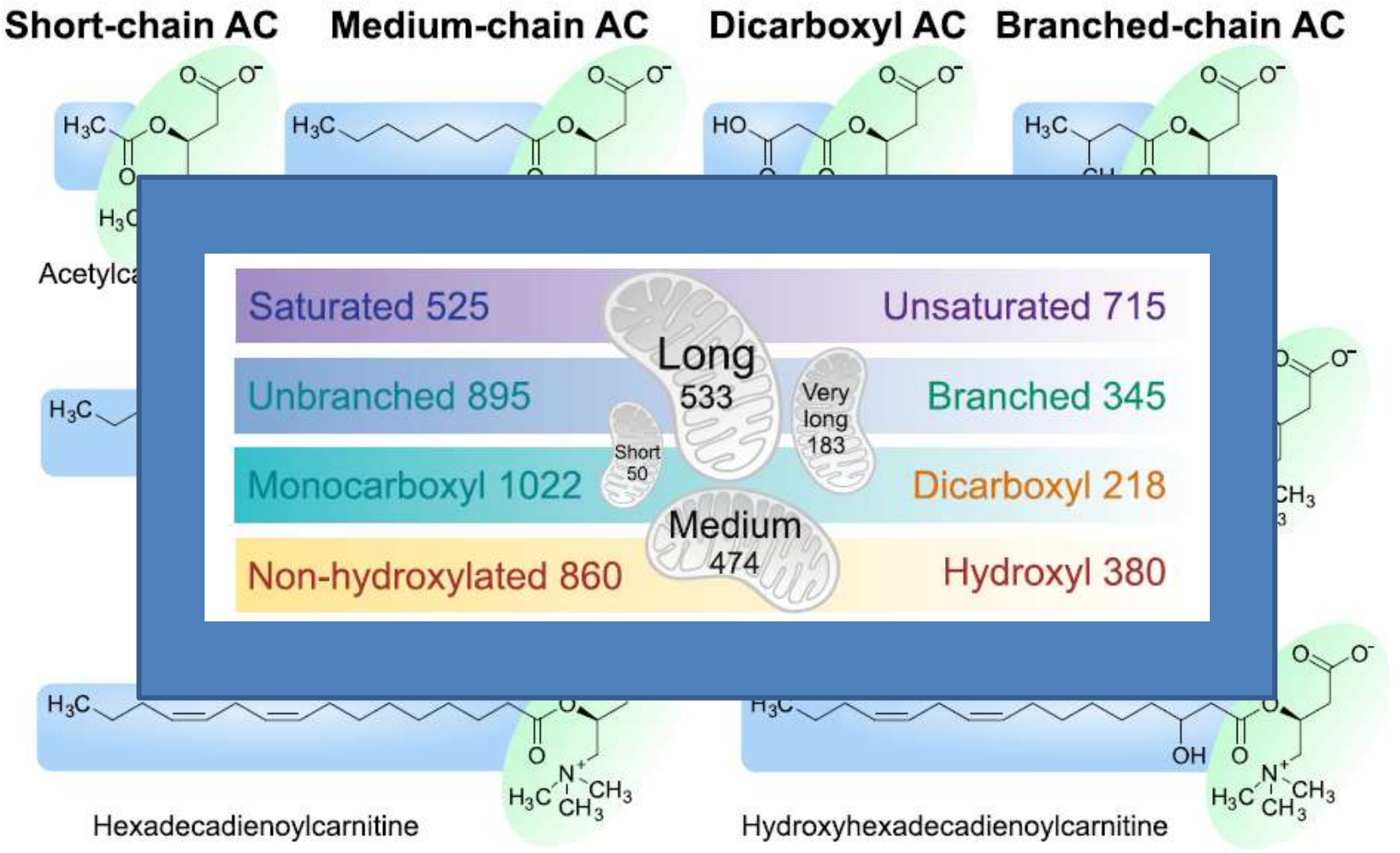
Formation of an acylcarnitine



Unnumbered figure pg 623b
Biochemistry, Sixth Edition

~75% diet (meat)
~25% endogenous synthesis from lysine (liver, brain, kidney)

Carnitine modulates the free CoA/acyl-CoA ratio

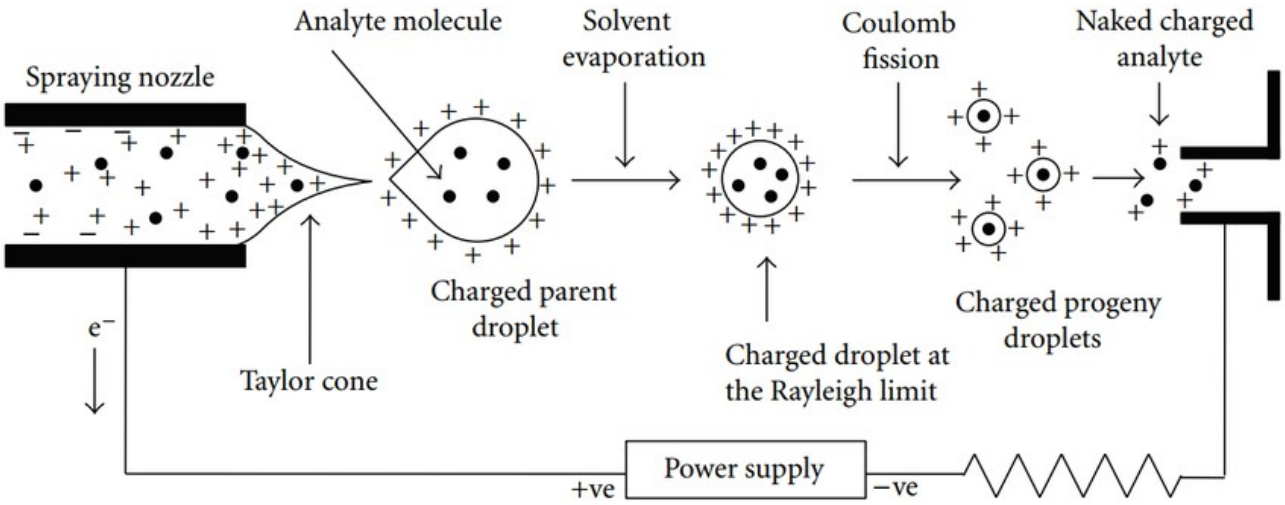


Pharmacol Rev 74:506–551, July 2022

Mass spectrometry

Mass spectrometry

Solvent ionisation, the electrospray ion source



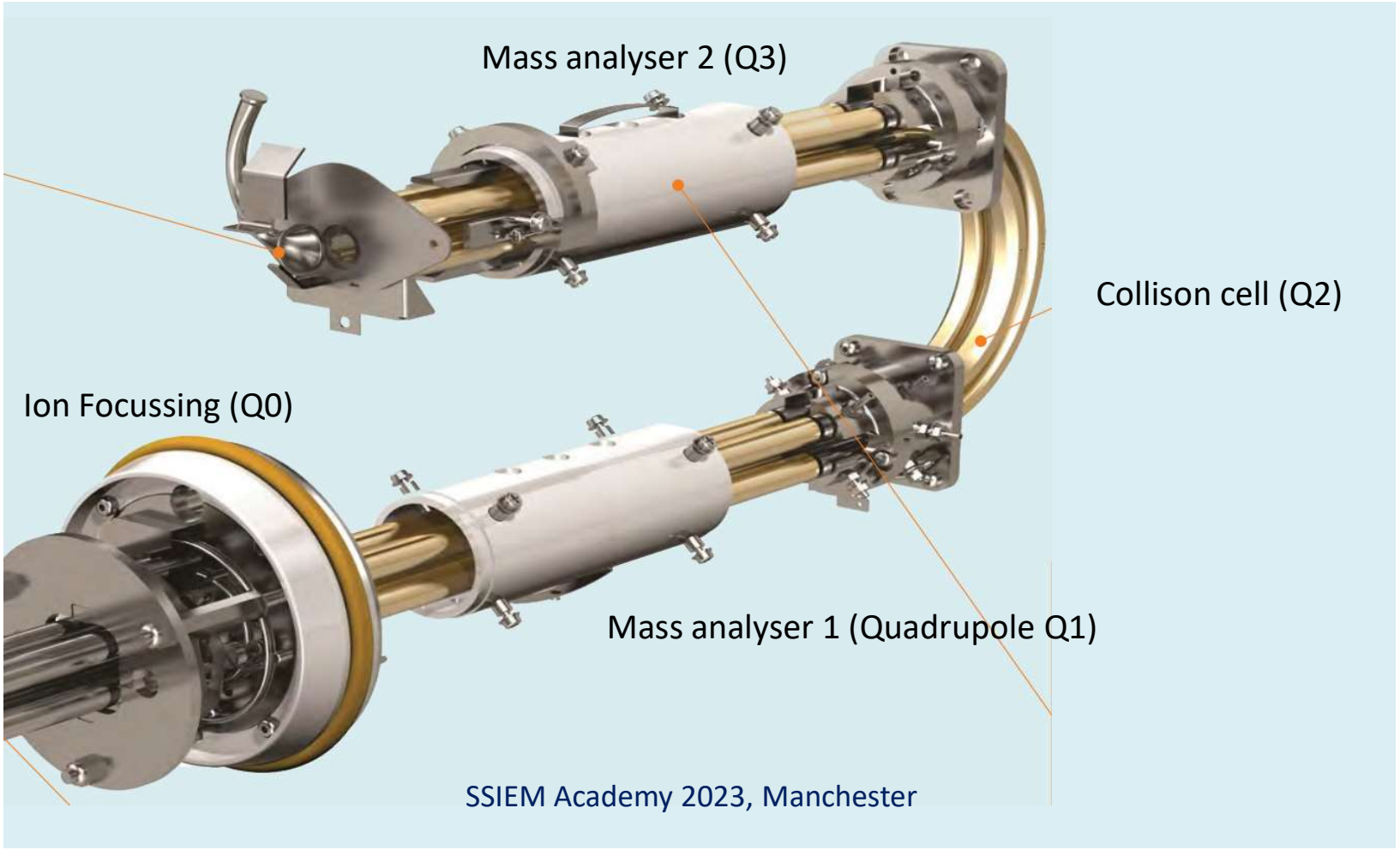
MS

HPLC

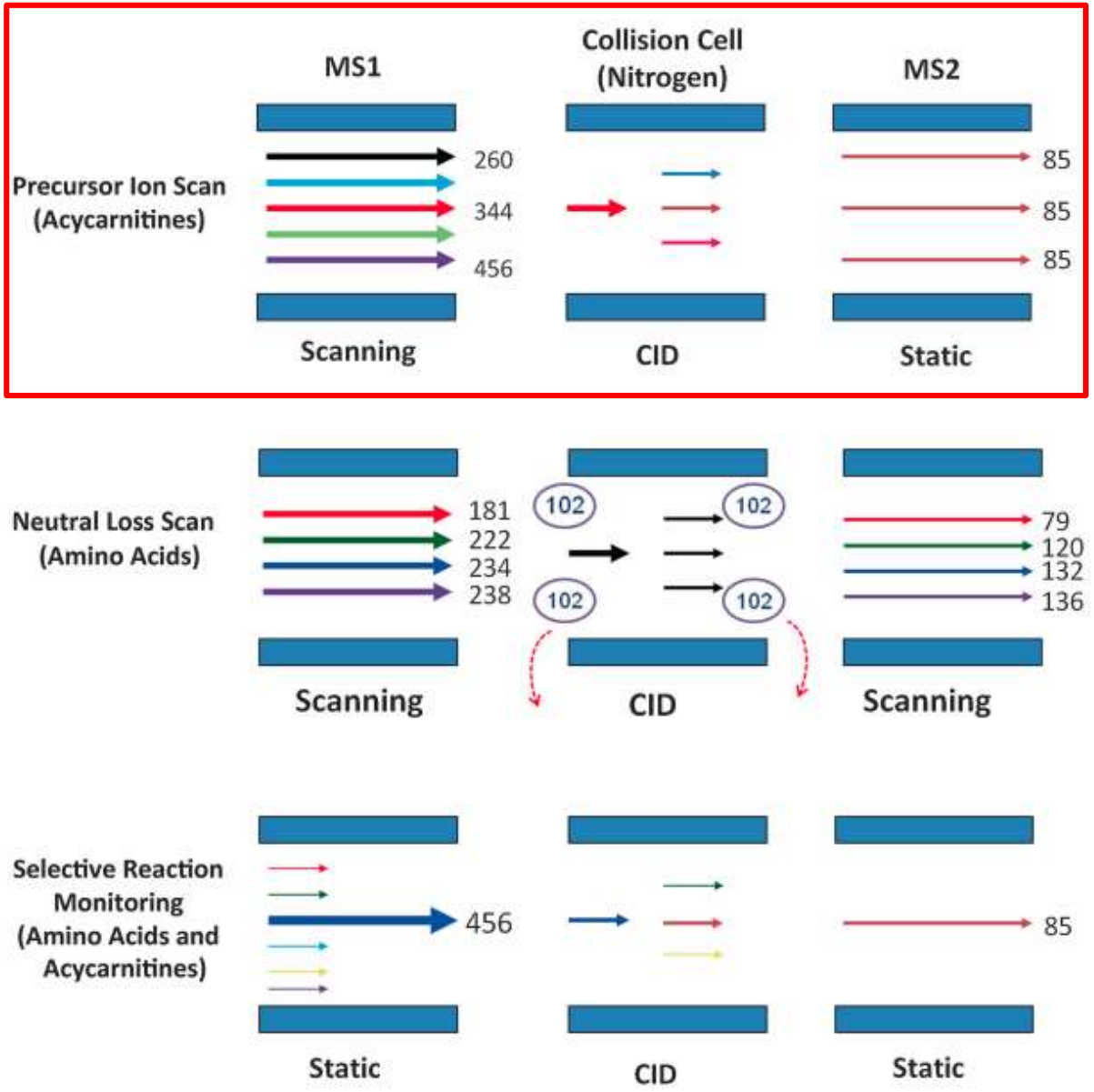
Mass spectrometer

Insite the mass analyser

(triple quadrupole or tandem MS)

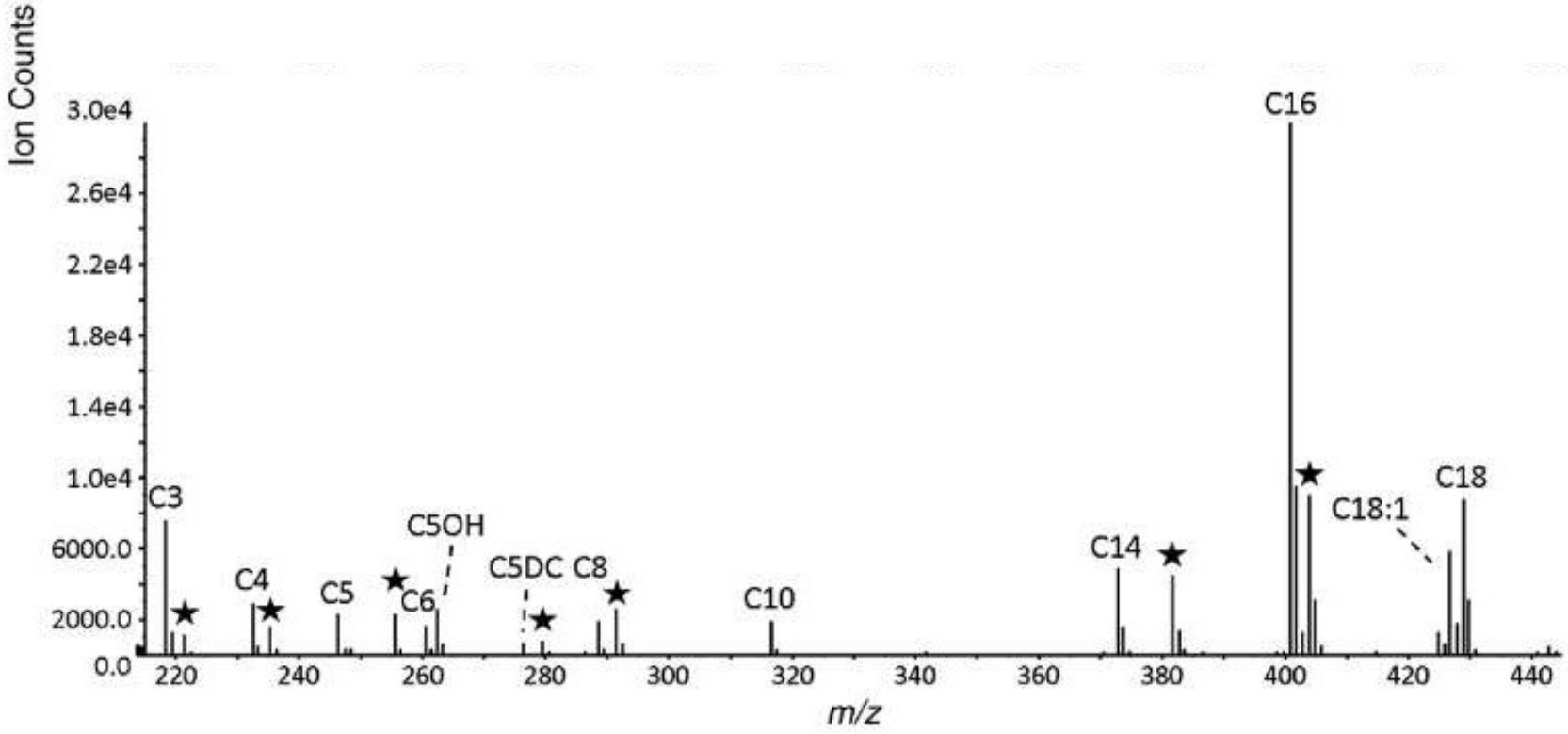


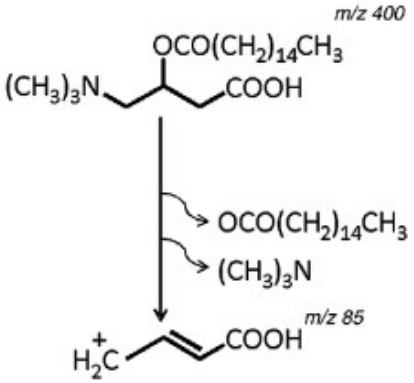
Operating modes of a tandem MS



L. Cheng, D.Y. Zhang, J.N. Eble (eds.), *Molecular Genetic Pathology*,

Mass spectrum of acylcarnitines





Palmitoylcarnitine

V.R. De Jesús et al. / Clinica Chimica Acta 411 (2010) 684–689

Underivatised vs butylated acylcarnitines

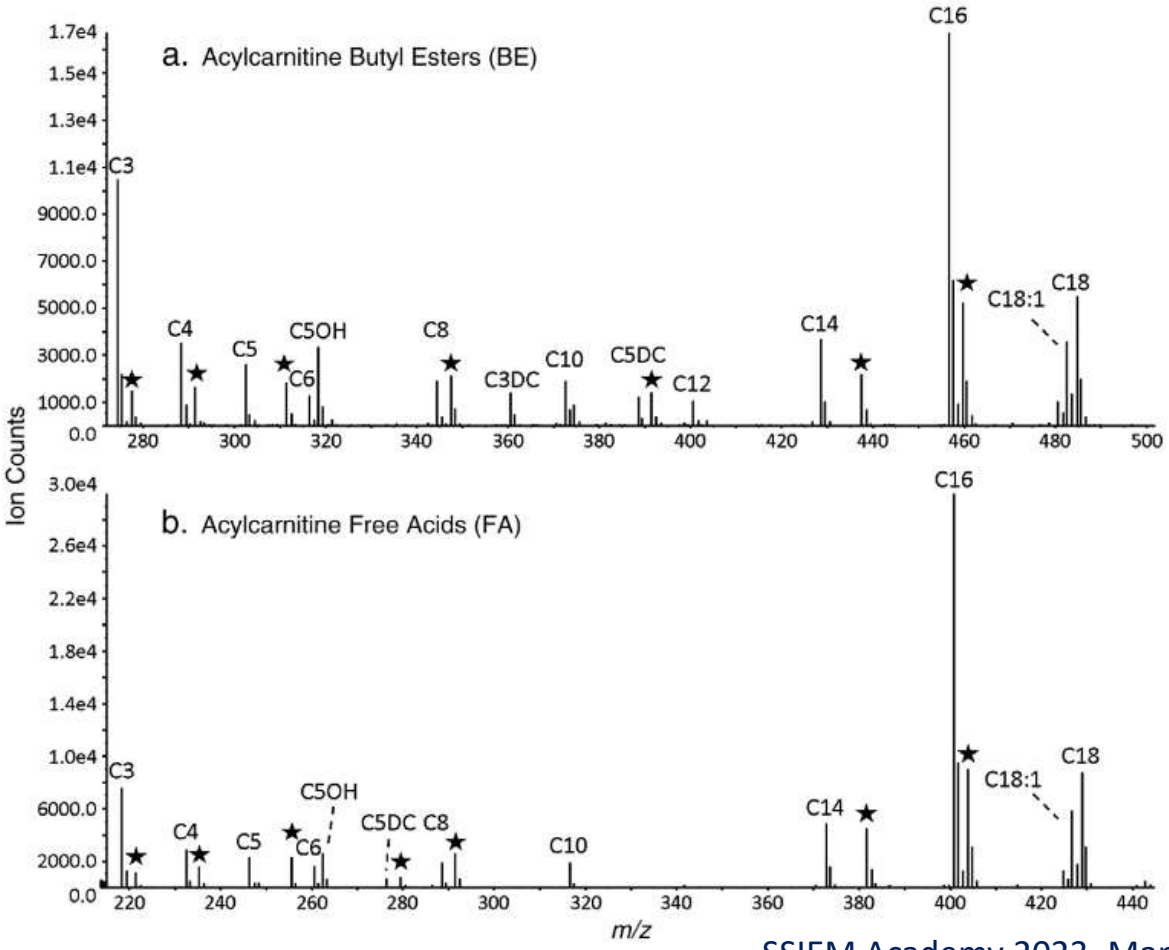
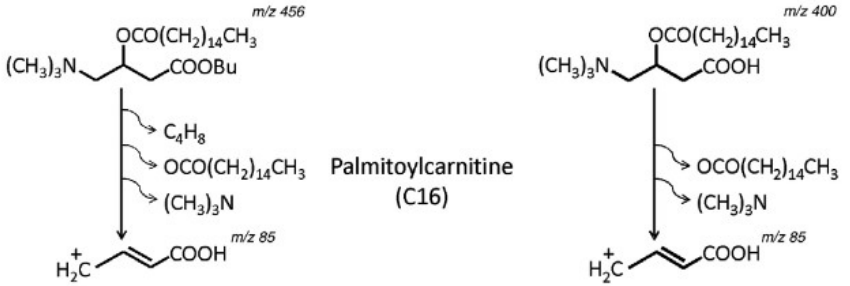


Fig. 2. Mass spectra of acylcarnitine butyl esters and free acids.

- Differences between methods <15%, except dicarboxylic acids (!)
- Underivatised: easy, but inadequate separation of isomers (C3DC/C4OH, C4DC/C5OH etc)
- Derivatised: risk of hydrolysis, inadequate separation of isomers (C5DC/C10OH, C4/FIGLU, C16:1OH/cefoxatim etc)

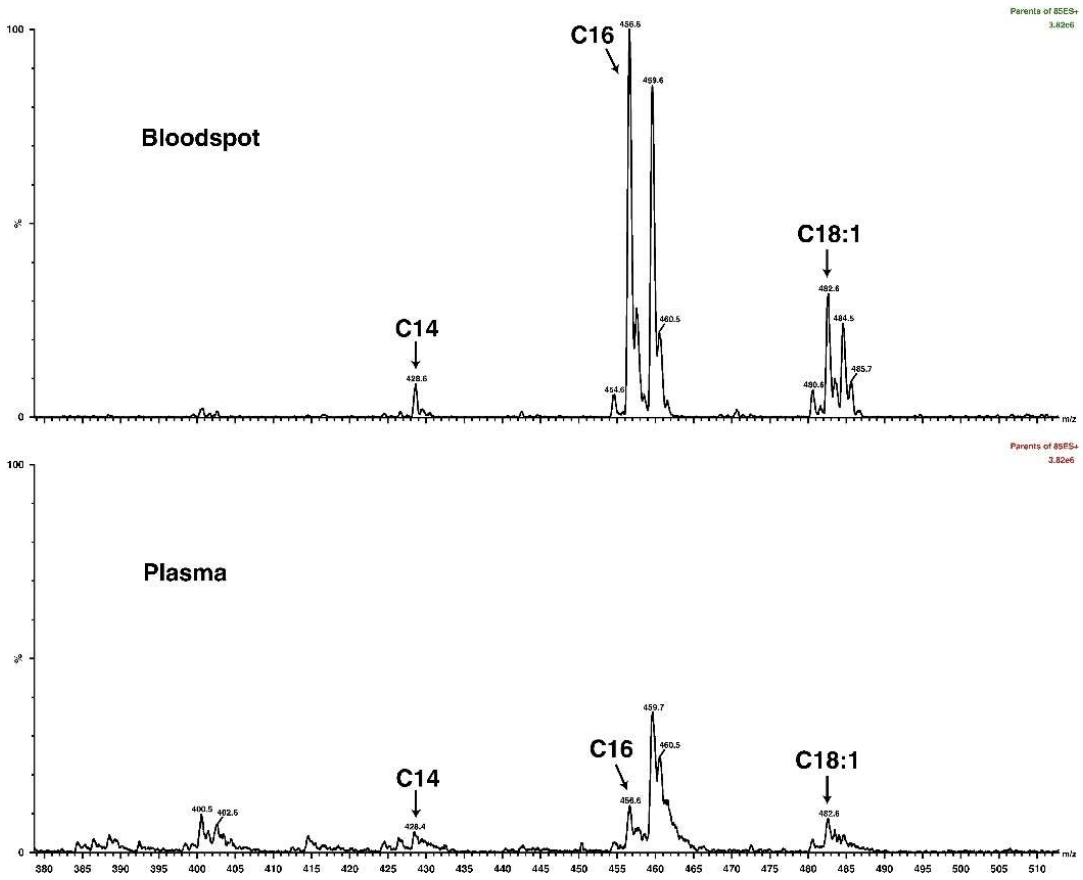


V.R. De Jesús et al. / Clinica Chimica Acta 411 (2010) 684–689

Possible pitfalls

- Flow-injection acylcarnitine interpretation (isomers)
- Low carnitine concentrations
  - check mass spectrum or acylcarnitine ratio's
- Samples collected after adequate treatment of crisis moment
- Interferences
  - C8: valproylcarnitine (-2-propylvaleric acid) or 2-ethylhexanoic acid
  - C5: pivalyolcarnitine (=C5) from antibiotica and (nipple) creams
  - Some interferences differ for butylated vs non-butylated methods (!)
  - Hemolysis
- Renal failure (SC/MC dicarboxylic acid carnitines), liver failure (LC dicarboxylic acid carnitines)
- Blood spot ≠ plasma ≠ urine

Blood spot vs plasma



DBS >3 * plasma

Table 1
Comparison of total carnitine, free carnitine and acylcarnitines in plasma and corresponding DBS from controls.

	Plasma (n = 54)	DBS (n = 54)	P (paired *t*-test)
Total carnitine	33.3 ± 16.0	31.4 ± 12.3	0.11
Free carnitine	26.8 ± 14.0	19.2 ± 8.5	<0.0001
Acyl carnitine (AC)	6.5 ± 3.7	12.1 ± 5.1	<0.0001
C2-carnitine	4.4 ± 3.1	7.2 ± 3.3	<0.0001
C3-carnitine	0.31 ± 0.21	0.86 ± 0.53	<0.0001
C4-carnitine	0.16 ± 0.09	0.16 ± 0.11	0.34
C5:1-carnitine	0.01 ± 0.01	0.02 ± 0.02	0.002
C5-carnitine	0.14 ± 0.10	0.12 ± 0.07	0.04
C4:3-OH-carnitine	0.03 ± 0.04	0.07 ± 0.06	<0.0001
C6-carnitine	0.04 ± 0.02	0.03 ± 0.02	0.0001
C5-OH-carnitine	0.03 ± 0.03	0.16 ± 0.19	<0.0001
C8:1-carnitine	0.17 ± 0.11	0.07 ± 0.05	<0.0001
C8 carnitine	0.07 ± 0.04	0.04 ± 0.03	<0.0001
C3-DC-carnitine	0.02 ± 0.01	0.01 ± 0.01	<0.0001
C10:2-carnitine	0.06 ± 0.04	0.01 ± 0.01	<0.0001
C10:1-carnitine	0.10 ± 0.06	0.04 ± 0.03	<0.0001
C10-carnitine	0.06 ± 0.08	0.06 ± 0.04	0.37
C4-DC-carnitine	0.04 ± 0.02	0.28 ± 0.17	<0.0001
C5-DC-carnitine	0.03 ± 0.01	0.02 ± 0.02	<0.0001
12:1-carnitine	0.04 ± 0.03	0.02 ± 0.02	<0.0001
12-carnitine	0.06 ± 0.03	0.04 ± 0.02	<0.0001
C6-DC-carnitine	0.05 ± 0.03	0.02 ± 0.02	<0.0001
C14:2-carnitine	0.03 ± 0.02	0.03 ± 0.01	0.13
C14:1-carnitine	0.04 ± 0.03	0.03 ± 0.02	0.002
C14-carnitine	0.04 ± 0.02	0.08 ± 0.04	<0.0001
C8-DC-carnitine	0.01 ± 0.01	0.01 ± 0.01	0.38
C14-OH-carnitine	0.01 ± 0.01	0.02 ± 0.01	<0.0001
C16:1-carnitine	0.03 ± 0.02	0.06 ± 0.04	<0.0001
C16-carnitine	0.11 ± 0.06	0.93 ± 0.58	<0.0001
C10-DC-carnitine	0.01 ± 0.01	0.05 ± 0.02	<0.0001
C16:1-OH-carnitine	0.01 ± 0.01	0.03 ± 0.02	<0.0001
C16-OH-carnitine	0.01 ± 0.01	0.02 ± 0.02	0.008
C18:2-carnitine	0.06 ± 0.05	0.25 ± 0.21	<0.0001
C18:1-carnitine	0.15 ± 0.09	0.83 ± 0.49	<0.0001
C18-carnitine	0.04 ± 0.02	0.46 ± 0.24	<0.0001
C18:2-OH-carnitine	0.0 ± 0.01	0.01 ± 0.01	0.001
C18:1- OH-carnitine	0.01 ± 0.01	0.02 ± 0.01	0.007
C18- OH-carnitine	0.01 ± 0.01	0.02 ± 0.01	0.36
C16-DC-carnitine	0.01 ± 0.01	0.02 ± 0.01	0.27
C18:1-DC-carnitine	0.01 ± 0.01	0.02 ± 0.01	0.27

Mean values ± standard deviation of the concentrations (in µmol/L); AC sum of the measured individual acylcarnitines; total carnitine: sum of free carnitine plus AC. DC; dicarbonic acid.

De Sain-van der Velden et al. MGM 2013;110:116-21

Blood spot vs plasma

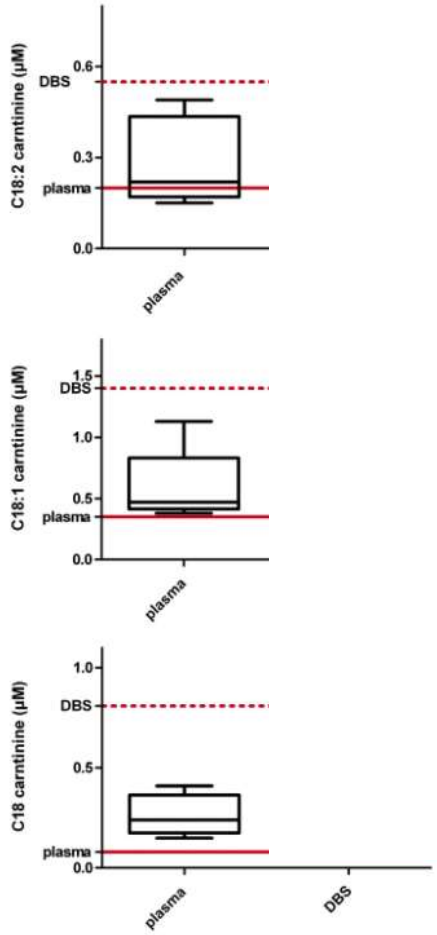


Fig. 3. Box-plots for C18:2-carnitine, C18:1-carnitine and C18-carnitine in plasma and DBS in four patients diagnosed with CPT-2 deficiency. Straight line represents 95th percentile of (age related) controls in plasma. Dotted line represents 95th percentile of (age related) controls in DBS.

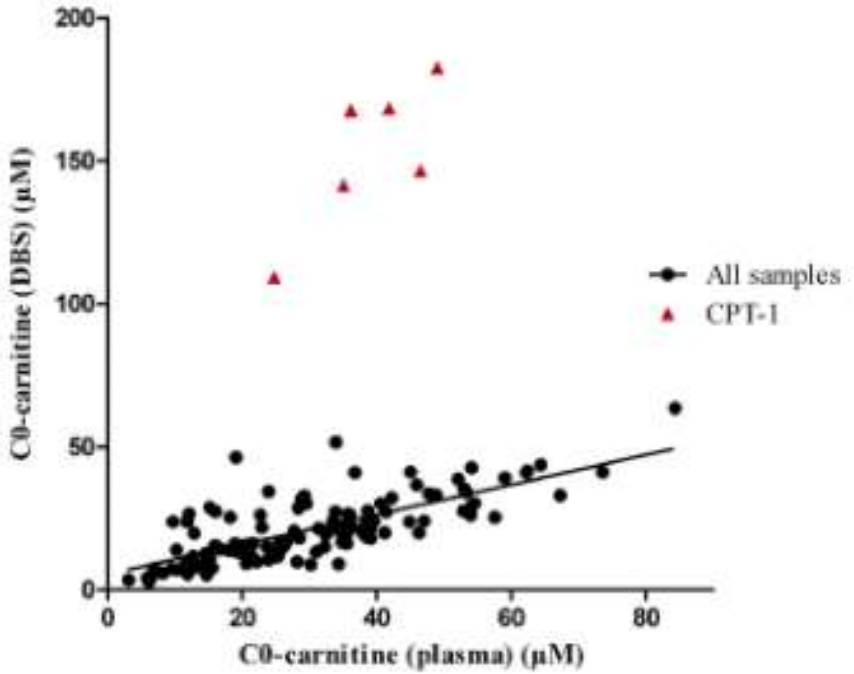


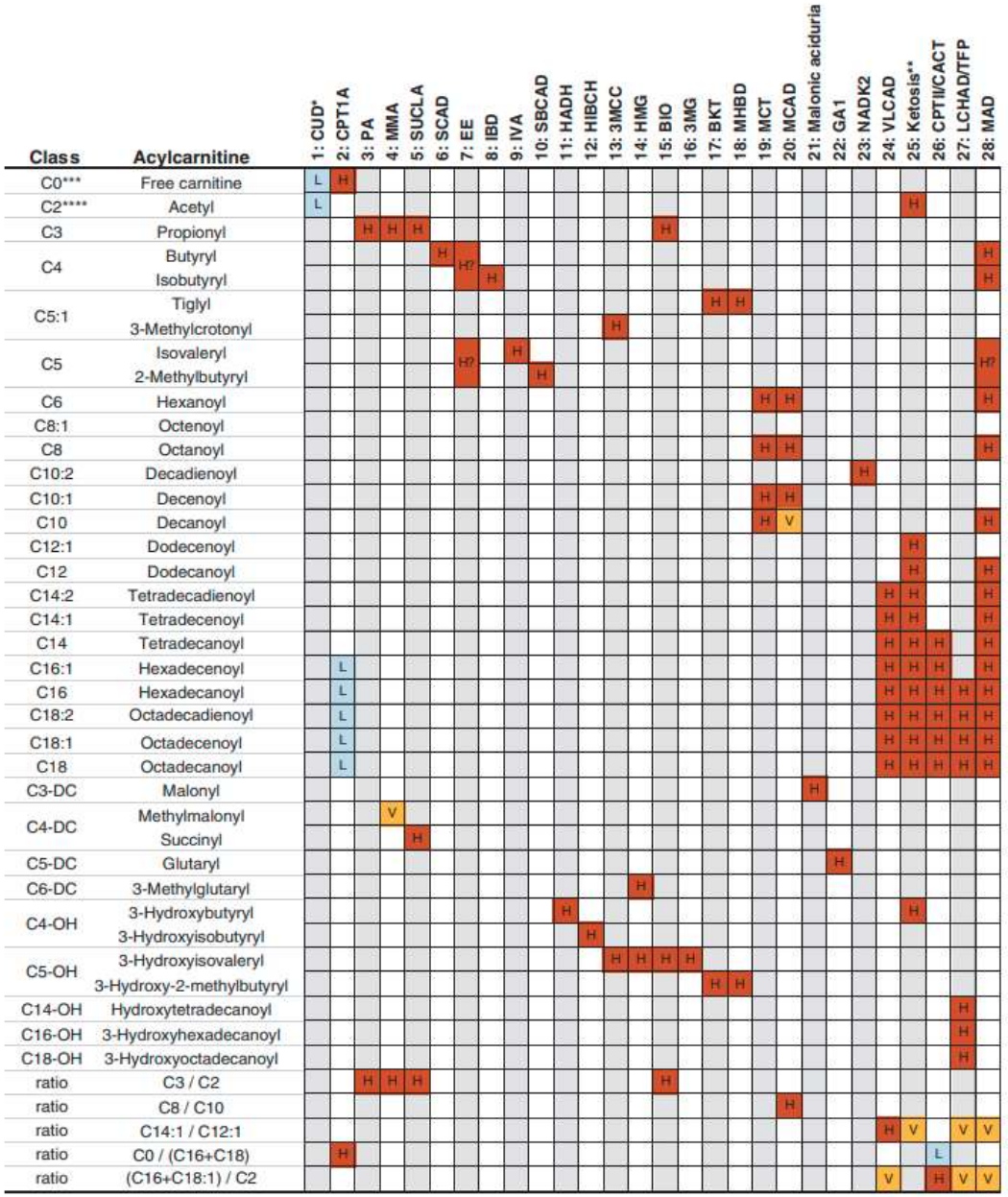
Fig. 2. Correlation between free carnitine in DBS specimen and their corresponding plasma sample (n = 125). ▲ represents free carnitine concentration in patients with proven CPT-1 deficiency. ● represents free carnitine concentration in all samples.

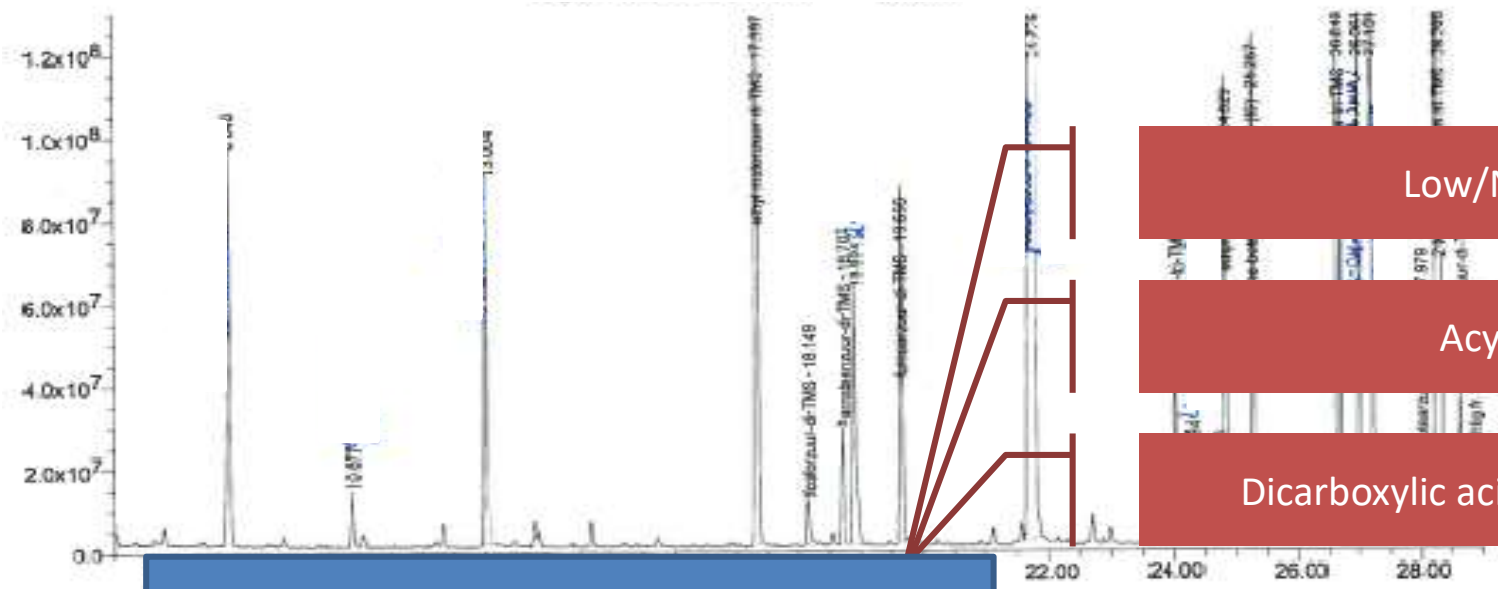
SSIEM Academy 2023, Manchester

De Sain-van der Velden et al. MGM 2013;110:116-21

American College of Medical Genetics

Laboratory diagnosis of acylcarnitines, 2020 update





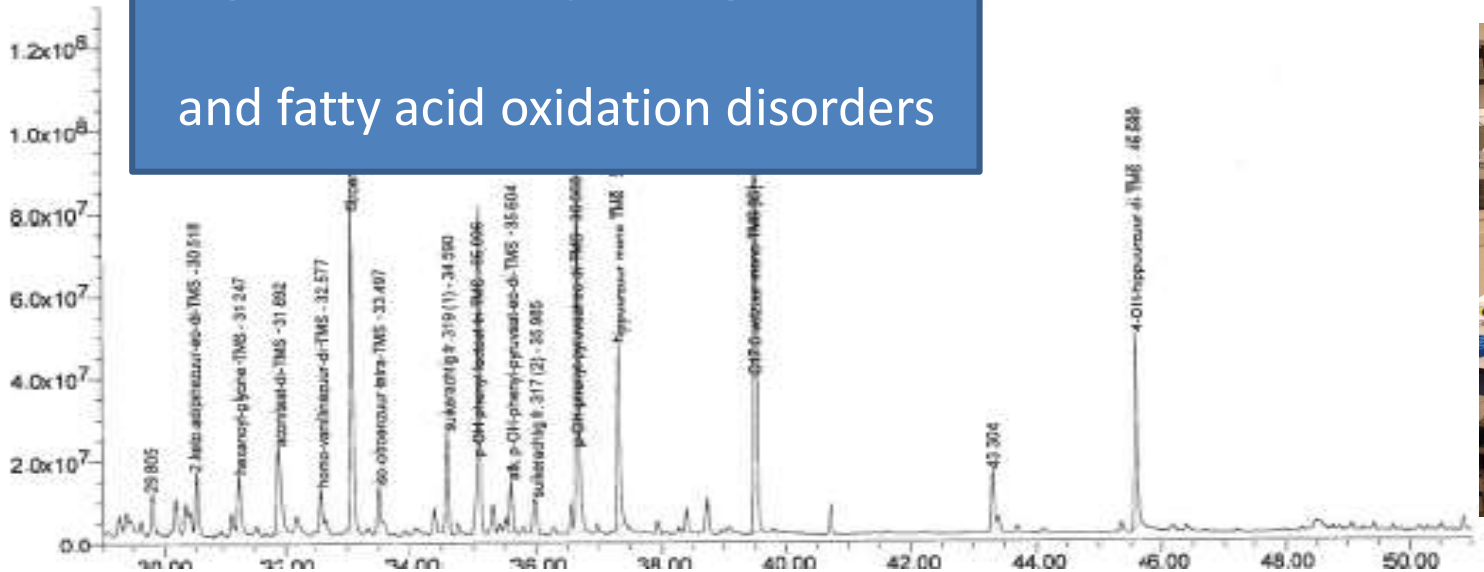
Low/No ketones

Acylglycines

Dicarboxylic acids from ω-oxidation

Organic acid analysis (e.g. GC-MS)

and fatty acid oxidation disorders



FAOX enzymology and genetics

- Single enzyme activity assays (lymfocytes/leukocytes or skin fibroblasts)
- Overall β-oxidation flux studies (lymfocytes/leukocytes or skin fibroblasts)
  - Fast in blood cells!
  - Low false-positives and false-negatives

- Genetics nowadays often first-line confirmation tests
  - Be aware of variance of unknown significance (VUS) and false-negatives
  - Fibroblast studies better predict functional consequences of mutations and patient outcomes

Wanders et al. J Inherit Metab Dis. 2010 Oct;33(5):479-94
Wanders et al. J Lipid Atheroscler. 2020 Sep;9(3):313-333

Pathophysiology

Energy deficit

- Fasting-induced
- OXPHOS defect
  - Lack of e^- to Respiratory chain
- Hypoketosis
- Hypoglycaemia

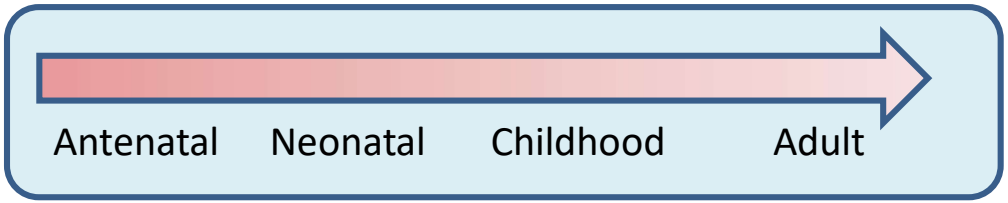
- Affecting liver, heart, muscle, brain

Fatty acid accumulation

- Toxic intermediates affecting liver, heart

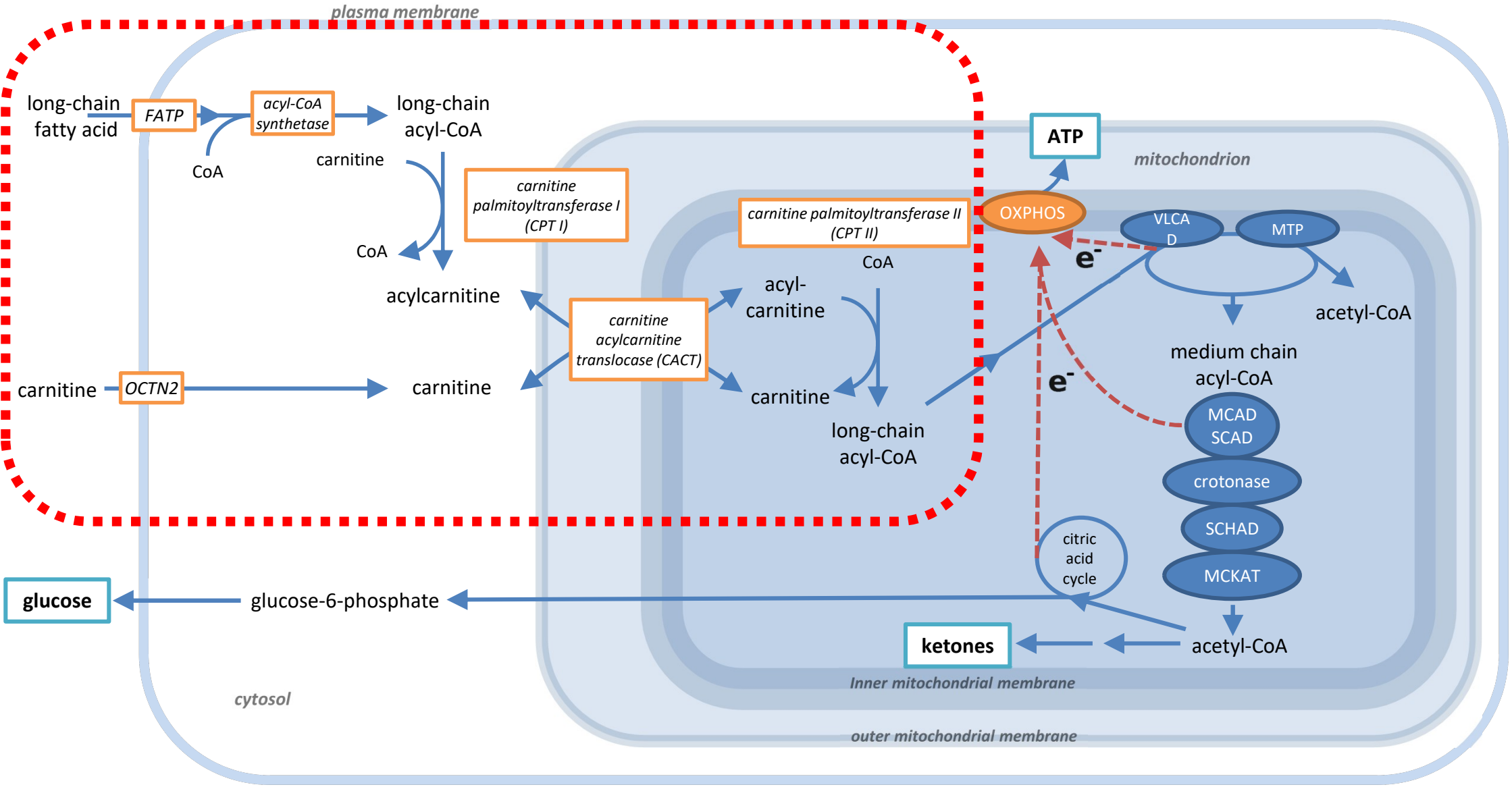
Pathophysiology

- **Hepatic/Encephalopathic**
  - Fasting hypoglycaemia
  - Hypoketotic
  - Hyperammonaemia
  - Hepatitis/hepatomegaly
- **Skeletal Muscle**
  - Exercise induced myalgia
  - Acute rhabdomyolysis
- **Cardiac**
  - Cardiomyopathy
  - Heart failure
  - Arrhythmia
- **Congenital Defects**



Carnitine Cycle

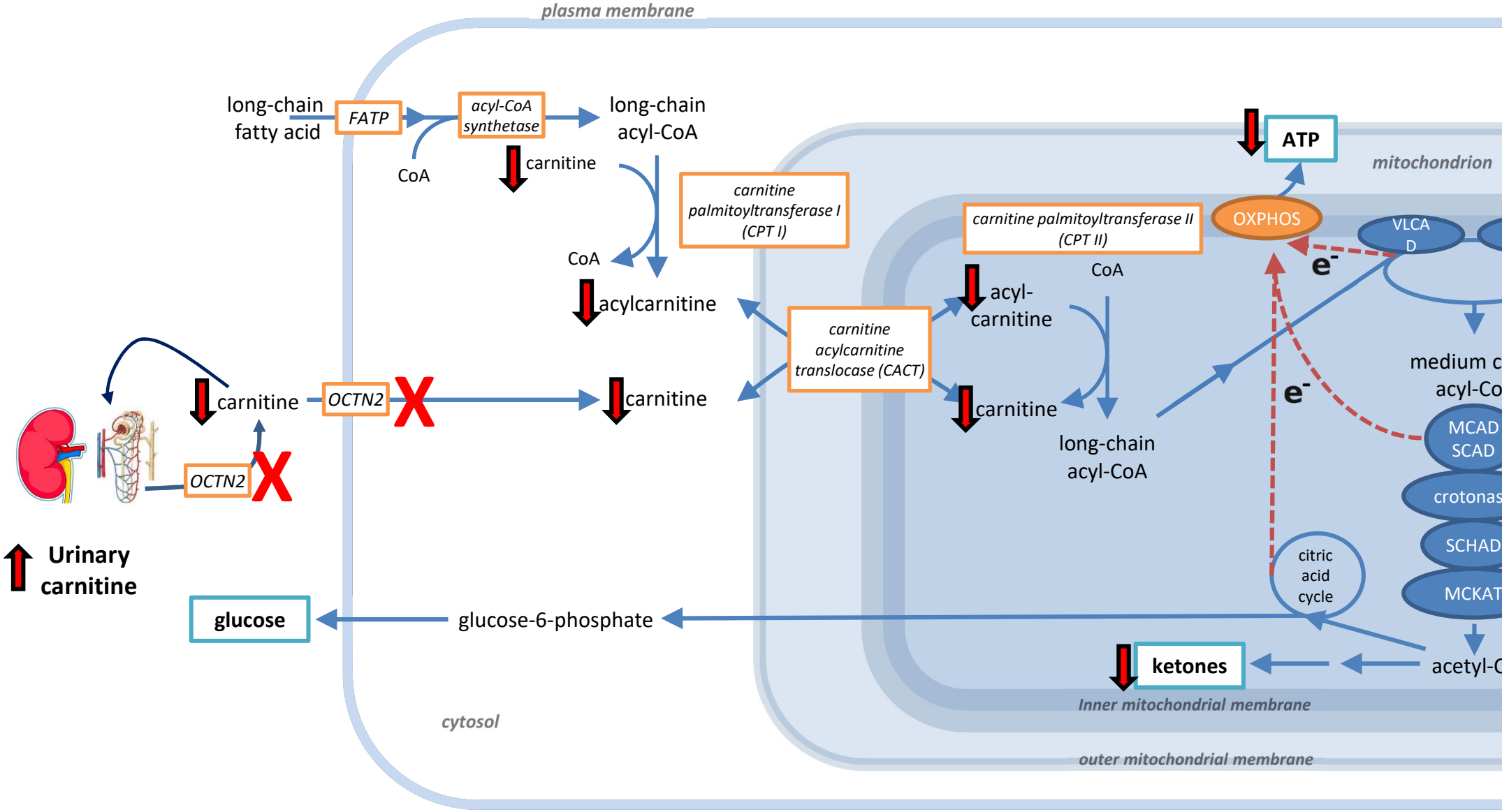
Mitochondrial fatty acid β-oxidation



Carnitine Transporter Defect

- SLC22A5/ OCTN2
  - High-affinity carnitine transporter
  - Cellular carnitine uptake
  - Renal tubular reabsorption of filtered carnitine

Mitochondrial fatty acid β-oxidation



Carnitine Transporter Defect

- **Renal wasting of carnitine**
  - Increased fractional excretion of carnitine
  - Low free plasma carnitine

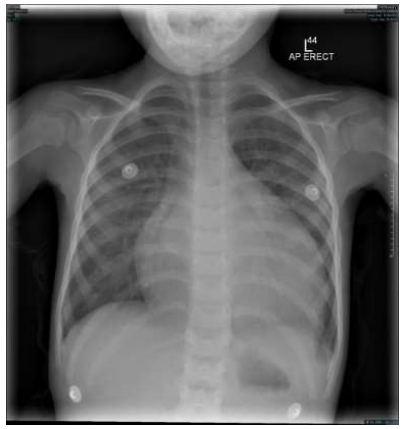
- **Skeletal & cardiac muscle:** impaired fatty acid oxidation
  - Cardiomyopathy, ventricular arrhythmia
  - Myopathy

- Impaired **hepatic uptake and ketogenesis**
  - Hypoketotic hypoglycaemia
  - Hyperammonaemia

3year old female

- Progressive dyspnoea
  - Noted to have cardiomegaly on chest radiograph
  - Echocardiogram: severe dilated cardiomyopathy
  - Heart failure drugs commenced
- Mildly raised ammonia (159 µmol/L)
- Low free carnitine + raised urinary carnitine excretion
- *SLC22A5* c.824G>A, p.Trp275* homozygous

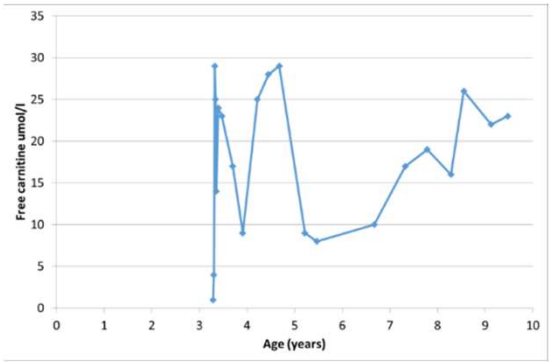
- Treatment: Oral Carnitine 100mg/kg/day
- Gradual resolution of cardiomyopathy

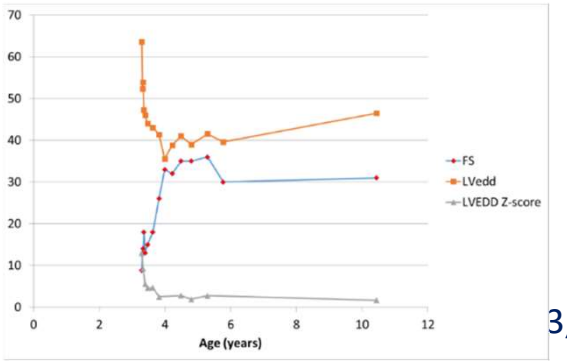


SSIEM ACADEMY 2023

Bloodspot acylcarnitine	µmol/L	Ref
Free carnitine C0	1	17-55
Acetyl carnitine C2	3.4	10-27.8
Propionyl carnitine C3	0.09	0.27-1.84
Octanoyl carnitine C8	0.06	0-0.18
Palmitoyl carnitine	0.2	0.4-1.7

Urine acylcarnitine	
Creatinine	6.4 mmol/L
Free carnitine	197 µmol/L
Free carnitine excretion	31 µmol/mmol creat

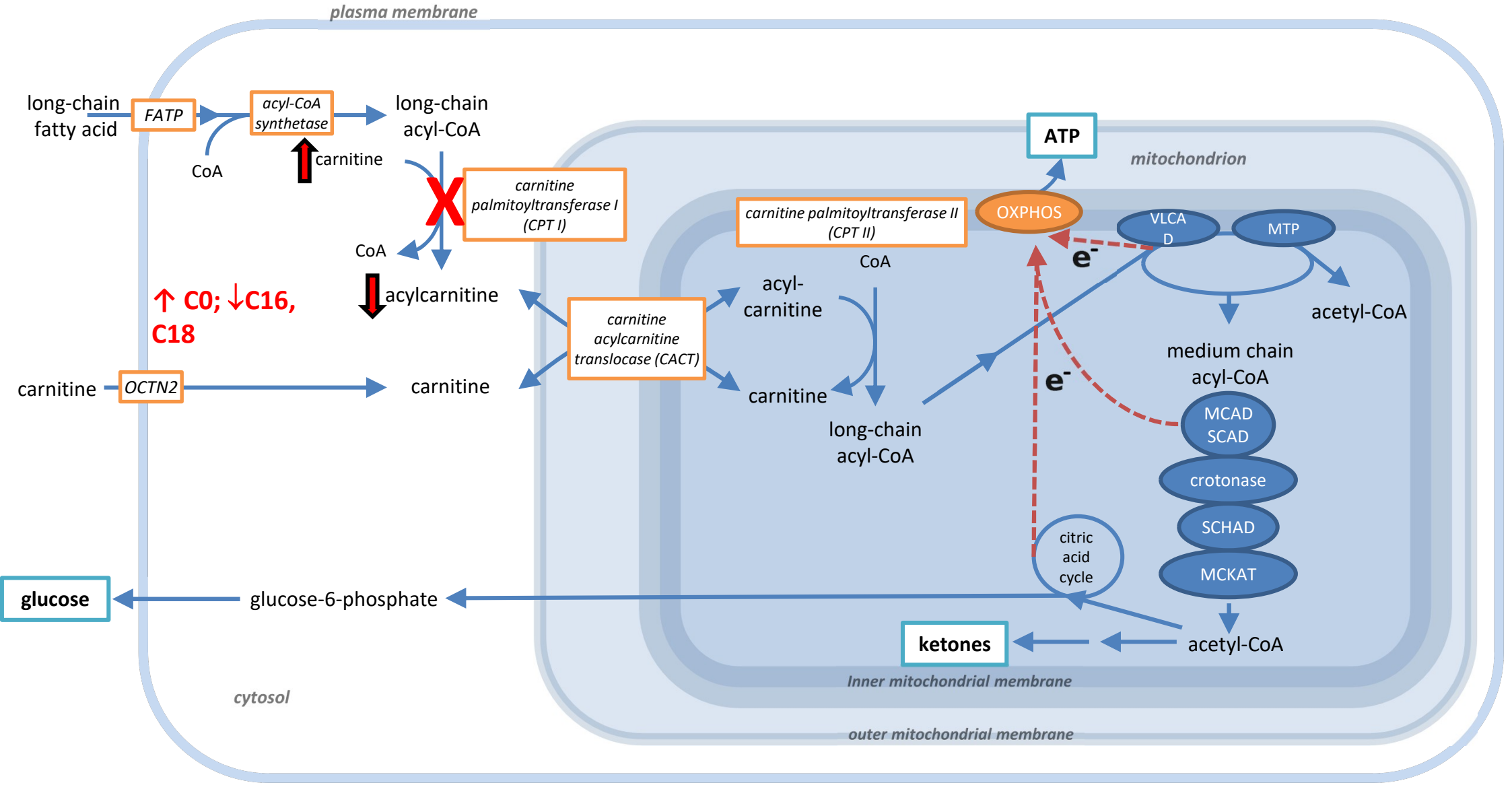




3, M

CPT1 deficiency

Mitochondrial fatty acid β-oxidation



CPT1 deficiency

Isoforms

- CPT1A: Liver-kidney
- CPT1B: muscle-heart
  - No reported phenotype
- CPT1C: neuronal/brain
  - ?Spastic paraplegia type 73 (AD)

Clinical phenotype

- Illness- or fasting-induced Hypoketotic hypoglycaemia
- Hepatomegaly/hepatitis
- Hypertriglyceridaemia /renal tubular acidosis

Diagnostics

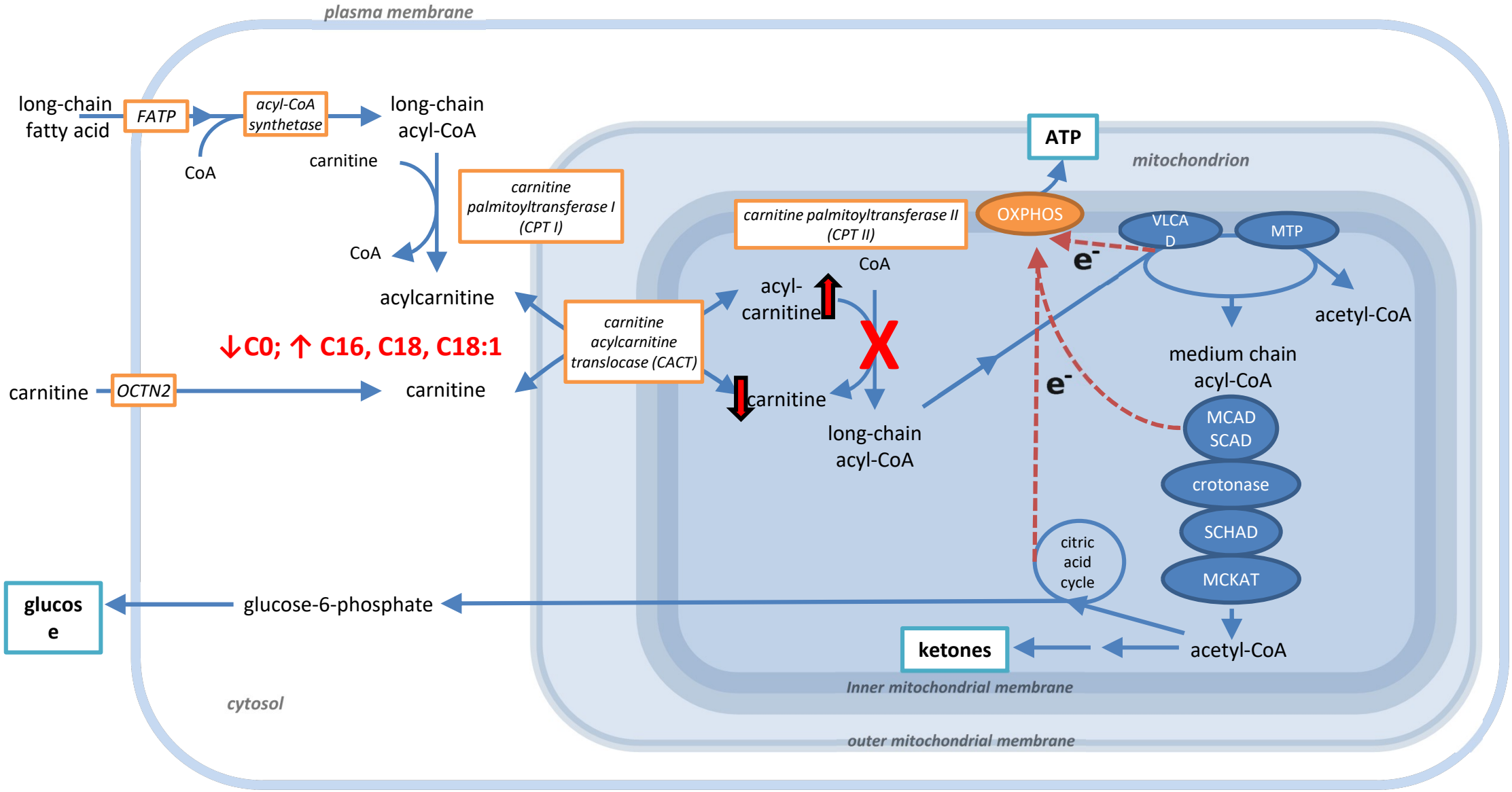
- Acylcarnitine (DBS better than Plasma)
  - ↑C0; ↓C16, 18
  - ↑C0 / (C16+C18)
- Urine organic acids: non specific (usually no dicarboxylic aciduria)
- *CPT1A* molecular genetics

Management

- Avoid prolonged fasting
- Low LCT, high MCT
- Glucose polymer emergency regimen

CPT2 Deficiency

Mitochondrial fatty acid β-oxidation

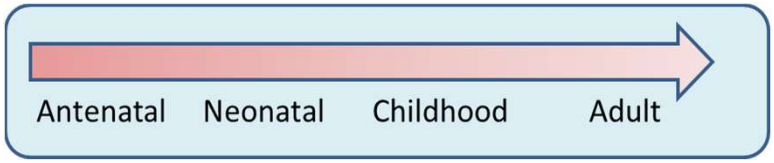


CPT2 deficiency: *Phenotypes*

"Mild"

- Recurrent exercise-induced rhabdomyolysis, often adult onset
- +/- myoglobinuria, acute renal impairment

Intermediate phenotype



Severe neonatal onset

- Usually fatal
- Hypoketotic hypoglycaemia
- Hyperammonaemia
- Cardiomyopathy, AV block and arrhythmias
- Congenital malformations (renal cysts, neuronal migration defects)

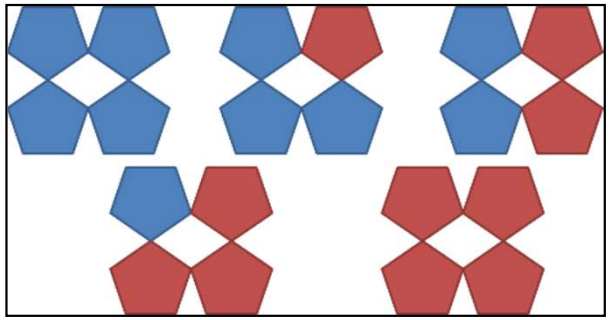
CPT2 deficiency: *Diagnostics*

- **Acylcarnitine** profile (=CACT deficiency)
  - ***Plasma*** preferred (RBC membrane interferes with C16, C18:1)
  - ↓ C0
  - ↑ C18:1, C18:2. C16, C16-DC. C18:2-DC. C18:1-DC
- Mild form: look at (C16+C18:1)/C2 ratio

- **Urine organic acids:** +/- Dicarboxylic aciduria

CPT2 deficiency: *Genetics*

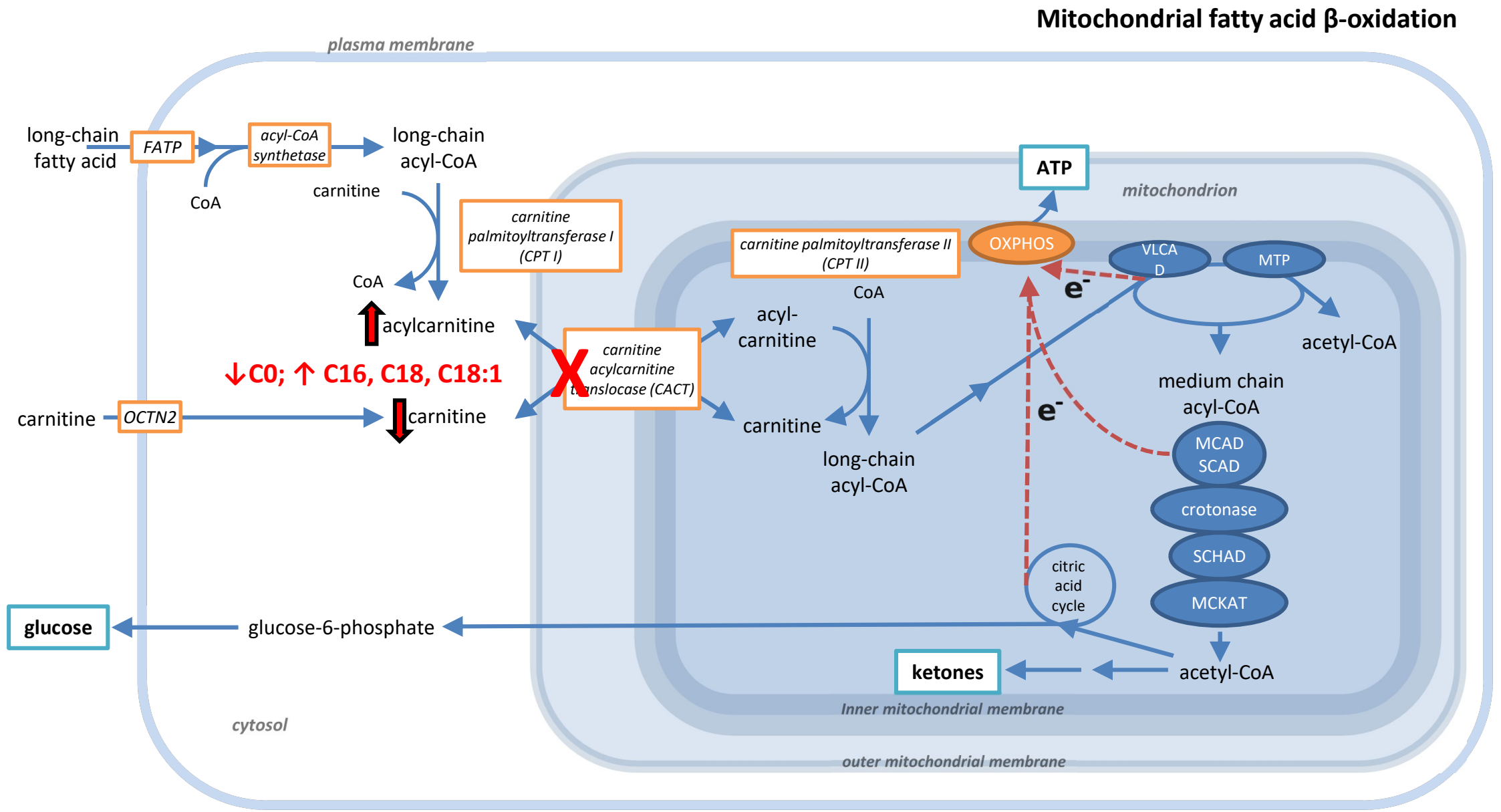
- CPT2 homotetrameric structure
- Common p.S113L mutation (70% mutant alleles)
  - Thermolabile → loss of function at higher temperatures
  - ***Inhibition of CPT2 in conditions when activity most needed***
- **Heterozygotes**
  - Symptomatic *in extremis*
  - Risk of statin-induced myopathy



CPT2 deficiency: *Management*

- Avoid prolonged fasting
- Glucose polymer pre-exercise/ during illness
- Dietary LCT restriction/MCT supplementation in severe cases
- Triheptanoin?

CACT deficiency


Mitochondrial fatty acid β-oxidation
plasma membrane
long-chain fatty acid
FATP
acyl-CoA synthetase
CoA
long-chain acyl-CoA
carnitine
carnitine palmitoyltransferase I (CPT I)
CoA
acylcarnitine
↓C0; ↑ C16, C18, C18:1
carnitine
OCTN2
carnitine
carnitine acylcarnitine translocase (CACT)
ATP
mitochondrion
carnitine palmitoyltransferase II (CPT II)
OXPHOS
CoA
acyl-carnitine
carnitine
long-chain acyl-CoA
VLCAD
MTP
e-
e-
acetyl-CoA
medium chain acyl-CoA
MCAD
SCAD
crotonase
SCHAD
MCKAT
citric acid cycle
acetyl-CoA
ketones
glucose
glucose-6-phosphate
cytosol
Inner mitochondrial membrane
outer mitochondrial membrane

CACT Deficiency

Clinical Phenotype

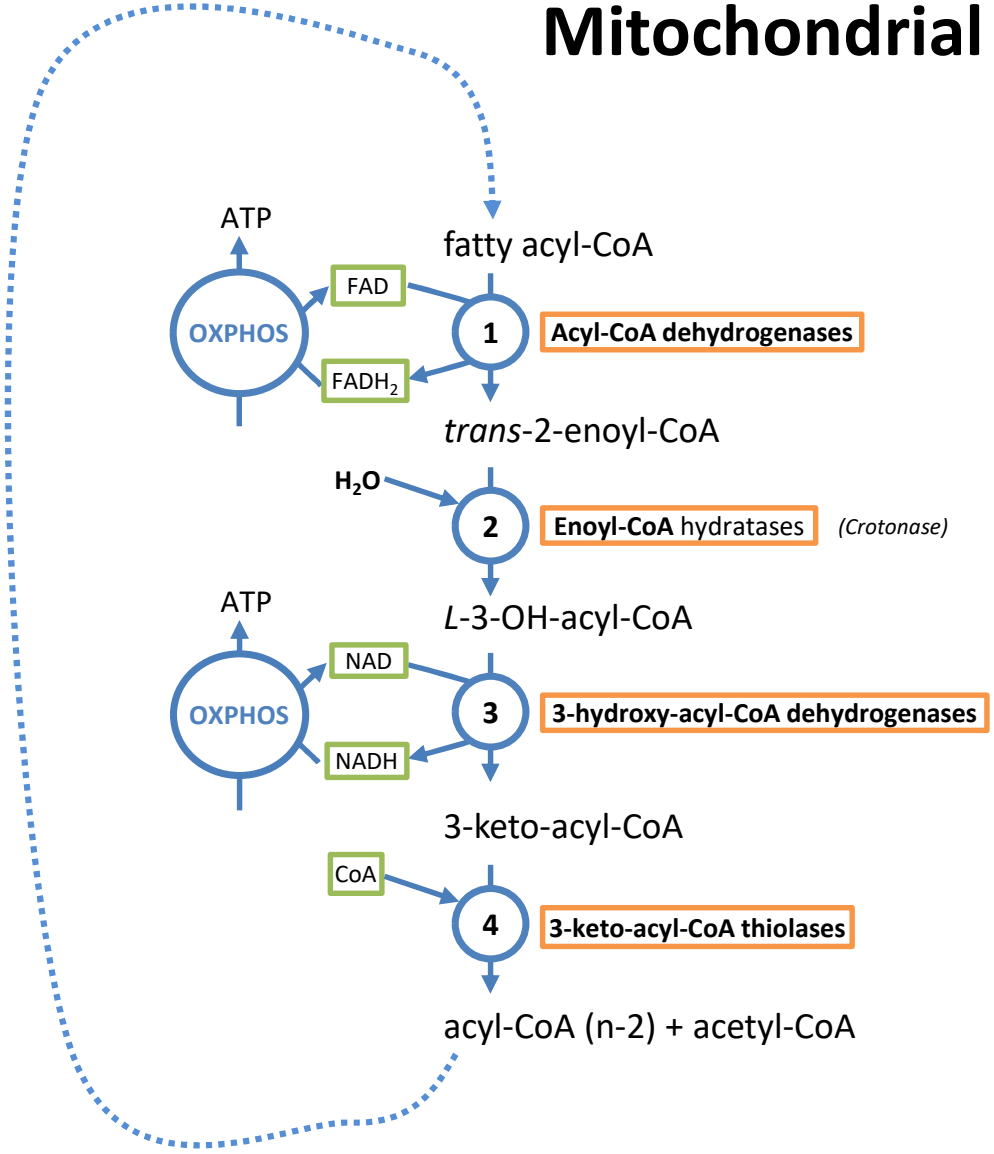
- Most neonatal onset and risk of early mortality
  - Hypoketotic hypoglycaemia, hyperammonaemia
  - Cardiomyopathy, AV block and arrythmias
- Milder presentation with fasting/illness- induced hypoglycaemia

Diagnostics

- Acylcarnitine profile
  - ↓ C0
  - ↑ C18:1, C18:2. C16, C16-DC. C18:2-DC. C18:1-DC
- Urine organic acids:
  - +/- Dicarboxylic aciduria
- *SLC25A20* molecular genetics

Beta-oxidation defects

Mitochondrial β-oxidation



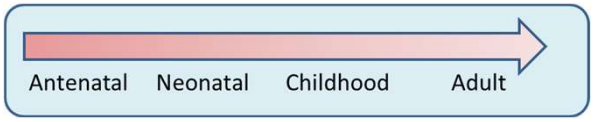
metabolite
enzyme
cofactor

	Long Chain	Medium/Short
	ACADVL	*ACADM* *ACADS*
	HADHA	*ECHS1*
***MTP**: Mitochondrial Trifunctional Protein*	*HADHA*	*HADH*
	HADHB	(Thiolase)

VLCAD Deficiency

Clinical Phenotypes

- Fatal neonatal hypoglycaemia, cardiomyopathy
- Infantile hepatic presentation
- Late-onset muscle presentation
  - Exercise intolerance, rhabdomyolysis
  - Common c.848T>C, p.V283A mutation



Diagnostics

- Acylcarnitine:
  - ↑C14:1, (C16:1, C14:2, C18:1)
  - May be masked by low free carnitine
  - May be normal in milder cases
- Urine organic acids: dicarboxylic aciduria
- *ACADVL* molecular genetics
- (Enzymology)

VLCAD Deficiency

Management

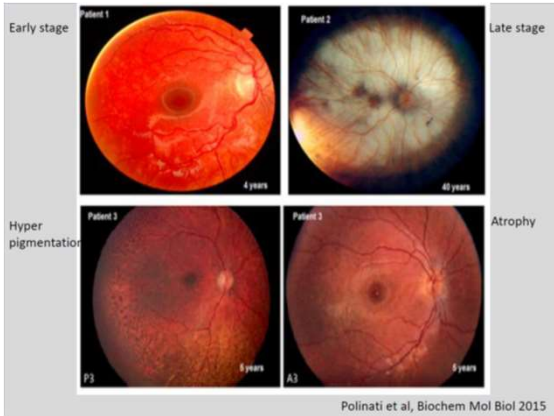
- Avoid prolonged fasting
- Emergency regimen glucose polymer
- High MCT/ Low LCT diet for severe cases
- Essential fatty acid supplementation
- C7 Triheptanoin
- Peri-exercise advice

Van Calcar et al 2020; Mol Genet Metab 131, 23-37. Nutrition management guideline for very-long chain acyl-CoA dehydrogenase deficiency (VLCAD): An evidence- and consensus-based approach

LCHADD/MTP Deficiency

Isolated LCHADD

- *HADHA* c.1528G>C (in dehydrogenase domain)
- Single enzyme function defect
- Infantile onset hypoglycaemia, liver dysfunction, lactic acidosis, cardiomyopathy
- Later onset retinopathy, chorioretinal atrophy
- Peripheral neuropathy



Trifunctional protein deficiency

- *HAHDA* or *HADHB* gene
- Severe fatal neonatal presentation with hypoglycaemia, liver dysfunction, progressive cardiomyopathy
- Milder neuromyopathic form

Maternal (heterozygous) carriers

- Risk of Haemolysis, Elevated Liver enzymes, Low Platelets (HELLP)
- Acute Fatty Liver of Pregnancy (AFLP)

LCHADD/MTP Deficiency

Isolated LCHADD

- *HADHA* c.1528G>C (in dehydrogenase domain)
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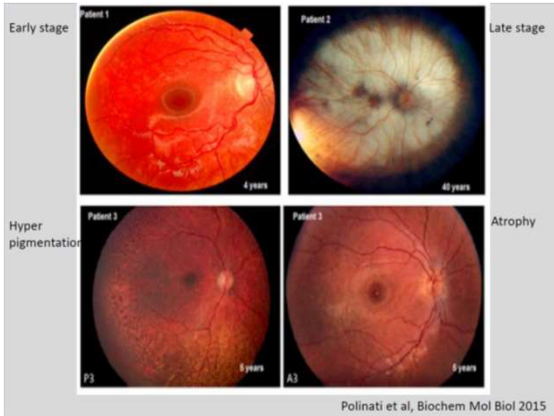

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- Risk of Haemolysis, Elevated Liver enzymes, Low Platelets (HELLP)
- Acute Fatty Liver of Pregnancy (AFLP)

LCHADD/MTP Deficiency

Diagnostics

- Acylcarnitine:
  - ↑C18:1-OH, C18-OH, C16:1-OH, C16-OH
- Urine organic acids: (hydroxy)dicarboxylic aciduria
- *HADHA/HADHB* molecular genetics

Management

- Avoid prolonged fasting
- Emergency regimen glucose polymer
- High MCT/ Low LCT diet
- Essential fatty acid supplementation
- C7 Triheptanoin?

- **Surveillance for neuropathy, retinopathy, cardiomyopathy**

Treatment: Long chain defects

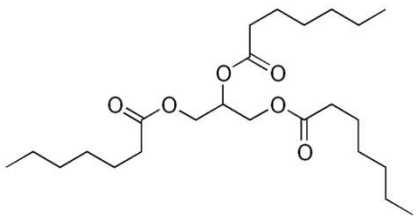
- Limit lipolysis /avoid prolonged fasts
- Provide adequate energy (CHO - 60% energy)
- Limit long chain triglyceride (LCT) intake
- Supplement MCT (20-25% energy)

- Glucose polymer emergency regimen for illness
- Prevent nutrient deficiencies of low LCT diet
  - EFA, LCPUFA
  - fat soluble vitamins

- Triheptanoin
  - C7 medium chain triglyceride

Spiekerkoetter et al. Treatment recommendations in long-chain fatty acid oxidation defects: consensus from a workshop. J Inherit Metab Dis. 2009;32:498–505.

Triheptanoin

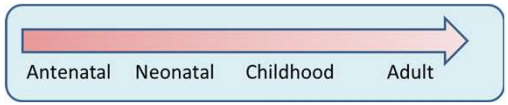


- Triheptanoin
  - Glycerol + 3x C7 (heptanoate)
  - C7 metabolised via short and medium chain FAO system
  - C7 → C2 acetyl-CoA + C3 propionyl-CoA
  - C2→ TCA cycle or ketogenesis
  - C3 → anaplerosis of TCA cycle
- Phase 2 (CL201) study
  - Reduced incidence and frequency of hospital days due to major clinical events (rhabdomyolysis, hypoglycaemia, cardiomyopathy)
  - Improved exercise tolerance
- CL202 open label extension
  - Confirmed benefit
  - Gastrointestinal side effects

Vockley J et al. Results from a 78-week, single-arm, open-label phase 2 study to evaluate UX007 in pediatric and adult patients with severe long-chain fatty acid oxidation disorders (LC-FAOD). J Inherit Metab Dis. 2018;42: 169-177.

Vockley et al, Effects of triheptanoin (UX007) in patients with long-chain fatty acid oxidation disorders: Results from an open-label, long-term extension study. J Inherit Metab Dis. 2021;44:253–263.

MCAD Deficiency



Commonest FAOD (1:6000-8000)
Common *ACADM* mutation c.985A>G

Clinical Phenotypes

- Lethargy, nausea, vomiting progressing to coma, seizures
- Acute cardiac event/ Sudden unexplained death in infancy
- Hypoglycaemia – late sign
- Acute liver dysfunction
- Can present later in adulthood

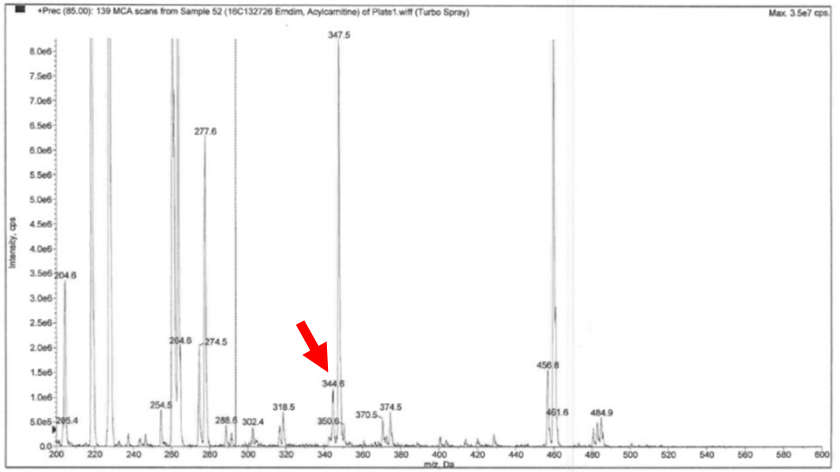
Diagnosis

- Acylcarnitines
  - ↑C8, ↑C8/C10 ratio, C10:1
- Urine hexanoyl-, suberyl-, phenylpropionylglycine
- *ACADM* molecular genetics

Newborn Screening

Management

- Avoid prolonged fasting
- Emergency regimen glucose polymer
- **Prospective management for subsequent infants at risk**



Short chain defects

- **SCAD deficiency**
  - *ACADS*
  - Majority asymptomatic
  - Reported associations with failure to thrive, developmental delay
- **Diagnostics**
  - Acylcarnitines: ↑C4
  - Urine butyrylglycine
  - Urine organic acids: ethylmalonic

- **SCHAD deficiency = Hydroxyacyl-CoA dehydrogenase deficiency**
  - *HADH*
  - Association with hyperinsulinemic hypoglycaemia
  - Regulation of insulin secretion via GDH in pancreatic islet cells.
  - Risk of hypoglycaemia
- **Diagnostics**
  - Acylcarnitines: ↑C4-OH
  - Urine organic acids: ↑3-OH-glutarate
  - Responsive to diazoxide

Short Chain Enoyl Hydratase deficiency

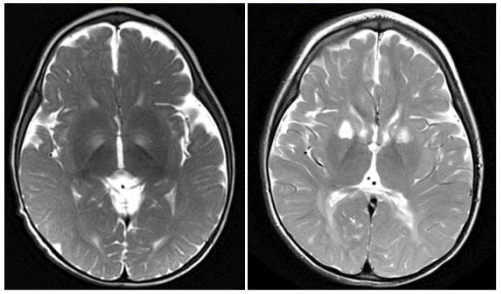
Clinical Phenotypes

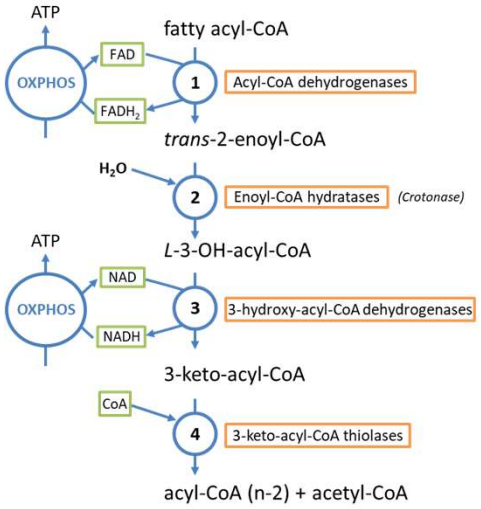
- Neonatal lactic acidosis/ encephalopathy
- Leigh/Leigh-like disease
- Severe neurodevelopmental disorder
- Isolated paroxysmal dystonia cohort

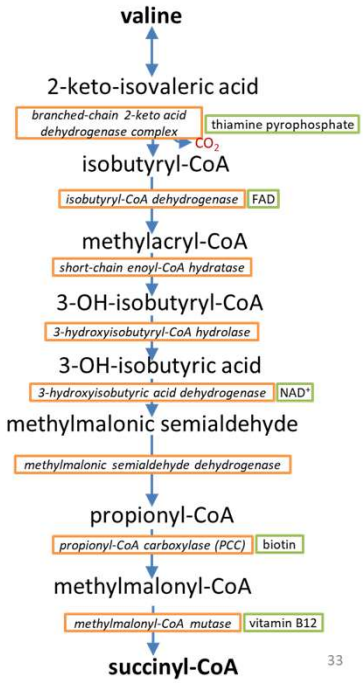
Diagnostics

- Lactic acidosis
- Urine organic acids:
  - 2-methyl-2,3-dihydoxybutyrate, branched chain ketoacids, 3-OH-isovalerate, 3-methylglutaconate, ketones, lactate
- Urine acryloyl-cysteamine, methacryl-cysteamine
- Acylcarnitines: +/- ↑C4
- Secondary respiratory chain enzyme deficiencies
- *ECHS1* molecular genetics

- **Treatment**
  - ?Valine restricted diet

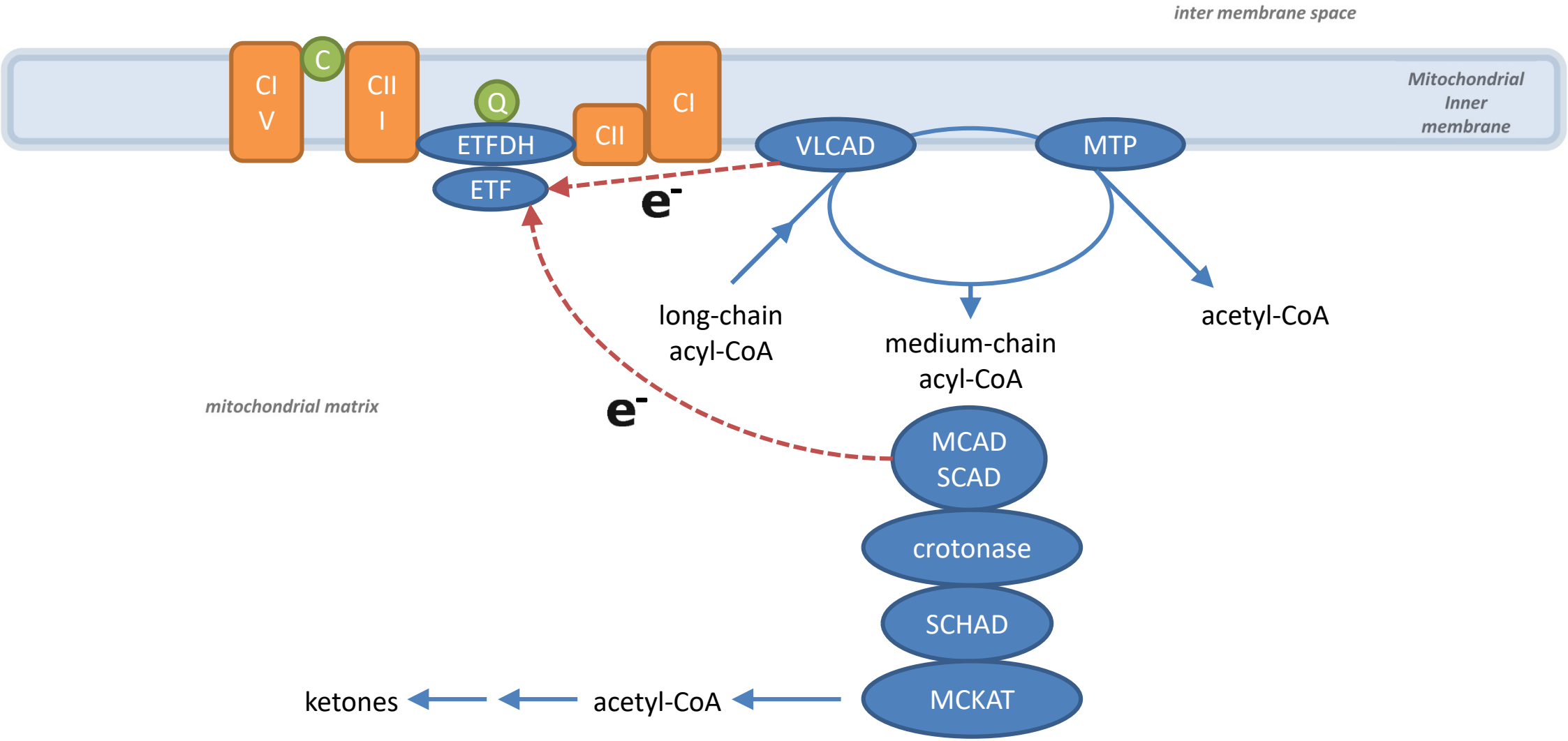






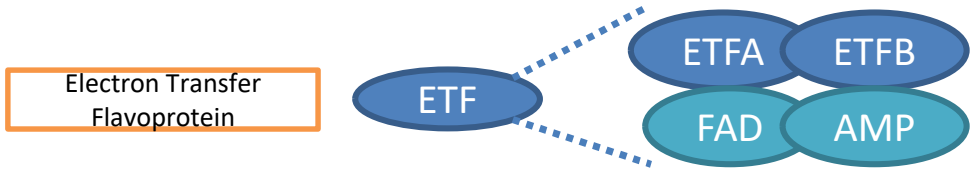
Peters et al 2014; ECHS1 mutations in Leigh disease: a new inborn error of metabolism affecting valine metabolism. Brain, 137(11),2903–2908

Electron Transfer defects

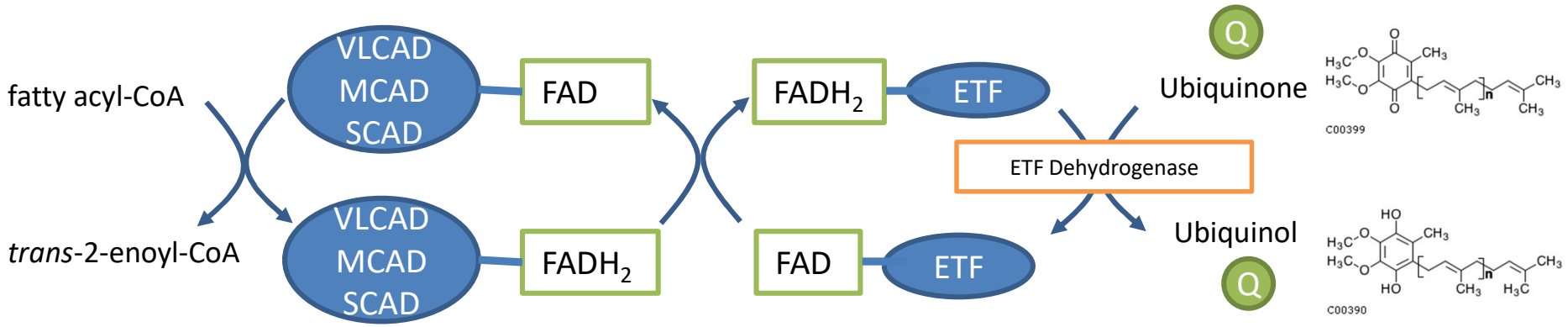

inter membrane space
Mitochondrial Inner membrane
CI V
C
CII I
Q
ETFDH
CII
CI
ETF
e-
VLCAD
MTP
long-chain acyl-CoA
medium-chain acyl-CoA
acetyl-CoA
mitochondrial matrix
e-
MCAD SCAD
crotonase
SCHAD
MCKAT
ketones
acetyl-CoA

FAD-linked dehydrogenases

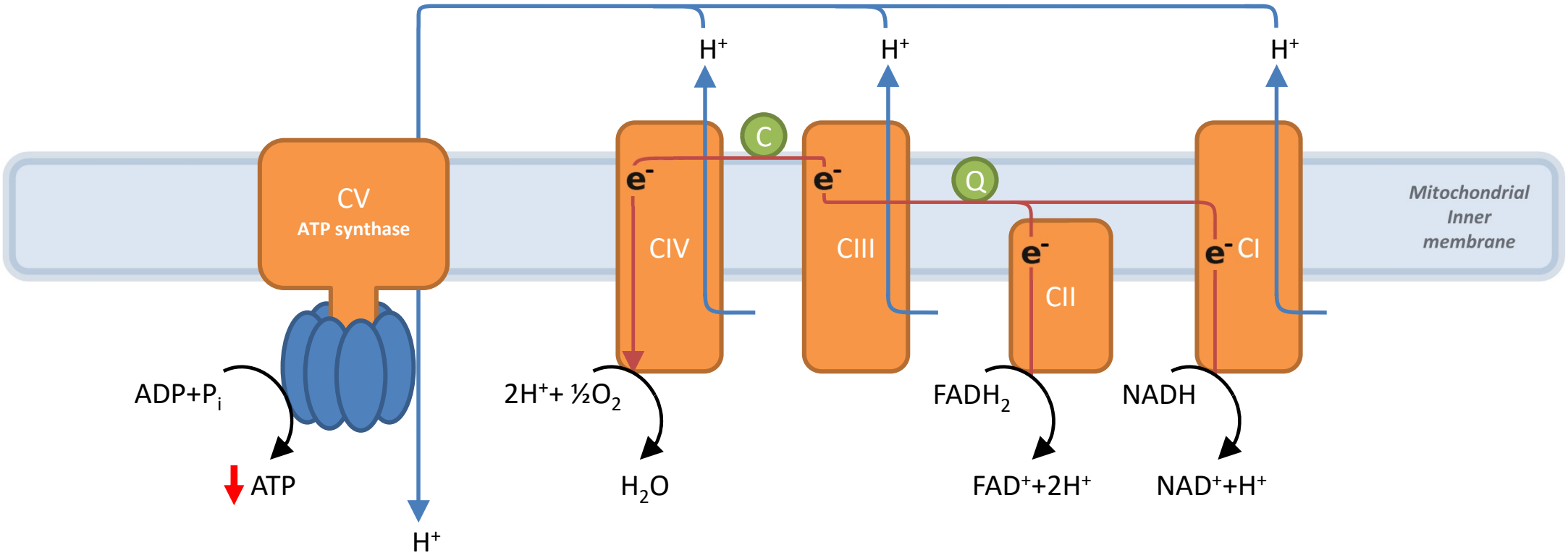
- Fatty acyl-CoA dehydrogenases
- Branched chain amino acid pathway
- Choline pathway
- Other



Heterodimer of ETFA & ETFB subunits
Flavin adenine dinucleotide
Adenosine monophosphate



the mitochondrial oxidative phosphorylation system (OXPHOS)



Multiple Acyl-CoA Dehydrogenase Deficiency (MADD, Glutaric aciduria type II)

- **Clinical Phenotypes**
  - **Type 1**: neonatal onset with congenital anomalies (kidneys, neuronal migration), cardiomyopathy
  - **Type 2**: neonatal onset without congenital anomalies, cardiomyopathy
  - **Type 3**: later-onset
    - Hypoglycaemia, liver dysfunction

- Hypoketotic hypoglycaemia, hyperammonaemia metabolic acidosis
- Hypotonia/ myopathic
  - Respiratory insufficiency
- Liver dysfunction, hepatomegaly
- Cardiomyopathy
- Pancreatitis

- **Diagnostics**
  - Acylcarnitines: ↑C4, C5, C5-DC, C6, C8, C10, C12, C14:1, C16, C18:1
  - Urine Organic acids: Ethylmalonic, glutaric, 2-OH-glutaric acids, dicarboxylic aciduria
  - Fatty acid oxidation flux studies
  - Molecular genetics *ETFA, ETFB, ETFDH*

- **Differentials**
  - Riboflavin transporters, FAD synthetase, (severe) riboflavin deficiency

- **Treatment**
  - Riboflavin
  - Avoid prolonged fasting
  - Dietary: Low-fat, CHO predominant
  - 3-OH-butyrate

Summary

- All stages of fatty acid oxidation process can be affected
- Common clinical/biochemical features

- Key diagnostics
  - Acylcarnitine profile (bloodspot, plasma)
  - Urine organic acids
  - Molecular genetics (and/or enzymology)
  - Abnormalities can be variable/subtle

- All disorders display range of severity from antenatal onset to late-onset adult or asymptomatic forms