# Metabolic Muscle Diseases

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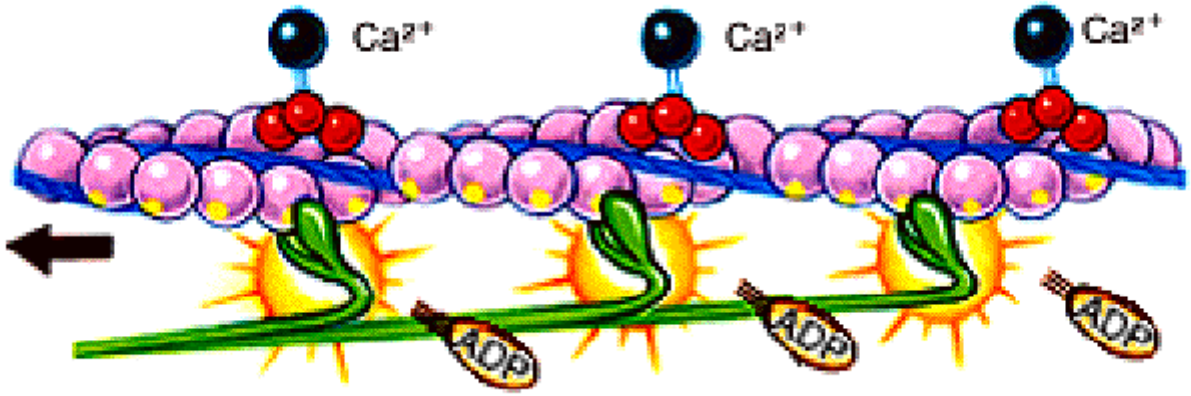
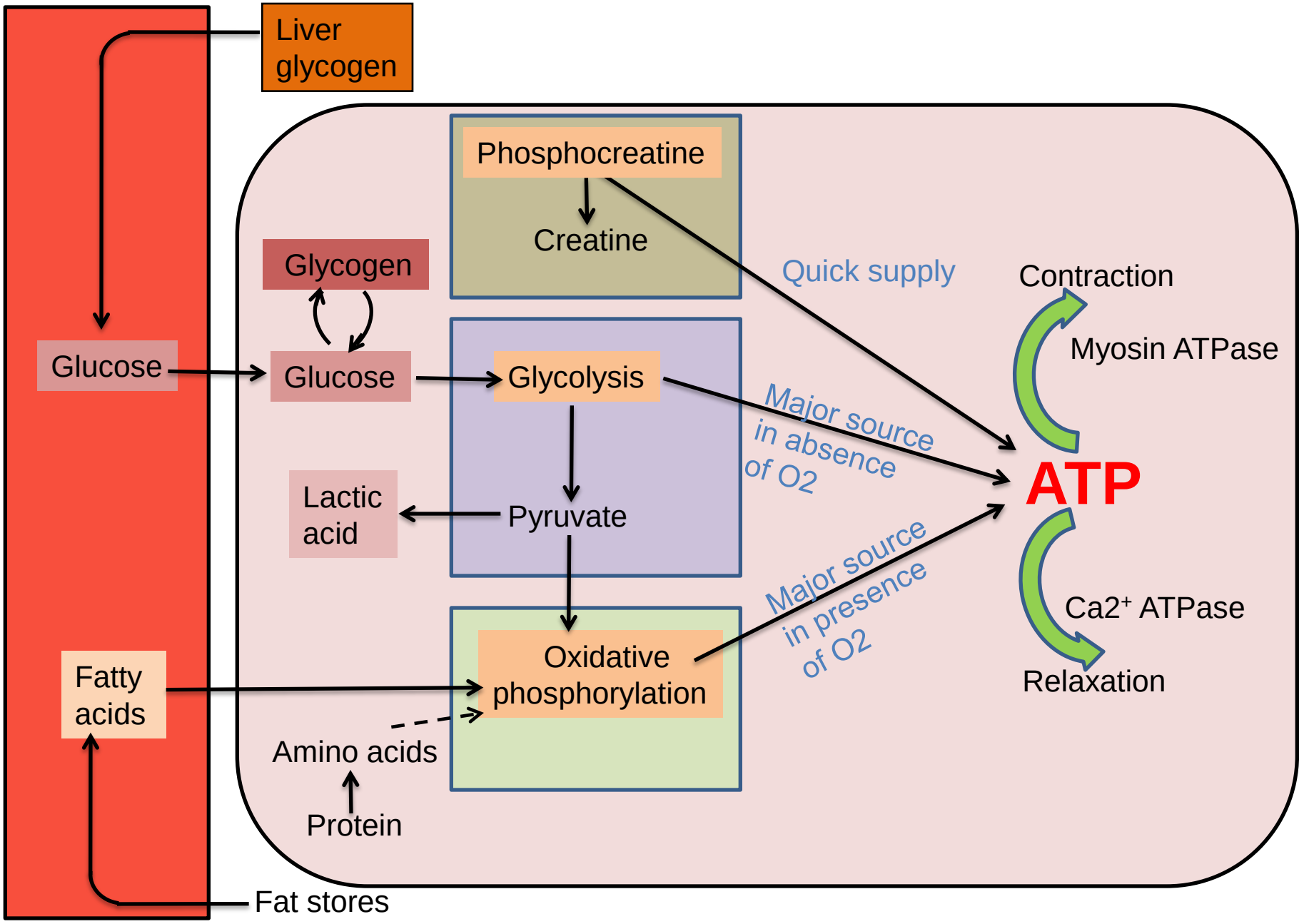
Metabolic myopathies are heterogeneous conditions with defects of muscle energy metabolism that result in predominantly skeletal muscle dysfunction but other muscles may be affected.

Most are considered primary inborn errors of metabolism and are associated with enzymatic defects that affect the ability of muscle fibres to maintain adequate ATP supplies.

Muscle contraction and relaxation require ATP



# Sources of ATP for muscle



# Three types of muscle:

Smooth muscle or "involuntary muscle" is found within the walls of organs and structures such as the oesophagus, stomach, intestines, uterus, bladder, blood vessels.
No real energy stores.

Cardiac muscle an "involuntary muscle" but more akin in structure to skeletal muscle. It contracts quite slowly, but it is used continuously and the total energy consumption is high.
Totally specialized for energy production (30-40% of ventricular mass is made up of mitochondria).
No real energy stores.

Skeletal muscle or "voluntary muscle" is used to effect skeletal movement such as locomotion and in maintaining posture.
Main energy stores are glycogen (3/4 of body's glycogen)

# 3 major pathways supply exercising muscle with ATP

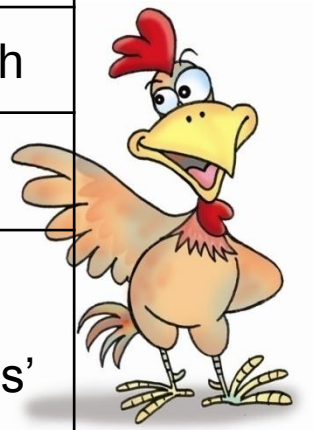
1. Phosphocreatine stores provide rapid but very brief supply (~1-5 minutes)

2. Glycogen metabolism: anaerobic metabolism can then supply ATP but for more sustained activity aerobic metabolism is utilised as long as oxygen supplies meet demand.

3. Fatty acid metabolism is utilised for sustained submaximal exercise (ie >40 minutes).

# Muscle Fibres for Different Jobs

| | Type I fibres | Type II a fibres | Type II b fibres |
|---|---|---|---|
| Contraction time | Slow twitch | Fast twitch | Very fast twitch |
| Resistance to fatigue | High | Fairly high | Low |
| Used for | Aerobic 'Marathon runners fibres' | Long-term anaerobic 'General purpose fibres' | Short-term anaerobic 'Sprinters fibres' |
| Mitochondrial density | High | High | Low |
| Oxidative capacity | High | High | Low |
| Glycolytic capacity | Low | High | High |
| Myoglobin | High | High | Low |
| Glycogen content | Low | Intermediate | High |
| Major storage fuel | Triglycerides | Creatine phosphate, glycogen | Creatine phosphate, glycogen |



# Inherited Disorders of Muscle Disease

- Structural Defects
  - Defects in proteins involved in maintaining muscle tone and the contraction process (myopathies) e.g. muscular dystrophies, congenital myopathies.
- Membrane Transport Defects
  - Defects in ion or neurotransmitter transport proteins or receptors (Channelopathies), e.g. myotonia congenita, hyper and hypokalemic periodic paralysis
- Metabolic Myopathies
  - Defects in enzymes involved in muscle metabolism leading to energy depletion or structural damage.

# Metabolic Muscle Disease

Inherited disorders of metabolic pathways.

Muscle is an ATP generating factory.

Metabolic muscle disease causes either:

- Energy (ATP) depletion:
  - Anaerobic (glycogenolysis, glycolysis)
  - Aerobic (fatty acid oxidation, electron transport chain)

- Structural damage:
  - Accumulation of abnormal glycogen (lysosomal or cytoplasmic)
  - Free radical damage

# Symptoms of Metabolic Muscle Disease

Metabolic myopathies have a wide range of symptom onset.

Most present early in life (infancy to adolescence)

Symptoms may be very mild (exercise intolerance) to fatal

Generally, onset and severity depends on the disorder and degree of enzyme deficiency (complete or partial)

Symptoms may be treatable

# Symptoms of Metabolic Muscle Disease

- Exercise intolerance
- Muscle pain (myalgia) after exercise
- Cramps
- Muscle damage
- Myoglobinuria
- Rhabdomyolysis (↑CK) leading to renal failure
- Proximal muscle weakness
- Hypotonia
- Other organs may be affected

# Further Symptoms of Metabolic Muscle Diseases

## Myoglobinuria:

When overexertion triggers acute muscle breakdown (rhabdomyolysis), muscle proteins like creatine kinase and myoglobin are released into the blood and ultimately appear in the urine. Myoglobinuria can cause severe kidney damage if untreated.

## Malignant Hyperthermia:

People with metabolic muscle disorders may be at higher risk for a potentially fatal reaction to certain common general anaesthetics.

## Cardiac Care:

Some patients may develop significant heart problems.

## Respiratory Care:

Some disorders may weaken the respiratory muscles that operate the lungs. These patients may require supplemental oxygen at some point.

# Causes of metabolic muscle disease

Glycogen storage disorders

Chronic, progressive weakness with atrophy, cardiomegaly, hepatomegaly, macroglossia, respiratory dysfunction. Symptoms usually present after short period of exercise but may experience a “second wind”

Lipid storage disorders

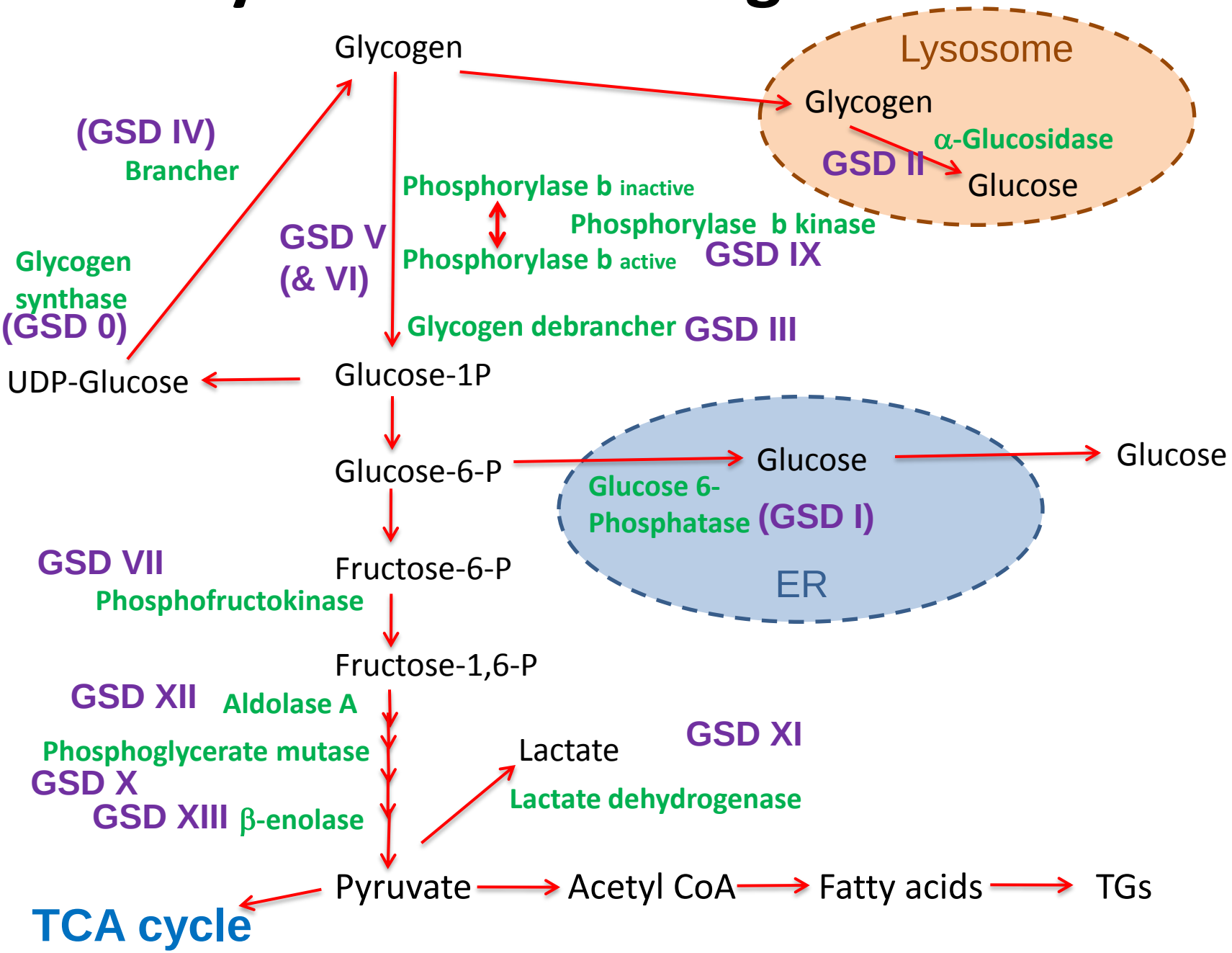
Muscle weakness and pain, myoglobinuria, exercise intolerance. Symptoms usually present after prolonged period of exercise

Purine recycling disorders

Mitochondrial Enzyme deficiencies

Multisystemic disorders. Very variable. Muscle weakness, exercise intolerance, hearing loss, seizures, ataxia, pigmentary retinopathy, cardiomyopathy

# Carbohydrate Processing Disorders



# Glycogen Storage Disorders

## Predominantly muscle

GSD II - acid $\alpha$-glucosidase - *Proximal muscle weakness More severe infantile form (cardiomegaly & hypotonia)*

GSD V - muscle phosphorylase - *Exertional muscle weakness*

GSD VII - muscle phosphfoructokinase - *Exertional muscle weakness*

GSD IXd - muscle phosphorylase b kinase - *Exertional muscle weakness and cardiomyopathy*

## Liver and Muscle

GSD IIIa - debranching enzyme

GSD IXb - phosphorylase b kinase

## Predominantly hepatic

GSD 0 - glycogen synthase

GSD I - glucose 6-phosphatatase or transport systems in ER

GSD IIIb - debranching enzyme

GSD IV - branching enzyme

GSD VI - liver phosphorylase

GSD IXa,c - liver phosphorylase b kinase

# Glycogen storage disease II (Pompe)

| | |
|---|---|
| **Clinical** | **Infantile:** Hypotonia, macroglossia, hepatomegaly, cardiomegaly and congestive heart failure, FTT. Death within 2 years due to cardiorespiratory failure. Incidence 1:130,000<br>**Juvenile:** Weakness, developmental delay, respiratory muscle affected but not cardiac.<br>**Adult:** Slowly progressive myopathy after 20 years of age, symptoms of respiratory failure, diaphragm involvement leads to sleep apnea.<br>Cardiac is normal. Incidence 1:57,000 |
| **Onset** | Infantile to adulthood |
| **Defect** | Acid $\alpha$-glucosidase (Acid maltase).<br>Lysosomal enzyme that breaks down glycogen |
| **Inheritance** | Autosomal recessive |
| **Laboratory findings** | Elevated CK, AST, LDH, particularly the infantile onset.<br>Glycogen storage on histology. |

# Glycogen storage disease V (McArdle's)

| | |
|---|---|
| **Clinical** | Muscle cramps/ pain after brief exercise<br>Resting may lead to a "second wind"<br>Rhabdomyolysis<br>Myoglobinuria – "coke cola" urine<br>Most common GSD- 1:350,000 to 1:100,000.<br>Susceptible to malignant hyperthermia.<br>Phenotype modulated by myoadenylate deaminase gene |
| **Onset** | Childhood to adulthood (usually diagnosed in adulthood) |
| **Defect** | Muscle glycogen phosphorylase (*PYGM*).<br>Removes glucose residues from $\alpha$-(1,4)-linkages in glycogen |
| **Inheritance** | Autosomal recessive (R50X mutation accounts for 60% of Caucasian mutations) |
| **Laboratory findings** | Raised CK (up to 13,000), even at rest<br>Raised ammonia, potassium and uric acid with exercise<br>No increase in lactate in ischaemic forearm test |

# Glycogen storage disease III (Cori or Forbes)

| | |
|---|---|
| **Clinical** | Type IIIa (85%) liver and muscle involvement<br>Type IIIb (15%) liver only<br><br>Hepatomegaly<br>Muscle weakness<br>Cardiomyopathy<br>Growth retardation<br>Hypoglycaemic seizures |
| **Onset** | Childhood - adulthood |
| **Defect** | Defect in amylo-1,6-glucosidase (*AGL*) gene- Debrancher<br>Removes glucose from $\alpha$-(1,6)-linkages in glycogen |
| **Inheritance** | Autosomal recessive |
| **Laboratory findings** | Hypoglycaemia<br>Hyperlipidaemia<br>Amino acids decreased- Ala, Leu, Ile, Val<br>↑Transaminases<br>↑Cholesterol<br>CK may be raised |

# Glycogen storage disease VII (Tarui)

| | |
|---|---|
| **Clinical** | Jaundice (due to haemolytic anaemia)<br>Exercise intolerance<br>Muscle weakness<br>Muscle cramps with exertion<br>Occasionally myoglobinuria<br>Similar to McArdles but less likely to experience “second wind”<br>Gout due to uric acid |
| **Onset** | Childhood to adulthood |
| **Defect** | Phosphofructokinase<br>(Fructose-6-P → Fructose-1,6-P) |
| **Inheritance** | Autosomal recessive |
| **Laboratory findings** | Myoglobinuria with extreme exertion<br>Increased uric acid, CK, bilirubin, reticulocyte count<br>Increased ammonia but not lactate with ischaemic exercise test |

# Glycogen phosphorylase b kinase

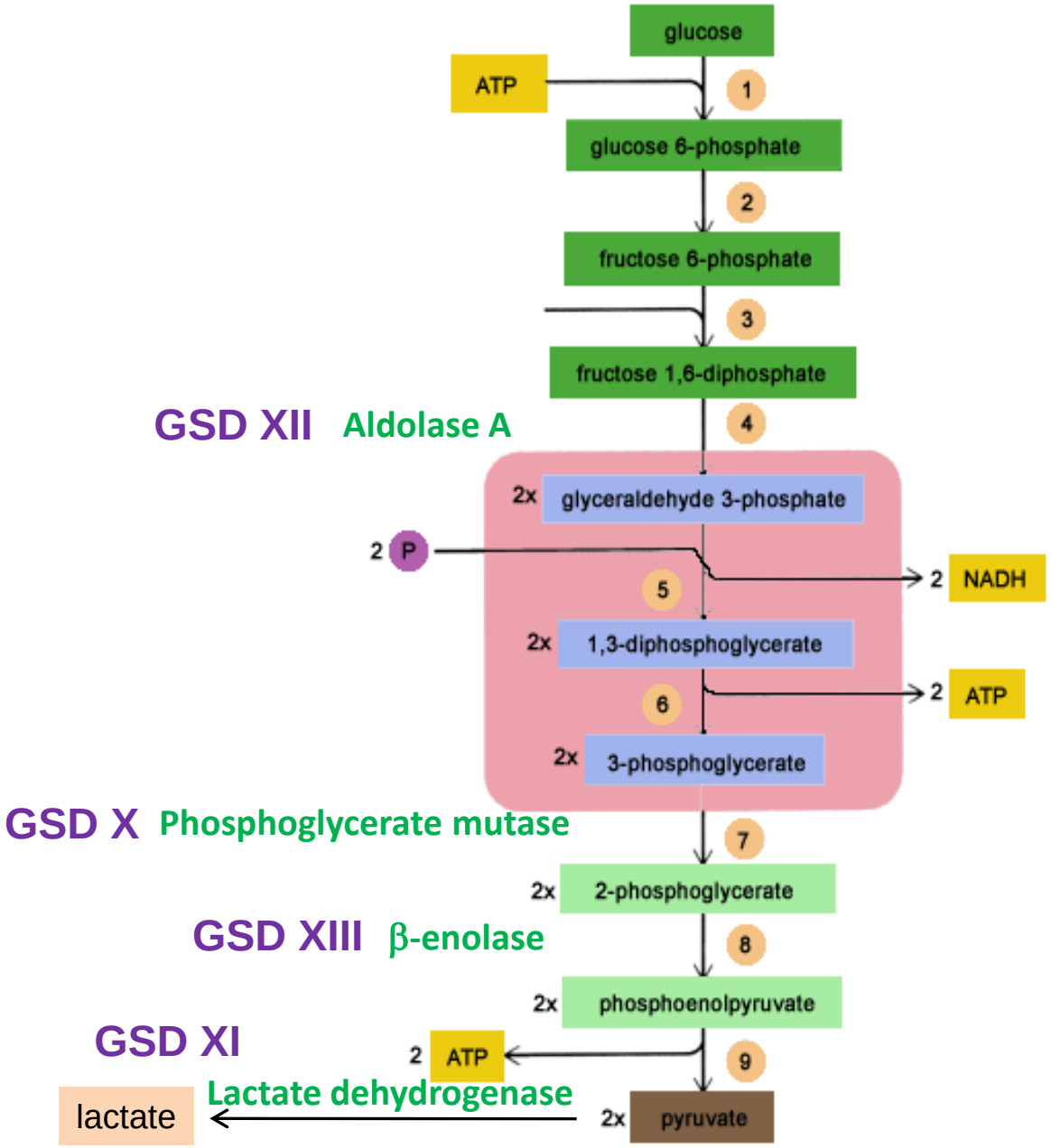
Hexadecameric enzyme composed of 4 copies of 4 subunits. Activates glycogen phosphorylase in response to neuronal or hormonal stimuli

| Subunit | Gene | Expression | Disorder | Inheritance | Affected tissues |
|---|---|---|---|---|---|
| α | *PHKA1* | Muscle | GSD IXd | X-linked | Muscle |
| | *PHKA2* | Liver | GSD IXa | X-linked | Liver |
| β | *PHKB* | Muscle and liver | GSD IXb | Autosomal recessive | Muscle and liver |
| γ | *PHKG1* | Muscle | - | Autosomal | - |
| | *PHFG2* | Liver | GSD IXc | Autosomal recessive | Liver |
| δ | *CALM1* | Ubiquitous | - | Autosomal | - |

# Glycogen storage disease IX (Phosphorylase kinase)

| | |
|---|---|
| **Clinical** | Variable, relatively mild<br>Myalgia, cramps and weakness with exercise<br>Myoglobinuria<br>Some forms with hepatomegaly |
| **Onset** | Childhood to adolescence |
| **Defect** | Glycogen phosphorylase b kinase (activates glycogen phosphorylase). |
| **Inheritance** | Autosomal recessive or X-linked |
| **Laboratory findings** | Mild elevation of cholesterol, triglycerides, CK.<br>Variable hypoglycaemia |

# Glycolytic Pathway Disorders



# Glycolytic Pathway Disorders

Very rare, often only handful of cases reported.

Usually present childhood to adolescence

Autosomal recessive

Multiple Isoforms of many enzymes

Features may include:

- Exercise Intolerance
- Rhabdomyolysis
- Haemolytic Anaemias
- Increased CK

# Glycolytic Pathway Disorders

***Phosphoglycerate Mutase deficiency (GSD X)***
Exercise intolerance, cramps, muscle pains.
Sometimes myoglobinuria with intense exercise

***Lactate Dehydrogenase deficiency (GSD XI)***
Exercise intolerance, cramps, pains
Rhabdomyolysis/ Myoglobinuria
Skin rash

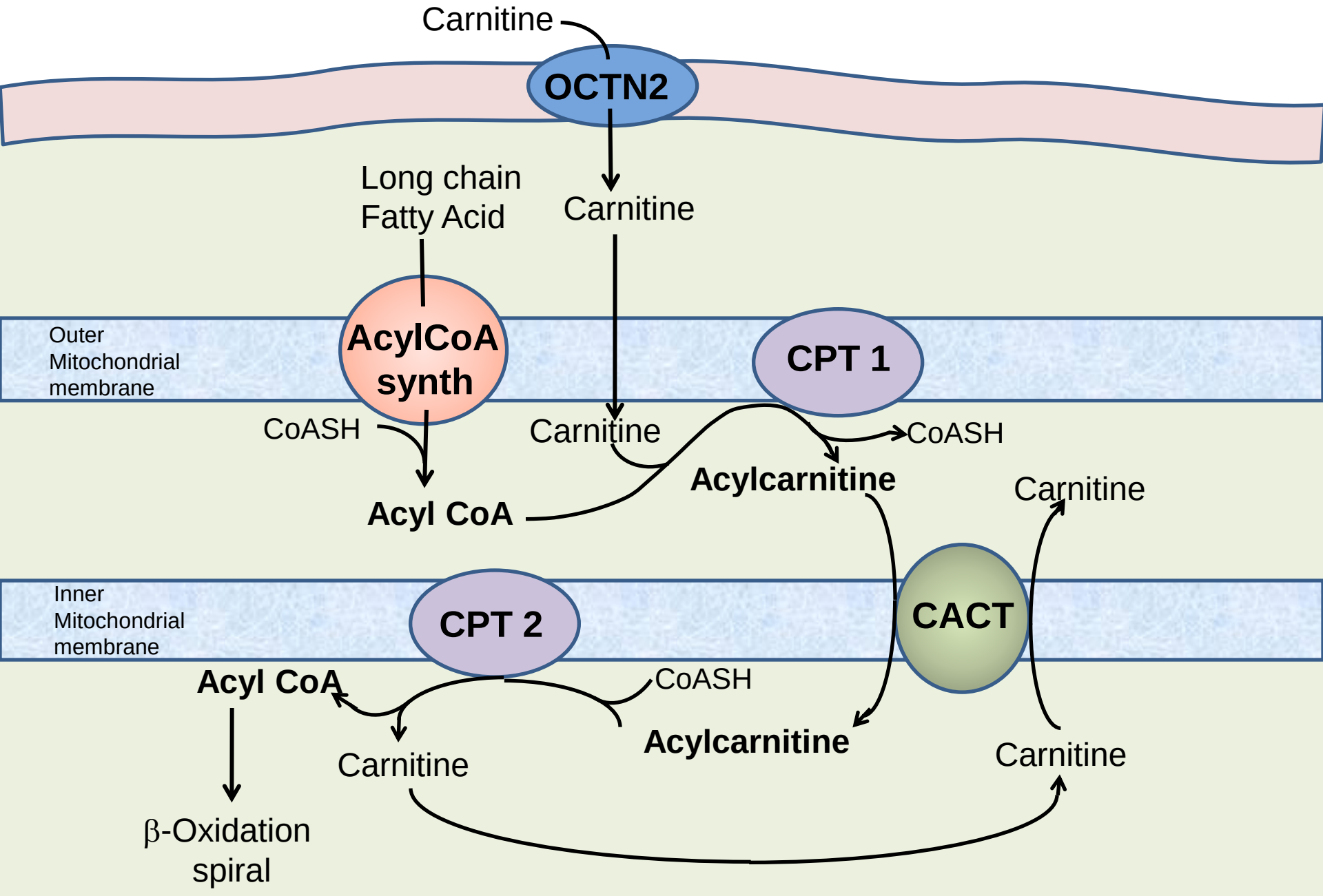
***Aldolase deficiency A (GSD XII)***
Exercise intolerance and proximal weakness
Jaundice + anaemia
Episodic myalgias and haemolysis

***β Enolase deficiency (GSD XIII)***
Myalgias

# Fatty Acid Oxidation Defects

- Only defects affecting long chain fatty acid oxidation give muscle disease
- Paediatric forms usually have severe hypoglycaemia and may also have a hypertrophic cardiomyopathy and liver disease.
- Adult-onset forms often present without hypoglycaemia or cardiomyopathy. They usually have exercise intolerance and muscle weakness sometimes presenting with myoglobinuria or rhabdomyolysis. Metabolites are often normal even on fasting.

# Carnitine and Fatty Acid Oxidation



# Carnitine

Essential for the transport of fatty acids into the mitochondrion for oxidation.

Deficient patients present with severe progressive cardiomyopathy and/or recurrent episodes of encephalopathy associated with hypoketotic hypoglycaemia and liver dysfunction.
Skeletal muscle involvement may manifest as motor delay, hypotonia, or proximal limb weakness.
Symptoms may be corrected when carnitine levels are raised with L-carnitine replacement

## Primary deficiency

Defect in transport of carnitine into the cell. Can be systemic due to OCTN2 defect or restricted to muscle (? muscle carnitine transporter)

## Secondary

Carnitine levels may be reduced by other disorders (fatty acid oxidation, organic acidurias, mitochondrial), malnutrition, renal failure (eg valproate therapy)

# OCTN2

| | |
|---|---|
| Clinical | Cardiomyopathy<br>Hepatomegaly<br>Fatigability/ Muscle weakness<br>Vomiting<br>Abdominal pain<br>Hypoglyaemia<br>Episodic encephalomyopathy |
| Onset | Infancy to first decade |
| Defect | Organic Cation Transporter (*OCTN2*)- $Na^{2+}$-dependent carnitine transporter- transports carnitine across cell membranes |
| Inheritance | Autosomal recessive |
| Laboratory findings | Plasma carnitine (total and free) low or absent<br>Hyperammonaemia<br>Hypoglycaemia |

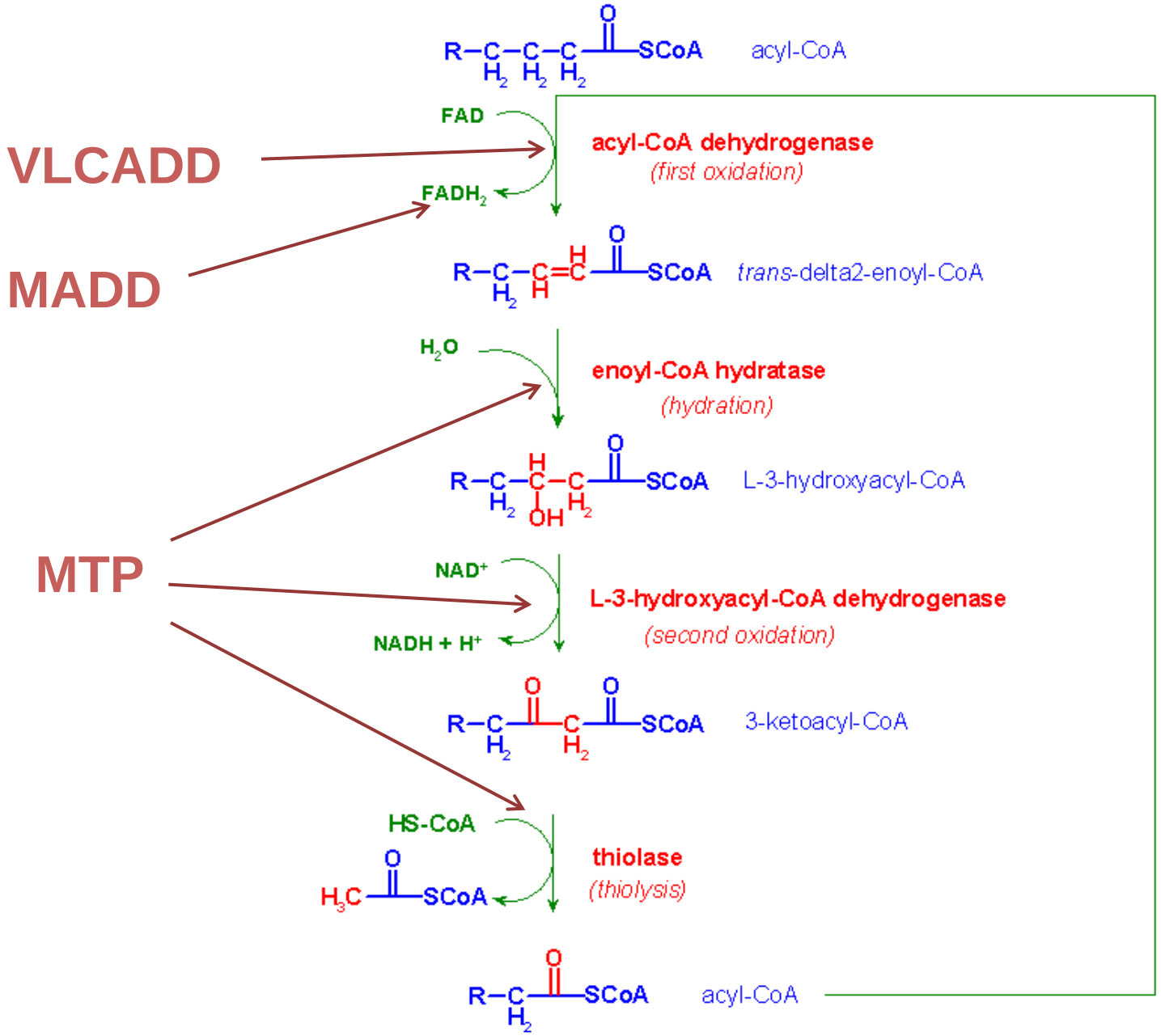
# CACT Deficiency

| | |
|---|---|
| **Clinical** | Encephalopathy<br>Cardiomyopathy<br>Muscle weakness<br>Episodic neonatal apnoea |
| **Onset** | Neonatal- usually fatal within months |
| **Defect** | Carnitine-acylcarnitine translocase (*SLC25A20*) deficiency. Shuttles substrates between cytosol and intramitochondrial matrix space |
| **Inheritance** | Autosomal recessive |
| **Laboratory findings** | Hypoketosis (low ketones)<br>Hypoglycaemia<br>Hyperammonaemia<br>Increase in plasma acylcarnitines (C16, C18) and low carnitine |

# Carnitine Palmitoyltransferase II- Late onset

| | |
|---|---|
| **Clinical** | Muscle weakness, stiffness, cramps, pain following prolonged exercise or other stress (heat, cold, illness, fasting)<br>Rhabdomyolysis (most common inherited cause) |
| **Onset** | Adolescence or adulthood.<br>Triggered by prolonged exercise or metabolic stresses, illness, cold |
| **Defect** | Carnitine palmitoyl transferase II |
| **Inheritance** | Autosomal recessive |
| **Laboratory findings** | Raised CK after an attack<br>Low free carnitine, normal total<br>Increased phosphates, uric acid, AST.<br>Increased ratio (C16+C18)/C2 |

# Fatty Acid Oxidation Defects



# VLCAD Deficiency

| | |
|---|---|
| **Clinical** | i) Severe **early onset** form with cardiomyopathy and hepatopathy<br>ii) Hepatic phenotype manifests in **infancy** with recurrent episodes of hypoketotic hyperglycinaemia<br>iii) Milder **later onset** myopathic form with episodic muscle weakness, myalgia and myoglobinuria with prolonged exercise |
| **Defect** | Very long chain Acyl-CoA dehydrogenase |
| **Inheritance** | Autosomal recessive |
| **Laboratory findings** | Increased acylcarnitines C14, ratio C14:1/C12:1<br>Dicarboxylic aciduria |

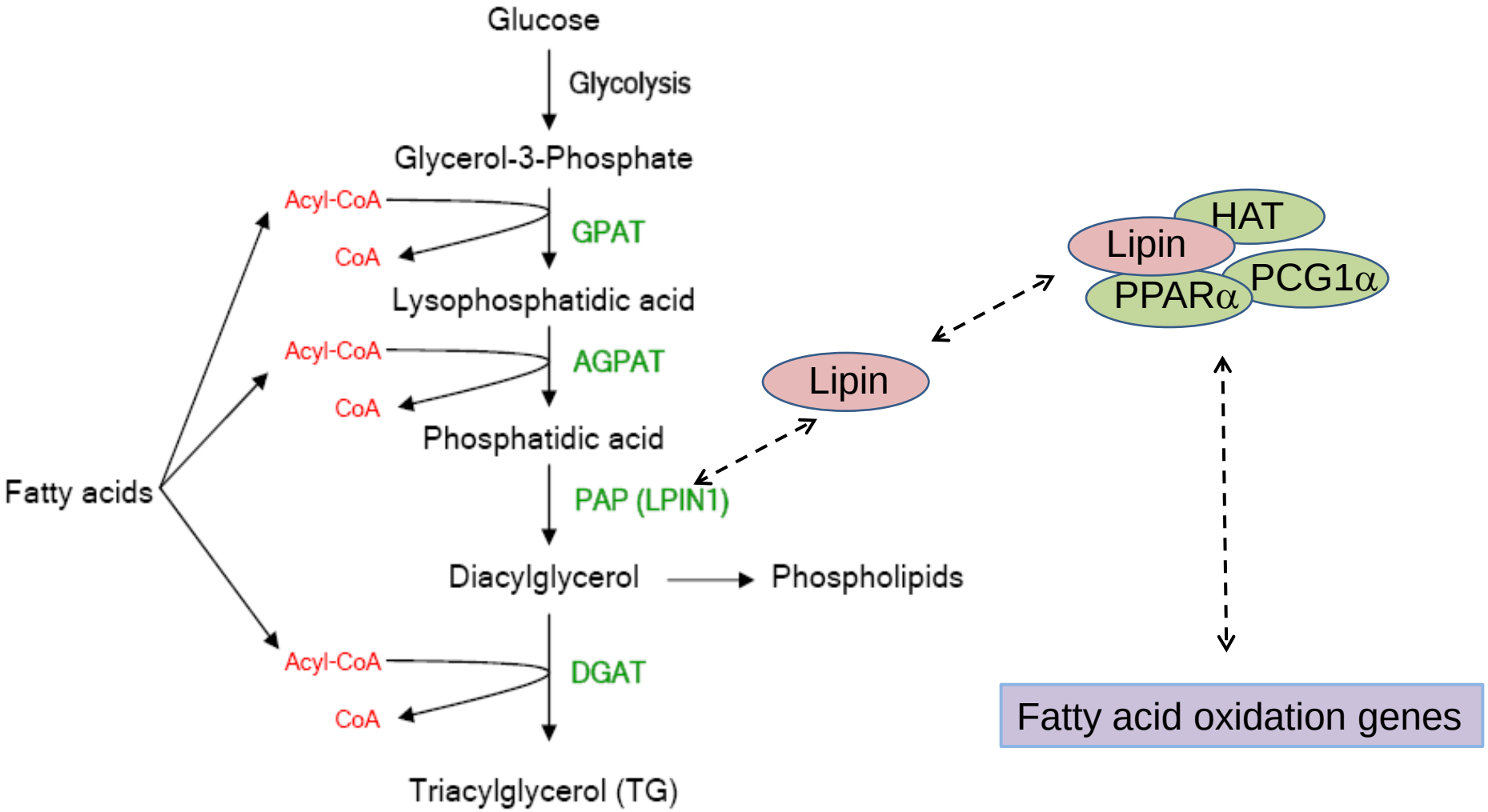
# Mild mitochondrial Tri-functional protein/ LCHAD

| | |
|---|---|
| **Clinical** | i) Rapidly progressive **neonatal onset**, early death<br>ii) **Infantile onset** with hepatic involvement<br>iii) **Childhood/ adolescent onset** with myopathy and neuropathy<br>Most patients die from heart failure |
| **Defect** | $\alpha$ and $\beta$ subunits of mitochondrial trifunctional protein- catalyses 3 reactions in fatty acid oxidation inc LCHAD |
| **Inheritance** | Autosomal recessive |
| **Laboratory findings** | Increased acylcarnitines C14- C18 |

# Riboflavin responsive MADD (Glutaric Aciduria 2)

| | |
|---|---|
| **Clinical** | Recurrent vomiting<br>Encephalopathy<br>Muscle weakness – proximal limbs, respiratory, dysphagia |
| **Onset** | Infant to adulthood |
| **Defect** | Multiple Acyl CoA Dehydrogenase<br>(Electron Transfer Flavoprotein *ETFDH*).<br>May be precipitated by poor diet of riboflavin |
| **Inheritance** | Autosomal recessive |
| **Laboratory findings** | Low plasma carnitine<br>Ketosis<br>MADD specific organic acid when symptomatic- Increased lactic, glutaric, ethylmalonic, dicarboxylic acids<br>MADD specific carnitines (C4-C18) even when asymptomatic |

# Lipin 1 - a phosphatidate phosphatase in triglyceride and phospholipid synthesis and transcriptional co-activator for fatty acid oxidation

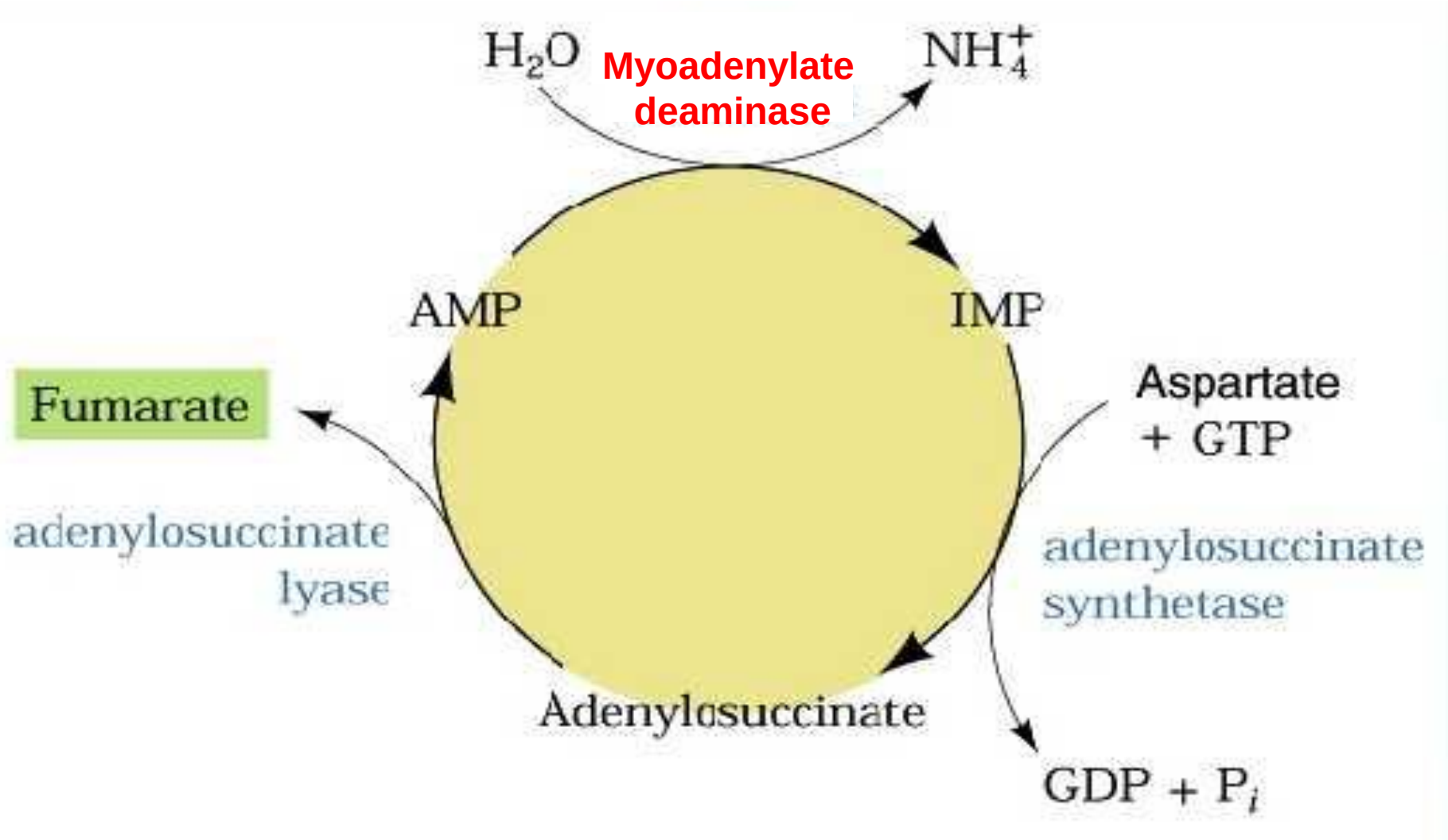



GPAT = glycerol-3-phosphate acyltransferase
AGPAT = 1-acylglycerol-3-phosphate acyltransferase
DGAT = diacylglycerol acyltransferase

# LPIN1 Deficiency

| | |
|---|---|
| **Clinical** | Repeated attacks of rhabdomyolysis with myoglobinuria.<br>Often precipitated by febrile illness, anaesthetic or fasting. |
| **Onset** | Early childhood |
| **Defect** | Lipin 1(*LPIN1*)- a phosphatidate phosphatase in triglyceride and<br>phospholipid synthesis and a transcriptional co-activator for fatty acid oxidation |
| **Inheritance** | Autosomal recessive.<br>A moderately common gene deletion |
| **Laboratory findings** | Increased CK |

# The Purine Nucleotide Cycle



# Disorders of Purine Nucleotide Metabolism

The purine nucleotide cycle serves to replenish TCA and glycolytic intermediates when energy demand is high.

Reaction occurs mainly during aerobic exercise to replenish ATP.

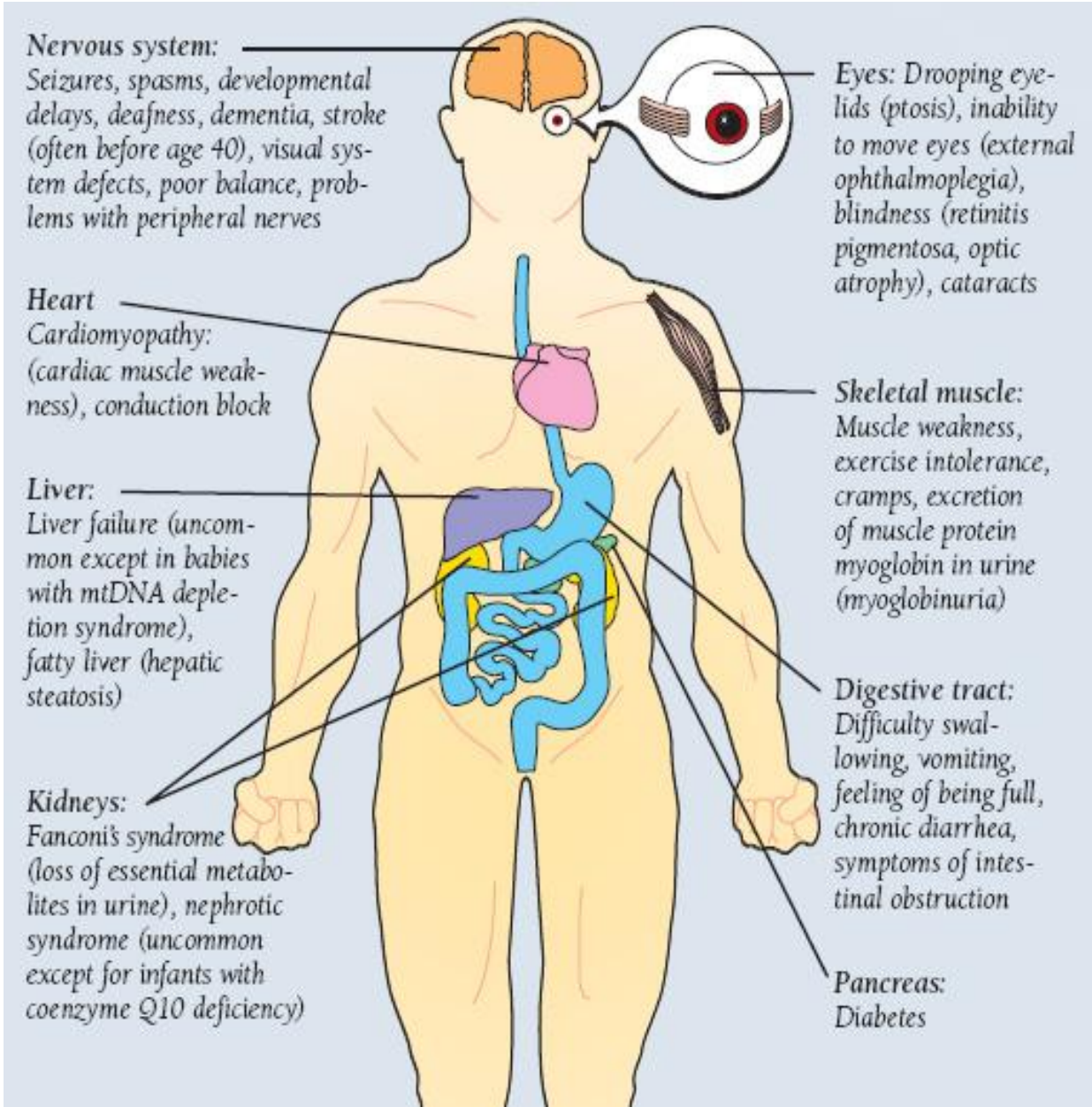
Supply of aspartate is high and is constantly replenished from blood or internal muscle protein stores.

# Myoadenylate Deaminase Deficiency

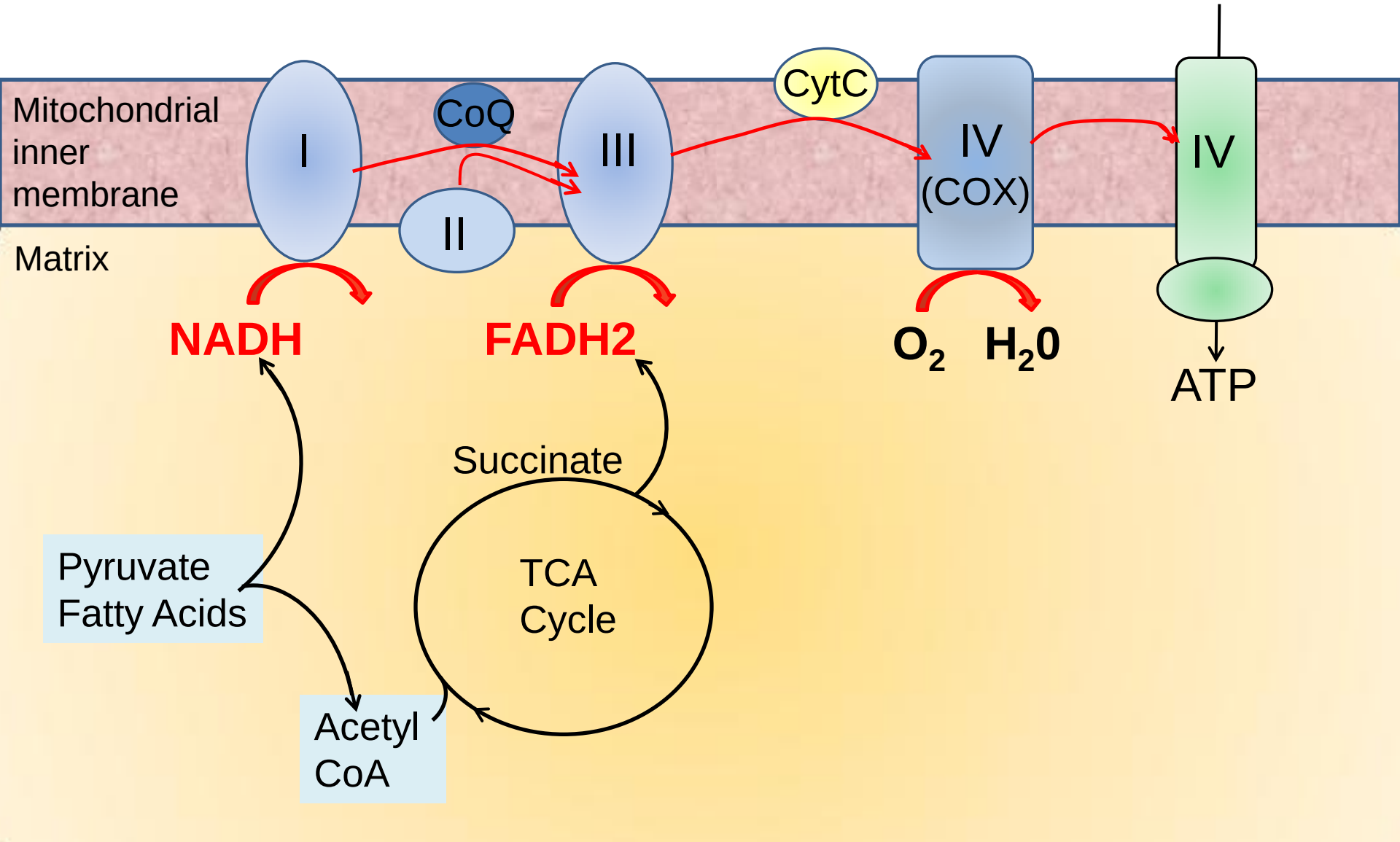
| | |
|---|---|
| **Clinical** | Most patients asymptomatic (1-2% of Europeans are homozygous for a mutation giving <10% activity)<br>Exercise induced myopathy<br>Post-exertional muscle weakness or cramping<br>Prolonged fatigue after exercise |
| **Onset** | Adulthood |
| **Defect** | Myoadenylate deaminase<br>(adenosine monophosphate deaminase) |
| **Inheritance** | Autosomal recessive.<br>Common mutation (can also modulate disease severity in McArdle's disease) |
| **Laboratory findings** | Increased CK.<br>No increase in ammonia in ischaemic forearm test |

# Symptoms of Respiratory Chain Disorders

- Exercise Intolerance
- Cardiomyopathy
- Neurological Symptoms
- Ophthalmoplegia
- Endocrine Abnormalities
- Failure to thrive
- Impaired gut motility
- Dysmorphic Features

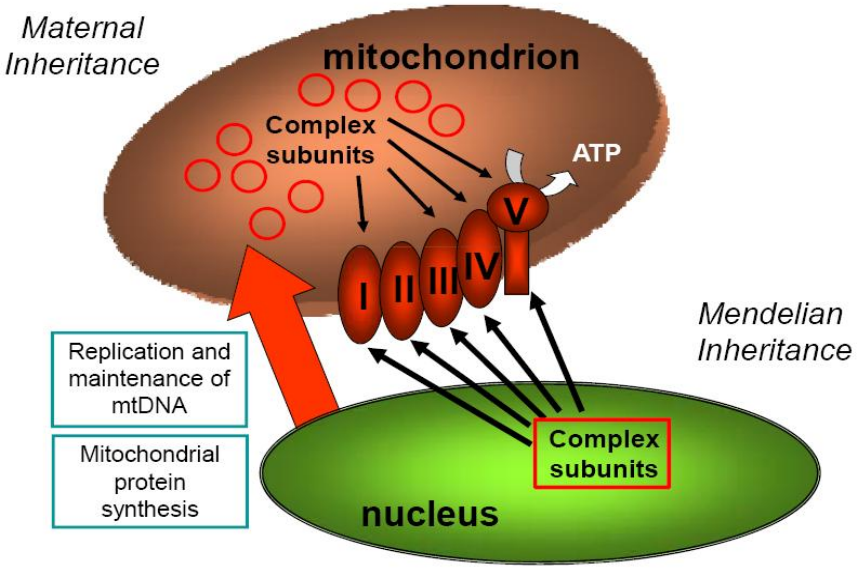


# Electron Transport Chain



# Genetic Classification of Mitochondrial Diseases

Nuclear mitochondrial interactions




## Defects of mtDNA

- **Mutations in protein synthesis genes**
  - mt-tRNA mutations
    - m.3243A>G, m.8344A>G
  - mt-rRNA mutations
  - single, large-scale mtDNA rearrangements
- **Mutations in protein-coding genes**
  - Multisystemic (NARP/MILS)
  - Tissue-specific (LHON)

## Defects of nuclear DNA

- **Mutations in respiratory chain subunits**
  - Complex I (*NDUFS1, NDUFS2* etc..), Complex II (*SDHA*), Complex IV
- **Mutations in ancillary proteins**
  - *C20orf7, NDUFAF2…* (Complex I)
  - *BCS1L* (Complex III)
  - *SURF1, SCO2, COX10* (Complex IV)
- **Defects of intergenomic signalling**
  - ad/ar-PEO and multiple mtDNA deletions
    - *POLG, POLG2, PEO1, RRM2B….*
  - mtDNA depletion syndromes
    - *TK2, DGUOK, MPV17, SUCLA2….*
  - Defective mitochondrial translation
- **Defects of protein transport**
- **Defects of the lipid milieu**
- **Defects of chaperone proteins**
- **Defects of fusion/fission** (*OPA1, MFN2*)
- **Defects of apoptosis**

# Mutations of mtDNA can cause muscle disease

**MELAS: mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes**

*Inheritance pattern*: maternal
*Onset*: childhood to early adulthood
*Features*: Recurrent stroke-like episodes, migraine-like headaches, vomiting and seizures. Other symptoms include PEO, general muscle weakness, exercise intolerance, hearing loss, diabetes and short stature.

**MERRF: myoclonus epilepsy with ragged red fibres**

*Inheritance pattern*: maternal
*Onset*: late childhood to adolescence
*Features*: myoclonus (muscle jerks), seizures, ataxia and muscle weakness. Can cause hearing impairment and short stature.

**KSS: Kearns-Sayre syndrome**

*Inheritance pattern*: sporadic (deletions in mtDNA)
*Onset*: before age 20
*Features*: Defined by PEO and pigmentary retinopathy. Other symptoms include cardiac conduction block, ataxia and proximal muscle weakness.

# mtDNA Depletion Syndromes

Characterized by a reduction in mtDNA copy number (15-20% of normal).

May be relatively common neurogenetic disorder of infancy (up to 10% of referrals for weakness, hypotonia and developmental delay)

Phenotypically heterogeneous:

- Hepatocerebral form
- Myopathic form
- Benign later onset myopathic form
- Cardiomyopathic form

Muscle weakness, and/or liver failure, and more rarely, brain abnormalities. Lactic acidosis, hypotonia, feeding difficulties, and developmental delays are common; PEO and seizures are less common.

Typically early onset and death

# mtDNA Depletion Syndromes

Primarily due to enzymes involved in maintenance of mtDNA copy number, e.g. nucleotide synthesis or mtDNA replication.

Inheritance: Many causes, usually recessive, can be dominant or sporadic.

Biochemical features may include:

- Lactic acidosis in more severe cases.
- Methylmalonic aciduria in some forms
- Serum CK: Mildly, or Prominently elevated to > 1,000
- Mitochondrial changes in muscle
  - Low activity: Complex I, III, IV
  - Normal activity: Complex II

# mtDNA Depletion Syndromes

| Disorder | Gene | Product | Function | Phenotype |
|---|---|---|---|---|
| MTDPS1 | *TYMP* | Thymidine phosphorylase | dNTP pools | MNGIE (mitochondrial neurogastrointestinal encephalomyopathy) |
| MTDPS2 | *TK2* | Thymidine kinase | dNTP pools | Myopathic |
| MTDPS3 | *DGUOK* | Deoxyguanosine kinase | dNTP pools | Hepatocerebral |
| MTDPS4 | *POLG* | Polymerase gamma | mtDNA replication | Hepatocerebral/ Alpers |
| MTDPS5 | *SUCLA2* | Succinyl-CoA synthase | dNTP pools | Encephalomyopathic with MMA |
| MTDPS6 | *MPV17* | - | ? | Hepatocerebral |
| MTDPS7 | *PEO1 (Twinkle)* | ? DNA Helicase | mtDNA replication | Hepatocerebral |
| MTDPS8 | *RRM2B* | Ribonucleotide reductase M2B | dNTP pools | Encephalomyopathic with renal tubulopathy |
| MTDPS9 | *SUCLG1* | Succinate-CoA ligase $\alpha$ subunit | dNTP pools | Fatal infantile lactic acidosis with MMA |

# Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

| | |
|---|---|
| **Clinical** | PEO<br>Ptosis<br>Limb weakness<br>Gastrointestinal (digestive) problems, including pseudo-obstruction, chronic diarrhoea and abdominal pain.<br>Peripheral neuropathy. |
| **Onset** | Childhood to adulthood |
| **Defect** | Thymidine phosphorylase (*TYMP*) |
| **Inheritance** | Autosomal recessive |
| **Laboratory findings** | Increased serum thymidine and deoxyuridine |

# Diagnosis of Muscle Disease

## A multi-disciplinary approach

- Clinical
- Physiology / Electrophysiology (can rule out other disorders)
- Magnetic Resonance Imaging & Spectroscopy
- Histopathology (histology & immunocytochemistry)
- Biochemistry (metabolites and enzymes)
- Genetics (can allow genetic counselling and testing in family members)
- Haematology

# Biochemical Abnormalities

- Elevated creatine kinase (intermittent)
- Elevated troponin (Heart or Muscle?)
- Hypoglycaemia
- Abnormal LFTs (sometimes due to muscle damage!)
- Myoglobinuria (cola- coloured urine)
- Increased plasma lactate
- Increased cholesterol & triglycerides
- Increased plasma urate.
- Abnormal acylcarnitines

Abnormalities may be present only during an attack

## Clinical Investigations

Family history
Neurological
Cardiac
*Gastrointestinal
*Ophthalmology
*Audiology

1st line Biochemical Investigations

| Plasma | Urine | CSF* |
|---|---|---|
| Lactate | Amino acids | Lactate |
| Creatine kinase | Organic acids | |
| Amino Acids | | |
| Acylcarnitines | | |
| Free carnitine | | |

*esp for mitochondrial

## Consider additional testing (non invasive)

Exercise testing
Forearm exercise test
EMG, ECG, MRS

## Glycogenoses

- Early exercise intolerance (e.g. cramps/ pain/ myoglobinuria)
- CK usually chronically raised
- Other first line tests normal
- Respiratory muscles may be involved,
- e.g. late onset Pompe

### Biochemistry

Glucose
Urate
LFTs
Lipids
FBC

### Blood

Mutation analysis for GSD V
GSD enzymes

### Muscle biopsy

Histology and enzyme assay where indicated

# Fatty Acid Oxidation defects

•Exercise intolerance (e.g. pain/stiffness/ myoglobinuria)- typically on prolonged/ sustained exercise.
Exacerbated by poor food intake/ stress/ illness
•CK usually normal between episodes
•Plasma acylcarnitines may be abnormal
•Urine organic acids may be abnormal

## Blood

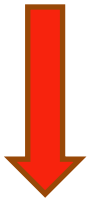
Common mutation in CPT2

## Skin biopsy

Fatty acid oxidation flux assays
Specific CPT2 enzyme assay

## Purine cycle defects

- Exercise intolerance (e.g. cramps/pain)
- CK usually normal between episodes
- Other first line tests normal



## Blood

Mutation analysis for myoadenylate deaminase (*AMPD1*)

## Muscle biopsy

Need to exclude other causes as this is common

## Mitochondrial Respiratory Chain defects

- Exercise intolerance, occasionally myoglobinuria
- Often more than one organ affected
- Normal or raised lactate (plasma and CSF) and CK
- May have abnormal organic acids (e.g. TCA intermediates, MMA)
- Normal or raised plasma alanine, reflecting lactic acidaemia
- May have generalised amino aciduria

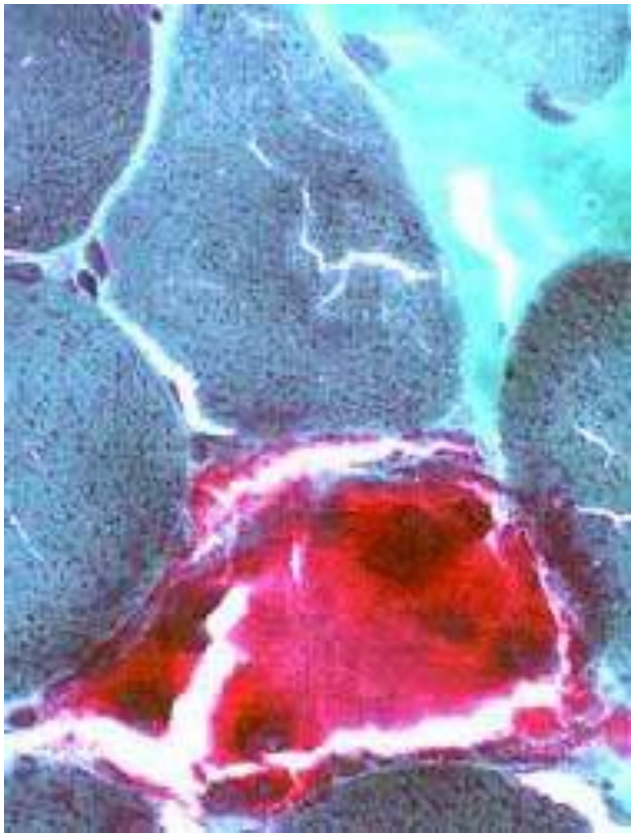
## Blood

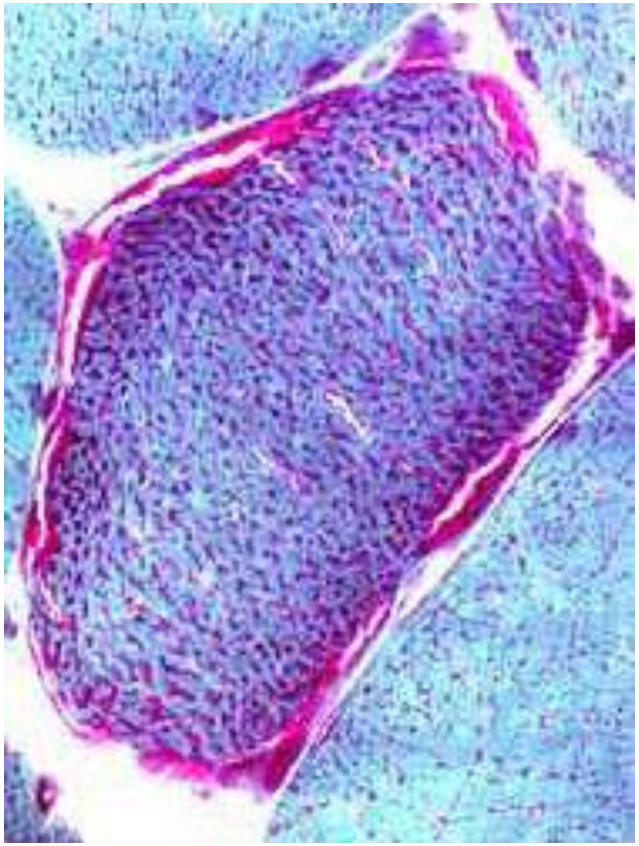
Mutation analysis for common mtDNA mutations

## Muscle Biopsy

Respiratory chain complexes assay
May include ubiquinone and mtDNA depletion studies
Histology – may have ragged red fibres or show decreased staining for some complexes

# Ragged Red Fibres



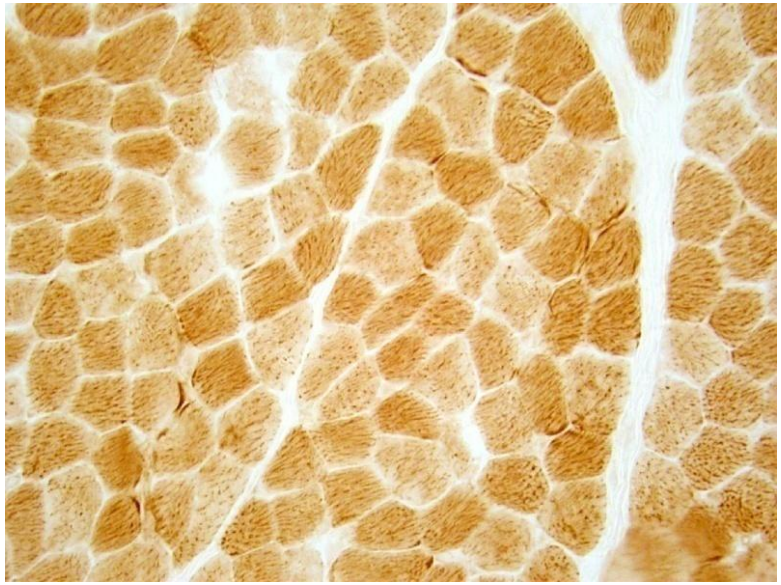


Gomori trichrome stain

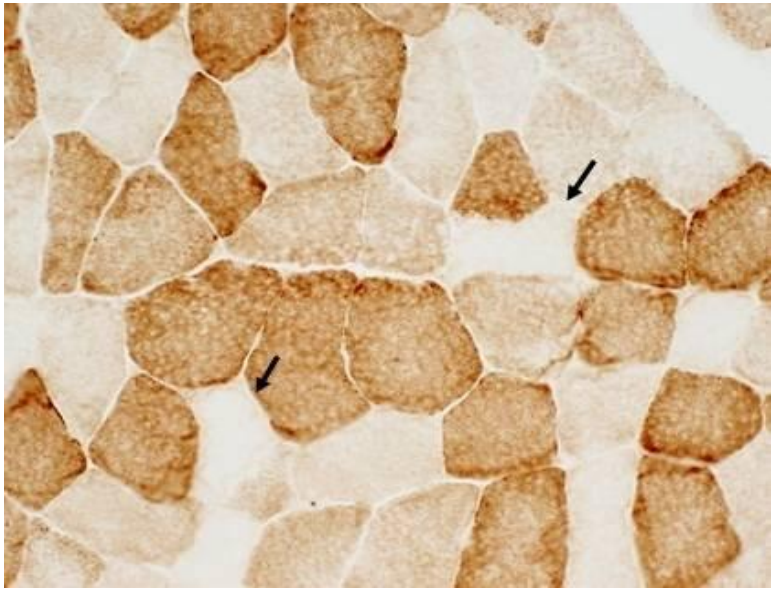
Muscle fibres with mitochondrial proliferation stain as red

# Cytochrome Oxidase staining

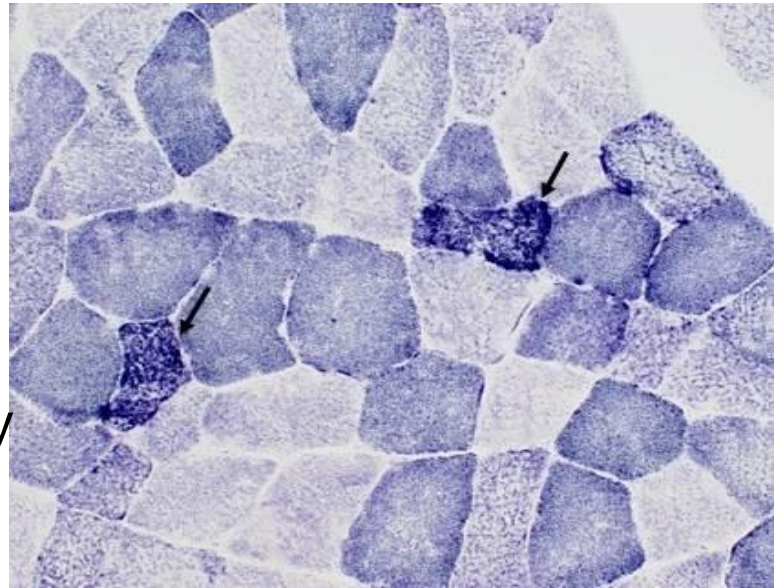
**Normal**



**COX deficient**



•Type I fibres stain more darkly than type II.



COX negative muscle fibres may have increased staining of SDH

# The Ischaemic Exercise Test

- Test for glycolytic defects, esp McArdles

- Restrict blood flow to arm muscle
- Ask patient to exercise arm
- Collect blood samples pre and at specified intervals post exercise.
- Measure lactate, creatine kinase, ammonia:

Normal response: 3-5 fold rise in lactate and ammonia.
Glycolytic defect: No increase in lactate
MAD defect: No increase in ammonia
Fatty Acid defect: Normal response

# Treatment of Metabolic Myopathies

- Dietary/ supplements
  - Glucose
  - Medium Chain Triglycerides
  - Carnitine supplements
  - CoQ10
  - Creatine
- Enzyme replacement therapy, e.g. Pompe Disease
- Exercise training to stimulate anaerobic or aerobic pathways

# Other factors to note

Lipid lowering drugs (e.g. statins) can induce myopathy/ rhabdomyolysis in some muscle disorders such as MAD, GSD V and CPT2.

Patients with muscle disorders such as McArdles and CPT2 may be at risk of malignant hyperthermia (causes a fast rise in body temperature and severe muscle contractions when the affected person gets general anaesthesia).

The common  MAD mutation can worsen the phenotype of some muscle disease patients.

# SUMMARY

Muscle function requires ATP.

Sources of ATP are creatine kinase, carbohydrates (aerobic and anaerobic) and fatty acids.

Defects in supply of ATP can cause muscle disease.

Symptoms and onset vary widely and may include:

- Exercise intolerance (after brief exercise in carbohydrate disorders or sustained exercise in fatty acid disorders)
- Cramps/ pains
- Rhabdomyolysis

Diagnosis requires a multidisciplinary approach:

- Physiology
- Biochemistry/ enzymology
- Histology
- DNA