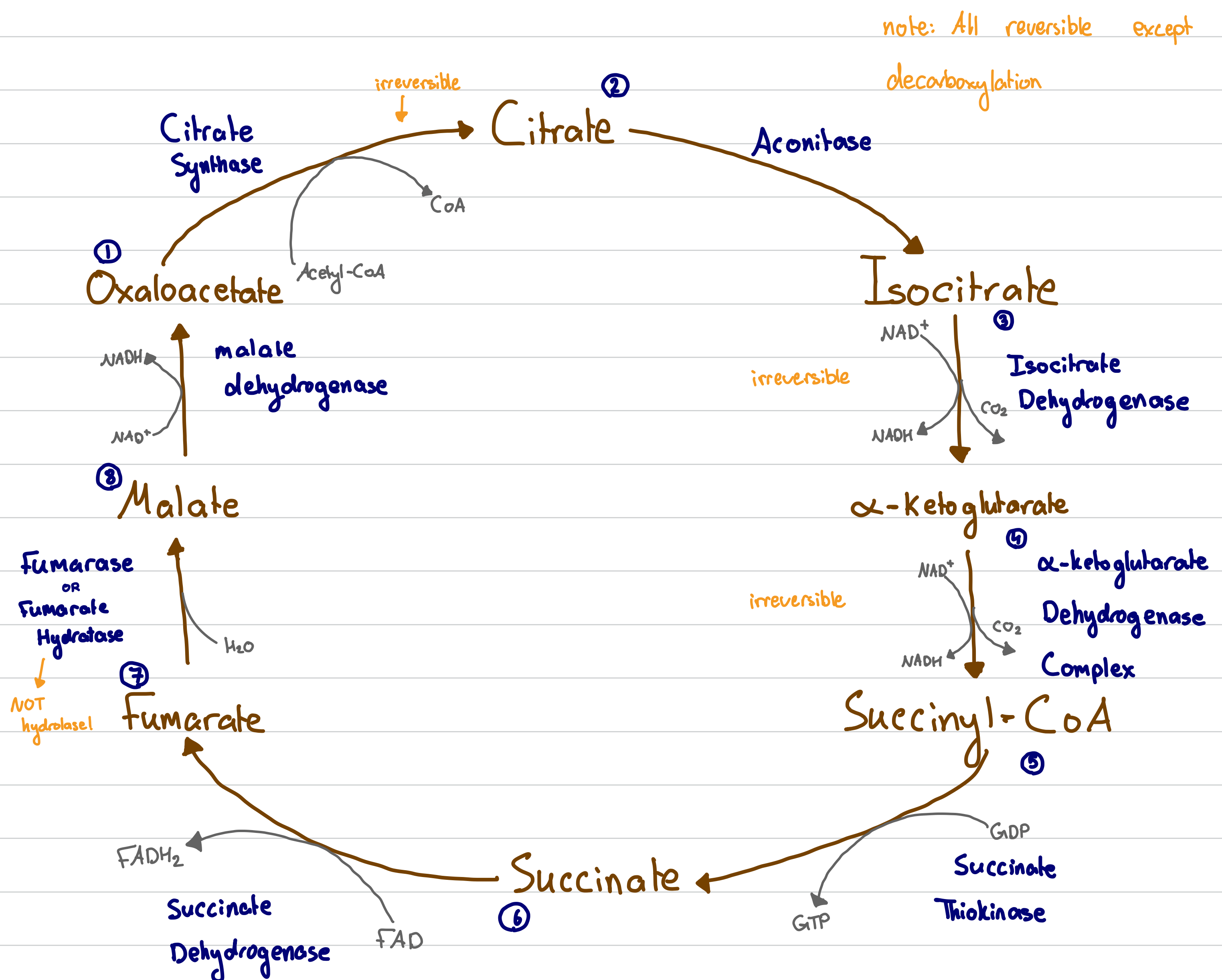
Krebs Cycle

General:

Mnemonic → Citrate Is Krebs Starting Substrate For Making Oxaloacetate

Products → 3 NADH + 1 GTP (GTP → ATP) + 1 $FADH_2$ + 2 CO_2

Total ATP = 3×(2.5) + 1×1 + 1×1.5 = 10



FAD vs NAD:

① → FAD gains e^- one by one, sequential. By different sources. form of H•

→ NAD gains pair of electrons at once by same source. form of hydride $\ddot{H}^-$

② → FAD used in succinate dehydrogenase.

→ FAD used in α-ketoglutarate dehydrogenase complex, FAD oxidized disulfide bridge in Lipoic acid in Transacylase to form $FADH_2$ then transfers electrons to NAD^+

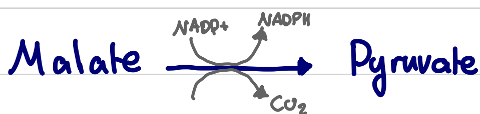
→ NAD used in most dehydrogenases. Oxidizes alcohol to ketones

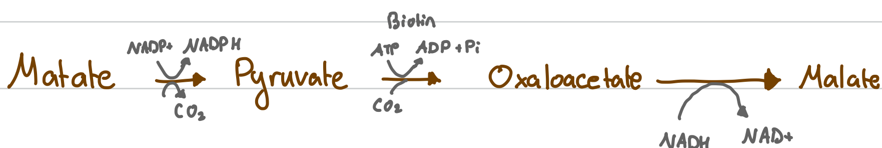
③ → Since FAD forms free radicals, it forms tight covalent bonds to enzymes. This changes the $E^\ominus$

→ NAD can be free

④ → NADH used in regulating krebs cycle, acting as inhibitor. While $FADH_2$ not used

⑤ → $NADP^+$ used to convert malate to pyruvate





Details of steps:

Step 1 :

Reaction: Oxaloacetate + Acetyl CoA ⟶ Citrate + CoASH

Enzyme: Citrate synthase

Regulation: Activation / Inhibition of enzyme

→ Activated by oxaloacetate which results in conformational shape change allowing Acetyl - CoA to bind to enzyme.

→ Inhibited by citrate

→ Inhibited by ATP allosterically

→ Inhibited by NADH

→ Inhibited by succinyl- CoA

Other regulations using citrate:

→ Inhibiting rate -limiting step of glycolysis. Inhibiting phosphofructokinase

→ In gluconeogenisis, it stimulates fructose-1,6- Bisphosphatase

→ Plays role in fatty acid synthesis

↳ Provides Acetyl CoA source

↳ Activates acetyl CoA carboxylase

↳ Inside mitochondria, fatty acid oxidized. Outside mitochondria fatty acid synthesized

↳ Citrate breaks down to Acetyl CoA + oxaloacetate. Oxaloacetate reduced to malate to cross mitochondrial membrane then oxidized again to oxaloacetate

Step 2:

Enzyme: Aconitase

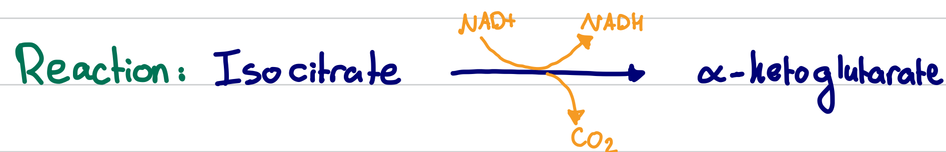
Regulation:

→ Inhibited by Fluoroacetate. Toxic, stops Krebs cycle. Non-competitive

→ Aconitase enzyme contains Fe- S clusters

→ isomerization RXN

Step 3:



Enzyme: Isocitrate dehydrogenase

Regulation:

→ Dehydration + decarboxylation.

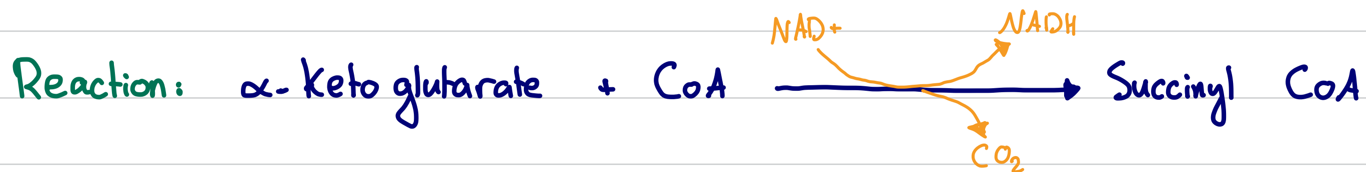
→ Rate - Limiting Step !! Best regulation

→ Inhibited by NADH
→ Inhibited by ATP

→ Activated allosterically by ADP
→ Activated allosterically by Ca^{2+}
↳ muscle -contraction ⇒ active ⇒ more ATP

} ⇒ shift to left. Lower Km. Higher affinity

Step 4:



Enzyme: α-ketoglutarate complex

Mechanism of α-keto acid dehydrogenase complexes:

→ Include α-ketoglutarate / pyruvate / branched chain keto acid DH complexes
(↳ alanine keto acid)

→ Three enzymes. 5 cofactors → Take (TPP) Loving (Lipoic acid) Care (CoA) For (FAD) Nancy (NAD). TLCFN

① Decarboxylase (E1). Cofactors: Thiamin Pyrophosphate TPP

② Trans acylase. (E2) Adds CoA and uses -S-S- to transfer H to FAD. Cofactors: Lipoic acid

③ Dehydrogenase. (E3) FAD takes H from Lipoic acid on transacylase then it transfers them to NAD+. NADH formed.

→ **Mechanism:**

1: CO_2 removed from α-KG. TPP used. Decarboxylase

2: -S-S- oxidize α-KG to form -SH + -SH. Lipoic acid used. Transacylase

3: CoA is added & Succinyl CoA released. Transacylase

4: FAD takes H from -SH & forms -S-S- again

5: FAD transfers H to NAD+ forming NADH

6: Energy conserved in NADH & thioester of CoA

Regulation:

→ Activated by Ca^{2+}

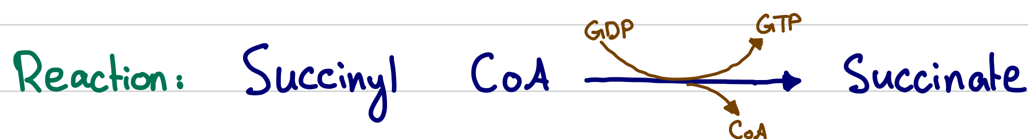
→ Inhibited by NADH

→ Inhibited by GTP

→ Inhibited by Succinyl-CoA

→ Inhibited by Arsenite. Toxic. Non-competitive

Step 5:

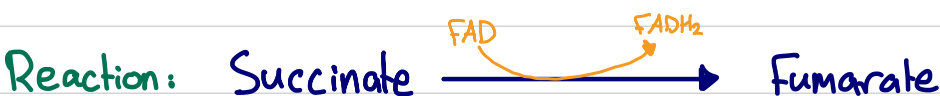


Enzyme: Succinate thiokinase

Mechanism:

* Cleavage of high energy thioester bond & using energy to add P_i to GDP via substrate level phosphorylation

Step 6:



Enzyme: Succinate Dehydrogenase

Mechanism

→ Succinate Dehydrogenase only enzyme in inner membrane in Krebs cycle

→ FAD is used rather than NAD+ because FAD gets reduced more easily than NAD+. FAD larger E° value. NAD+ not enough to oxidize succinate.

→ Succinate Dehydrogenase = Complex II of ETC

Regulation:

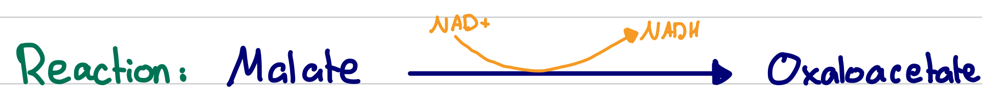
* Inhibited by Malonate. Toxic. Competitive

Step 7:

Reaction:

Enzyme: Fumarase

Step 8:

Reaction: 

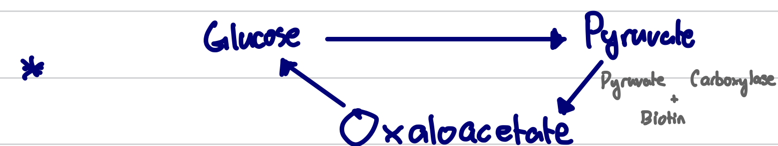
Enzyme: Malate Dehydrogenase

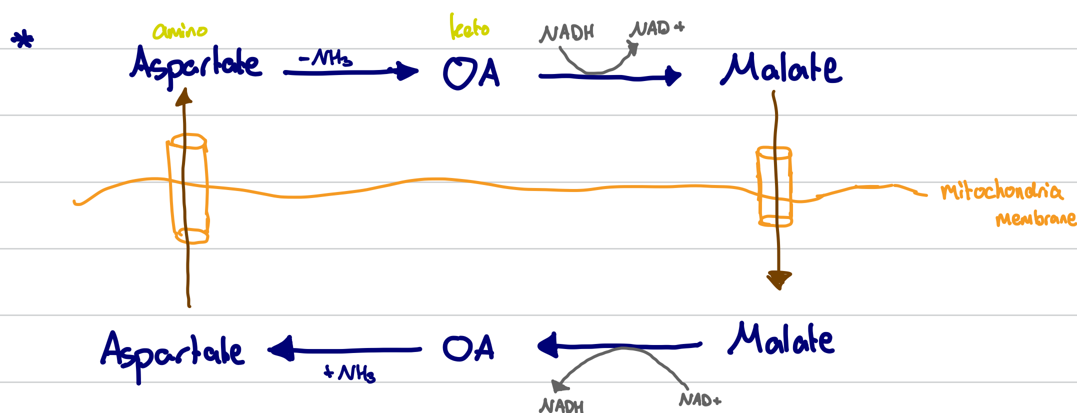
Mechanism:

→ -OH on alcohol oxidized to keto group

→ ΔG° = positive. Reaction driven by step 1. Citric synthase. Which has ΔG° = -ve

Oxaloacetate Junctions:

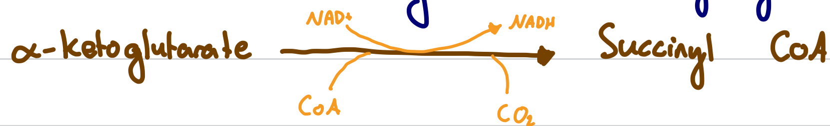
* 

* 

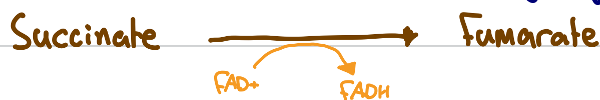
Toxins on the Krebs cycle:

* Flouroacetate: Aconitase non-competitive inhibitor

* Arsenite: α-ketoglutarate dehydrogenase non-competitive inhibitor



* Malonate: Succinate Dehydrogenase competitive inhibitor



Krebs Cycle intermediates used in other pathways:

* Citrate:
  - ↳ fatty acid synthesis in liver
  - ↳ Activates Acetyl CoA carboxylase
  - ↳ Breaks down to form Acetyl CoA, building blood of fatty acids.
  - ↳ Occurs in cytosol NOT mitochondria

* α-Ketoglutarate:
  - ↳ Converted to glutamate
  - ↳ Forming GABA
  - ↳ Neurotransmitter on NS

* α-ketoglutarate:
  - ↳ Converted to glutamine
  - ↳ skeletal muscle & other tissues
  - ↳ Protein synthesis

* Succinyl - CoA:
↳ Heme synthesis in bone marrow

* Malate:
↳ Increase blood glucose when fasting via gluconeogenisis
↳ In liver

* Oxaloacetate:
↳ Amino acid synthesis

Anaplerotic Reactions:

→ Since intermediates can be used, we need reactions that replenish those intermediates called anaplerotic reactions.

* Aspartate → Oxaloacetate

* Alanine → Pyruvate + HCO_3^- → Oxaloacetate !! imp

* Glutamate → α-Ketoglutarate

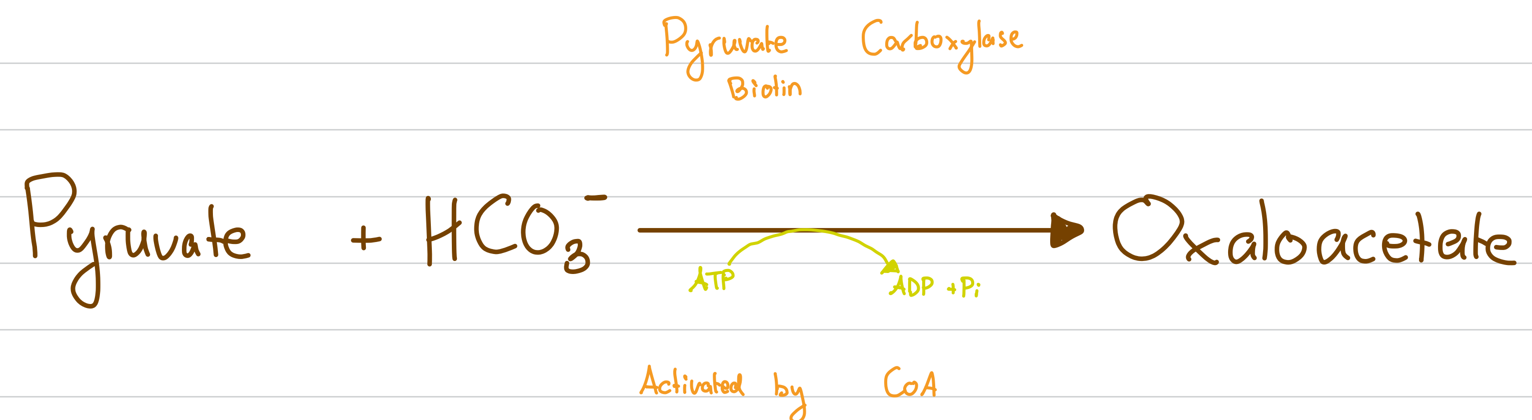
* Amino Acids → Propionyl CoA → Succinyl CoA

* Amino Acids → Fumarate

→ All anaplerotic reactions use amino acid except pyruvate to oxaloacetate
↓
both pyruvate & oxaloacetate are keto acids.

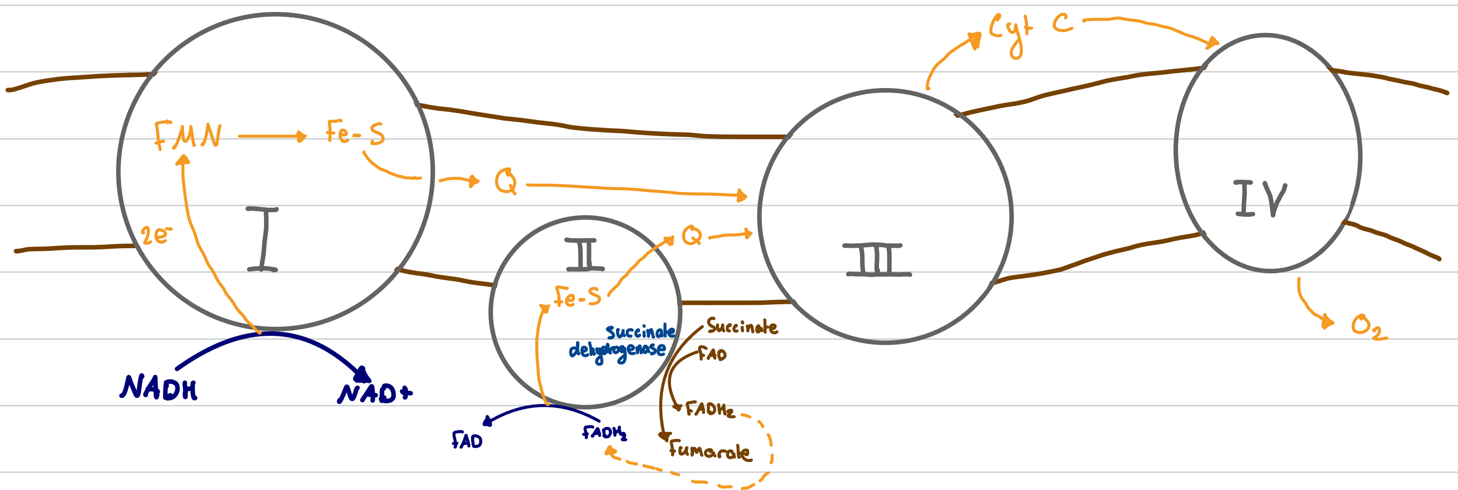
Pyruvate Carboxylase:

- Carboxylation of pyruvate to form oxaloacetate. Anaplerotic reaction
- Needs biotin Coenzyme
- Activated by Co A
- Found in kidneys + liver + brain + adipocytes + fibroblasts
- High conc. in liver & kidney



Oxidative Phosphorylation

ETC in inner mitochondrial membrane:



Complex I:

→ NADH dehydrogenase OR NADH CoQ oxidoreductase

→ Flavoprotein. FMN. FMN takes $2e^-$ from NADH. FMN $\xrightarrow{NADH \rightarrow NAD^+}$ $FMNH_2$
↳ tightly bound to protein

→ FMN gives e^- to Fe-S iron-sulfur complex. (7 complexes. ≥ 2 types)
↳ bound to protein NADH dehydrogenase on Cys

→ Lipid-soluble Co-enzyme Q / ubiquinone / Q takes e^- from complex I. Ubiquinole / QH_2 forms.

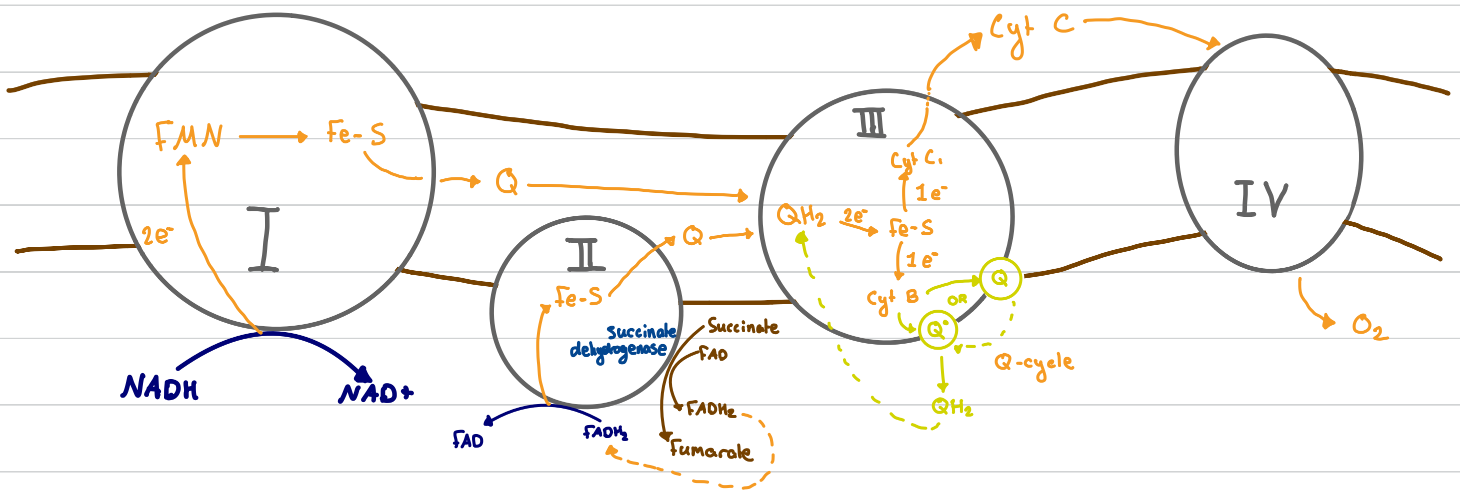
Complex II:

→ Has succinate dehydrogenase part of it. FAD. part of enzyme

→ Succinate $\xrightarrow{FAD \rightarrow FADH_2}$ Fumarate. $FADH_2$ produced is directly used. Electron transfer flavoprotein, ETF-CoQ oxireductase.

→ $FADH_2 \rightarrow FAD + 2H$. FAD part of the complex. Flavoprotein (like complex I)

→ Fe-S takes e^- and gives it to CoQ



Complex III :

→ Cytochrome b-c_1 complex. Q - Cyt C oxireductase

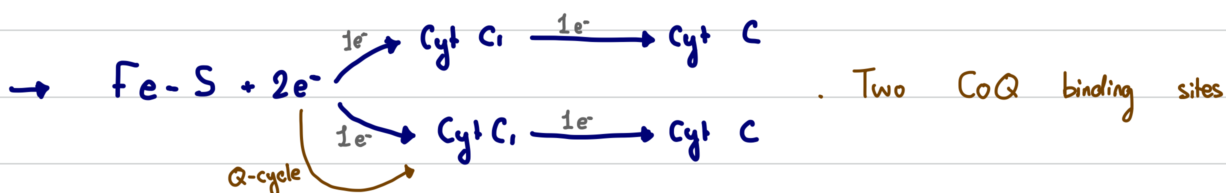
→ QH_2 /ubiquanole gives 2 e^- to Fe-S

→ Fe-S gives 1 e^- to Cyt c_1. Cyt C_1 gives e^- to Cyt. C

→ Fe-S gives 1 e^- to Cyt b

→ Cyt B gives e^- back to Q. Q cycle

→ Cyt C_1 takes e^- one at a time Cytochromes carry e^- via heme groups so each Fe only holds one e^-.

→ 

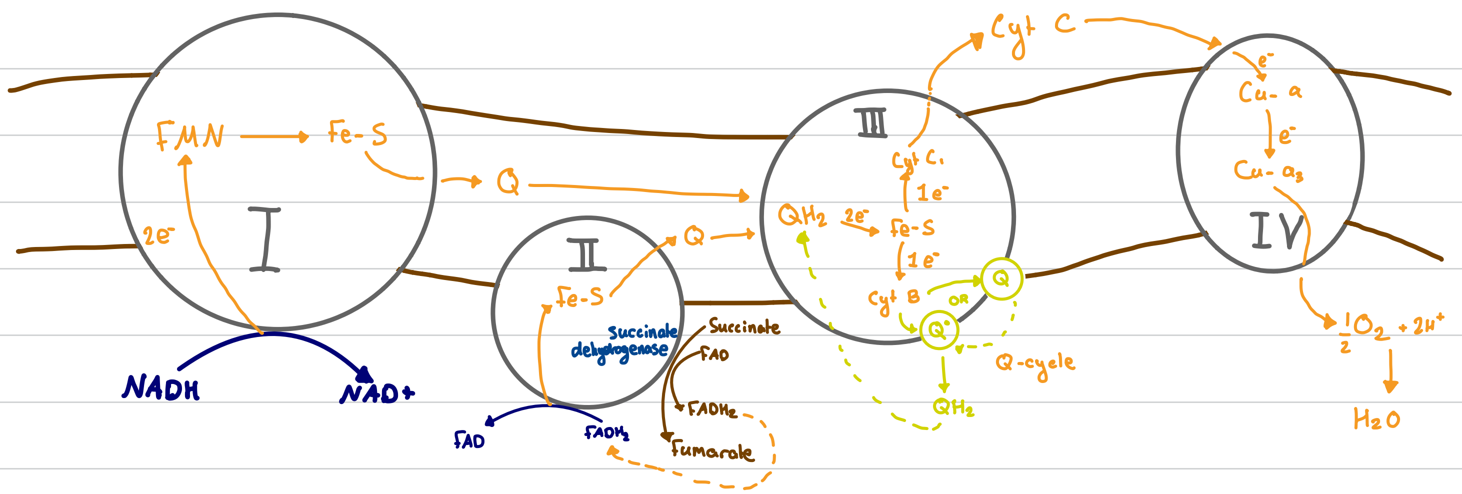
. Two CoQ binding sites

→ Cyt C is water soluble & doesn't move via membrane

→ 3 total heme prosthetic groups

↳ Cyt-c_1 = 1 c-type heme

↳ Cyt-b = 1 b_L heme + 1 b_H heme



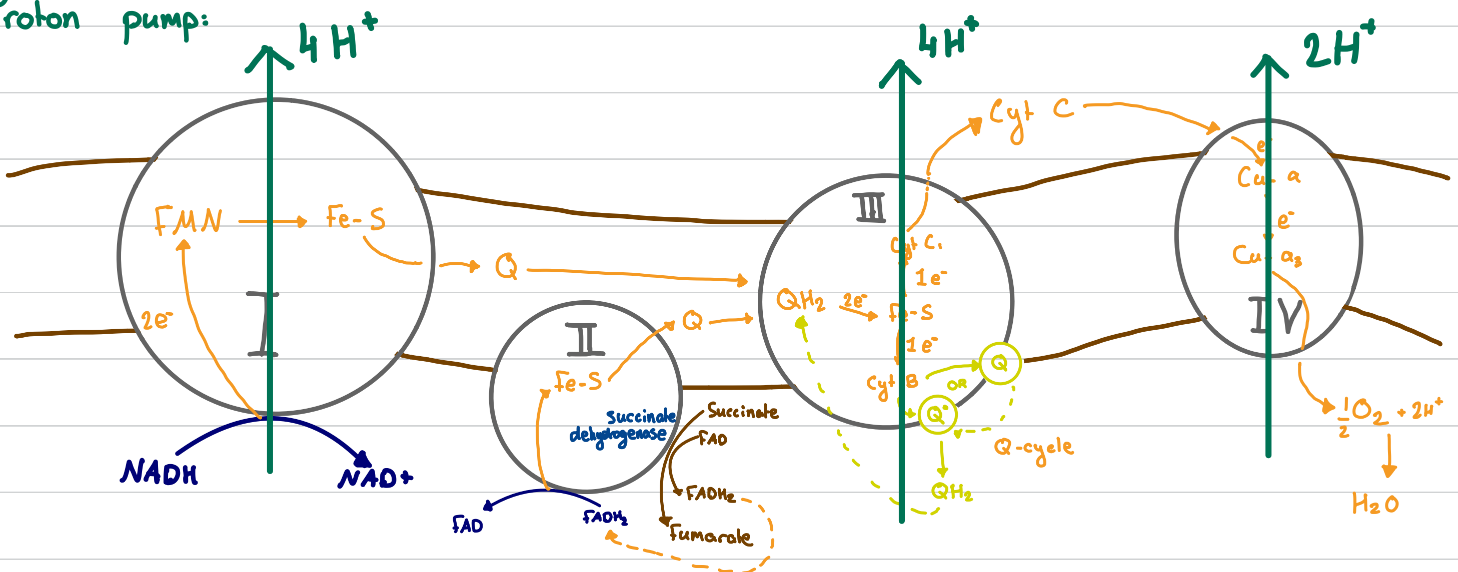
Complex IV:

→ Uses Cu-a , Cu-a_3 , Cyt-a , Cyt-a_3. NO Fe-S

→ Transfers e^- to O_2. Final e^- acceptor. (1 O_2 needs 4 e^-). We need full reduction because partial reduction gives radicals.

→ Binds to O_2 to reduce it. Very very high affinity. Km for IV lower than Hb & myoglobin!

Proton pump:



→ Complex II doesn't pump e^-. ≈ 0 kcal

→ Each 4 e^- produce 1 ATP.

→ NADH: Complex I ($4H^+$) —CoQ→ Complex III ($4H^+$) —Cyt C→ Complex IV ($2H^+$) = 4 + 4 + 2 = 10 = 2.5 ATP

→ $FADH_2$: Complex II ($0H^+$) —CoQ→ Complex III ($4H^+$) —Cyt C→ Complex IV ($2H^+$) = 0 + 4 + 2 = 6 = 1.5 ATP

Mitochondrial membrane composition:

Inner membrane:

→ High amount of cardiolipin. 22 %.

→ NO cholesterol

→ Impermeable. NOT permeable to H^+, need specific transporters. Why? to maintain an H^+ gradient

Outer membrane:

→ Similar to plasma membrane. Permeable

→ Has cholesterol 45%.

→ Low cardiolipin 3%.

Electron Carriers:

Ubiquinone:

→ Lipid solube & carries e⁻ from I / II to III through inner membrane

→ Has benzoquinone and isoprenoid (long)

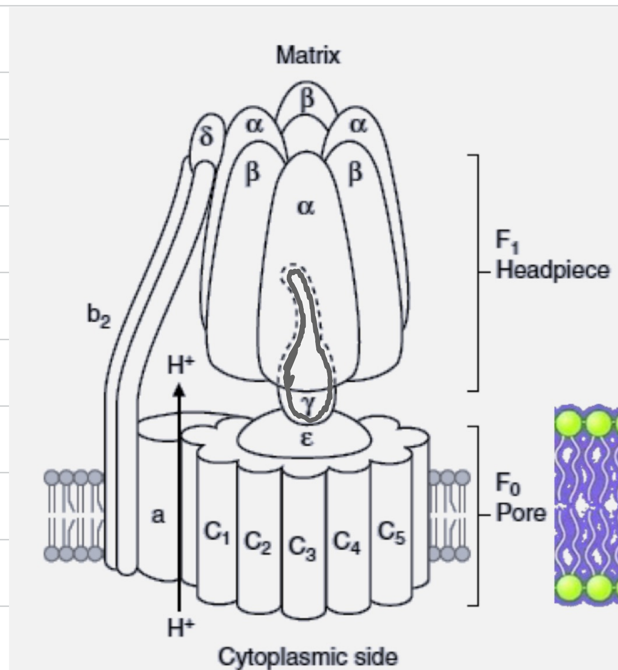
→ Can carry 1 e⁻ (semiquanone radical ·QH) or 2 e⁻ (Ubiquinol) thus used in Q cycle of complex III

→ Prescriped for myocardial infraction patients

Cytochrome:

- Cyt C is water soluble. e^- transport from III to IV. Cyt C contains -SH groups
- Cyt are proteins containing heme prosthetic groups with Fe.
- Carry only one e^-
- Cyt-c_1 & Cyt-b in complex III
- Cyt-C transports from III to IV (Cyt-C has -SH)
- Cyt-a & Cyt-a_3 in complex IV (IV has no Fe-S complex but Cu instead but cyt-a & cyt-a_3 have iron heme groups.)
- Named according to light absorbtion of α-band in Fe^{2+} state
- ΔE° value depends on protein
- Movement of e^- in ETC from lower E° to higher E°. Different cytochromes have different E° values.

ATP Synthase:



F_0:

→ a subunit where H^+ enters and goes to c subunits then goes back to a subunit to exit into matrix

→ 12 c subunits which rotate when H^+ enters

F_1:

→ Middle γ subunit which is bent & rotates when c subunits rotate.

→ γ subunits hit the β-subunits & ATP produced

→ α subunits present for support

→ β subunits have:

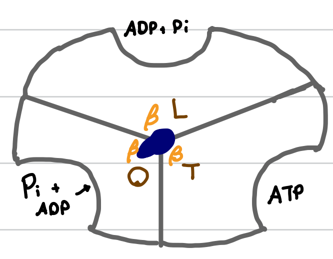
T - tense

L - loose

O - open

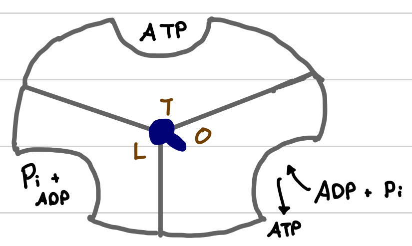
β - subunits & ATP production:

①



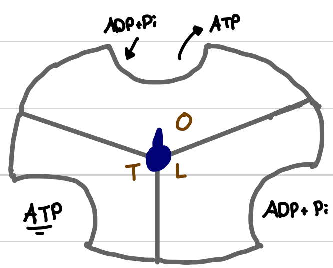
anti-clock, 4 H^+

②



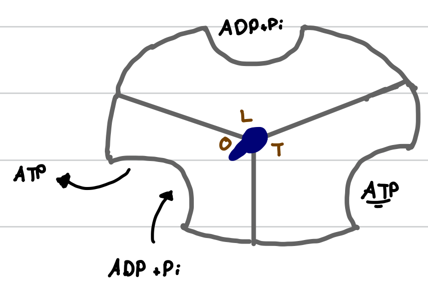
4 H^+

③



4 H^+

④



* Where gamma is pointing is open
* Clockwise order: O → L → T
* ADP + Pi enter in open
* ATP form in Tense
* ATP exit in O & ADP + Pi enter in its place
* Every 4 H^+ rotate 120°
* 12 H^+ make full rotation
* Full rotation = 3 ATP.

IMPORTANT:

→ ATP synthase is reversible!

Can act as H^+-pump!

ATP used & H^+ pumped into intermembrane space

ATP / ADP translocase mitochondrial shuffling system:

→ Coupled transport. ADP in & ATP out

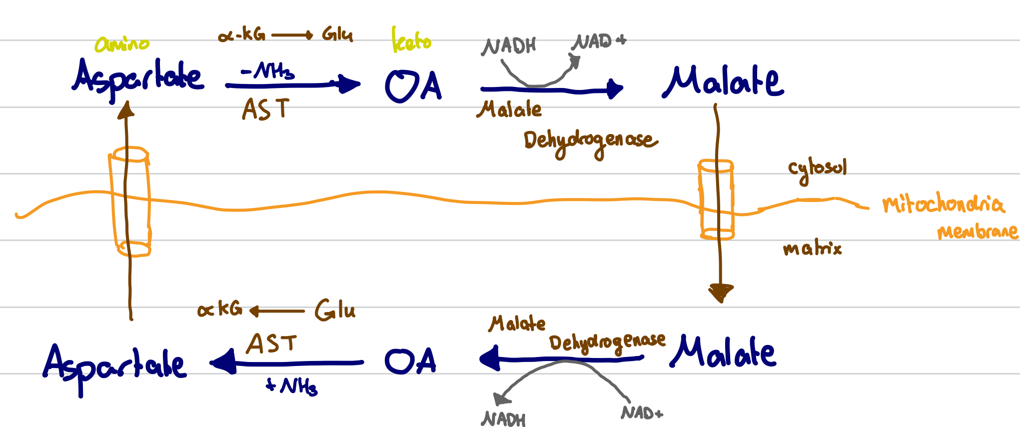
→ Inner membrane. 14 %. . Abundant

→ Called ANT, adenine nucleotide translocase

→ If its inhibited, then no ADP in matrix. Low ADP inhibits cellular respiration

→ Phosphate carrier used to transport P_i into mitochondria

Asp- Malate shuttle of NADH:



* Transporting e^- / H^+ inside mitochondrial matrix from cytosol

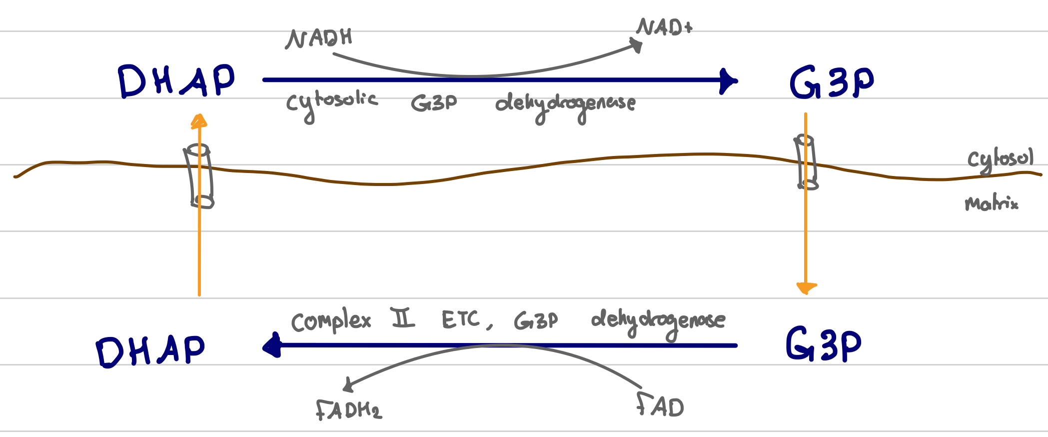
→ Liver / Kidney / Heart

→ NADH : NAD+ ratio higher in cytosol (more NADH in cytosol than matrix)

→ Readily reversible unlike G3P shuttle.

→ Uses NAD throughout

G3P - DHAP shuttle of NADH:



→ 1 NADH = 2 ATP

→ Less effective due to NAD to FAD

→ In matrix, complex II G3P DH part is used!

→ Complex II : ETC + Krebs + G3P shuttle + fatty acyl CoA dehydrogenase

→ In skeletal muscles & brain

ETC bioenergetics:

→ Less efficient than krebs cycle

→ ATP needs ΔG° : 7 k cal

→ NADH has ΔG° = -53. $FADH_2$ ΔG° = -41. ΔG for entire oxd. phosph. so negative so it is irreversible! ATP synthase is reversible

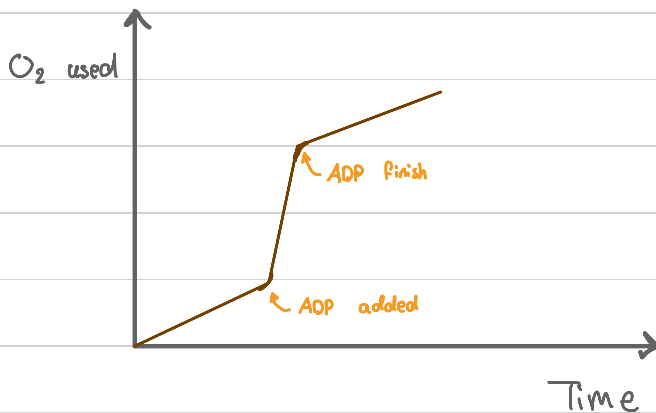
→ NADH = 2.5 ATP → 17.5. 53 - 17.5 = 35.5
→ $FADH_2$ = 1.5 ATP → 10.5. 40 - 10.5 = 30

} ⇒ Lost as heat!
↓
non-shivering thermogenesis.
ATP production releases heat
ATP usage releases heat

Regulation - ADP

→ ADP most important. ADP increases oxd. Phos. rate

→ Called Respiratory control / Acceptor control



Regulation. Inhibitor Toxins

R A ⁝ A ⁝ C A C ⁝ O

Inhibit:

→ Rotenone
→ Amytal
Complex I

→ Antimycin A — Complex III

→ CO
→ Azide — complex IV, mimic O_2
→ CN

→ Oligomycin — ATP synthase

R [1] A | A [3] | C [4] A C | O synthase

→ Cyanoglycosides (amygdalin, misnomer B17) act as cyanide inhibitors & inhibit complex IV.

Regulation - Uncoupling Proteins (UCP_s) So important! Exam question

→ Short circuit the ETC, H^+ enters through UCPs, not ATP synthase.

→ No ATP produced, heat produced instead! non-shivering thermogenesis

→ UCP1
↳ Thermogenin
↳ Brown adipose tissue in neck / breast / around kidney
↳ Activated by fatty acids

→ UCP2 most cells

→ UCP3 skeletal muscles

→ UCP4, UCP5 brain

→ UCP mutations increase cardiometabolic disease risks

→ Dinitrophenol, DNP, & other acidic aromatic compounds can act like UCPs.
DNP takes H^+ in intermembrane space & DNP in matrix release H^+, functioning like UCP & no ATP produced. Heat produced

→ DNP and UCP use NADH & O_2 but dont produce ATP. Heat instead

→ FDA banned DNP

Genetic Oxolidative Phosphorylation diseases:

Complex I:

nDNA: Leigh syndrome / Leukodystrophy 35 proteins
mt DNA: LHON / Dystonia / Sporadic myopathy 7 "

Complex II:

nDNA: Leigh syndrome / Paraganglioma 4
mt DNA: none 0

Complex III:

nDNA: none 10
mt DNA: Sporadic myopathy 1

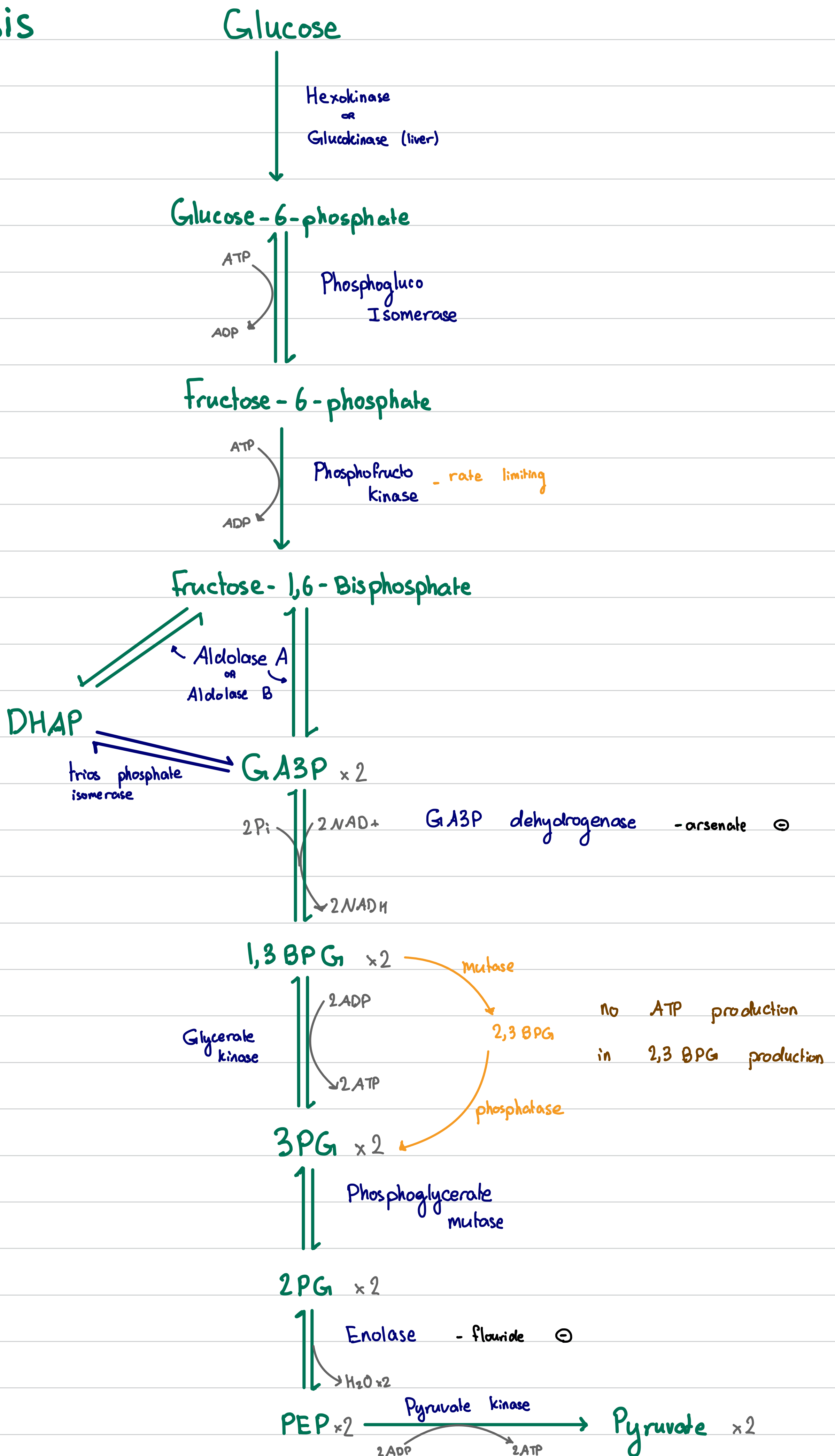
Complex IV:

nDNA: Leigh syndrome / cardioencephalomyopathy / Leukoencephalomyopathy 10
mt DNA: Sporadic myopathy / Sporadic anemia / encephalomyopathy 3

Complex V:

nDNA: none 14
mt DNA: NARP / MILS / FBSN 4

Glycolysis



Lactic Acidosis:

- Inhibiting oxidative phosphorylation:

→ Glycolysis take over, anaerobically. O_2 cant be used

- Alcohol intoxication:

→ Causes high NADH : NAD+ ratio.

→ Many NADH, low NAD+.

→ Pyruvate to lactic acid to regenerate NAD+.

- ↓ Pyruvate dehydrogenase activity: (arsenite)

→ No acetyl CoA formation

→ Pyruvate accumulate & turn to lactic acid

- ↓ Krebs cycle:

→ Pyruvate accumulate & turn to lactic acid

- ↓ Pyruvate carboxylase (pyruvate to oxaloacetate)

→ Pyruvate accumulate & turn to lactic acid

- ↓ Gluconeogenesis

→ Pyruvate accumulate & turn to lactic acid

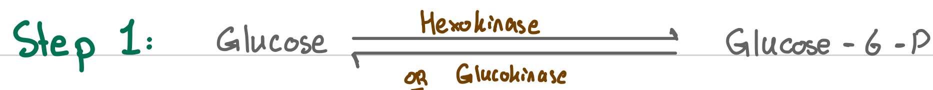
- Hypoxia

→ Hemorrhage

→ Respiratory failure

→ Impaired O_2 transport

Enzyme Regulation:



Hexokinase	vs	Glucokinase
- Low km, high affinity		- High km, low affinity
- works at all glucose conc.		- Works at high glucose conc. >100
- In all tissues		- In liver. Turn glucose to glycogen
- Not affected by insulin & glycogen		- Affected by insulin (+) & glucagon (−)
- Feed back inhibitor by Glu-6-P		- Feedback inhibitor from Fru-6-P → GKRP
- Glu. / Man. / Gal. / Fru.		- Only on glucose

Glucokinase:

GK - GKRP enter nucleus. GK not active

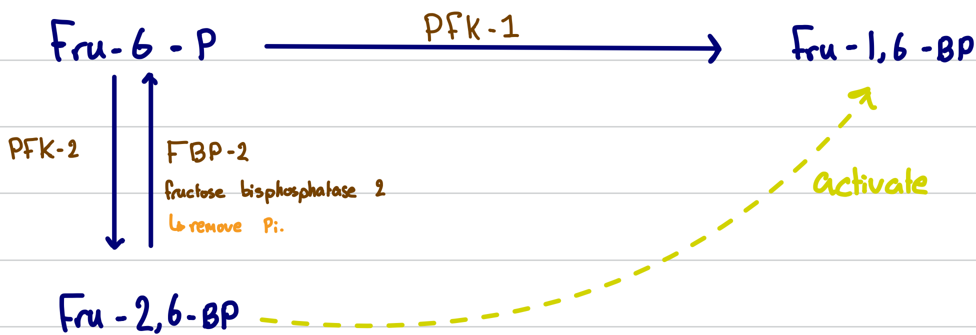
Hexokinase:

Directly inhibited by Glu-6-P

Step 3: Fructose - 6 - Phosphate —Phospho fructo kinase (PFK-1), rate limiting→ Fru - 1,6 - Bisphosphate

Activators ⊕	Inhibitors ⊖
- AMP NOTTT ADP!!	- ATP
- Fru-2,6-BP ⇒ PFK-2 produces Fru-2,6-BP when fructose accumulates so its like reactant activation but other pathway	- Citrate
	- H^+ ⇒ From lactic acid. Lactic acid toxic so alot of lactic acid stops glycolysis. Thats why we can't anaerobically respire for ever
- Insulin	- Glucagon

Fru-2,6-BP, PFK, Insulin & Glucagon:



Enzyme ↑ Glucose + Pi = Activated (Glucagon adds Pi via PKA from cAMP)

Enzyme ↓ Glucose + Pi = Deactivated (Insulin removes Pi via phosphatase)

Glucagon:

FBP + Pi → FBP - Pi Activate - F-2,6-P ↓ so PFK-1 ↓ so Glucose ↑ so activate

PFK-2 + Pi → PFK-2 - Pi Deactivate - F-2,6-P ↑ so PFK-1 ↑ & Glucose ↓ so deactivate

So glucagon activates FBP by adding Pi, less F-2,6-BP so more glucose! Less glycolysis rate.

Activated via cAMP & PKA

Insulin:

$FBP-P_i \longrightarrow FBP + P_i$ Deactivate - FBP will ↑ Glucose so deactivated with no P_i

$PFK\text{-}2-P_i \longrightarrow PFK\text{-}2 + P_i$ Activate - PFK-2 will ↓ Glucose so activated with no P_i

So Insulin activates PFK-2 by removing P_i, more F-2,6-BP so less glucose!

More glycolysis rate.

Decreases cAMP & PKA

PFK-2 ⇒ Decrease Glucose. Active no P_i (Insulin) / Inactive with P_i (Glucagon)

FBP-2 ⇒ Increase Glucose. Inactive no P_i / Active with P_i

Step 10: PEP $\underset{}{\overset{\text{Pyruvate kinase (Pk)}}{\rightleftharpoons}}$ Pyruvate

Activators ⊕	vs	Inhibitors ⊖
- Insulin		- Glucagon
- Fru-1,6-BP feedforward activation		- Alanine
		- ATP

Insulin & Glucagon:

PK will lower glucose. So with Pi inactive.

Glucagon: PK - Pi inactive

Insulin: Pk active

2,3 BPG:

→ Low O_2 causes Glycolysis to increase. ↑ 1,3 BPG which becomes 2,3 BPG

→ 2,3 BPG lowers Hb affinity to O_2. O_2 released into tissues more

→ Mutase & phosphatase

External inhibitors of glycolysis: non-physiological

A. Flouride:

→ Inhibits enolase.

→ Inhibits glycolysis in bacteria!

→ In toothpaste & flouridated water

B. Arsenite: (krebs cycle!)

→ Trivalent Arsenic

→ Inhibits keto acids dehydrogenases. Pyruvate dehydrogenase & α-keto dehydrogenase

→ How? It forms stable complex with -SH of lipoic acid!

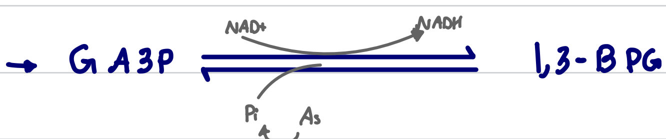
→ Causes neurological disturbances & death

C. Arsenate:

→ Pentavalent arsenic. Looks like P_i

→ Since similar to P_i. Competes with P_i for GA3P dehydrogenase. Less 1,3 BPG

→



→ Less ATP produced

Pyruvate kinase Deficiency / Abnormality:

→ Most common

→ RBC's most affected because no mitochondria

→ Low ATP = ↓ Na^+-K^+ pump = cell swell & die

→ Mild to severe chronic hemolytic anemia

→ Due to altered kinetic properties. Varies mutant forms of pyruvate kinase.

- Abnormal response to Fru-1,6-BP activator
- Weird km or Vmax values
- Decreased amount of enzyme
- Stability / Activity lower

PDH:

Keto acid dehydrogenases:

* Pyruvate → Acetyl CoA + NADH + CO_2
* α-keto glutarate → Succinyl CoA + NADH + CO_2

Enzyme complex:

E1 :

* Decarboxylase
* Uses TPP.
* CO_2 removed from pyruvate & alcohol formed

E2 :

* Dihydrolipoyl transacetylase
* Uses lipoic acid. -L(S–S) → -L(SH)(SH) . e^- carrier!
* Takes H & e^- from alcohol, ketone formed
* Adds CoA to ketone. Acetyl CoA formed

E3 :

* Dihydrolipoyl dehydrogenase
* Uses FAD to take H & e^- from reduced lipoic acid.
* Transfers H & e^- from FAD to NAD^+.
* NADH formed & -L(S–S) regenerated

Regulation:

A. Feed back inhibition:

* ⊖ Acetyl CoA
* ⊖ NADH

B. Regulation by Phosphoprotein phosphatase:

* Remove Pi. (insulin). So activates PDH
* Activated by Ca^{2+}
* Ca^{2+} = more ATP = activate phosphatase = activate PDH

C. Regulation by Protein kinase:

* Add Pi. (Glucagon). So inactivates PDH
* Activated by: ATP / NADH / Acetyl CoA
* Inhibited by: Pyruvate

Diseases:

Pyruvate dehydrogenase deficiency:

→ Most common is E_1 deficiency. No decarboxylation

→ X-linked genetic

→ More anaerobic respiration. Lactic acidosis

→ Brain most affected

→ Neurodegeneration

→ Muscle spasms

→ Neonatal form → early death

→ Reduce carb intake

→ Take TPP supplements

Arsenic poisoning:

→ Arsenite / Trivalent affects keto acid dehydrogenases by binding to lipoic acid.

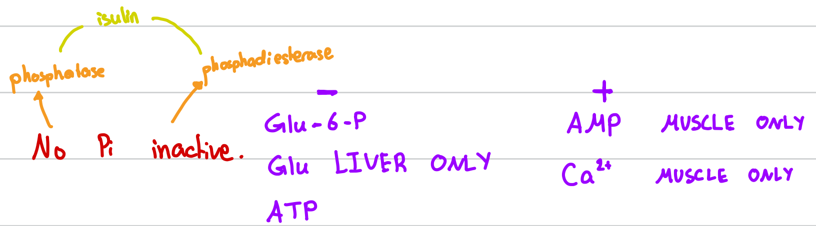
→ Arsenate / Pentavalent affects GA3P dehydrogenase by mimicking P_i

Glycogen Metabolism:

Glycogen Catabolism / Glycogenolysis:

Enzymes:

A. Glycogen phosphorylase Pi active.



→ Breaks glucose at non-reducing end

→ Produce glucose-1-P

→ ONLY works on α-1,4

→ Does NOT use ATP. Catabolism release energy... used to add free Pi.

B. Phosphoglucomutase

→ Convert Glu-1-P to Glu-6-P

C. Debranching enzyme

→ Works on "limit dextrin"

① Transferase: Transfers branch from α-1,6 to α-1,4. Only works on α-1,4 bonds

② α-1,6 glucosidase: Breaks the single α-1,6 glucose using H_2O. No Pi!

D. Glucose-6-Phosphatase

→ ONLY in liver. NOT in muscle.

→ Liver can release glucose in blood. Muscle is greedy & holds Glu-6-P

→ Glucose-6-Phosphate ⟶ Glucose → To blood

E. α-1,4 Glucosidase

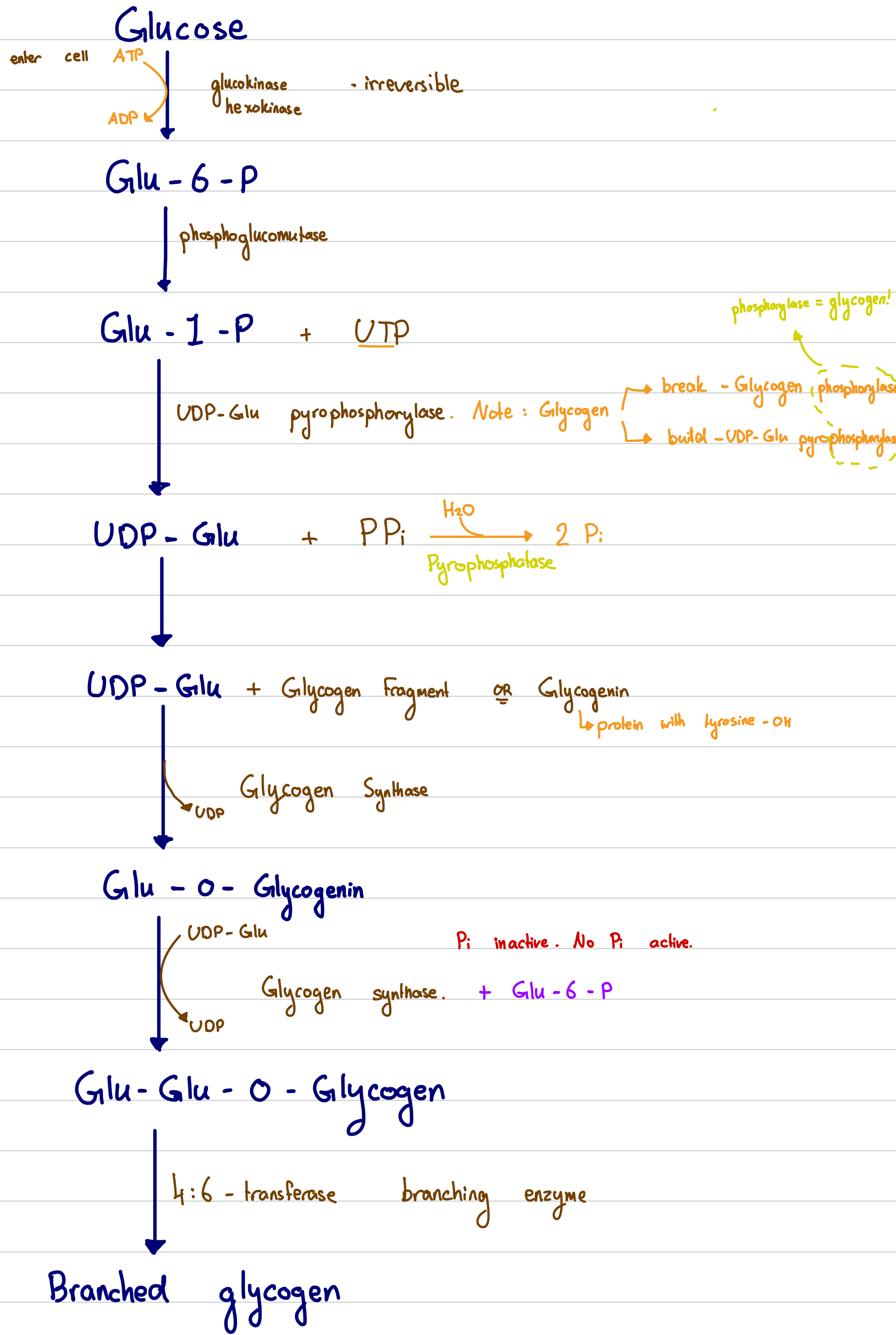
→ 3% of glycogen metabolism

→ in lysosomes

→ Removes α-1,4 glucose at non-reducing end. Use H_2O, no Pi.

→ Deficiency in Pompe disease.

Glycogen Anabolism / Glycogenesis :



Energy Usage → 1 ATP + 1 UTP

Glycogen storage Diseases:

→ Affects synthesis & degradation enzymes

synthesis ↓ accumulation of faulty glycogen

degradation ↓ accumulation of normal glycogen

→ Genetic .. Many tissues.. Fatal in infants

A. Type I / Von Gierke disease:

* Glu-6-Phosphatase

* Glu-6-P ⟶ (blocked) Glu

* Cant release Glucose to blood. Severe fasting hypoglycemia

* Accumulate Glu-6-P. Inhibit glycogen phosphorylase. normal Glycogen accumulation

* Affects intestines

* Affects liver... Hepatomegaly fatty liver

* Affects kidneys... progressive renal diseases

* Growth retardation... since low glucose in blood but high glycogen storage.

* Tip: Von Gierke = G = glucose-6-phosphatase

B. Type II / Pompe Disease:

* Lysosomal α-1,4 glucosidase deficiency (3% of glycogenolysis)

* normal Glycogen accumulation IN Lysosomal vacuoles. Affects entire lysosome.

* Due to lysosomal failure & NOT blood glucose. Normal blood glucose levels

* Affects Heart + Liver + muscle

* Death from heart failure. Massive cardiomegaly

* Tip = Pompe disease = om = Lysosomal α-1,4 glucosidase

C. Type V / McArdle:

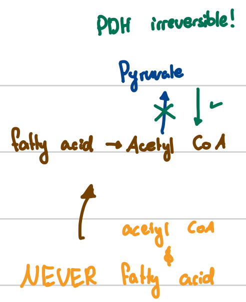
* No muscle glycogen phosphorylase

* Low glucose & ATP in muscle. Muscle weakness & cramping

* NO lactate production cuz low glucose

* Ca^{2+} release. Ca^{2+} - Calmodulin complex, activates phosphorylase kinase, no glycogen phosphorylase to be phosphorylated.

* Tip = McArdle = M = muscle glycogen phosphorylase



Gluconeogenesis:

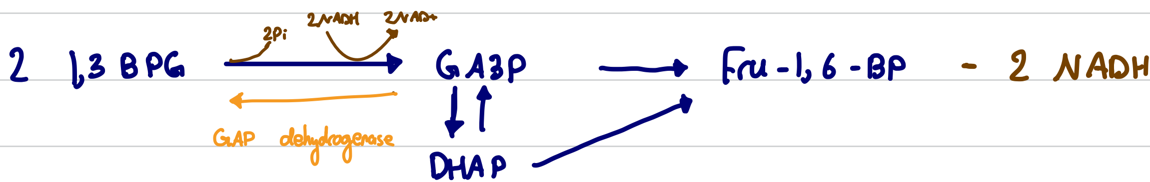
Lactate
Non-carb. Amino acid... Glycerol NEVER fatty acid

Reverse of glycolysis except irreversible steps. Use other substances to produce pyruvate

Liver & kidneys → prolonged fasting (+ fatty acid to ketone bodies)
↳ NOT gluconeogenesis

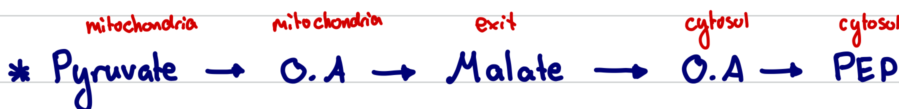
Pyruvate carboxylase & malate dehydrogenase. Glu-6-phosphatase
In cytosol EXCEPT pyruvate to PEP in mitochondria. & Glu-6-P to Glu in SER
→ PEP carboxykinase in cytosol

Total = 4 ATP + 2 GTP + 2NADH
USED

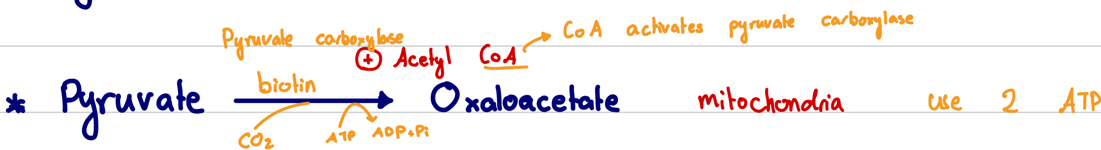


- 2 NADH

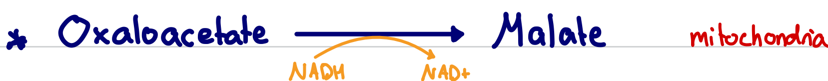
1. Pyruvate to PEP: ⊕ Acetyl CoA → imagine it one of reactants... but its not!



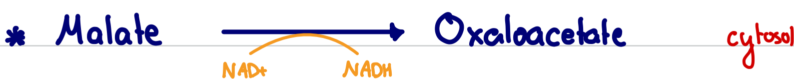
CoA activates pyruvate carboxylase



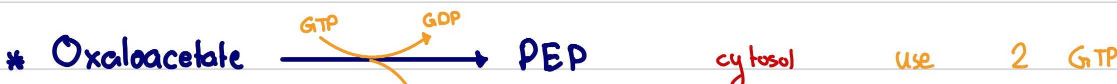
mitochondria use 2 ATP



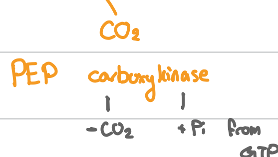
mitochondria



cytosol



cytosol use 2 GTP



↳ 3PG to 1,3BPG uses 2 ATP.

Total: 6 ATP used. None produced

AMP = products

gluconeogenesis requires ATP.

2. Fru-1,6-BP to Fru-6-P: (−) → AMP, Fru-2,6-BP

* Uses Fru-1,6-Bisphosphatase

* DOES NOT produce ATP!

* AMP & Fru-2,6-BP which activate PFK-1 WILL INHIBIT Fru-1,6-Bisphosphatase
  PFK2 & FBP

3. Glu-6-P to Glu:

* Uses Glu-6-phosphatase

* Only Liver (& kidneys). Not muscles

* Also used in glycogen breakdown to release Glu into blood from liver. Muscle are greedy & hold onto the Glu-6-P

* Glu-6-phosphatase is bound to ER membrane, so Glu-6-P translocase is needed to transport Glu-6-P across ER membrane to the phosphatase since Glu-6-P cant cross membranes

Regulation:

Regulation of gluconeogenesis

Gluconeogenesis Activated by Glucagon.

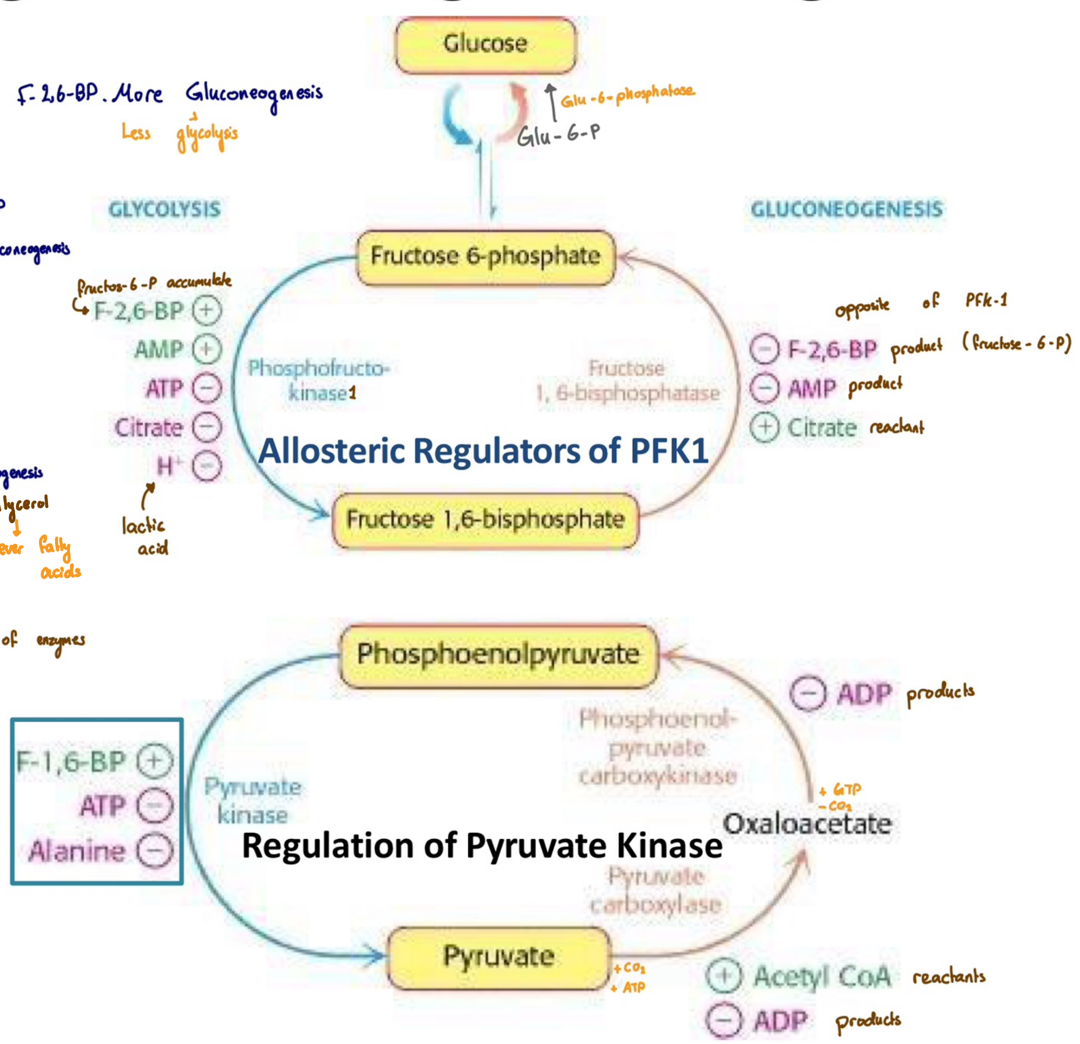
Pi + PFK2 ⇒ inactive
Pi + FBP2 ⇒ active
} ⇒ Lower F-2,6-BP. More Gluconeogenesis, Less glycolysis

Pi + Pyr.K ⇒ inactive ⇒ more PEP ⇒ More gluconeogenesis

Increase PEP carbokinase

Increase substrates for gluconeogenesis
↳ Amino acids, Lactate, Glycerate, Glycerol
Alanine, aspartate — Never fatty acids

Slow changes
↳ ↑ or ↓ synthesis & degregation of enzymes



Monosaccharide Metabolism:

Fructose Kinases:

Hexokinase:

* Most tissue types
* Fructose to Fructose-6-P... continue like glycolysis, PFK-1

Fructokinase:

* Liver (& kidney & small intestine) like glucokinase
* Fructose to Fructose-1-P... turned then into DHAP & GA via aldolase B
* Bypass PFK-1 step. So fructose metabolism faster than glucose metabolism
  (PFK-1 ↓ Glycolysis. Rate limiting)

Aldolases:

Aldolase A:

* Most tissue types
* Only works on F-1,6-BP
* Doesn't work on F-1-P
  (Hexokinase Fru-6-P & PFK-1 Fru-1,6-P)
* Fru-1,6-BP to GA3P & DHAP

Tip: Aldolase A = First letter = more esential = Glycolysis pathway = work on Fru-1,6-BP

Aldolase B:

* Only liver (+ kidney + small intestine)
* Both Fru-1,6-BP & Fru-1-BP ← Fructokinase
* Either GA3P + DHAP OR GA + DHAP

Tip: Aldolase B = Both Fru-1-BP & Fru-1,6-BP

Fructokinase Deficiency:

→ Benign. Not too dangerous. Hexokinase pathway

→ Accumulation of fructose => fructosuria

Aldolase B deficiency:

→ Heridatory

→ No Fru-1-P cleavage

→ Fructose intolerance / poisoning

→ ↑ Fru-1-P → ↓ ATP ⟶ ↑↑ AMP ⟶ Degrade AMP

→ Aldolase B in Liver (+ kidney + SI)

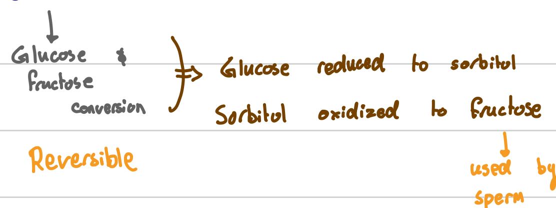
→ ↑ AMP, so activate glucose metabolism => Hypoglycemia

→ ↑ AMP, so ↑ Glycolysis => Lactic acidosis

→ ↓ ATP, so hepatic failure

→ ↑ AMP => ↑ AMP degradation => ↑ Uric acid => Hyperuricemia

→ Avoid fructose, sucrose, sorbitol



Aldose reductase:

→ Glucose to sorbitol

→ Think of places affected by diabetes:

* Lens
* Retina
* Schwann cells
* Liver
* kidneys
* Seminal vesicles } sperm use fructose
* Ovaries

Sorbitol Dehydrogenase:

→ Sorbitol to fructose

→ Places that need fructose ~ sperm

* Seminal vesicles
* Ovaries

Diabetes:

→ Glucose enters cells NOT via GLUT. Insulin independant

→ Glucose to sorbitol via aldose reductase

→ Sorbitol retains water & causes cell swelling.

→ Affects tissues with aldose reductase mentioned above.

Eyes, nerves, kidneys, liver etc.

Glucuronic Acid Metabolism:

Glucose oxidation = Glucuronic Acid | UDP-Glu dehydrogenase

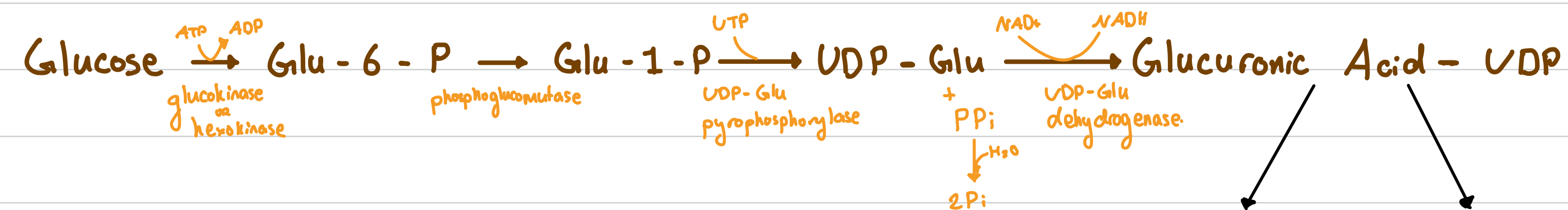
Minor route. Produce precursors for other pathways.

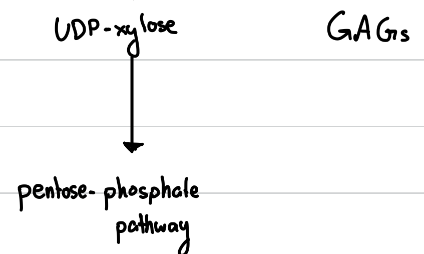
Similar to glycogen synthesis

Use 1 ATP & 1 UTP. Requires energy to produce Glucuronic Acid - UDP

Used to produce GAGs

Used in pentose phosphate pathway





Uses of UDP-Glucose:

→ Glycogen synthesis

→ Oxidation into glucuronic acid

→ Galactose metabolism.

Galactose metabolism diseases:

Galactokinase defecency:

→ NO Gala to Gala-1-P

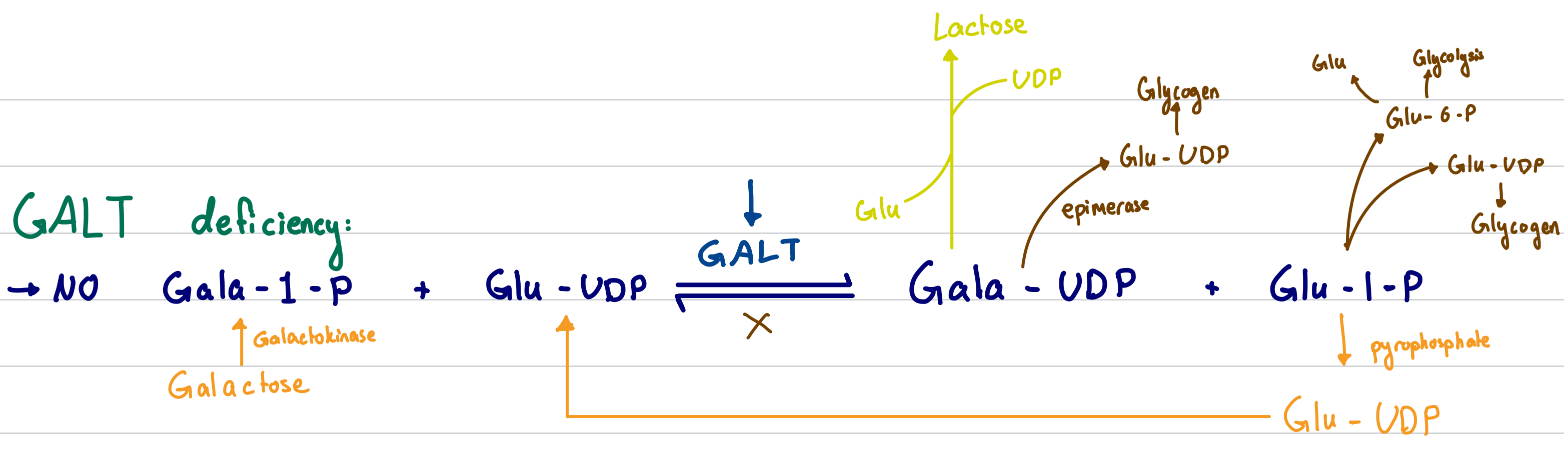
→ Galactose accumulation.

→ Cause glactosemia & galactosuria.

→ Galactose --Aldose reductase--> Galacitol. Aldose reductase also in Glu & Fru conversion. Glu to sorbitol. It is in places affected by diabetes

→ Excess galacticol can cause Cataracts

GALT deficiency:



→ Gala-1-P & Gala accumulate

→ Cause glactosemia & galactosuria. Classic galactosemia

→ Same idea as aldolase B deficiency. ATP ↓ & AMP ↑. Problems.

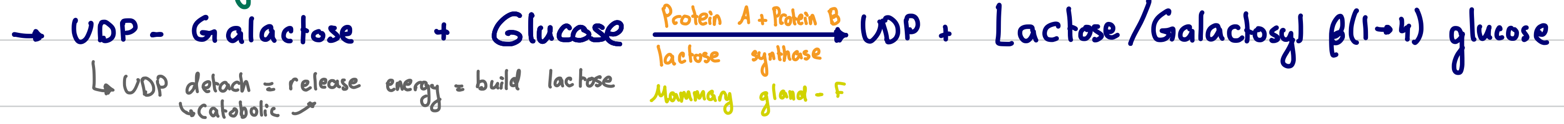
→ Increase galacticol. Gala $\xrightarrow{\text{Aldose reductase}}$ Galacticol

→ Galacticol accumulate where Aldose reductase is present. Think places where aldose reductase is present

→ Jaundice

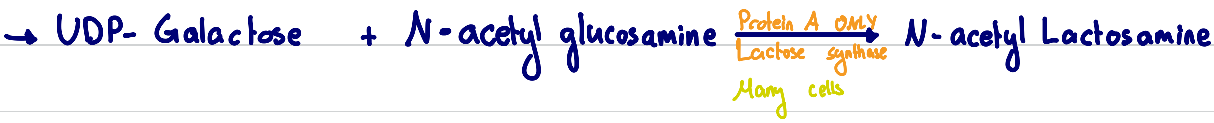
→ Vommiting + diarrhea

Lactose synthase protein complex:



→ Both males & females. Females use for milk production when prolactin high. Both use for glycolipids & glycoproteins!

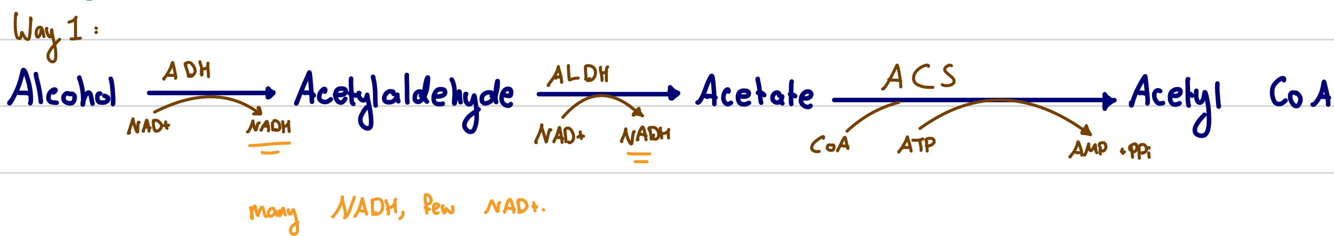
* Protein A = Galactosyl transferase ⇒ A only (all cells) = Lactose in glycolipid & glycoprotein (M + F)
* Protein B = α-lactal albumin A + B = Lactose in milk, mammary gland. Prolactin (females)
  ↳ mammary gland



Alcohol Metabolism:

Large Alcohol consumption:

Way 1 :



many NADH, few NAD+.

Bad. Alot of NADH. No NAD+. Glycolysis stop. krebs stop. NADH → NAD+ Pyruvate → Lactate

- ✓ High NADH/NAD+
- ✓ Inhibition of FA oxidation
  - ↳ FA → CoA. CoA products. ↑ CoA so inhibition
- ✓ Inhibition of gluconeogenesis
  - CYP450 & liver busy dealing with alcohol. So not free to deal with gluconeogenesis. → Pyruvate to OA stop
- ✓ Lactic acidosis
  - ↳ Lactate ↑ cuz NADH ↑. Pyr. → Lactate (LDH; NADH → NAD+)

A. ↑ Acetyl CoA ⊕

B. ↑ H^+ ⊕ (outweighs)

C. Pyruvate ↑ ⊕ → Pyruvate decrease. So less substrate so less gluconeogenesis

Way 2:

MEOS, use CYP2E1. Produce free radicals. 10%. NADPH give H to MEOS, this forms free radicals

Way 3:

Catalase, use H_2O_2 oxidizing agent instead of NAD+ & MEOS