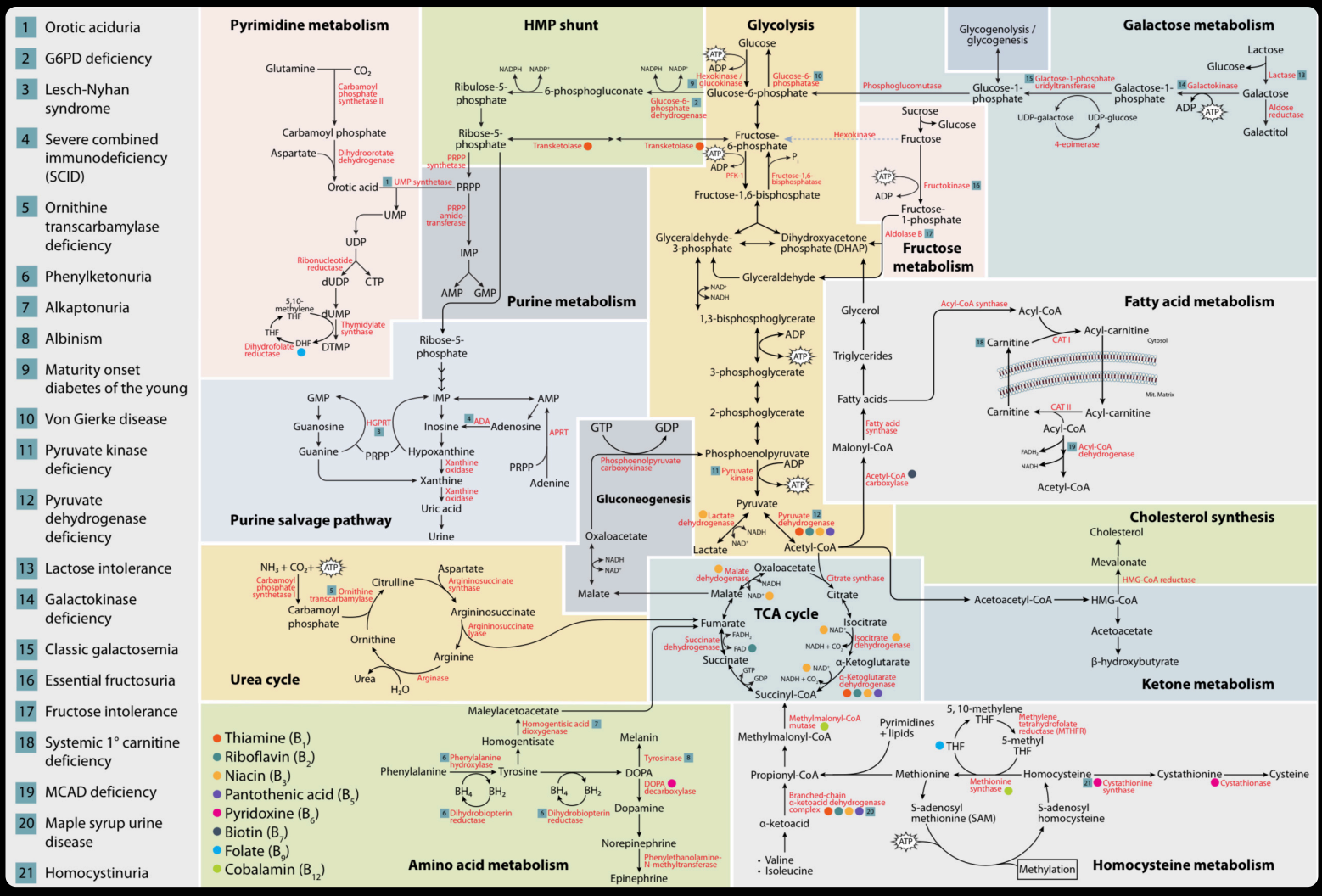
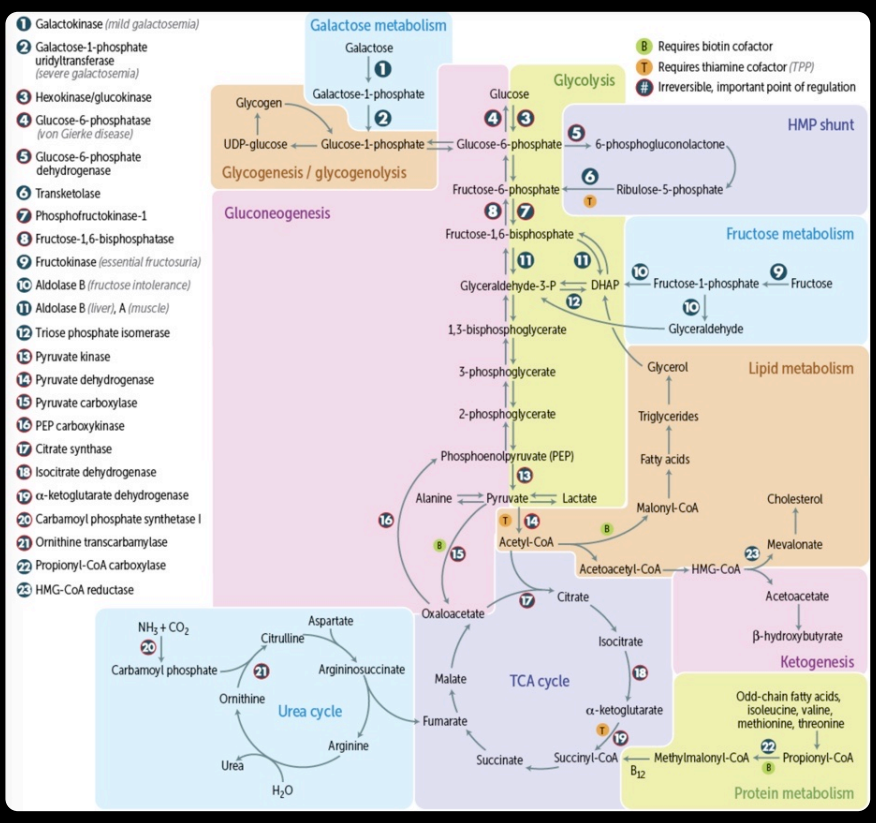
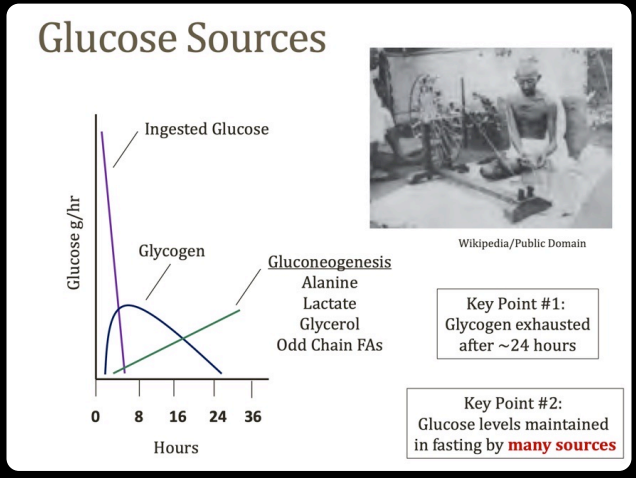
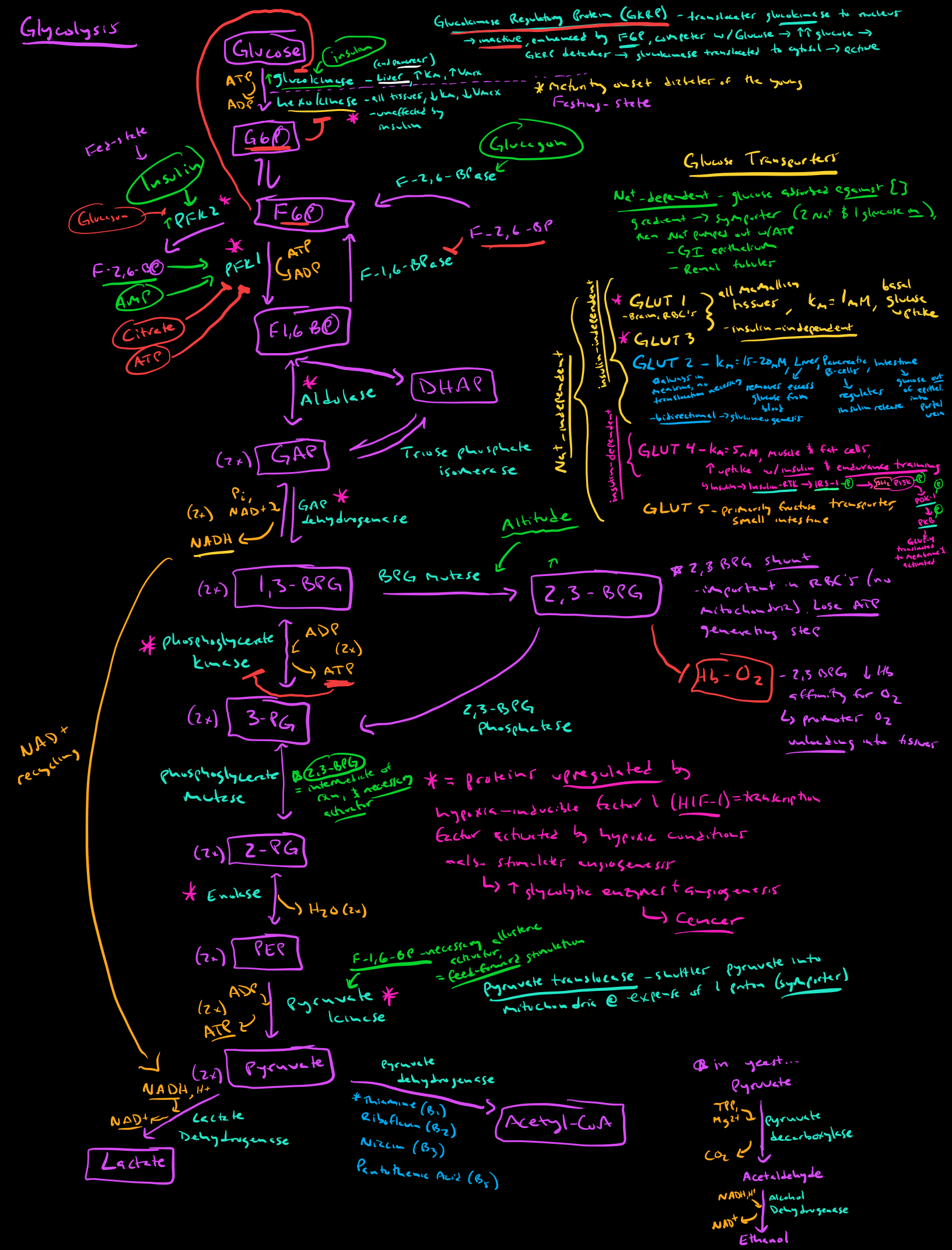

1 Orotic aciduria
2 G6PD deficiency
3 Lesch-Nyhan syndrome
4 Severe combined immunodeficiency (SCID)
5 Ornithine transcarbamylase deficiency
6 Phenylketonuria
7 Alkaptonuria
8 Albinism
9 Maturity onset diabetes of the young
10 Von Gierke disease
11 Pyruvate kinase deficiency
12 Pyruvate dehydrogenase deficiency
13 Lactose intolerance
14 Galactokinase deficiency
15 Classic galactosemia
16 Essential fructosuria
17 Fructose intolerance
18 Systemic 1° carnitine deficiency
19 MCAD deficiency
20 Maple syrup urine disease
21 Homocystinuria
Pyrimidine metabolism
HMP shunt
Glycolysis
Galactose metabolism
Purine metabolism
Fructose metabolism
Fatty acid metabolism
Purine salvage pathway
Gluconeogenesis
Cholesterol synthesis
Urea cycle
TCA cycle
Ketone metabolism
Thiamine (B1)
Riboflavin (B2)
Niacin (B3)
Pantothenic acid (B5)
Pyridoxine (B6)
Biotin (B7)
Folate (B9)
Cobalamin (B12)
Amino acid metabolism
Homocysteine metabolism

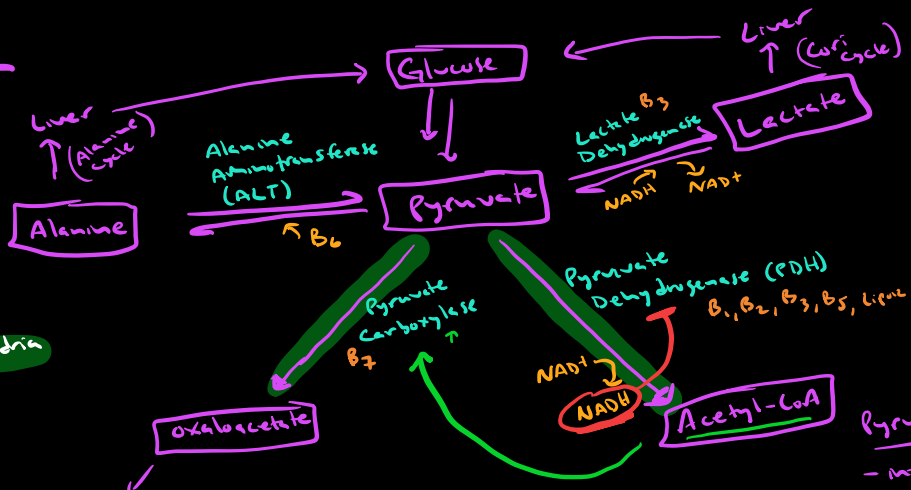

1 Galactokinase (mild galactosemia)
2 Galactose-1-phosphate uridyltransferase (severe galactosemia)
3 Hexokinase/glucokinase
4 Glucose-6-phosphatase (von Gierke disease)
5 Glucose-6-phosphate dehydrogenase
6 Transketolase
7 Phosphofructokinase-1
8 Fructose-1,6-bisphosphatase
9 Fructokinase (essential fructosuria)
10 Aldolase B (fructose intolerance)
11 Aldolase B (liver), A (muscle)
12 Triose phosphate isomerase
13 Pyruvate kinase
14 Pyruvate dehydrogenase
15 Pyruvate carboxylase
16 PEP carboxykinase
17 Citrate synthase
18 Isocitrate dehydrogenase
19 α-ketoglutarate dehydrogenase
20 Carbamoyl phosphate synthetase I
21 Ornithine transcarbamylase
22 Propionyl-CoA carboxylase
23 HMG-CoA reductase
B Requires biotin cofactor
T Requires thiamine cofactor (TPP)
Irreversible, important point of regulation
Galactose metabolism
Glycolysis
HMP shunt
Glycogenesis / glycogenolysis
Gluconeogenesis
Fructose metabolism
Lipid metabolism
Ketogenesis
Urea cycle
TCA cycle
Protein metabolism
Odd-chain fatty acids, isoleucine, valine, methionine, threonine


Glucose Sources
Ingested Glucose
Glycogen
Gluconeogenesis
Alanine
Lactate
Glycerol
Odd Chain FAs
Glucose g/hr
0
8
16
24
36
Hours
Wikipedia/Public Domain
Key Point #1: Glycogen exhausted after ~24 hours
Key Point #2: Glucose levels maintained in fasting by many sources

Glycolysis


Glucose
Insulin
ATP
ADP
↑Glucokinase – Liver, ↑Km, ↑Vmax
Hexokinase – all tissues, ↓Km, ↓Vmax
– unaffected by insulin
* Maturity onset diabetes of the young
Fasting-state
G6P
Fed-state
Insulin
Glucose
TPFK2*
Glucagon
F-2,6-BPase
F6P
F-2,6-BP
F-2,6-BP
AMP
Citrate
ATP
PFK1*
ATP
ADP
F-1,6-BPase
F1,6BP
*Aldulase
DHAP
(2x) GAP
Triose phosphate isomerase
Pi, NAD+2
(2x) NADH
GAP* dehydrogenase
Altitude
(2x) 1,3-BPG
BPG Mutase
2,3-BPG
* Phosphoglycerate kinase
ADP (2x)
ATP
(2x) 3-PG
2,3-BPG phosphatase
Phosphoglycerate Mutase
2,3-BPG = intermediate of Rbc, & necessary activator
(2x) 2-PG
* Enolase
H2O (2x)
(2x) PEP
F-1,6-BP – necessary allosteric activator, = feed-forward stimulation
Pyruvate kinase*
(2x) ADP
(2x) ATP
(2x) Pyruvate
NAD+ recycling
NADH, H+
NAD+
Lactate Dehydrogenase
Lactate
Pyruvate dehydrogenase
* Thiamine (B1)
Riboflavin (B2)
Niacin (B3)
Pantothenic Acid (B5)
Acetyl-CoA
Pyruvate translocase – shuttles Pyruvate into mitochondria @ expense of 1 proton (symporter)
Glucokinase Regulating Protein (GKRP) – translocates glucokinase to nucleus → inactive, enhanced by F6P, competes w/ Glucose → ↑↑ glucose → GKRP detaches → glucokinase translocated to cytosol → active
Glucose Transporters
Na+-dependent – glucose absorbed against [ ]
gradient → symporter (2 Na+ & 1 glucose in), then Na+ pumped out w/ ATP
– GI epithelium
– Renal tubules
Na+-independent
insulin-independent
* GLUT 1 – Brain, RBC's – all metabolizing tissues, Km = 1 mM, basal glucose uptake
* GLUT 3
– insulin-independent
insulin-dependent
GLUT 2 – Km = 15-20 mM, Liver, Pancreatic B-cells, Intestine
always in membrane, no translocation necessary
removes excess glucose from blood
↓ regulates insulin release
glucose out of epithel. into portal vein
– bidirectional → gluconeogenesis
GLUT 4 – Km = 5 mM, muscle & fat cells, ↑ uptake w/ insulin & endurance training
↓ Insulin → Insulin-RTK → IRS-1 → PI3K → PDK-1 → PKB
GLUT 5 – primarily fructose transporter, small intestine
Glut 4 translocated to membrane & activated
* 2,3 BPG shunt – important in RBC's (no mitochondria). Lose ATP generating step
Hb-O2 – 2,3 BPG ↓ Hb affinity for O2 → promotes O2 unloading into tissues
* = proteins upregulated by Hypoxia-inducible factor 1 (HIF-1) = transcription factor activated by hypoxic conditions
also stimulates angiogenesis
↳ ↑ glycolytic enzymes & angiogenesis
↳ Cancer
In yeast...
Pyruvate
TPP, Mg2+
Pyruvate decarboxylase
CO2
Acetaldehyde
NADH, H+
NAD+
Alcohol Dehydrogenase
Ethanol

Pyruvate



PDH cofactors:

TLC for Nancy

- Thiamine (B_1)
- Lipoic Acid
- CoA (B_5, Pantothenic acid)
- FAD (B_2, riboflavin)
- NAD (B_3, niacin)

Pyruvate transport

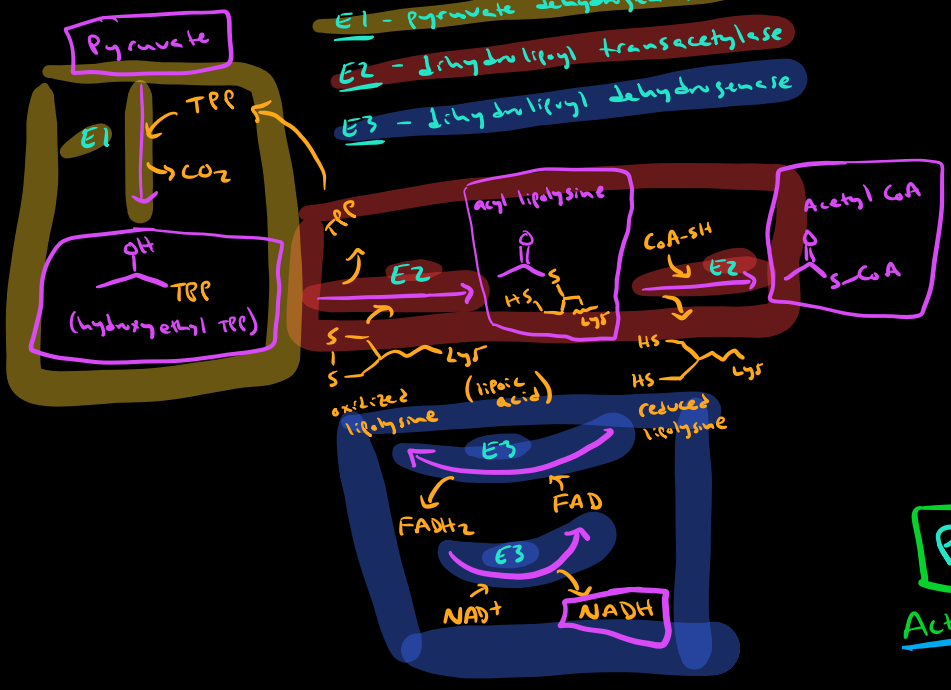
- into mitochondria for:
  - TCA cycle
  - Gluconeogenesis
- outer-membrane transport
  - voltage-gated porin complex
- inner-membrane transport
  - mitochondrial pyruvate carrier (MPC)

PDH Complex – Mitochondria

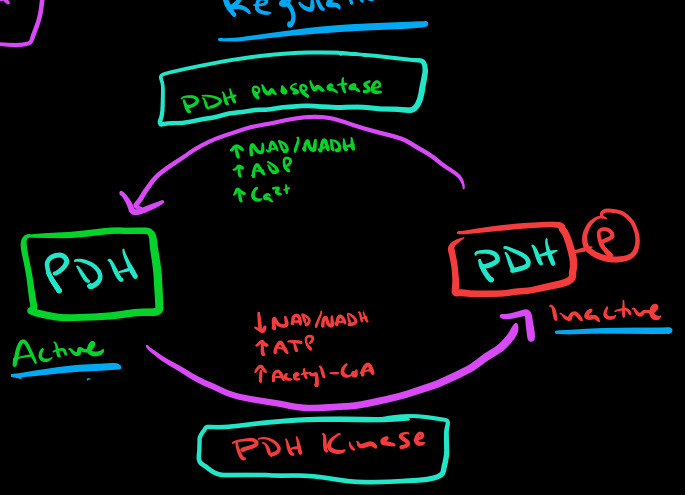
E1 – Pyruvate dehydrogenase

E2 – dihydrolipoyl transacetylase

E3 – dihydrolipoyl dehydrogenase



Regulation



PDH deficiency

- Mitochondrial disorder
- often X-linked
- Common mutation = PDHA1 = E1 α-subunit
- ↑ shunting of pyruvate → ↑alanine & lactate → lactic acidosis
- Carbs & AA's metabolized to pyruvate → ↑ lactic acidosis
- Poor feeding, growth failure, developmental delays
- Labs: ↑alanine & lactic acidosis
- treatment:
  1. Give thiamine & lipoic acid (optimize any remaining PDH)
  2. ketogenic diet
     - low carbohydrates → avoid pyruvate precursors
     - ↑fat → converted directly to acetyl CoA
     - Lys & Leu ⇒ ketogenic AA's that bypass pyruvate
       - Leucine → acetoacetate = ketone body
       - Lysine → acetyl-CoA = used in TCA cycle & cannot be used for gluconeogenesis → cannot be converted back into pyruvate

PDH Cofactors

Thiamine (B_1)

- active form = Thiamine Pyrophosphate (TPP)

Thiamine $\xrightarrow{ATP \rightarrow AMP}$ TPP

- used by:
  - Pyruvate Dehydrogenase
  - α-KG Dehydrogenase
    - TCA cycle
  - α-ketoacid Dehydrogenase
    - branched chain AA's
  - Transketolase
    - HMP shunt

- Thiamine deficiency - ↓ ATP
  - Beriberi
    1. Dry-type → polyneuritis, muscle weakness
    2. Wet-type → tachycardia, high-output heart failure, edema
  - Wernicke-Korsakoff Syndrome
    - alcoholics (malnourished, poor vitamin absorption)
    - Confusion, confabulation
    - ⚠ If give glucose first to malnourished pt's → unable to metabolize
      ↳ must administer thiamine first

Lipoic Acid

- Binds w/ lysine → lipoamide
- Cofactor for E2
- Inhibited by arsenic
  - Poison (Metal)
  - Binds lipoic acid → inhibits PDH
  - Oxidized to arsenous oxide - smells like garlic breath
  - vomiting, diarrhea, coma, death
  - theory that Napoleon Bonaparte poisoned by arsenic

Nucleotide Coenzymes

FAD (Flavin Adenine Dinucleotide)

- Synthesized from riboflavin (B_2)
  ↳ Riboflavin + Adenosine → FAD
- accepts 2 e^-'s → $FADH_2$
- B_2 deficiency:
  - cheilosis - fissures @ corners of mouth
    - inflamed lips
  - Corneal vascularization → corneal clouding
  - commonly seen in anorexia nervosa

NAD (Nicotinamide Adenine Dinucleotide)

- Synthesized from Niacin (B_3)
  - Niacin synthesized from tryptophan
  - can also obtain niacin from diet

Coenzyme A

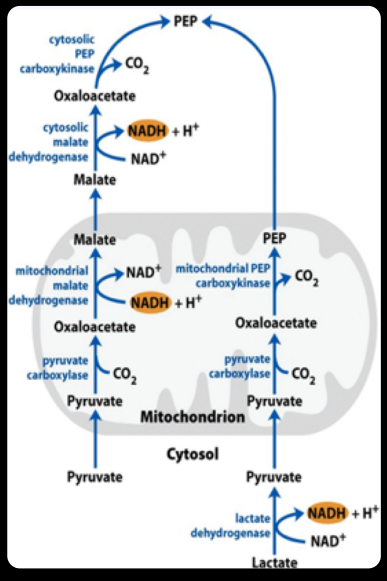
- Synthesized from pantothenic acid (B_5)
- accepts/donates acyl groups

Gluconeogenesis – Liver ONLY

- Non-carbohydrates → glucose
  - lactate, glycerol, propionyl-CoA
  - ALL AAs except leucine, lysine

↑ Gluconeogenesis

- Glucagon
- Epinephrine
- Cortisol
- Thyroid Hormone



Glucose

ADP ↑ / ATP ↓ — G-6-Pase ← Glucagon

* Endoplasmic Reticulum of liver & kidney

– in other tissues, G6P → glycogen → deliver to liver

G-6-P

Glucagon, ATP

F-6-P ← F-2,6-Bpase — F-2,6-BP

F-1,6-Bpase * RLS ↑AMP

F-1,6-BP

Aldolase

TAG → FAs (Hormone Sensitive Lipase (HSL)) / Glycerol (ATP ↓ ADP ↑ Glycerol Kinase)

GAP ⇌ (Triose Phosphate Isomerase) DHAP ⇌ (G3P Dehydrogenase; NADH, H^+ ↑ / NAD^+ ↓) Glycerol-3-P (G3P)

NAD^+ ↑ / H_2O, NADH ↓ — GAP Dehydrogenase

1,3 BPG

ADP ↑ / H_2O, ATP ↓ — Phosphoglycerate kinase

3PG

Phosphoglycerate Mutase

2PG

Enolase (H_2O) → PEP

Phosphoenol pyruvate Carboxykinase (PEPCK) (GTP ↓ GDP)

Insulin ↑

Oxaloacetate ⇌ (NAD^+ ↑ / NADH ↓) Malate

Malate shuttle: cytosol / mitochondria

Malate dehydrogenase (NAD^+ ↑ / NADH ↓)

Oxaloacetate ← (ATP, CO_2 ↓) Pyruvate Carboxylase * B_7 (biotin)

Pyruvate ← AAs, Alanine, Lactate

Pyruvate → Acetyl-CoA

* Pyruvate carboxylase cannot function w/o Acetyl-CoA

odd-chain FA's → Propionyl-CoA → Oxaloacetate

AAs → Oxaloacetate

Pyruvate Carboxylase deficiency

- Presents in infancy → failure to thrive
- ↑ Pyruvate → ↑ lactate → lactic acidosis

Biotin

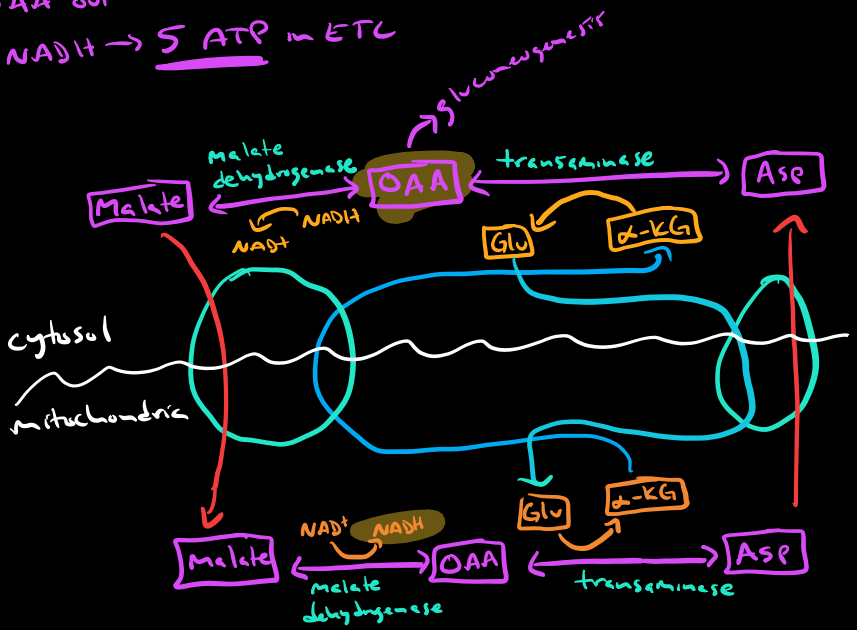
- Cofactor for carboxylation enzymes:
  - Pyruvate Carboxylase
  - Acetyl-CoA Carboxylase
  - Propionyl-CoA Carboxylase
- Deficiency:
  - raw (avidin widely distributed)
  - massive consumption of raw egg whites → Avidin (glycoprotein) → binds biotin

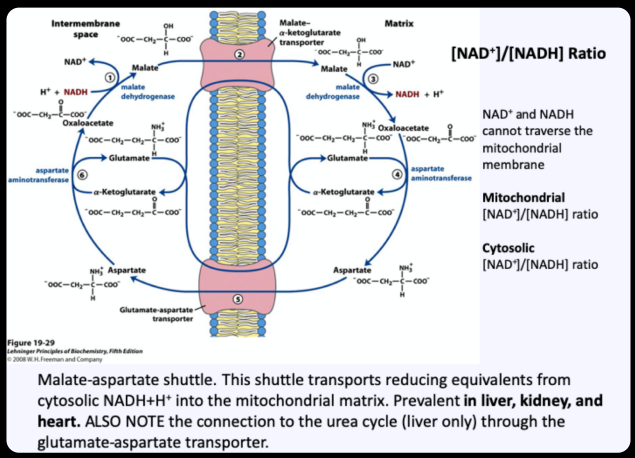
Shuttles:

Malate-Aspartate - liver, kidney, heart

- Malate = Membrane Permeable
- NADH & Oxaloacetate = Impermeable
- NADH in
  OAA out
- 2 NADH → 5 ATP in ETC

Total ATP per glucose in cellular respiration = 30-32
↳ # varies depending on which shuttle mechanism is used
↳ Malate-aspartate shuttle user NADH → 2.5 ATP per molecule
↳ glycerol-phosphate shuttle user $FADH_2$ → 1.5 ATP per molecule



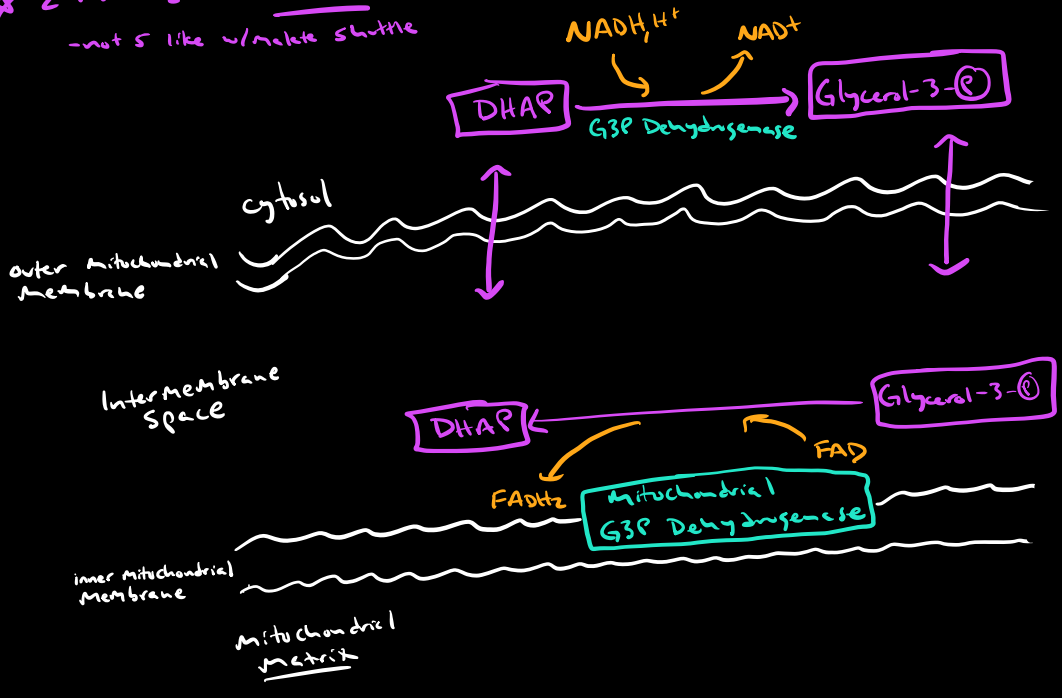


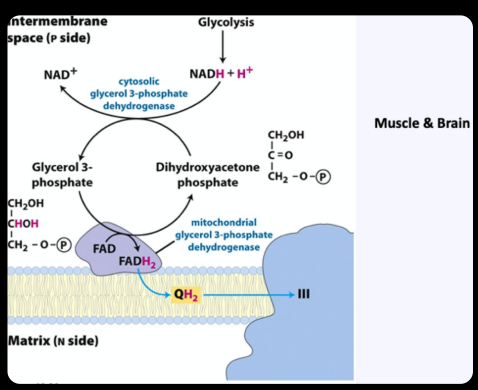
Malate-aspartate shuttle. This shuttle transports reducing equivalents from cytosolic NADH+H⁺ into the mitochondrial matrix. Prevalent **in liver, kidney, and heart.** ALSO NOTE the connection to the urea cycle (liver only) through the glutamate-aspartate transporter.

Glycerol-Phosphate - Muscle & Brain

- Moves e^-'s on NADH into mitochondria via oxidation of G3P → DHAP to yield 2 $FADH_2$
  → carries e^-'s to ETC on outer surface of inner mitochondrial membrane

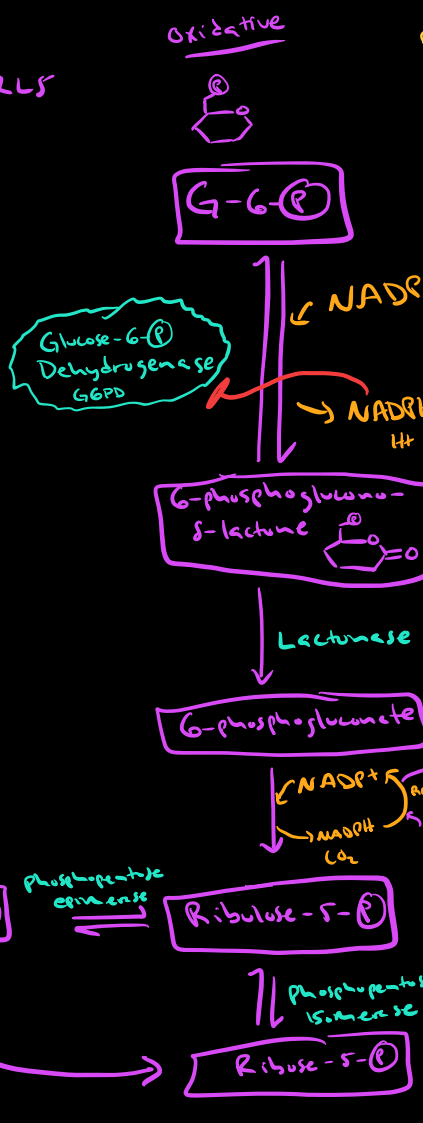
2 $FADH_2$ → 3 ATP in ETC
- not 5 like w/malate shuttle





Pentose Phosphate Pathway

- aka Hexose Monophosphate Shunt (HMP Shunt)
- Produces NADPH
  - Reductive Synthesis (cholesterol, steroids, fatty acids)
  - Protects cells from oxidative stress (Glutathione reduction)
  - Assists Phagocytic cells (respiratory burst)
- Produces Ribose-5-P
  - ↳ nucleotide synthesis
- Exclusively in cytoplasm
- Oxidative Phase = irreversible, RLS
- Reductive phase = reversible



Transketolase requires Thiamine Pyrophosphate (TPP)

Abnormal transketolase pt's may be predisposed to Wernicke-Korsakoff Syndrome

Beriberi
- deficient transketolase function
  - can be due to Thiamine deficiency

Oxidative Burst

- Phagocytes (neutrophils & monocytes) using O_2-dependent bacterial killing

O_2 → (NADPH, H+ → NADP+) NADPH oxidase → $O_2^{-}\cdot$

$O_2^{-}\cdot$ → Superoxide Dismutase → H_2O_2

H_2O_2 → Bacterial Death

H_2O_2 → (catalase) → $2\,H_2O$ → catalase + bacteria can use enzymes b/c don't have myeloperoxidase

H_2O_2 → (myeloperoxidase) → HOCl (bleach)

GSH

2 Glutathione (GSH) → (GSH Reductase) → Glutathione Disulfide (GSSG) → (GSH peroxidase) → H_2O

GSH peroxidase ← H_2O_2

↑ H_2O_2 in RBC's
- Infections
- Fava Beans → Toxidants
- Sulfa Drugs

↳ can form Cross-linkages → aggregation in RBCs → bad

GSH very important for protection against oxidative stress

G6PD deficiency

→ ↓ NADPH → ↓ GSH → hemolysis → hemolytic anemia (destroying RBCs faster than regeneration)

→ ↓ NADPH → ↓ immune system (↓ respiratory burst)

- X-linked → affects mostly males
- Most common human enzyme disorder
- Africa, Asia, Mediterranean
- Recurrent hemolysis after exposure to trigger
  - may present as dark urine

Confers Malaria resistance in RBC's b/c RBCs have defective structure → don't uptake malaria disease

- other areas of HMP shunt OK
  - Damage usually localized to oxidative stress in RBC's
- Heinz bodies - oxidized Hb precipitated in RBCs as aggregates
- Bite cells - phagocytic removal by splenic macrophages of Heinz bodies
- Typical presentation:
  - tachycardia & ↑ BP
  - b/c hemolytic anemia → ↓ O_2 to tissues → ↑ HR & BP to ↑ Cardiac Output
  - fatigue
  - splenomegaly
- Triggers: (all generate oxidants - ROS)
  - Infections → Macrophages generate free radicals
  - Fava Beans → Contain oxidants → Favism in People w/ G6PD deficiency
  - Drugs:
    - Antibiotics (e.g., sulfa)
    - Anti-malarials (primaquine, quinidine)
    - Aspirin, acetaminophen (rare)

Pyruvate kinase deficiency can present w/ similar symptoms as G6PD deficiency, however would see ↑ [lactate] → lactic acidosis which is possible in G6PD deficiency but not as much of a hallmark

↳ to distinguish between PK deficiency & G6PD deficiency, look @ [lactate]

TCA Cycle

↑ATP
↑Acetyl-CoA
↑NADH
→ PDH

Ketones ← Acetyl-CoA ← Pyruvate

↓glycolysis ← ↓PFK-1

↑FA synthesis ← ↑Acetyl-CoA Carboxylase
- by inhibits citrate synthase
→ ↑OAA → ↑Acetyl-CoA
PEPCK → → Glucose
↑ Gluconeogenesis

Glucose ← Amino Acids ← Oxaloacetate

H_2O → CoA → Citrate Synthase → Citrate

Fluoroacetate (rat poison) → Aconitase → Citrate

Citrate → Isocitrate

↑ATP → ↓ Isocitrate dehydrogenase
↑ADP → ↑ Isocitrate dehydrogenase

NAD+ → Isocitrate dehydrogenase → NADH, H+ + CO_2

↑NADH → ↓ Isocitrate dehydrogenase

↑Ca^{2+} (Skeletal muscle) → ↑ Isocitrate dehydrogenase

Isocitrate dehydrogenase → α-Ketoglutarate

α-Ketoglutarate → α-KG dehydrogenase

* TLC For Nancy
- Thiamine (B_1)
- Lipoic Acid
- Pantothenic Acid (B_5) (CoA)
- FADH2 - Riboflavin (B_2)
- NAD+ - Niacin (B_3)

α-KG dehydrogenase ← NADH, CoA
→ NADH, H+, CO_2

Oxaloacetate ← NADH, H+ ← Malate Dehydrogenase ← NAD+
* Niacin (B_3)

Malate Dehydrogenase → rxn usually favors formation of Malate (very low driving force for conversion to OAA UNTIL Citrate Synthase stimulated → ↓OAA → drives Malate dehydrogenase forward → forward OAA production

Malate ⇄ Fumarate
H_2O ↑ Fumarase * Riboflavin (B_2)

Malate ⇄ Pyruvate
NAD+ ↑ NADH
Malic enzyme (cytosolic only)

Fumarate ← -Urea cycle
- Purine Synthesis (IMP)
- Phe & Tyr metabolism

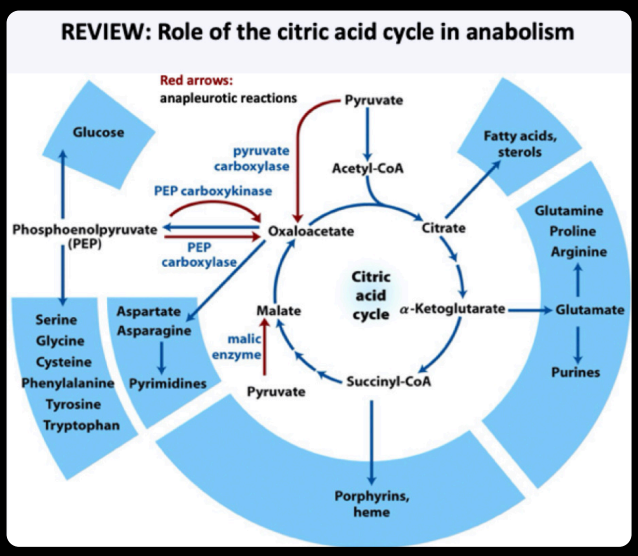
Fumarate → Succinate
Succinate dehydrogenase (complex II)
$FADH_2$ ↑ FAD

Succinate → Succinyl-CoA
Succinyl-CoA Synthetase
GDP, P_i → GTP, CoA

Succinyl-CoA → Heme Synthesis

Odd chain FA's
Branched chain AA's
→ Methyl Malonyl CoA → Succinyl-CoA

* Both CO_2 molecules released from 1 turn of cycle originated from 2 carbonyl groups of oxaloacetate

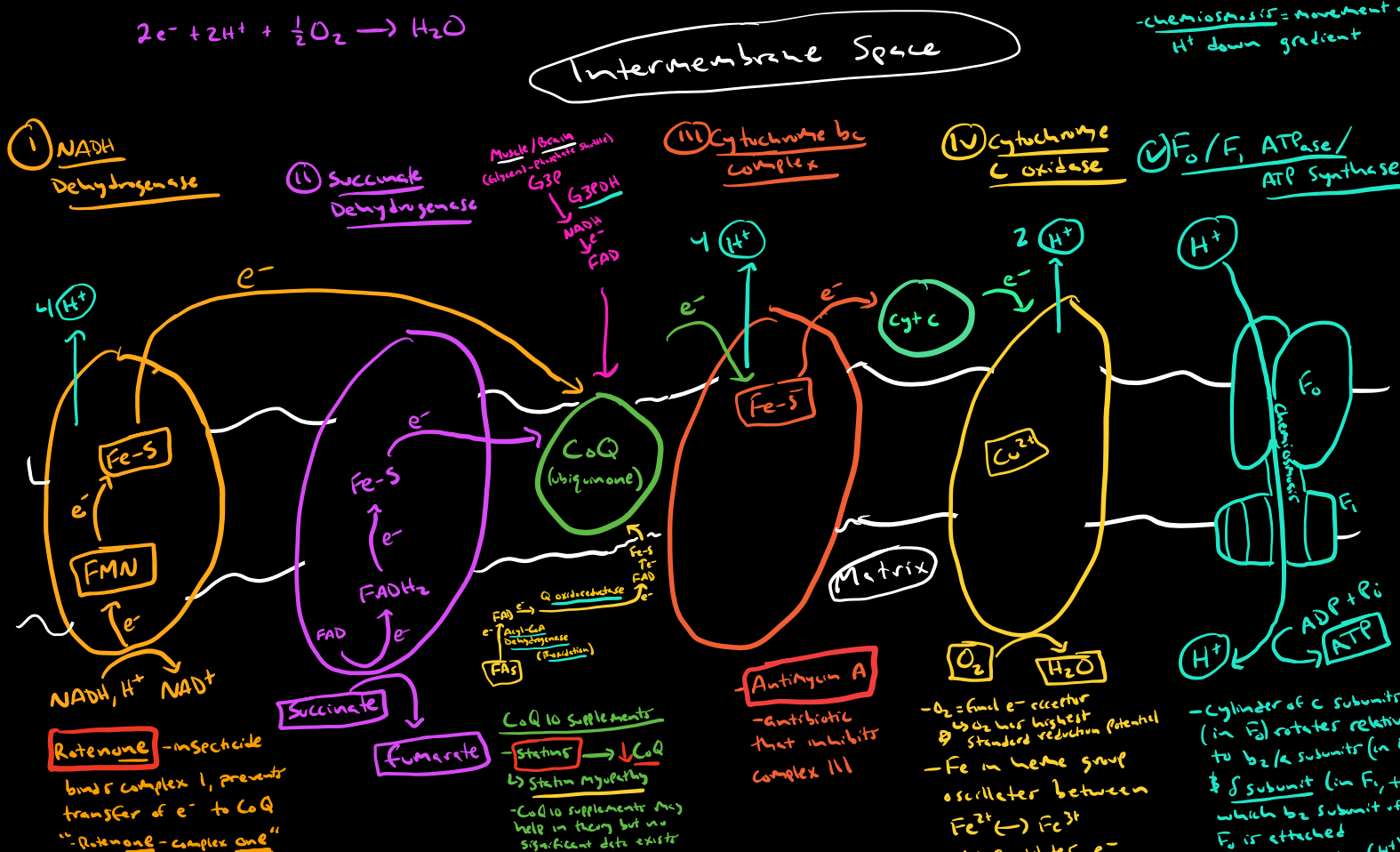


Electron Transport Chain

- extract e^-'s from NADH & $FADH_2$ → transfer to O_2 → generate/capture energy
  - NADH → $NAD^+ + H^+ + 2e^-$ → 2.5 ATP
  - $FADH_2$ → $FAD + 2H^+ + 2e^-$ → 1.5 ATP
  - $2e^- + 2H^+ + \frac{1}{2}O_2 \rightarrow H_2O$

Complex V converts proton charge gradient → ATP
- "electrochemical gradient"
- "proton motive force"

-chemiosmosis = movement of H^+ down gradient



Rotenone - insecticide
- binds complex I, prevents transfer of e^- to CoQ
- "-Rotenone - complex one"

CoQ 10 Supplements
- Statins → ↓CoQ
  - ↳ Statin Myopathy
- CoQ 10 supplements may help in theory but no significant data exists

Antimycin A
- antibiotic that inhibits complex III

- O_2 = final e^- acceptor
  - ↳ O_2 has highest Standard reduction Potential
- Fe in heme group oscillates between $Fe^{2+} \leftrightarrow Fe^{3+}$
  - ↳ facilitates e^- movement

- **CN⁻** - binds Fe^{3+}
  - ↳ inhibits IV
  - part of nitroprusside
  - ↳ ↑ risk CN poisoning
- **CO** - binds Fe^{2+}
  - ↳ inhibits IV & Hb in RBC's

- F_o = Chemiosmosis
- Cylinder of c subunits (in F_o) rotates relative to b_2/a subunits (in F_o)
  - & δ subunit (in F_1, to which b_2 subunit of F_o is attached
  - ↳ For each proton (H^+) passing through, assembly rotates by 1 c subunit
- γ subunit acts as shaft

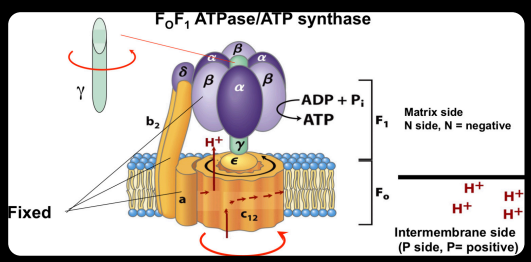
Oligomycin A
- macrolide antibiotic
- inhibits ATP Synthase
  - ↳ traps protons in intermembrane space
  - ↳ ATP cannot be produced

Cytochrome Proteins

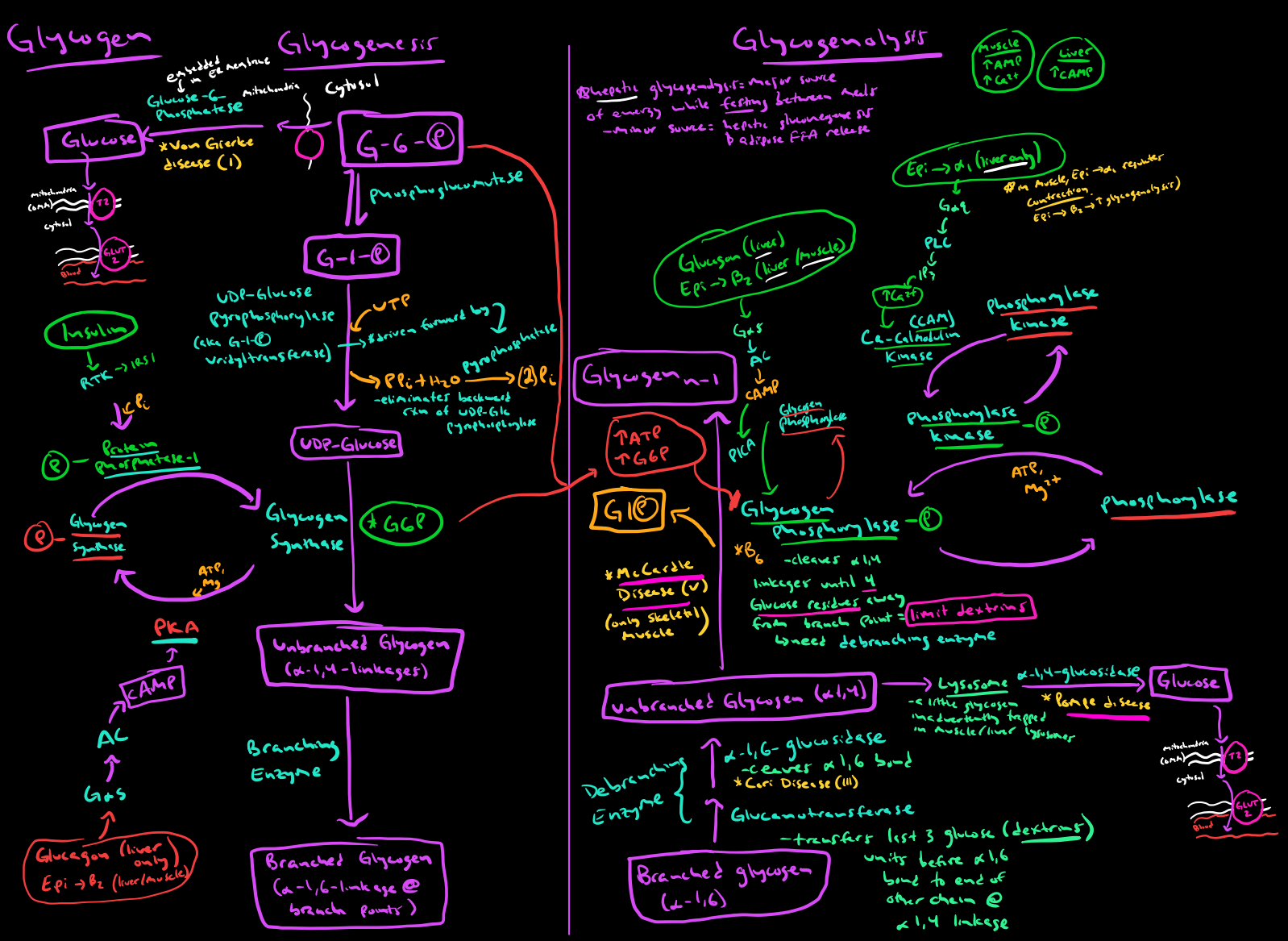
- contain heme
  - heme = porphyrin ring + Fe
    - in Hb: Fe^{2+}
    - cytochromes: $Fe^{2+} \leftrightarrow Fe^{3+}$
      - oscillation of oxidation state facilitates e^- movement
- Cytochromes in e^- transport:
  - a, b, c
- Cyt P450 - drug metabolism

- **Carbon Monoxide (CO)** - ↑ affinity for Fe^{2+}
  - ↳ inhibits both IV & Hb in RBC's

- **Cyanide (CN^-)** - ↑ affinity for Fe^{3+}
  - ↳ inhibits Cyt. c oxidase (IV) but not Hb in RBC's
  - headache, confusion, initial tachycardia, HTN, initial tachypnea
  - bright red venous blood b/c less TO_2 content b/c not extracted b/c electron transport inhibited by CO
  - Almond smell
  - Anaerobic metabolism → lactic acidosis
- **Nitroprusside** - anti hypertensive
  - contains CN^- side groups in molecular structure
    - ↳ ↑ risk for CN^- toxicity
- Tx: Nitrite - oxidizes Fe in Hb from $Fe^{2+} \rightarrow Fe^{3+}$ = Methemoglobin
  - ↳ CN^- dissociates from IV → binds to Fe^{3+} in Met Hb → aerobic metabolism can continue
  - ↳ causes Methemoglobinemia = chocolate-colored blood



Uncoupling Agents → ↑O_2 consumption b/c ↓ATP drives Metabolic rxns forward → ↑ NADH & $FADH_2$ produced → ↑ delivery to O_2, however ATP won't be generated
- Shuttle H^+ across inner membrane by ↑ permeability to H^+
  - ↳ destroys H^+ gradient → ↓ATP
  - ↳ heat produced as byproduct of uncoupled rxns
- Aspirin
- 2,4-Dinitrophenol (2,4 DNP)
- Brown Fat - newborns & hibernating animals
  - Uncoupling protein 1 (UCP-1, thermogenin)
  - SNS stimulation (NE → β-receptors → lipolysis
  - Electron transport → heat (not ATP)



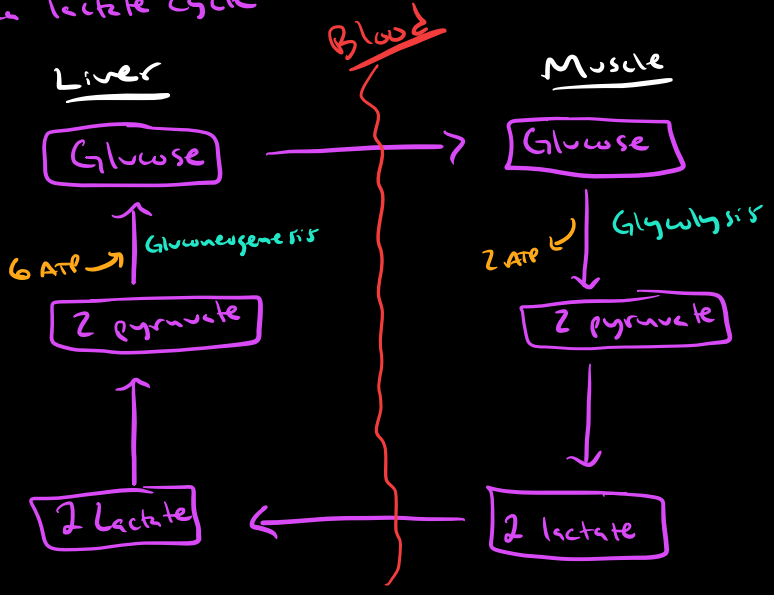
Glycogen Storage Disease

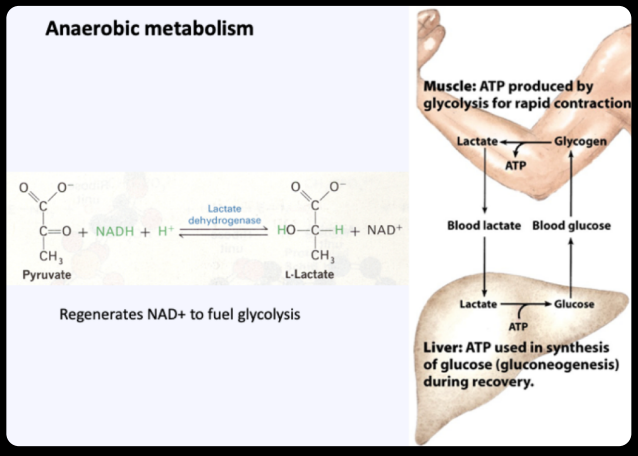
Disease (GSD)	Enzyme	Findings	Mnemonics
Von Gierke disease (type I)	Glucose-6-phosphatase	• Liver cannot release glucose into blood → hypoglycemia • Accumulation of hepatic glycogen → hepatomegaly • Cori cycle defective → lactic acidosis	"Gierke breaks Gluconeogenesis"
Pompe disease (type II)	α-1,4-glucosidase (acid α-glucosidase)	• Lysosomal accumulation of glycogen in liver and muscle → cardiomegaly, hepatomegaly, and hypotonia. • Gluconeogenesis and glycogenolysis mostly normal → normal blood glucose levels	Pump=heart "PomPe breaks the PumP" 4 P's= α-1,4-glucosidase
Cori disease (type III)	α-1,6-glucosidase	• Glycogen accumulation → hepatomegaly and hypotonia • ↓ glycogen mobilization → hypoglycemia → ↑ compensation via gluconeogenesis (i.e. fat metabolism) → ketoacidosis	"Cori breaks the Corner"
McArdle disease (type V)	Glycogen phosphorylase (only skeletal Muscle)	• ↓ glycogen breakdown → ↓ ATP → muscle cramps, muscle weakness, exercise intolerance, and rhabdomyolysis • Liver unaffected → normal blood glucose levels	"McArdle breaks the Muscle"

- avoid fructose & galactose
- ↑ liver glycogen visible on biopsy using PAS stain
= only GSD that damages heart
- ketoacidosis = unique to Cori disease

Cori Cycle

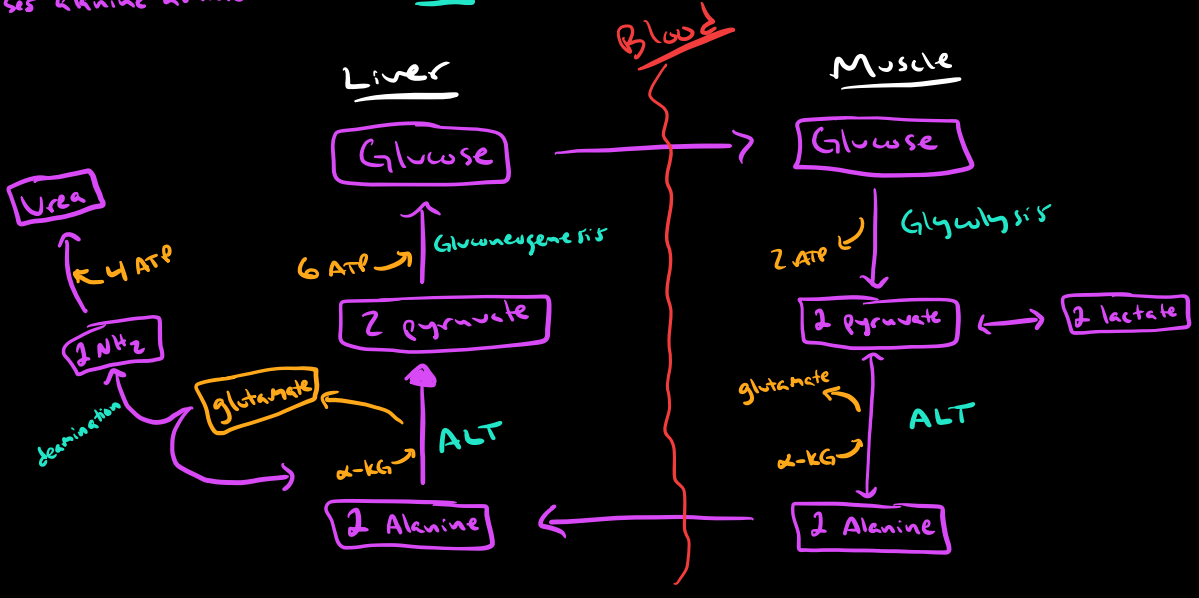
- aka lactate cycle





Alanine Cycle

- aka Cahill cycle
- during extended fasting, skeletal muscle degraded as energy source
  - alanine = major AA present in muscle degradation
  - by eliminates nitrogen as waste via urea cycle while ATP regenerated for muscle energy
- uses alanine aminotransferase (ALT)



Lactose / Galactose Metabolism

Lactose

Lactase (β-galactosidase) → glucose + galactose

Aldose Reductase: galactose → galactitol (NADPH → NADP+)

Galactose Dehydrogenase: galactose → galactonate (NAD+ → NADH, H+)

Galactitol: membrane impermeable → ↑galactitol → ↑osmolarity → osmotic damage (in lens of eye) → Cataracts / cerebral edema

UDP-glucose

- used for glycosylation of proteins & lipids (e.g., proteoglycans, glycoproteins, glycolipids)
- same role as glycogenesis

Galactose → (SGLT-1 = Na+-dependent transporter) → galactokinase (Mg2+, ATP → ADP) → galactose-1-P

*Type II galactosemia → ↑[galactose] in blood & urine
- Milder than type I b/c not depleting liver [ATP] stores → can still perform gluconeogenesis & glycogen breakdown
↳ ↑[galactose] → ↑galactitol → Cataracts

Galactose → Xylose → (Fructokinase) → Xylulose-1-P → DHAP + Glyceraldehyde (Aldolase)

Glyceraldehyde → (Aldehyde Dehydrogenase) → glycolate → (glycolate oxidase) → glycoxylate → (Lactate Dehydrogenase) → Oxylate → (Ca^{2+}) → Ca^{2+}-oxylate → Kidney Stones

Glucose-1-P → (UDP-glucose Pyrophosphorylase = aka G-1-P uridyltransferase; UTP → PPi + H2O; 2Pi ← Pyrophosphatase) → UDP-glucose

UDP-galactose 4-epimerase: UDP-glucose ⇄ UDP-galactose

Galactose-1-P + UDP-glucose → (GALT = galactose-1-P uridyltransferase) → glucose-1-P + UDP-galactose

*Type I galactosemia

UDP-galactose → Biosynthesis of Glycoconjugates:
- galactoproteins
- galactolipids
- Mucopolysaccharides

Glucose-1-P → (UDP-glucose Pyrophosphorylase; UTP → PPi + H2O → 2Pi Pyrophosphatase) → UDP-glucose → UDP-glucuronate

Phosphoglucomutase: Glucose-1-P ⇄ Glucose-6-P ⇄ Gal-1-P

Glucose-6-P → glycolysis

Gal-1-P → (GGPase) → Glucose

Gal-1-P → (GGP Dehydrogenase; NADP+ → NADPH) → 6-Phospho-gluconolactone → Pentose Phosphate Pathway / HMP shunt

Heme degradation → Unconjugated Bilirubin

Bilirubin glucuronyl transferase (UDP-glucuronate → UDP): Bilirubin → Bilirubin monoglucuronide → Bilirubin diglucuronide = conjugated (water soluble) → excretion

↑Bilirubin → kernicterus (accumulation of bilirubin in basal ganglia, pons, & cerebellum), potentially fatal. Jaundice

- Unconjugated bilirubin = hydrophobic → can cross BBB
- treat w/ blue light phototherapy → oxidation → conjugation

Type I Galactosemia

- aka classic galactosemia
- defective GALT (remember, ALT = liver enzyme, type I causes liver damage)
- ↑[Gal-1-P] → ties up P supply in liver
  ↳↓ gluconeogenesis & glycogen breakdown (just like w/ hereditary fructose intolerance)
- ↑ risk of E. Coli sepsis

Both Type I & II Galactosemias

① ↑[galactose] → ↑[galactitol] (via polyol pathway) → Cataracts in eye

② ↓ glucose from galactose → ↓ glycosylation of proteins & lipids
↳↓ glycosylation of glycosphingolipids (important part of myelin sheath) → impaired signal conduction down axon → cognitive impairment, ataxia, tremors, abnormal gait/coordination, speech/language problems
↳↓ glycosylation of gonadotropins & gonadotropin receptors

Galactokinase deficiency (type II) is kinder (more benign) than classic galactosemia (type I)

Fructose Metabolism

- Enters enterocyte in intestine via facilitated diffusion through GLUT-5
- Leaves enterocyte via GLUT-2
- Fructose found in sucrose (glucose + fructose)

FAB GUT
↳ Fructose is to Aldolase B as Galactose is to UridylTransferase

Essential Fructosuria

- deficient fructokinase
  ↳ Fructose excreted in urine b/c not taken up by hepatocytes
- benign condition

Fructose --(very small amount hexokinase, ATP)--> F-6-P → glycolysis (going through ↑ therefore limited by PFK-1) - useful for pt's deficient in other fructose metabolic enzymes

Fructose --(ATP, Fructokinase (liver))--> F-1-P
*Essential Fructosuria

F-1-P → Glyceraldehyde (Aldolase B *Hereditary Fructose Intolerance) + DHAP
Glyceraldehyde --(NAD+ → NADH)--> Glycerol
Glyceraldehyde --(Triose Kinase)--> GAP
DHAP ⇄ GAP (Triose Phosphate Isomerase)
GAP → Glycolysis

*B/c enters glycolytic pathway after PFK step (not counting small amount that can go through hexokinase) → PFK has no rate-limiting effect on Fructose metabolism
↳ Fructose metabolized much faster than glucose or galactose

Hereditary Fructose Intolerance

- deficient aldolase B
  ↳ ↑ accumulation of F-1-P in liver
    ↳ ↓ [ATP] in liver b/c uses to convert fructose → F-1-P but then not metabolized any further for ATP regeneration
      ↳ not enough ATP around to perform other liver functions
        ↳ ↓ gluconeogenesis
        ↓ glycogen breakdown

⇒ ↑ [F-1-P] → ↓ [ATP]
- ↓ gluconeogenesis → Hypoglycemia/Vomiting (especially after meals w/ ↑ fructose)
- ↓ glycogen breakdown → hepatomegaly → Liver failure

- Classic presentation:
  - baby just weaned from breast milk
  - Failure to thrive
  - Hypoglycemia → seizures
  - Enlarged liver
- Tx: avoid fructose, sucrose, Sorbitol (polyol pathway)

Polyol Pathway - Glucose → Fructose

- alternative pathway for glucose metabolism (instead of glycolysis) used by some cells
- In diabetics w/ ↑ [Glucose] → ↑ accumulation [Sorbitol]
  ↳ responsible for some complications of diabetes

Glucose --(NADPH → NADP+, Aldose Reductase)--> Sorbitol
Galactose --(Aldose Reductase)--> Galactitol
Sorbitol --(NAD+ → NADH, Sorbitol Dehydrogenase)--> Fructose

- Polyol pathway also used for galactose → galactitol
  ↳ ↑ [galactitol] can cause cataracts just like ↑ sorbitol can cause cataracts (e.g., in diabetics)

Copper Reduction Test

- non-specific → detects any reducing sugar present (e.g., fructose, glucose, galactose)

Fatty Acid Synthesis

- occurs primarily in liver, mammary glands, & small amount in adipose tissue
- stored as triglyceride in adipocytes
- during ↑energy states, ↑[ATP] & ↑[NADH]
  inhibit isocitrate dehydrogenase → ↑[citrate]
  → up-regulates ↑Acetyl-CoA carboxylase (ACC) activity (requires biotin - B_7) → ↑ FA synthesis
- Malonyl-CoA synthesized during FA synthesis
  → inhibits FA catabolism via inhibition of carnitine acyl-transferase I (CAT I)
- NADPH produced from HMP shunt necessary

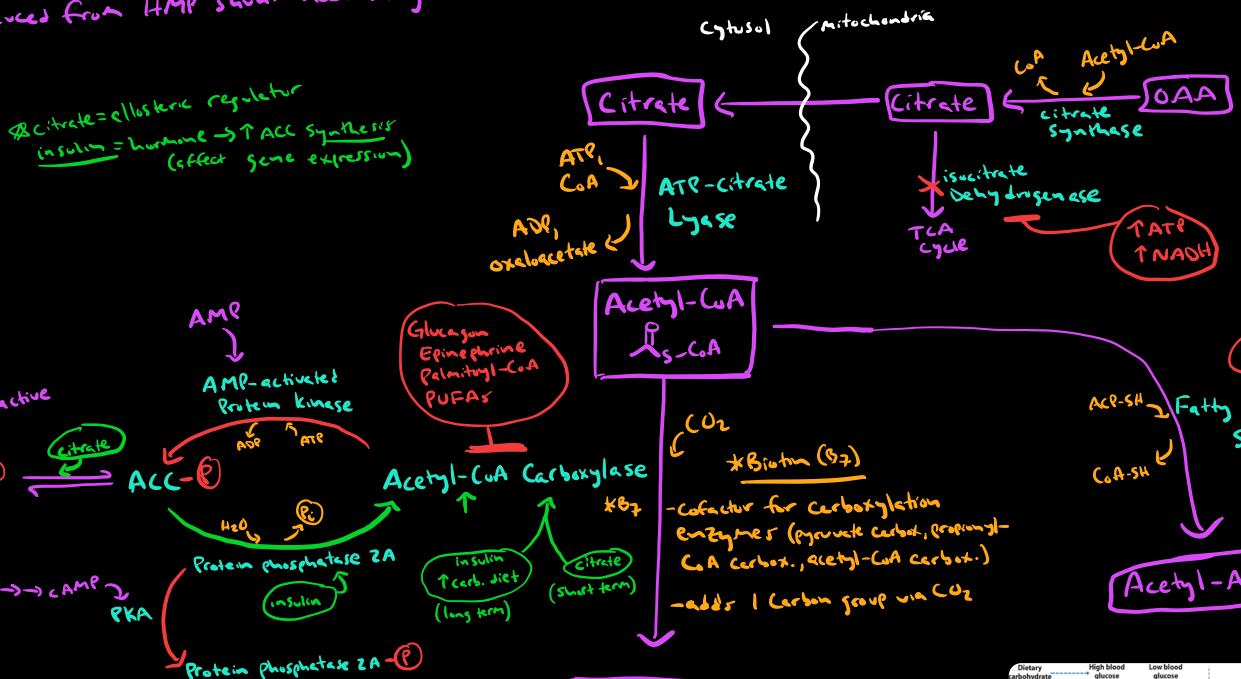
*citrate = allosteric regulator
insulin = hormone → ↑ ACC synthesis (effect gene expression)

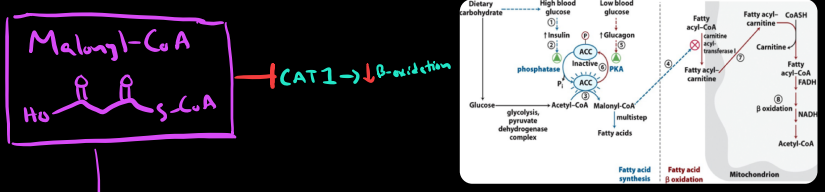
Biosynthesis of Unsaturated FAs

Saturated Fatty Acyl-CoA —(O_2, 2 H^+ → 2 H_2O)→ Monounsaturated Fatty Acyl-CoA
Fatty Acyl-CoA desaturase (PUFA)

(2) Cyt. b_5 (Fe^{2+}) ⇄ (2) Cyt. b_5 (Fe^{3+}) — Endoplasmic Reticulum

NADPH, H^+ → NADP+ → Cyt. b_5 reductase → FADH2 → Cyt. b_5 reductase → FAD





Malonyl-CoA
Malonyl CoA-ACP Transacylase (ACP-SH → CoA-SH)
Malonyl-ACP
β-ketoacyl-ACP Synthase (S-acetyl → CO_2)
Acetoacetyl-ACP
β-ketoacyl-ACP Reductase (NADPH, H^+ → NADP+)
D-β-hydroxybutyryl-ACP
β-hydroxyacetyl-ACP dehydratase (↓H_2O)
Crotonyl-ACP
Enoyl-ACP Reductase (NADPH, H^+ → NADP+)
Butyryl-ACP
Malonyl-ACP (x6)
Palmitoyl-ACP (16-C)
Thioesterase (ACP-SH)
Fatty Acid (Palmitate, 16-C)

*Biosynthesis of Palmitoyl-ACP requires:
8 acetyl CoA
8 Malonyl CoA
14 NADPH

PUFAs ⊣ reductase

Fatty Acid Synthase Complex
= Reductive Biosynthesis
Bc NADPH used to reduce intermediates to synthesize FA

NADPH, H^+ → NADP+ (reductase)
NADPH, H^+ → NADP+ (reductase)

Regulation

- omega-3 PUFAs (EPA & DHA) bind LXR (nuclear receptor txn factor) → binds SREP-1c (sterol regulator element binding Protein) ⊣ txn of lipogenic enzymes:
  ↓Acetyl CoA carboxylase
  ↓Fatty Acid Synthase
  ↓Stearoyl CoA (acetyl CoA?) desaturase

- Palmitate can be modified to other FA's
- Stored as triacylglycerols in adipose tissue

Triacylglyceride (TAG) Synthesis

- Formed from 1 Fatty Acyl CoA + 2 Glycerol-3-Phosphates ($G3P_s$)

① Glycerol 3 phosphate from glucose, glycerol, or pyruvate (glyceroneogenesis)

- ✱ Glyceroneogenesis converts Pyruvate → DHAP
  - during lipolysis (stimulated by glucagon or epinephrine) → glycolysis inhibited
    - ↳ need alternate source of DHAP ✱ explains why adipose cells have pyruvate carboxylase & PEPCK even though they do not perform gluconeogenesis
  - **Liver** – has glycerol kinase → uses glycerol
  - **Adipose** – no glycerol kinase → gets G3P from DHAP

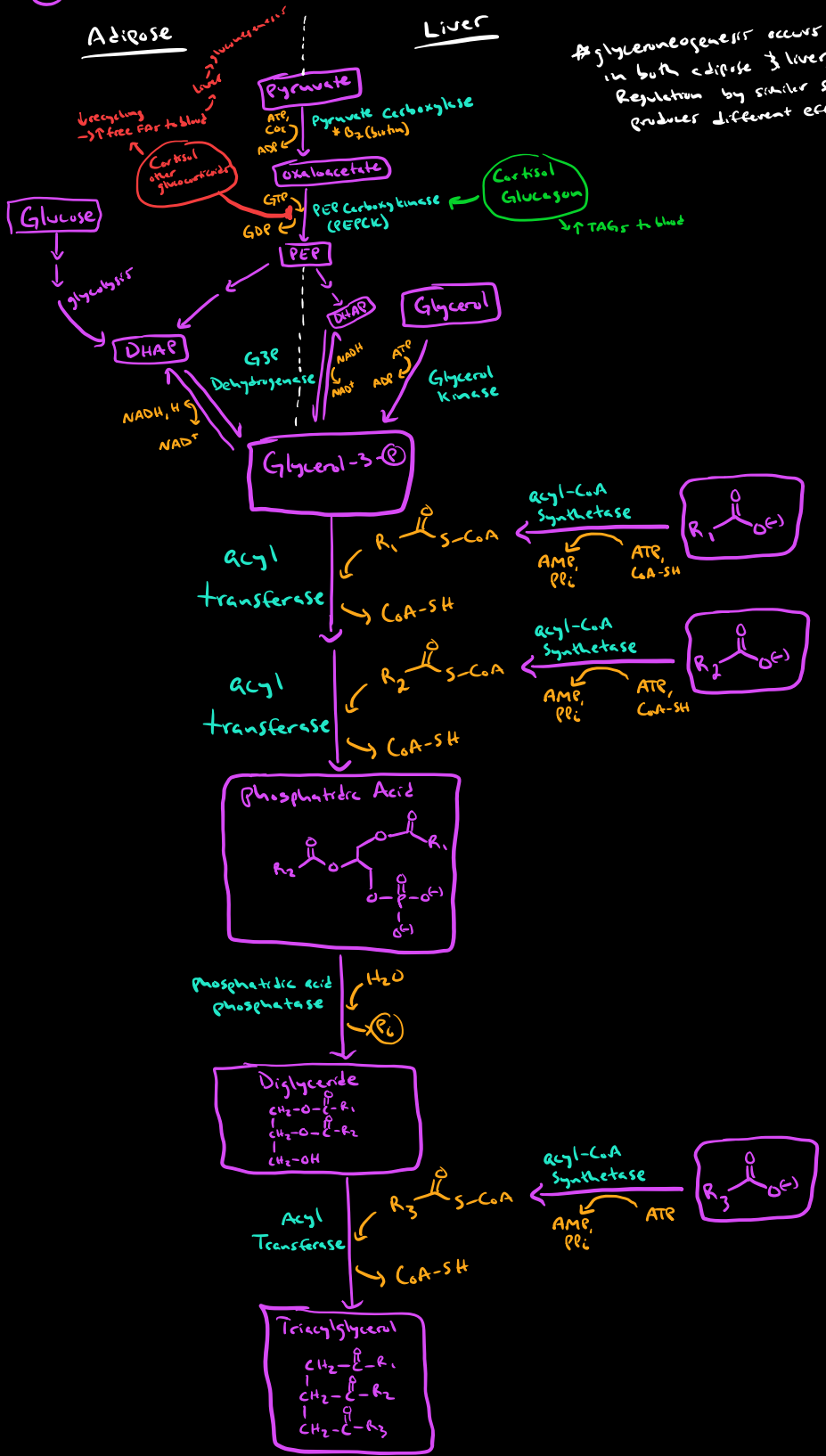
② Addition of 2 FA's to GAP (acyl transferase (x2)) → Phosphatidic Acid

③ Hydrolysis of phosphatidic acid (Phosphatidic acid phosphatase) → diglyceride

④ Addition of 1 FA to diglyceride (acyl transferase) → TAG

✱ 75% of free FAs generated from lipolysis are re-esterified to form TAGs rather than be used for fuel (via β-oxidation)
- some recycling in adipose
- some free FAs from adipose transported into liver → remade into TAG → redeposited in adipose

✱ The total # of free FAs in flux may vary, but % recycled ALWAYS remains @ 75% (unless pharmacological intervention like thiazolidinediones)



✱ glyceroneogenesis occurs in both adipose & liver, however, Regulation by similar substances produces different effects

Regulation by Polyunsaturated Fatty Acids (PUFA)

- many PUFAs exist that regulate lipid metabolism
  - ↳ ↓ lipogenesis
  - ↳ ↑ lipolysis
- e.g., omega-3 PUFAs:
  - eicosapentaenoic acid (EPA)
  - docosahexaenoic acid (DHA)

- EPA & DHA bind nuclear receptor transcription factors:
  - ↳ LXR
  - HNF-4α
  - FXR
  - PPARs

↳ steral regulator element binding protein (SREP-1)
= hepatic txn factor that regulates txn of lipogenic enzymes:
- ↓ Acetyl-CoA Carboxylase
- ↓ Fatty Acid Synthase
- ↓ Acyl CoA desaturase

↳ SREP-1 regulated by LXR receptor, which is regulated by PUFAs

- PUFAs ↑ txn of genes in FA catabolism:
  - ↑ acetyl-CoA synthetase
  - ↑ Carnitine palmityl transferase I (CAT I)
  - ↑ Uncoupling protein 1 (UCP-1)

Fatty Acid Catabolism: β-oxidation

- lipids from diet → degraded into free FAs
  - ↳ Enterocytes convert free FAs → triacylglycerides (TAGs)
  - ↳ TAG's travel in plasma in chylomicrons (lipoprotein)
  - ↳ reach target tissue → degraded back to FA's via lipoprotein lipase found on endothelial surfaces of capillaries (abundant in adipocytes & muscle tissue)
- FA's can be transported via albumin (after release by tissue lipases)
- occurs in muscle, liver, & other tissues w/ mitochondria
  - does not occur in:
    - brain - must rely on glucose & ketones
    - RBCs - no mitochondria
- Triglycerides (triacylglycerol; TAG) stored in adipocytes
  - Hormone-Sensitive lipase (HSL) metabolizes TAG → FA + glycerol (→ liver)
    - activated by glucagon, catecholamines (epi), ACTH
    - inhibited by insulin
- ① FA → Fatty acyl CoA via Long-chain fatty acyl CoA synthetase
- ② Transport Fatty acyl CoA into mitochondria using Carnitine shuttle
  - Carnitine acyltransferase (CAT), aka Carnitine palmitoyl transferase (CPT)
- ③ β-oxidation, each cycle:
- 2 carbons cleaved from FA → $FADH_2$, NADH, Acetyl-CoA
- Acyl-CoA dehydrogenase
  - adds double bond between α & β carbons
  - Family of 4 enzymes - use based on FA-length
    - Short (2-6 C) } Diffusion
    - Medium (6-12 C) } Diffusion → Mitochondria
    - long (12-20 C) → Carnitine
    - very long (>20 C) → ATP Binding Cassette (ABC) → Peroxisome

β-oxidation disorders → hypoketotic hypoglycemia
- ↓ β-oxidation → ↓ ketones (hypoketosis)
- ↓ tissue overuse glucose → hypoglycemia
- seen in both MCAD & Carnitine Deficiency

Odd # chain FA's

- β-oxidation until 3 carbons left = propionyl CoA

- odd chain FA's
- cholesterol
- AA's:
  - Ile
  - Val
  - Thr
  - Met

→ Propionyl CoA

CO_2, ATP → Propionyl CoA Carboxylase (*Biotin)

ADP, P_i →

→ Methylmalonyl-CoA

Methylmalonyl CoA Mutase

*Cobalamin (B_{12}) - only synthesized by microorganisms, not plants or animals. Must consume. Intrinsic Factor secreted by stomach binds cobalamin in intestine.

→ Succinyl-CoA → TCA cycle / gluconeogenesis

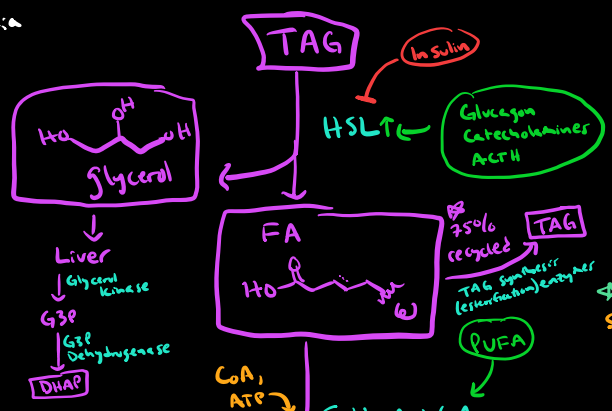
↳ even-chains give only acetyl CoA which can be used in TCA cycle for energy and also used to ↑ activity of pyruvate carboxylase in gluconeogenesis, but not directly used as a substrate to synthesize glucose

*Methylmalonic acidemia

*Pernicious Anemia
- intrinsic factor deficiency
→ impaired cobalamin absorption

Methylmalonic acidemia

- deficiency in methylmalonyl mutase
  - ↳ ↑ [methylmalonyl CoA] → dissociates → ↑ [methylmalonic acid] in blood = methylmalonic acidosis
  - ↳ can cause anion gap metabolic acidosis
  - ↳ CNS dysfunction
- often fatal early in life



Carnitine

- found in nature, consume in diet
- also synthesized by lysine & Methionine
  - *only liver can synthesize de novo
  - ↳ muscle & heart depend on diet or other tissues

- Carnitine Deficiencies
  - many 2° causes:
    - Malnutrition
    - Liver disease
    - ↑ requirements (trauma, burns, pregnant)
    - Hemodialysis (↓ synthesis, loss through membranes)
  - Major consequence = inability to transport long chain FAs (LCFA) into mitochondria → ↑ accumulation of LCFAs in cells
    - ↳ ↓ serum [carnitine] & [acyl carnitine]
  - Symptoms:
    - muscle weakness (esp. w/ exercise)
    - Cardiomyopathy
    - *Hypoketotic Hypoglycemia when fasting (when using FAs & glucose from gluconeogenesis)
      - ↳ Cannot metabolize FAs → overuse glucose (→ hypoglycemia)
      - ↳ ↓ Ketogenesis (= hypoketosis)

- Primary Systemic Carnitine Deficiency
  - rare inborn error of metabolism
  - mutation → ↓ carnitine uptake into cells due to dysfunctional carnitine transport protein
  - infantile phenotype in first 2 years related to buildup of FAs that can't be metabolized
    - encephalopathy (from ↑ NH_3 due to liver dysfunction)
    - Hepatomegaly (due to ↑ [LCFA] accumulating)
    - Hyperammonemia (from liver failure)
  - *Hypoketotic Hypoglycemia
  - *↓ serum [carnitine]: kidneys cannot reabsorb → become carnitine deficient b/c lost in urine
  - ↓ [carnitine] in muscles, liver, & heart

MCAD deficiency

- Medium chain acyl-CoA dehydrogenase deficiency
- Autosomal recessive, most common in white northern Europeans
- ↓ oxidation of 6-10 C FAs
- *Severe hypoketotic hypoglycemia during fasting b/c need to oversee glucose & ↓ FA oxidation → ↓ ketogenesis
  - ↓ [Acetyl-CoA] → ↓ gluconeogenesis b/c acetyl-CoA = substrate for pyruvate carboxylase
- *↳ ↑ dicarboxylic acids in urine

result of ↑ ω-oxidation of FA's b/c can't do β-oxidation
- ↑ [uric acid] b/c ↑ [NH_3] due to need to ↑ protein degradation for energy b/c not getting energy from MCFAs
- Hepatomegaly - due to buildup of MCFAs
- *↑ [acylcarnitine] in serum
- * breast milk is ↑ in medium-chain FAs → infants particularly susceptible → fatigue, seizures, coma, death

Tx: avoid fasting

Differentiate MCAD from 1° Systemic Carnitine deficiency based on serum [carnitine] & [acyl carnitine] & [LCFAs]

MCAD → ↑ [carnitine], normal [LCFA]

1°SCD → ↓ [carnitine], ↑ [LCFA]

Ketogenesis & Ketolysis

Ketone bodies - alternative fuel source in extra-hepatic cells

- acetoacetate, β-hydroxybutyrate, acetone
  - acetoacetate & β-hydroxybutyrate = byproduct of FA catabolism & fuel for tissues
  - acetone → exhaled by lungs → no energy gained
- Produced in mitochondria of liver
  - liver = only tissue w/ significant levels of HMG-CoA synthase
  - however, liver cannot metabolize ketone bodies further b/c no enzyme to form thio-ester w/ CoA
  - ↳ RBCs & hepatocytes cannot use ketones for energy (b/c RBCs don't have mitochondria for TCA cycle, liver is producing it for rest of body bc knows sense that it doesn't have Acetyl-CoA transferase)
- Acetoacetyl-CoA formed via
  - β-oxidation
  - reverse thiolase rxn
- Fasting/starving → ↑ FAs to liver → ↑ acetyl-CoA → ↑ [acetyl-CoA] exceeds TCA cycle capacity → acetyl-CoA shunted to ketone bodies
- ↳ Ketone synthesis upregulated during periods of intense gluconeogenesis (b/c ↓ OAA → ↑ acetyl-CoA not used in TCA cycle → shunted to ketones)
- used by muscles & heart, saves glucose for brain (which can still use ketone bodies if necessary)
- brain cannot use FAs, but reason why is unknown
- → ketone bodies allow brain to use energy from FA-catabolism indirectly

Diabetes

- ↓ insulin → ↑ FA breakdown for energy
- oxaloacetate depletion due to
  - ① ↑ Gluconeogenesis → ↓ oxaloacetate (substrate)
  - ② ↑ FA oxidation → ↑ [NADH] → drives Malate ⇌ OAA in TCA cycle (NAD+ → NADH)
- ↳ ↓ OAA → ↑ [acetyl CoA] (b/c ↓ TCA)
- → ↑ ketones

Alcoholism

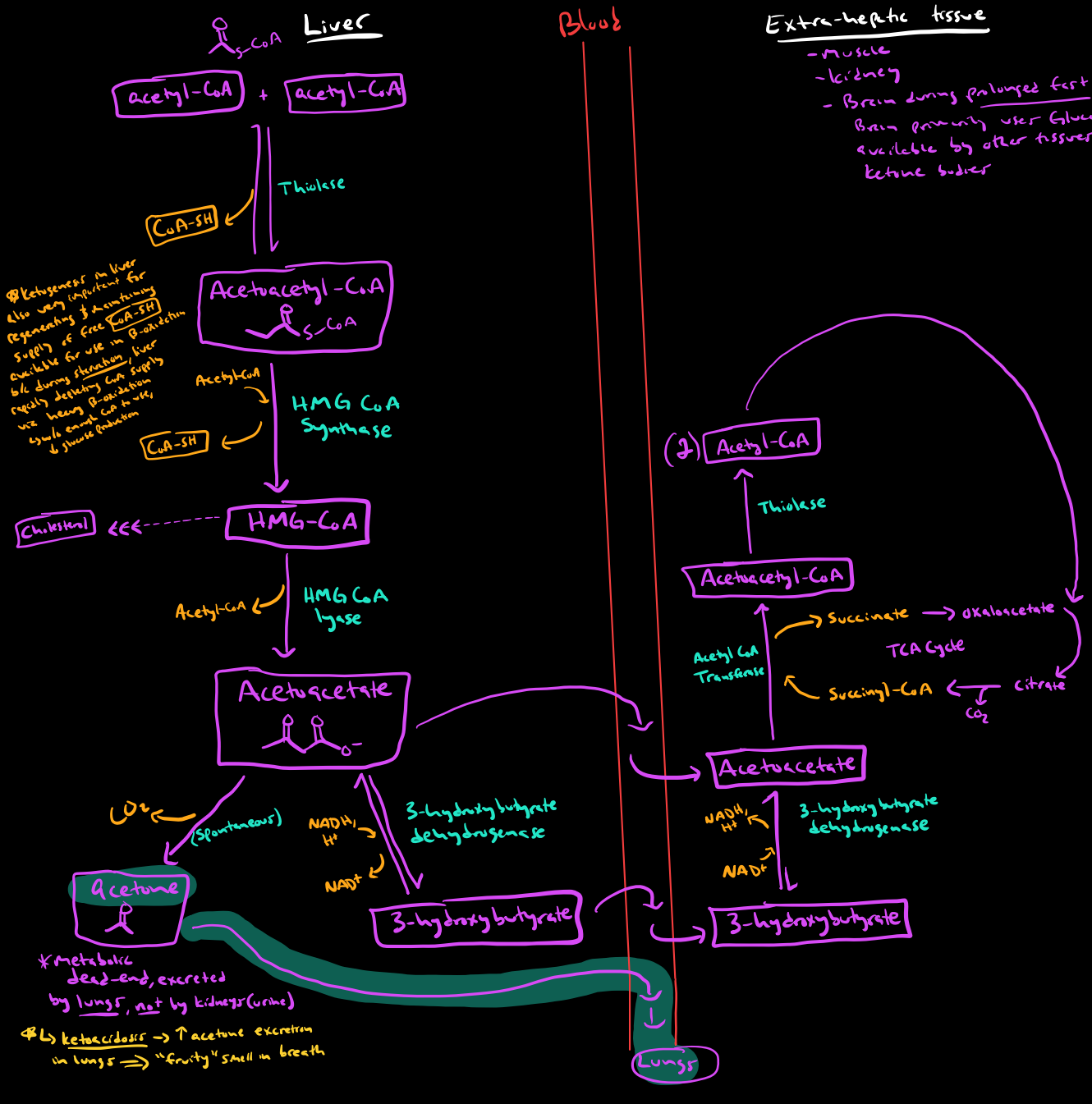
- ↑ EtOH Metabolism → ↑↑ [NADH] → OAA shunted → Malate
- ↳ Stalls TCA cycle → ↑ [acetyl-CoA] → ↑ ketones
- ↳ ↓ gluconeogenesis → hypoglycemia

Ketoacidosis

- ketone bodies have ↓ pKa ↳ release H^+ @ plasma pH
- ↳ ↑ ketones → anion-gap metabolic acidosis

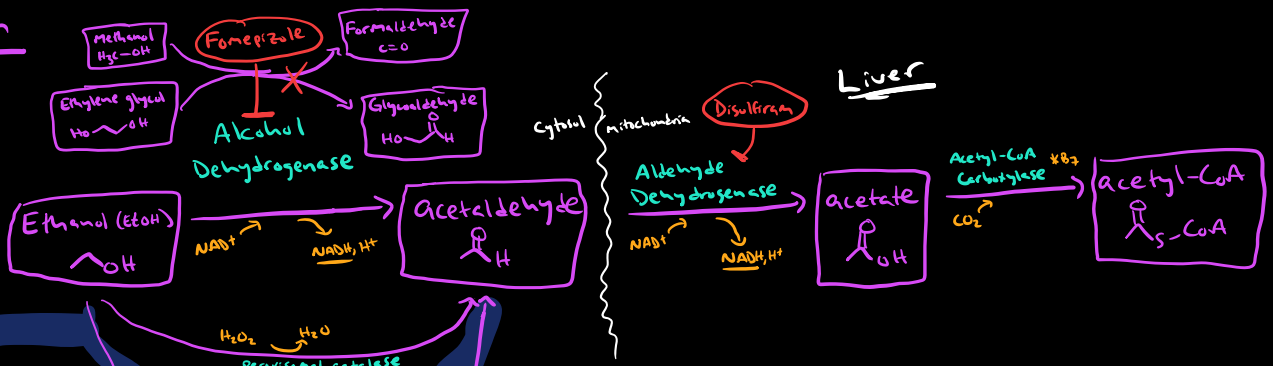
Ketone testing

- urine, usually no ketones excreted b/c any produced → utilized by body
- ↳ ketonuria = something wrong
  - Poorly controlled diabetes (insufficient insulin)
  - Diabetic Ketoacidosis
  - Prolonged Starvation
    - Present w/ extensive nausea & vomiting (malnourished)
  - Alcoholism



* Ketogenesis in liver also very important for regenerating & maintaining supply of free CoA-SH available for use in β-oxidation b/c during starvation, liver rapidly depleting CoA supply via heavy β-oxidation use, synth cannot CoA to use, ↓ glucose production

Ethanol Metabolism



Enzymes

- Alcohol Dehydrogenase
  - Zero order kinetics (constant rate)
  - Also metabolizes methanol & ethylene glycol

  - Fomepizole - inhibitor → used to treat methanol/ethylene glycol intoxication

- Aldehyde Dehydrogenase
  - Disulfiram - inhibitor → ↑acetaldehyde accumulation
    → triggers catecholamine release → sweating, palpitations, nausea, vomiting
    ↳ used to deter alcoholics from consuming alcohol
    ↳ aka antabuse

Alcohol Flushing

- EtOH consumption → skin flushing from slow metabolism of acetaldehyde
  ↳ inherited deficiency of acetaldehyde dehydrogenase 2
- Common among Asian populations
- Possible ↑ risk of esophageal & oropharyngeal cancer

Microsomal ethanol-oxidizing system (MEOS)

- alternative pathway for EtOH
  - normally metabolizes small amount of EtOH
    ↳ becomes important w/ ↑↑ EtOH consumption
- Cytochrome P450 - dependent pathway in liver
- generates acetaldehyde & acetate
- consumes NADPH & O_2
  ↳ O_2 generates free radicals ($O^{\cdot-}$, ROS)
  ↳ ↓NADPH → Glutathione cannot be regenerated → susceptible to oxidative stress

Thiamine (B_1) deficiency

- alcoholism → malabsorption & malnutrition → thiamine deficiency → ↓ activity of:
  - Pyruvate Dehydrogenase
  - α-KG Dehydrogenase
  - Transketolase
    - nucleotide & DNA synthesis (converts F6P to Ribose-5-P)
  - Branched-chain ketoacid Dehydrogenase

Chronic EtOH use → ROS formation

- ↑NADH → ↑ use of O_2 in ETC → ↑ likelihood of ROS formation
- Microsomal CYP uses O_2 → can generate ROS AND uses NADPH, ↓ Glutathione antioxidant capability
- Peroxisomes more focused on EtOH metabolism rather than combatting ROS

Acamprosate = NMDA-R inhibitor used to maintain abstinence in alcohol-dependent ptts
- "anti-craving" drug via modulation of neuronal excitability implicated in induction of alcohol dependence

↑NADH = source of problems from excessive EtOH consumption:
- CNS depressant
- Hypoglycemia
- ↑ ketones (ketosis)
- lactic acidosis
- FA accumulation
- Hyperuricemia
  ↳ Gout
- Hepatitis & Cirrhosis

→ Stalls TCA cycle → ↑NADH shunts OAA → malate
↳ ↓[OAA] → ↓ gluconeogenesis → hypoglycemia
- Glycogen = important source of glucose when fasting, esp. b/c gluconeogenesis not working
  ↳ Dangerous: - EtOH w/o eating b/c no eating → low glycogen stores
  - EtOH after running b/c running → glycogenolysis → ↓ glycogen & need ↑ glycogen to maintain appropriate blood [glucose]

↳ ↑[acetyl-CoA] → ↑ ketone body synthesis → ketosis

→ Lactic Acidosis
- EtOH metabolism → ↓[NAD+] & ↑↑EtOH overwhelms ETC → ↓NAD+ regeneration in ETC
  → pyruvate shunted to lactate to regenerate NAD+ (also ↑NADH → PDH)

→ Fatty Acid accumulation → Fatty Liver Disease
- ↑[NADH] → β-oxidation (which usually generates NADH like TCA cycle) & requires NAD+ to convert G3P → DHAP → ↓ FA breakdown + ↑TAG synthesis
- RLS in FA synthesis = Acetyl CoA carboxylase
  ↳ ↓TCA cycle → ↑[citrate] → ↑ Acetyl-CoA → Malonyl-CoA → β-oxidation
  FA synthase (NADPH, NADP+) → Palmitate
  ↳ Fatty liver - due to ↑TAGs → ↑[malate] (NADP+, NADPH) → Pyruvate (Malic Enzyme)

→ Hyperuricemia
- Uric acid & lactate excreted by proximal tubule (PT) using Uric acid transporter (URAT1)
  - URAT1 = antiporter that secretes lactic acid into urine / reabsorbs uric acid into blood
  ↳ ↑[lactate] in plasma → ↑ lactate secretion → ↑[uric acid] reabsorption → Gout attack
  ↳ acute gouty arthritis, often presents in big toe

→ Hepatitis & Cirrhosis
→ ↑[NADH] → ↓ EtOH metabolism → ↑ accumulation of [acetaldehyde]
↳ ↑[acetaldehyde] = toxic to hepatocytes
↳ acute: inflammation → Alcoholic hepatitis
chronic: scar tissue → Cirrhosis
↳ ↑MEOS pathway → ↑[acetaldehyde], ↑ROS, ↓[NADPH] → ↑ oxidative damage → hepatitis & cirrhosis