METABOLISM

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ARKAN ACADEMY

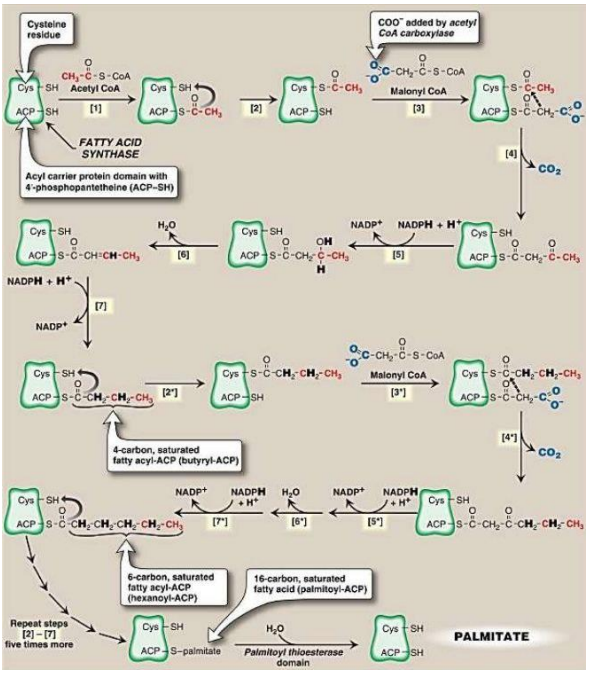
Fatty acids synthesis

- At low energy state, high ADP level leads for the activation of TCA cycle to generate energy
- FAs are synthesized in the *high energy state*, which causes:
  - Inhibition of TCA cycle, especially isocitrate dehydrogenase enzyme, causing the accumulation of citrate which is transported from the mitochondria into the cytosol by citrate transporter and cleaved into *oxaloacetate* and *acetyl CoA* by ***ATP citrate lyase***
  - Acetyl CoA is then used in the synthesis of FAs

- FAs synthesis occurs in the ***cytosol*** of ***liver*** and ***adipose tissues,*** by Fatty acid synthase (FAS)
- FAS is a multi-functional homo-dimeric enzyme
  - Each monomer has 6 enzymatic domains and 1 binding domain (ACP)

- **ACP** (Acyl-carrier protein) carries acyl groups and contains phosphopantetheine
  - *Phosphopantetheine* is a derivative of pantothenic acid (*vitamin B5*) with a terminal thiol group

- FAs synthesis steps:
  - *Acetyl CoA* is added to the ***ACP*** domain
  - Acetyl is transferred into the ***Cys*** residue
  - *Malonyl CoA* is added to the ***ACP*** domain
  - ***Condensation*** reaction producing ***4-carbon molecule*** on the *ACP* and decarboxylation of carboxyl group in malonyl CoA, ***released as CO_2***
  - ***Reduction*** (requires **NADPH**) which converts the carbonyl group into hydroxyl
  - ***Dehydration*** which involves the removal of H_2O
  - ***Reduction*** (requires **NADPH**) removes double bond
  - Addition of more malonyl CoA, and repeating the same steps for each ***malonyl CoA*** added increasing the length of the FA by ***2 carbons each turn***



  - *Palmitoyl thioesterase* domain of the FAS cleaves (releases) the palmitate from the ACP domain

- Synthesis of FAs in the ***liver*** and ***adipose*** tissue terminates by reaching 16 C molecule called **palmitate**
  - In the lactating ***mammary*** gland***,*** the reaction terminates early producing **SCFAs** and **MCFAs**

- The source of substances used in FA synthesis:
  - ***Acetyl CoA:*** from *pyruvate oxidation*
  - ***NADPH:*** from *PPP* and conversion of *malate into pyruvate*
  - ***NADH*** (important for the conversion of OAA into malate then into pyruvate)***:*** from *glycolysis*
  - ***Malonyl CoA:*** *Carboxylation of acetyl CoA* by ACC

- Carboxylation of acetyl CoA produces Malonyl CoA, where CO_2 is brought as a ***bicarbonate (HCO_3^-)***
  - This enzyme is catalyzed by ***acetyl CoA carboxylase (ACC)***, and it is ATP dependent
  - It requires *vitamin B7* as a coenzyme which is covalently bound to lysine in the ACC
  - It is the ***rate limiting step*** of FA synthesis

- ACC expression (production) requires the presence of 2 transcription factors:
  - Carbohydrate response element– binding protein (*ChREBP*)
  - Sterol regulatory element–binding protein-1c (*SREBP-1c*)

- Short term regulation of ACC activity:
  - Activated by ***citrate***, ***phosphatase*** (dephosphorylation) and ***insulin***
  - Inhibited by ***palmitoyl CoA***, ***AMP***, ***glucagon*** and ***epinephrine***
    - ✓ AMP, glucagon and epinephrin inhibit ACC by activating ***AMPK*** (phosphorylation) which phosphorylates ACC

AMPK: AMP-activated Protein Kinase

- Long term regulation of ACC activity:
  - PKA & AMPK phosphorylates ChREBP preventing its entry to the nucleus (reduces ACC synthesis)
  - Insulin activates SREBP-1c (increases ACC synthesis)

- Metformin (Glucophage) is a drug given for pre-diabetic patients which:
  - **Lowers plasma TAGs** by activating AMPK which inhibits ACC and FA synthase expression
  - **lowers blood glucose** by increasing AMP-mediated glucose uptake in the muscles

- For the production of 1 palmitate (16:0), it requires:
  - 1 acetyl CoA, 7 Malonyl CoA, 14 NADPH, 14 H^+
  - 8 Acetyl CoA, 7 CO2, 7 ATP, 14 NADPH, 14 H^+

- Further elongation of FAs occurs in:
  - SER: where the 2-carbon donor is *malonyl CoA* and the source of electrons is *NADPH*
  - Mitochondria: the 2-carbon donor is *acetyl CoA*, and the source of electrons is *NADH* & *NADPH*
    - ✓ Brain has enzymes allowing it to produce VLCFA

- Chain desaturation is done by ***fatty acyl CoA desaturases*** which act on LCFAs in the *SER*
  - The electron acceptor is *O_2* and *Cyt b5* (which have FAD-linked reductase)
  - Donor of electrons: *NADH*

- The first double bond is inserted between carbons 9 and 10, producing *oleic acid* (18:1), and small amounts of *palmitoleic acid (16:1)* by Δ^9 desaturase
- Humans have carbon **Δ^9, Δ^6, Δ^5 and Δ^4 desaturases**
- We cannot introduce double bonds from carbon 10 to the ω end of the chain, so they are essential
  - The polyunsaturated *ω-6 linoleic acid* and *ω-3 linolenic acid* are **essential**

- Notes
  - SCFAs and MCFAs usually do not require a carrier in plasma, but LCFAs ***requires albumin***
  - Glucose can be used to produce fats, but fats **can't** produce glucose
  - ACC2 Inhibitors can be used as wight loss agents
  - CoA also contains Vitamin B5

Glyceroneogenesis

- Glycerol production from *non-glucose precursors* such as lactate, alanine and aspartate
- It occurs in the adipose tissue and liver, and after synthesis glycerol leaves adipose to the liver
- It *regulates FA levels* in the blood
- Failure in regulating glyceroneogenesis may lead to ***Type 2 diabetes***
- Steps:
  - Precursor is converted into pyruvate which is converted into OAA by pyruvate carboxylase (PC), which is converted into PEP (phosphoenolpyruvate) by PEP-CK-C (PEP carboxykinase C)
  - PEP is converted into G3P then DHAP which is converted into glycerol 3-phosphate

TAGs synthesis

- Synthesis of TAGs in the liver and adipose tissue invloves:
  - Glycerol 3-phosphate synthesis, by 2 mechanisms:
    - ✓ *Conversion of DHAP* (from glycolysis) into glycerol 3-phosphate
    - ✓ *Phosphorylation of glycerol* into glycerol 3-phosphate by glycerol kinase
      - Liver can use both mechanisms; adipose tissue can only use the first one
      - Glucose enters the adipose tissue by GLUT4 transporter

  - Activation of fatty acids by adding CoA, by:
    - ✓ *Adding A*MP from ATP into FA producing acyl-adenylate and PP_i by Thiokinase
    - ✓ *AMP is replaced by CoA* producing Acyl CoA

  - Synthesis of triacylglycerol
    - ✓ Acyltransferase adds a FA-CoA to glycerol 3-phosphate on C1
    - ✓ Acyltransferase adds a FA-CoA to lysophosphatidic acid on C2
    - ✓ Phosphatase removes phosphate group from phosphatidic acid
    - ✓ Acyltransferase adds a FA-CoA to diacylglycerol on C3 forming TAG

- TAGs in the adipose tissue are produced to be *stored* as lipid droplets
- TAGs in the liver are produced mainly to be *packaged in VLDL* and a small portion for storage

- In the intestines, TAGs are synthesized by ***MAG pathway***, which involves:
  - Monoacylglycerol enters mucosal cells
  - 2 FAs are activated into FA-CoA, to be added into the monoglyceride producing TAG
  - TAGs are then packaged into *chylomicrons* into the lymph

Degradation of FAs and TAGs

- Lipids represent a *major storage site of energy* (long term storage), especially TAGs
  - Lipids are hydrophobic (stored without water), producing 9 Kcal per gram
  - Carbohydrates are hydrophilic (which attracts water), producing 4 Kcal per gram
    - ✓ *Glucose is the major circulating fuel*
- The release of FAs from TAGs:
  - *Adipose triglyceride lipase (ATGL)* releases the **1st** FA of TAG, producing diglyceride
  - *Hormone-sensitive lipase (HSL)* releases the **2nd** FA producing monoglyceride
  - *Monoacylglyceride lipase (MGL)* releases the **3rd** FA producing glycerol
- In well-fed state, ***insulin*** inhibits ATGL synthesis and activates phosphatase which inhibits HSL
  - ***Perilipin*** protein that coats fat droplets, act as an emulsifier and blocks HSL
- In fasting state, ***Glucagon*** and ***epinephrine*** increases cAMP which activates PKA that phosphorylates perilipin releasing (disassembles) it and activating HSL
  - ***Phosphodiesterase inhibitors*** activate the HSL

β-Oxidation of FAs

- It is the process of cleaving FAs on the **β-C**, producing *2-C fragments (**Acetyl CoA**)*
  - It occurs in the mitochondrial matrix
- SCFAs and MCFAs can enter the mitochondrial matrix **easily**
- LCFAs are shuttled from the cytosol into the mitochondrial matrix by the ***carnitine shuttle mechanism***
- Carnitine shuttle mechanism
  - FAs are **activated** by attaching CoA via *Acyl CoA synthetase* (***outer*** membrane), requiring *ATP*
  - Fatty acyl CoA passes through the outer mitochondrial membrane
  - *CPT I* (carnitine palmitoyl transferase I) in the ***outer*** membrane converts Fatty acyl CoA & carnitine into fatty *acyl-carnitine* and *CoA* and it is inhibited by ***malonyl CoA***
  - Fatty acyl carnitine is passed through the inner membrane by a translocase into the matrix
  - *CPT II* (***inner*** membrane) reform *fatty acyl-CoA*, and a translocase passes *carnitine* out

- Carnitine is originally synthesized from 2 amino acids L-methionine and L-lysine
  - The cardiac and skeletal **muscles** contain 97% of carnitine in the body
  - Muscles don't have ACC1 (no FA synthesis) but have mitochondrial ACC2 (regulate degradation)

- Sources of carnitine are meat and synthesis in the kidney and liver
- Carnitine deficiencies:
  - Primary carnitine deficiency
    - ✓ *Defects in membrane transporter:* No uptake of carnitine by muscles and the kidneys (excreted)
    - ✓ Treated by carnitine supplementation
  - Secondary carnitine deficiency
    - ✓ Taking *valproic acid (antiseizure)*, decreases renal reabsorption
    - ✓ *Liver diseases* cause decreased carnitine synthesis
    - ✓ *Defective fatty acid oxidation*, causes acyl-carnitines accumulation and its excretion into urine
    - ✓ *CPT-I deficiency:* affects the ***liver***, causing severe ***hypoglycemia***, ***coma***, and ***death***
    - ✓ *CPT-II deficiency:* affects the ***liver***, ***cardiac muscle***, and ***skeletal muscle***
      - Avoidance of fasting
      - A diet with high carbohydrates, low fat and supplemented with medium-chain TAG

- β-oxidation of FAs:
  - *Oxidation:* fatty acyl CoA is oxidized by ***Acyl CoA dehydrogenase*** which reduces FAD into ***$FADH_2$***
    - ✓ This enzyme has 4 isozymes SCAD, MCAD, LCAD, VLCAD
  - *Hydration:* addition of water by hydratase
  - *Oxidation:* by ***hydroxyacyl-CoA dehydrogenase***, reducing NAD^+ into ***NADH***
  - *Thiolytic cleavage:* by ***thiolase*** via breaking the bond between alpha and beta carbon
    - ✓ Inhibited by *Acetyl CoA*

- The number of cycles of β-oxidation and FA synthesis = **(n/2) – 1**
- Number of acetyl CoA produced during β-oxidation = **n/2**
  - NADH = 2.5 ATP, FADH2 = 1.5 ATP, Acetyl CoA = 12 ATP
  - **Net** ATP yield of oxidation of FA = the net ATP yield of oxidation of fatty acyl CoA **– 2**
  - Not all acetyl CoA are used to produce ATP, some are used in gluconeogenesis and ketogenesis

- Medium chain fatty-acyl CoA dehydrogenase ***(MCAD) deficiency*** is an autosomal-recessive disorder
  - Most common inborn error of β-oxidation (1:14,000 births worldwide)
  - Higher incidence among Caucasians of Northern European descent
  - Decreased ability to oxidize MCFAs (lack of energy) and severe hypoglycemia and hypoketonemia
  - Treatment: *avoidance of fasting* by regular and frequent meals and snacks and diet high in carbohydrates and low in fat

Oxidation of ODD FA

- Odd FAs undergo ***β-oxidation*** until reaching the last 3-C fragment which is called ***propionyl CoA***
  - Propionyl CoA is carboxylated by ***propionyl CoA carboxylase*** which requires *ATP* and CO_2 in the form of HCO_3^- and carried by biotin (*Vit. B7*) forming ***D-methylmalonyl CoA***
  - D-methylmalonyl CoA is converted into ***L-methylmalonyl*** CoA by ***epimerase***
  - L-methylmalonyl CoA is converted into ***Succinyl CoA*** by ***methylmalonyl CoA mutase*** which requires *vitamin B12* as a coenzyme
    - ✓ Deficiency in this enzyme or vitamin B12 causes neurological manifestations (developmental delay, seizures or intellectual disabilities) and metabolic acidosis
    - ✓ Succinyl CoA enters the TCA cycle

Oxidation of unsaturated FA

- **Monounsaturated** FAs are isomerized where the double bond is transferred between α and β carbons
  - It is done by *isomerase* and it causes the skip of the first step of β-oxidation leading to the loss of electrons (***loss of $FADH_2$***)
- Oxidation of **polyunsaturated** FAs such as linoleic acid (18:2) requires an NADPH dependent *2,4-dienoyl CoA reductase* in addition to the *isomerase*
  - It causes the loss of electrons (***loss of FADH2, NADPH***)

Peroxisomal β-oxidation

- Oxidation of ***VLCFAs into LCFAs*** then return to the mitochondrial β-oxidation
  - It is very similar to the mitochondrial β-oxidation, but it uses *acyl CoA oxidase* instead of dehydrogenase in the first step
    - ✓ $FADH_2$ is oxidized forming hydrogen peroxide (***H_2O_2***) causing the ***loss of electrons***
- *Zellweger syndrome* (peroxisomal biogenesis disorder) and *X-linked adrenoleukodystrophy* (dysfunctional transport VLCFA) causes VLCFAs accumulation

Peroxisomal α-oxidation

- Occurs in the ***phytanic acid metabolism***
  - Phytanic acid is a branched fatty acid produced from the breakdown of ***chlorophyll***
  - Cleaves the bond between the *1st and α carbons producing CO_2*
- Steps:
  - Phytanic acid is **activated** by CoA (requires *ATP*) then it is transported into the peroxisomes
  - It is hydroxylated by phytanoyl CoA α-hydroxylase (***PhyH***) which has Fe^{+2} as a prosthetic group

- 2-hydroxy phytanoyl-CoA lyase releases formyl-CoA which is then converted into formic acid and then CO_2 is released

- When fully degraded, it generates 4 byproducts: acetyl-CoA, 2-methyl-propionyl-CoA, formyl-CoA, propionyl-CoA

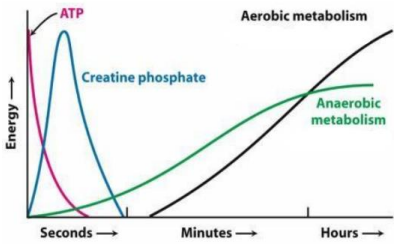
- *Refsum disease* is an autosomal-recessive disorder caused by a deficiency of peroxisomal PhyH

SER ω-oxidation

- ω-Oxidation is a minor pathway of the SER where FAs is converted into ***dicarboxylic*** acids by forming carboxyl group on the ω carbon
- It is upregulated in certain conditions such as MCAD deficiency

Sources of energy

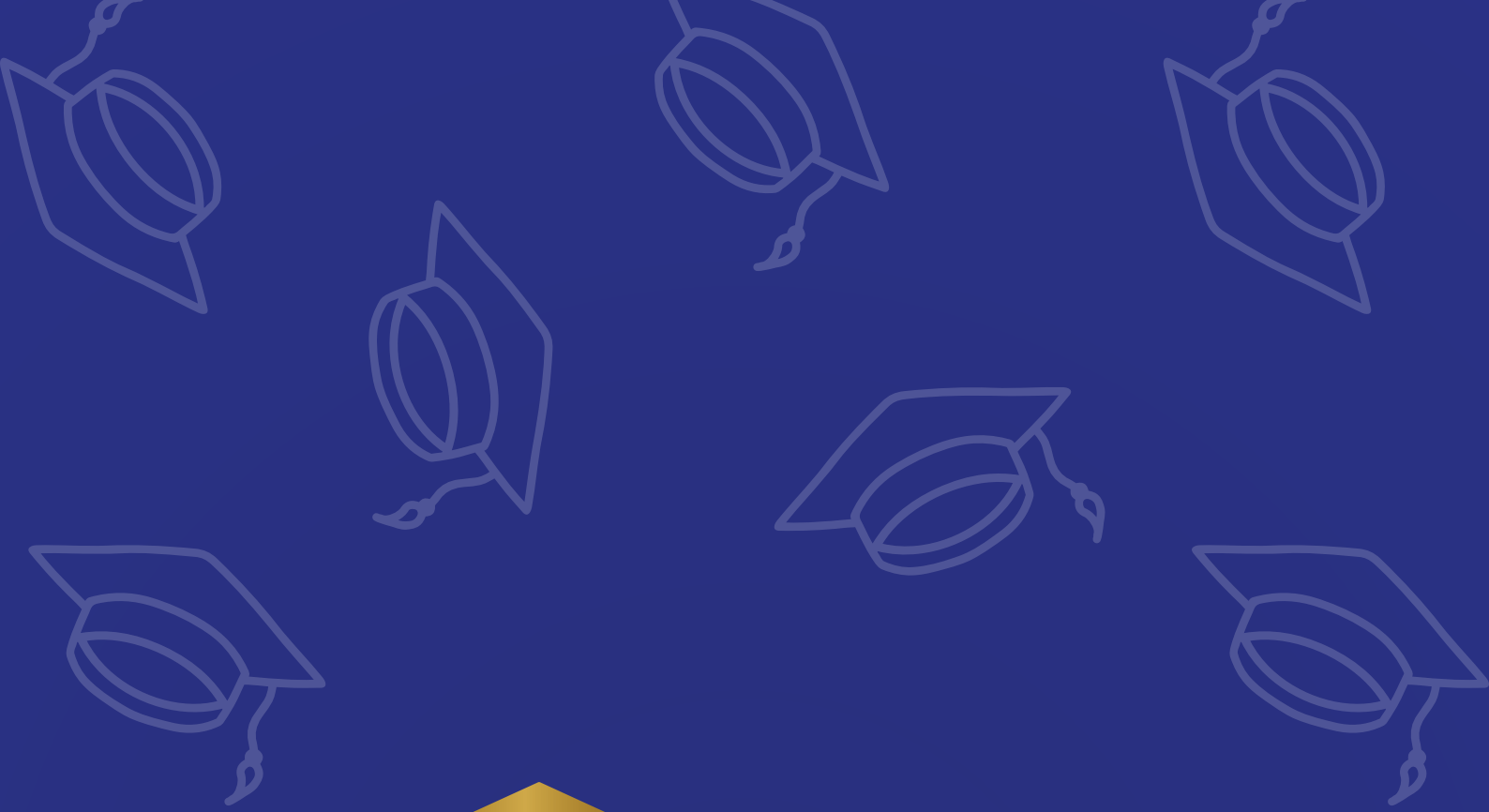
- Sources of energy during an exercise:
  - For the first 5 seconds, our reservoir of ATP is consumed
  - For the first 30 seconds, creatinine phosphate is used to replenish ATP reservoir by creatinine kinase
  - Aerobic and anaerobic metabolism starts:
    - ✓ Anaerobic can't continue for a long time because of the accumulation of lactic acid
    - ✓ Aerobic metabolism works after a while and persist for long periods



- For *short distance runners*, they rely on *ATP* and *creatinine phosphate*
- For *marathon runners*, they mostly rely on *aerobic metabolism* so must attain adequate oxygen

VARIABLE	SYNTHESIS	DEGRADATION
Greatest flux through pathway	After carbohydrate-rich meal	In starvation
Hormonal state favoring pathway	High insulin/glucagon ratio	Low insulin/glucagon ratio
Major tissue site	Primarily liver	Muscle, liver
Subcellular location	Cytosol	Primarily mitochondria
Carriers of acyl/acetyl groups between mitochondria and cytosol	Citrate (mitochondria to cytosol)	Carnitine (cytosol to mitochondria)
Phosphopantetheine-containing active carriers	Acyl carrier protein domain, coenzyme A	Coenzyme A
Oxidation/reduction coenzymes	NADPH (reduction)	NAD^+, FAD (oxidation)
Two-carbon donor/product	Malonyl CoA: donor of one acetyl group	Acetyl CoA: product of β-oxidation
Activator	Citrate	—
Inhibitor	Palmitoyl CoA (inhibits *acetyl CoA carboxylase*)	Malonyl CoA (inhibits *carnitine palmitoyltransferase-I*)
Product of pathway	Palmitate	Acetyl CoA
Repetitive four-step process	Condensation, reduction dehydration, reduction	Dehydrogenation, hydration dehydrogenation, thiolysis

	carbohydrates	lipids
Stored as...?	Starch - plants Glycogen - animals	Fats & oils (plants Fat (animals)
Long/short term storage?	Starch: long-term Gylcogen: short-term	Long term
Ease of digestion/ release of energy?	Easy to release energy	Harder to release energy (needs more oxygen)
Energy per gram?	17kJ/g	38kJ/g
Solubility in water? (and consequence)	Soluble	Not soluble
Use of oxygen in metabolism? (and consequence)	Needs less oxygen, useful for high-demand activity	Needs more oxygen, less efficient to release energy



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