METABOLISM

GLYCOLYSIS OVERVIEW

Glucose ⟶ 2 Pyruvate

Aerobic Glycolysis:

Pyruvate $\xrightarrow[O_2]{\text{oxidative decarboxylation}}$ Acetyl CoA → TCA

Anaerobic Glycolysis: (in RBCs)

Pyruvate $\xrightarrow{\text{Lactate Dehydrogenase}}$ Lactate / Lactic Acid

* Glycolysis takes place in cytosol

* Transport of Glucose from Interstitial spaces to cell is either by facilitated diffusion or is ATP-dependent through Na-Glucose co-transport.

* Facilitated diffusion is through GLUT transporters

* GLUT-1 : ~~Neurons~~ RBCs, Blood brain barrier

GLUT-2 : Liver, β cells of pancreas, kid.

GLUT-3 : ~~RBCs~~ Neurons

GLUT-4 : Adipose tissue, Muscle

GLUT-5 : Small intestine, testes

* GLUT-1, 2, 3, 4 transport glucose into the cell.
* GLUT-2 : bifunctional, may transport glucose into or out of cell
* GLUT-5 : transport Fructose

* Sodium-Glucose Co-Transport :
  - → Na moves along conc. gradient
  - → Glucose moves against conc. gradient
  - → ATP required
  - → $Na^+ - K^+$ ATPase
  - → Sodium-dependent Glucose Transporter (SGLT)

• Phosphorylation → Kinases

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• Dephosphorylation → Phosphatases

* Two phases of Glycolysis:

1- Energy Investment phase

2. Energy production phase

Step 1:

Glucose

ATP → ADP ↓ • Hexokinases • Glucokinases — Rate determining step — Irreversible step

Glucose-6-phosphate

Hexokinase	Glucokinase (Also called Hexokinase-IV)
• present in all tissues	• Liver, β cells of pancreas
• Km Small	• km ↑
• efficiency large	• Efficiency ↓
• Vmax small	• Vmax ↑
• Regulated by Glucose-6-phosphate	• Respond to hyperglycemia and hypoglycemia
	• Glucose sensor
	• Regulated by Fructose-6-phosphate

Scanned with CamScanner

- bisphosphate → phosphate on 2 diff positions
- 2,3 bisphosphoglycerate in RBCs serve to increase O_2 delivery

Glucose

↓ Hexokinase, Glucokinase

Glucose-6-phosphate

⇅ Phosphoglucoisomerase

Fructose-6-phosphate

PFK-2 bifunctional

ATP → ADP — Phosphofructokinase-1 (PFK-1)

Fructose 2,6 phosphate

Fructose-1,6-bisphosphate

Aldolase

DHAP ⇌ Glyceraldehyde-3-Phosphate

G3P

NADH + H⁺ ← NAD, Pi

(First oxidation-reduction reaction of glycolysis)

2,3 bisphosphoglycerate ← RBCs ← 1,3-Bisphosphoglycerate

↓ ADP → ATP (Substrate level energy production)

3 Phosphoglycerate

↓

2-Phosphoglycerate

Enolase → Phosphoenolpyruvate → Pyruvate

• Fructose 2,6-bis... inhibitor of fructose-1,6-bisphosphatase, an enzyme of gluconeogenesis.

* Regulators of Phosphofructokinase-1

1. ATP (high ATP inhibit enzyme)
2. Citrate (high levels inhibit enzyme)
3. AMP (high AMP enhance enzyme)
4. Fructose-2,6-bisphosphate (activator of enzyme)

* Phosphofructokinase-2 (PFK-2) is bifunctional ie it acts as kinase as well as phosphatase

• In well fed state, insulin level is high while Glucagon level is down.

Due to high insulin level, the PFK-2 is dephosphorylated due to which phosphatase activity of PFK-2 is inhibited while kinase activity is enhanced.

Due to increased kinase activity of PFK-2, glycolysis proceeds.

- In fasting state, increased glucagon leads to phosphorylation of PFK-2 due to which kinase activity is inhibited and phosphatase activity is enhanced. Glycolysis does not proceed.

* Phosphoenolpyruvate

ADP
ATP ↙ | Pyruvate kinase

↓

Pyruvate

* Pyruvate kinase main Regulator:

Fructose-1,6-bisphosphate (activator)

Feed Forward Regulation

(Remember: Decreased insulin level phosphorylates both PFK-2 and pyruvate kinase)

* Pyruvate Kinase is inhibited by ATP

* Regulation of pyruvate kinase in liver depends on kinase or phosphatase activity.

Decreased insulin level phosphorylates pyruvate kinase due to which kinase activity of pyruvate kinase is inhibited while phosphatase activity is enhanced. and PEP is not converted to pyruvate.

Increased insulin level dephosphorylate pyruvate kinase due to which phosphatase activity of pyruvate kinase is inhibited while kinase activity is activated and PEP is converted to pyruvate.

* Three main Regulatory steps of Glycolysis:

1- Formation of Glucose-6-phosphate.
2- Formation of Fructose-1,6-Bisphosphate
3- Conversion of PEP into pyruvate

Regulators of Enzymes

1. Glucokinase → Fructose-6-phosphate
2. Hexokinase → Glucose-6-phosphate
3. Phosphofructokinase-1:
   (i) ATP
   (ii) Citrate
   (iii) AMP
   (iv) Fructose-2,6-bisphosphate
4. Phosphofructokinase-2:
   (i) Insulin
   (ii) Glucagon
5. Pyruvate kinase
   (i) Fructose-1,6-bisphosphate (activator)
   (ii) ATP (inhibitor)

NADH = 3 ATP
FADH = 2 ATP

ENERGY PRODUCTION

* Glycolysis
  - → 2 ATP used
  - → 4 ATP produced
  - → 2 NADH produced
  - → Net ATP = 2 (through substrate level phosphorylation
  - → 2 NADH will produce 6 ATPs through oxidative phosphyration in ETC
  - → Product = 2 Pyruvate

2Pyruvate → 2Acetyl CoA → TCA cycle
(2NADH)

These 2 NADH = 6ATP in ETC

* TCA cycle

From each pyruvate =

3 NADH, 1 FADH, 1 ATP

(12 ATP per pyruvate)

(24 ATP per Glucose molecule)

Net ATP

Glycolysis = 8

Pyruvate - Acetyl CoA = 6

TCA = 24

Total = 38 ATP per Glucose

* Substrate level phosphorylation

Glycolysis = 2

TCA = 2

Total = 4

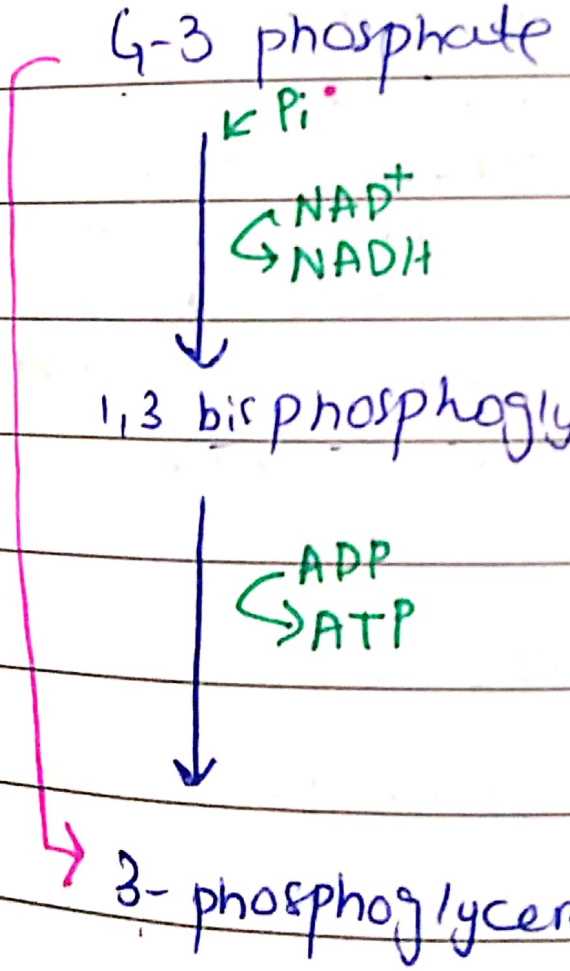
* Oxidative phosphorylation = 34

ARSENIC POISONING

Arsenic present in pentavalent (Arsenate) and trivalent form (Arsenite)

Arsenate → affect Glycolysis

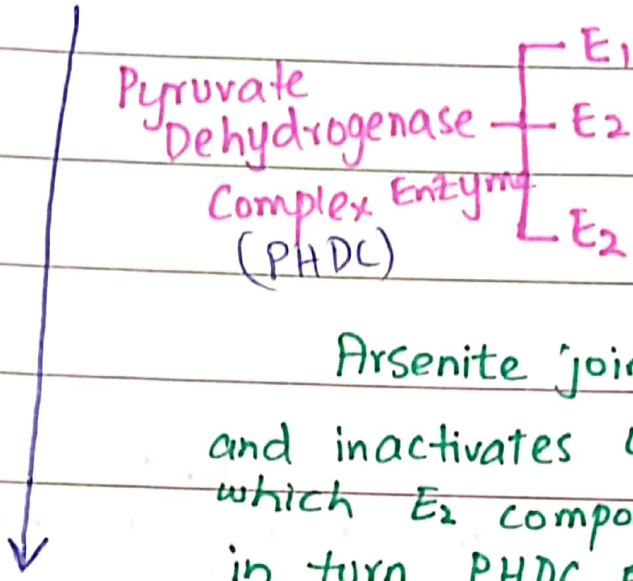
Arsenite → affect TCA



Arsenate compete with Pi and attack as substrate in place of Pi.
Due to Arsenate, G3P directly converts into 3-phosphoglycerate thus bypassing the energy producing processes of glycolysis and rendering glycolysis useless

Arsenite (~~pen~~ trivalent) inhibit TCA

Pyruvate



Arsenite joins with -SH group and inactivates lipoic acid. due to which E_2 component inactivates and in turn PHDC ~~com~~ inactivates.

Acetyl Co-A

Pyruvate can't convert to Acetyl CoA. Pyruvate level raises and it is dangerous in higher levels causing neurotoxicity leading to death.

Arsenite inhibit all enzymes which have lipoic acid as co-enzyme including PHDC and α-ketoglutarate

* Three regulatory enzymes of Glycolysis:

1- Glucokinase / Hexokinase

2- Phosphofructokinase

3- Pyruvate kinase

GLYCOLYSIS – LIPINCOTT POINTS

* GLUT are uniporters as they transport one molecule at a time.
* Number of ~~glu~~ GLUT-4 transports active in muscles and adipose tissues is increased by insulin.
* Transport through SGLT occurs in epithelial cells of the intestine, renal tubules and choroid plexus.
* Mammals have four isozymes of the enzyme hexokinase that catalyze the phosphorylation of glucose to Glucose-6-phosphate.
  - Hexokinases I-III : in most tissues
  - Hexokinase IV : also called Glucokinase, present in liver parenchymal cells and pancreatic β-cells.

  Glucokinase has a high Vmax, allowing the liver to effectively remove the flood of glucose delivered by the portal blood, thereby minimizing hyperglycemia.

* Glucokinase indirectly inhibited by Fructose-6-phorphate.
- Glucokinase indirectly stimulated by Glucose.
- In the presence of Fructose-6-phosphate, glucokinase binds tightly to ~~GKRP~~ GKRP (Glucokinase Regulatory Protein) and is translocated to the nucleus, thereby rendering the enzyme inactive.
- When glucose levels increase, glucokinase is released from GKRP and the enzyme reenters the cytosol where it phosphorylates glucose to glucose-6-phosphate.
* Fructose 2,6-bisphosphate is an activator of glycolysis (activator of PFK-1) while an inhibitor of gluconeogenesis (inhibitor of fructose 1,6 bisphosphatase) to ensure that both pathways are not fully active at the same time.

* Due to elevated level of insulin, PFK-2 is dephosphorylated. Kinase activity increased and glycolysis proceeds
* Due to elevated levels of glucagon and decreased levels of insulin, PFK-2 is phosphorylated; phosphatase activity increased and inhibition of glycolysis takes place.
* Mature RBCs lack mitochondria, so they are completely dependant on Glycolysis ~~mitochondria~~ for energy/ATP production
* Anaerobic Respiration takes place in RBCs, lens and cornea of eye and The kidney medulla
* During intense exercise, lactate accumulate in muscle, causing a drop in intracellular pH, potentially resulting in cramps

* The direction of Lactate Dehydrogenase (LDH) reaction i.e. anaerobic pathway depend on:

1. Relative intracellular conc. of pyruvate and lactate
2. NADH / NAD^+ ratio

- Liver and heart oxidize lactate to pyruvate.

In liver, pyruvate is either converted to glucose by gluconeogenesis or converted to Acetyl CoA that is oxidized in TCA cycle.

Heart muscle exclusively oxidize lactate to CO_2 and water via TCA cycle

* Elevated conc. of lactate in plasma termed Lactic Acidosis (a type of metabolic acidosis), occur when there is a collapse of circulatory system,

such as with MI, pulmonary embolism, and uncontrolled hemorrhage, when an individual is in shock.

The additional O_2 required to recover from a period when O_2 availability has been inadequate is termed the **O_2 debt**. [In many clinical situations, measuring the blood levels of lactic acid allows the rapid, early detection of O_2 debt]

* Increased insulin initiates an increase in amount of glucokinase, PFK-1 and pyruvate kinase in liver.

* Alternative Fates of Pyruvate:

1- Oxidative decarboxylation to Acetyl CoA by PDHC

2- Carboxylation to oxaloacetate by pyruvate ~~de~~ carboxylase (~~it~~ is a biotin dependent reaction)

3- Reduction to ethanol (occurs in microorganisms such as yeast)

* Acetyl CoA is a TCA cycle substrate and the carbon source for fatty acid synthesis.

* Oxaloacetate is a TCA cycle intermediate and substrate for gluconeogenesis

* Catabolism → Degradation of complex molecules to a few simple products with ATP production

* Anabolism → Synthesis of complex end product from simple precursors with ATP hydrolysis.

KREBS CYCLE / BRAINLESS

TCA / CITRIC ACID CYCLE

→ Main energy production

→ takes place in mitochondria

→ Aerobic pathway i.e. O_2 required

→ Acetyl CoA enters TCA cycle

* Conversion of Pyruvate to Acetyl CoA

Pyruvate

CO_2 ↙

NADH ↙

~~Acetyl~~ CoA →

↓

Acetyl CoA

PDHC —
- E_1 : Pyruvate Decarboxylase
- E_2 : Dihydrolipoil transacetylase
- E_3 : Dihydrolipoid dehydrogenase

* Coenzymes Required :

- E_1 → Thiamine Pyrophosphate
- E_2 → Lipoic Acid , CoA
- E_3 → FAD, NAD^+

* Deficiency of thiamine or niacin can cause serious CNS problems. This is bcz brain cell are unable to produce sufficient ATP if PDHC is inactive. resulting in Wernicke-Korsakoff, an encephalopathy-psychosis syndrome.

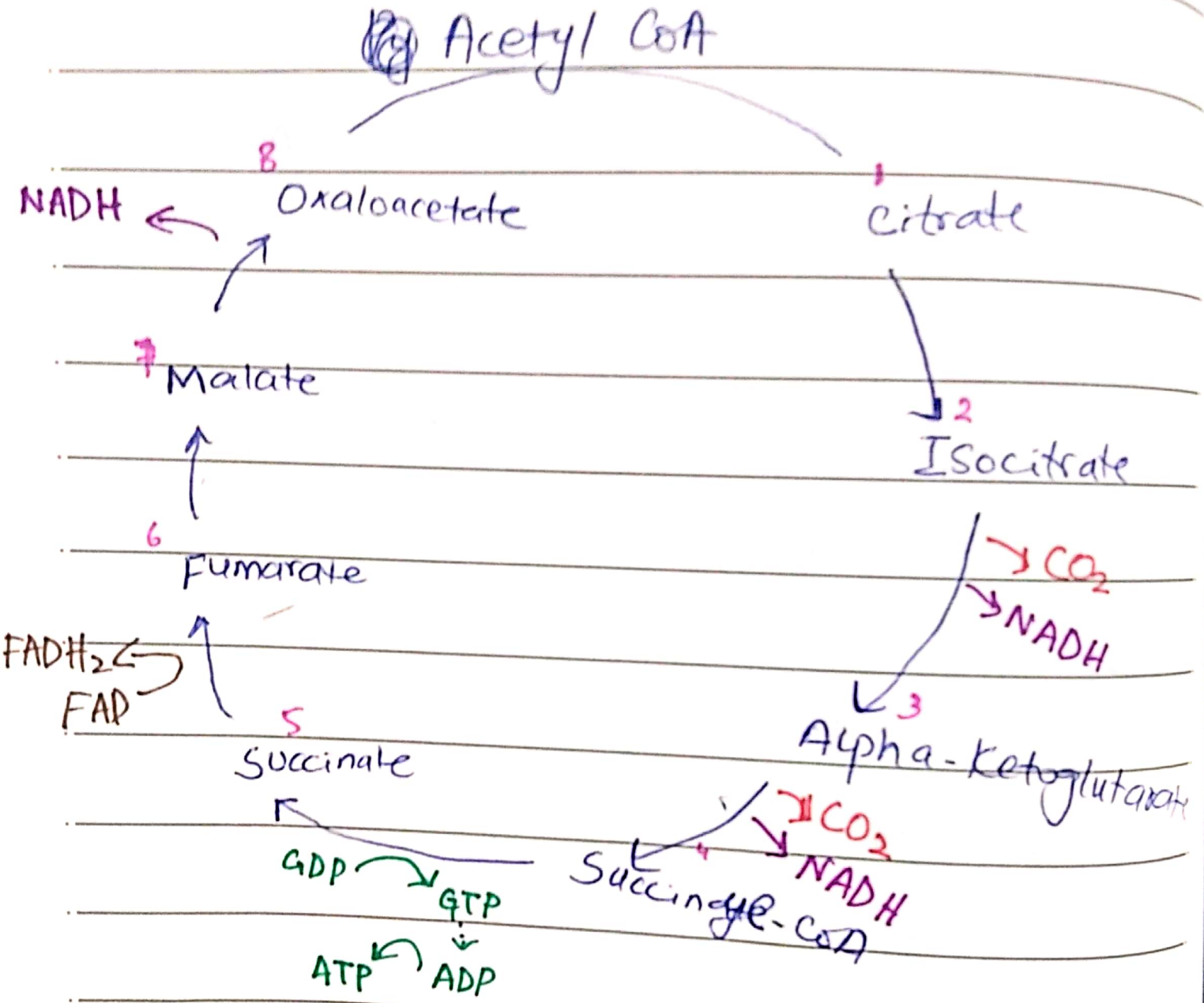
* Regulation of PDHC:
2 Regulatory Enzymes
1- Pyruvate Dehydrogenase Kinase
2- Pyruvate Dehydrogenase Phosphatase

* If ATP or NADPH levels are high, phosphorylation of E_1 component of PDHC takes place and E_1 component is inactivated. (stop reaction)

* If Ca^{+2} level or pyruvate level rises, dephosphorylation of E_1 component of PDHC takes place and E_1 component is activated. Hence reaction proceeds.

* Deficiency of PDHC: (X-Linked Dominant)
→ No conversion of pyruvate to Acetyl CoA
→ No TCA cycle
→ Pyruvate accumulates
→ Pyruvate converts into lactate and further lactic acid resulting in congenital lactic acidosis.
→ Pyruvate neurotoxic resulting in neonatal death

TCA Cycle



→ Nothing madde in 1st, 2nd, 2nd Last step

→ 3 NADH, 1 $FADH_2$, 2 CO_2, ATP

→

Pyruvate

↓ PDHC

Oxaloacetate + Acetyl CoA

↓ Citrate Synthase

Regulation:
- ATP, NADH ⊖, Citrate
- Energy ↓ ⊕

Citrate

Citrate inhibit PFK-1. Thereby inhibiting Glycolysis

↓ Aconitase → inhibited by fluoroacetate. found in drugs / plant toxins.

Fluoroacetate convert Acetyl CoA into fluorocitrate. Aconitase cannot act on fluoroacetate, thereby inhibiting TCA cycle

Isocitrate

CO_2 ↙
NADH ↙

↓ Isocitrate Dehydrogenase

Regulation
- ⊕ ADP + Ca^{2+} ↑
- ⊖ NADH, ATP ↑

Rate limiting step

α-Ketoglutarate

CO_2 ↙
NADH ↙
CoA ↘

↓ α-Ketoglutarate Dehydrogenase Complex (same complex as PDHC with same components and same coenzymes)

Regulation
- ⊖ NADH, ATP, ↑ Succinyl CoA
- ⊕ Ca^{+}, ADP ↑

Succinyl Co-A

Succinyl CoA

GTP → ATP

Succinate Thiokinase (also called succinyl CoA synthetase)

Succinate

$FADH_2$ ←

Succinate Dehydrogenase (present in inner mitochondrial matrix)

[FAD, rather than NAD^+, is the electron acceptor bcz reducing power of succinate is not sufficient to reduce NAD^+]

Fumarate

Hydration

Fumarase

Malate

Oxidation

NADH ←

Malate Dehydrogenase

Oxaloacetate

LIPINCOTT KREBS CYCLE

* Pyruvate is transported from cytosol into the mitochondrial matrix by the pyruvate mitochondrial carrier of the inner mitochondrial membrane.
* Citrate, in addition to being an intermediate in the TCA cycle, is a source of acetyl CoA for the cystosolic synthesis of fatty acids. and cholesterol.
* Citrate also inhibits PFK-1 (the rate-limiting enzyme of glycolysis), and activates acetyl CoA carboxylase (the rate-limiting enzyme of fatty acid synthesis)
* α-ketoglutarate is also produced by the oxidative deamination and transamination of amino acid glutamate.
* Succinyl CoA is also produced from propionyl CoA derived from metabolism of fatty acids with an odd number of carbon atoms and

from the metabolism of several amino acids. It can be converted to pyruvate for gluconeogenesis or used in heme synthesis.

* Succinate Dehydrogenase functions as Complex II of ETC.
* Fumarate is also produced by the urea cycle, in purine synthesis, and during catabolism of amino acids phenylalanine and tyrosine.
* Oxaloacetate is also produced by the transamination of amino acid aspartic acid
* Total 12 ATP produced from oxidation of 1 Acetyl CoA in TCA cycle

BRAINLESS

GLUCONEOGENES

* Glucose synthesis from non-carbohydrate sources.
* ~~Brain~~ CNS, RBCs, Adrenal medulla, lens of eye, testes, exercising muscles need continuous supply of glucose.
* Glycogen stored in liver is converted into glucose by Glycogenolysis.
* Three reactions of glycolytic pathway are not reversible:
  1. Glucose ⟶ Glucose-6-phorphate
  2. Fructose-6-phosphate → Fructose-1,6-Bisphorphate
  3. PEP → Pyruvate
* Non-Carbohydrate Substrate For Gluconeogenesis:
  1. Lactate
  2. Triglyceride
  3. Amino Acids

  All but two amino acids (leucine and lysine) are glucogenic

* Cori Cycle
  ↳ Pyruvate → Lactate → Liver → Pyruvate → Glucose

* Triglyceride → Glycerol → G3P → DHAP → Glucose

* Amino acids → α-Ketoglutarate → Oxaloacetate
  Glucose ← PEP ←

Glucose

↓ (3)

Glucose-6-phosphate

⇅

Fructose-6-phosphate (2)

↓ PFK-1

Fructose 1,6-bisphosphate

↙ ↘

DHAP ⇌ G-3-P

⇅

1,3 Bisphosphoglycerate

⇅

3 Phosphoglycerate

⇅

2-Phosphoglycerate

⇅

PEP (1)

↓ Pyruvate kinase

Pyruvate

① Pyruvate —(Pyruvate carboxylase, CO_2)→ Oxaloacetate

Oxaloacetate —(Malate dehydrogenase)→ Malate

Oxaloacetate cannot move out of mitochondria so it is first converted into malate. Malate is transported outside of mitochondria and converted into oxaloacetate.

Mitochondria

Malate

Mitochondria

cytosol

Oxaloacetate

P_i → , CO_2 ← (PEP-CK)

PEP

② Fructose-1,6-Bisphosphate

—(Fructose-1,6-Bisphosphatase)→

Fructose-6-phosphate

③ Glucose-6-phosphate

—(Translocase)→

Transported to Endoplasmic Reticulun

~~Glucose~~

—(Glucose-6-phosphatase)→

Glucose

* Regulation:

* Increased Glucagon increase cAMP. cAMP activates protein kinase A which further phosphorylate pyruvate kinase and PFK-2 and inactive both these enzymes, thereby stopping glycolysis to proceed further.

* Increased Acetyl CoA drives pyruvate to be converted into oxaloacetate

Lipincott

GLUCONEOGENESIS

* During an overnight fast, 90% of gluconeogenesis occurs in liver, with the remaining 10% occuring in kidneys.

During prolonged fastings, kidney become major glucose-producing organs, contributing 40% of total glucose production.

* Acetyl CoA and compounds that give rise to acetyl CoA (e.g acetoacetate, lysine, and leucine) cannot give rise to a net synthesis of glucose. This is bcz of the irreversible nature of PDHC, which converts pyruvate to acetyl CoA. These compounds give rise instead to ketone bodies and are termed ketogenic.

* Regulation of Fructose 1,6-bisphosphatase:

1. Rise in AMP/ATP ratio (inhibitory)
2. Rise in Fructose-2,6-bisphosphate (inhibitory)

* Specific Gluconeogenesis Reactions:

1- Pyruvate Carboxylation

2- Oxaloacetate transport to cytosol

3- Cytosolic oxaloacetate decarboxylation

4- Fructose-1,6-bisphosphate dephosphorylation

5- Glucose-6-phosphate dephosphorylation

* Pyruvate carboxylase enzyme requires biotin.

* Pyruvate carboxylase is allosterically activated by acetyl CoA.

* Enzymes of Glycolysis:

1- Hexokinase / Glucokinase

2- PFK-1

3- Pyruvate Kinase

* Enzymes of Gluconeogenesis

1- Glucose-6-phosphatase

2- Fructose 1,6-bisphosphatase

3- Pyruvate Carboxylase

4- PEPCK

* The stoichiometry of gluconeogenesis from two pyruvate molecules couples the cleavage of six high-energy phosphate bonds and the oxidation of two NADH with the formation of one glucose molecule.

* Glucagon :

→ Fructose 1,6-bisphosphatase activation

→ PFK-1 inhibition

→ Phosphorylate and inactivate pyruvate kinas

→ increase transcription of gene for PEPCK (Cortisol also increase expression for PEPCK while insulin decreases expression)

GLYCOGEN METABOLISM

→ Glycogen is a polysaccharide made of glucosyl residues

→ Two linkages in Glycogen: α1-4 and α,1-6

* Glycogenes: Synthesis of glycogen
* Glycogenolysis: Degradation of glycogen
* On well fed state, glucose being stored as glycogen in liver (100g) and muscles (400g)
* On fasting state, glycogen breaks down.
* Liver Glycogen → G-6-phosphate → Glucose
* Muscle Glycogen → G-6-phosphate → Glycolysis → Energy

* GLYCOGEN SYNTHESIS:

↳ Two enzymes to be used

1- Elongation enzyme: Glycogen Synthase

2- Branching enzyme: Transferase

Glucose

↓

Glucose-6-phosphate

⇅ Phosphoglucomutase

Glucose-1-phosphate

G-1-phosphate

UDP-Glucose pyrophosphorylase

UTP → UDP

→ Pyrophosphate (PP_i) —pyrophosphatase→ $2P_i$

UDP-Glucose

UDP

H^O

Glycogenin

Tyrosine Ring

Glucose [Glycogenin ~~chain~~ primer protein

↳ Many more glucose residues add up and form primer in presence of Glycogenin

Glycogen synthase

Long chain

α(1-4) Linkages

Branching Enzyme: 4-6 Transferase

α(1-6) Linkages form

GLYCOGEN DEGRADATION: GLYCOGENOLYSIS

* Enzymes used:
  1- Glycogen phosphorylase
  2- Debranching Enzyme
- Chain Shortening + Debranching
- Glycogen phosphorylase breaks α(1-4) linkages and convert it into Glucose-6-phosphate which is converted into Glucose in ER.
- Dextrin Limit
- α(1-6) linkages broken and direct glucose released.

GLYCOGEN METABOLISM ~~DEGRADATION~~ Regulation

Two ways of Regulation
1- Allosteric Regulation
2- Hormonal (Insulin, Glucagon)

- Allosteric Regulation:
  Increase level of
  → Glucose + Glucose-6-phosphate both are positive regulator of glycogen Synthase and negative regulators of glycogen phosphorylase.
  → High ATP activate glycogen synthase while inhibit glycogen phosphorylase.
- Hormonal Regulation:
  → when blood glucose level is down, glucagon and epinephrine is released. As a result GTP converts into GDP. Adenyl cyclase is activated

↓

ATP → cAMP

↓

Protein kinase A

↓

Phosphorylase kinase (active)

↓

Glycogen phosphorylase (active)

↓

Degradation of Glycogen into Glucose-6-phosphate

↓

Glucose in RE

GLYCOGEN METABOLISM

* Glycogen is synthesized from molecules of α-D-glucose. The process occurs in cytosol and requires energy supplied by ATP (for phosphorylation of glucose) and UTP.
* Glucose-1-phosphate is produced by degradation of glycogen, by enzyme glycogen phosphorylase.
This G-1-phosphate is isomerized in cytosol to G-6-phosphate by phosphoglucomutase.
* Muscles lack Glucose-6-phosphatase

FRUCTOSE METABOLISM

→ Sources : sucrose, fruits, honey

→ insulin-independent transport

→ Fructose can be converted into fats, Glycogen, pyruvate,

→ Can go through Glycolysis as well ar Gluconeogenes

→ doesnot promote insulin secretion

Fructose

ATP → Fructokinase

- Aldolase A found in most tissues
- Aldolase B in Liver, kidneys and small intestine
- Aldolase C in brain

Fructose 1-phosphate

Aldolase B

DHAP

Glyceraldehyde

Alcohol Dehydrogenase

G-3-P

Glycerol

G-1,3-bisphosphate

Glycerol-3-phosphate

Pyruvate

Glycolysis

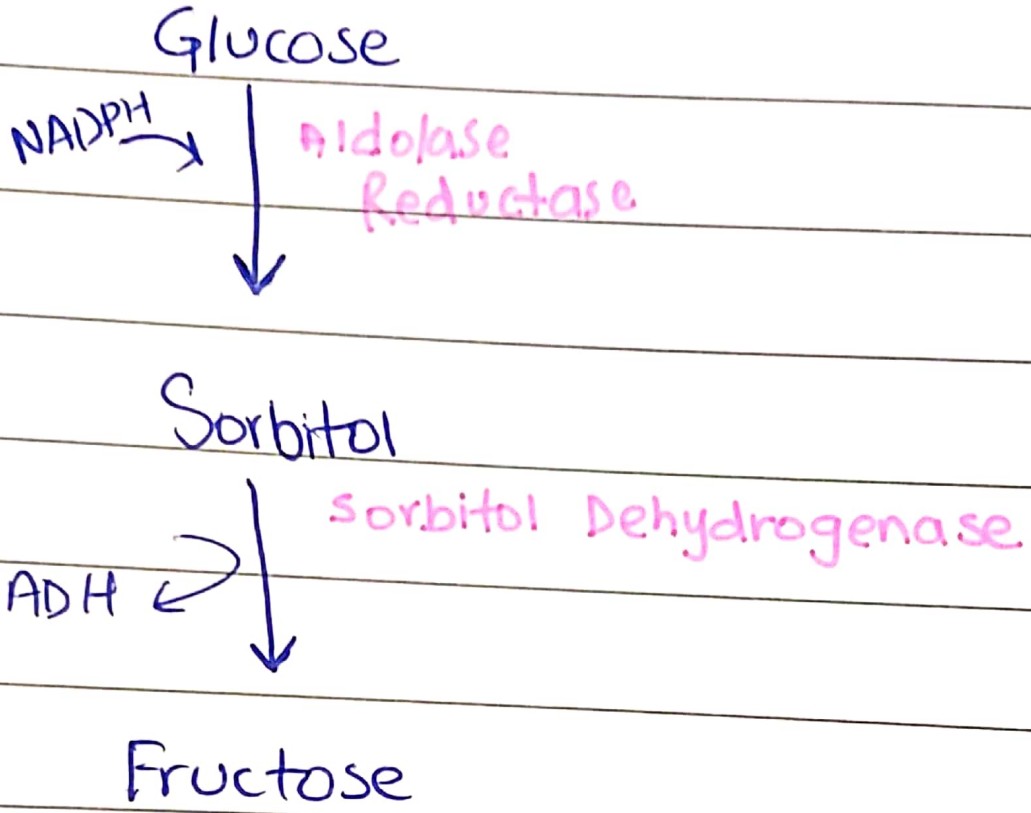
Fats

* Deficienciency of Fructokinase → Fructosourea
* Deficiency of Aldolase B → Heriditary Fructose Intolerance → accumulation of Fructose-1-phosphate

* Mannose
  → C-2 epimer of Glucose
  → important component of Glycoprotein

Mannose
↓ Hexokinase
Mannose-6-phosphate
⇕ Isomerase
Fructose-6-phosphate
↓ PFK-1
Fructose-1,6-bisphosphate
↓
Glycolysis

* GLUCOSE - SORBITOL CONVERSION



* Sorbitol can be used as diuretic

* Sorbitol may accumulate ~~in~~ ~~cells~~ following hyperglycemia in cells when sorbitol dehydrogenase is low or absent, causing strong osmotic effects and cell swelling due to water influx and retention.

GALACTOSE METABOLISM

→ Galactose obtained from lactose, glycoprotein, glycolipids, GAGs

Galactose

ATP → ADP

↓ Galactokinase

Galactose-1-phosphate

Galactose-1-phosphate uridyl transferase (GALT)

UDP-Glucose → UDP-Galactose

UDP-hexose-4-epimerase

Glucose 1-phosphate

↓

Glucose-6-phosphate

↓

UDP-Glucose

Glucose

↓

Glycogen synthesis

GALT is deficient in patient with classic galactosemia

* UDP Galactose can be used to synthesize lactose, glycoproteins, glycolipids, GAGs.

* Lactose intolerance → lack of enzyme β-galactosidase

LIPINCOTT

* The rate of fructose metabolism is more rapid than that of glucose b/c triose production from fructose 1-phosphate bypasses PFK-1, the major rate-limiting step in glycolysis

HMP SHUNT / PENTOSE-PHOSPHATE-PATHWAY

→ cytosol

→ Two phases :

1. Irreversible → Oxidative Phase [1 CO_2 removed, 2 NADPH produced]

2. Reversible → Sugar-phosphate interconversion

* NADPH needed in liver, lactating gland and adipose tissue for synthesis of fatty acids.

* NADPH needed in ovaries, testes, placenta, adrenal cortex for synthesis of steroid hormones

* In RBCs, glutathione is reduced in presence of NADPH

* IRREVERSIBLE REACTION

→ 1 CO_2 removed

→ 2 NADPH produced

→ Ribulose-5-phosphate produced which is converted into Ribose-5-phosphate to be used in nucleotide synthesis

Irreversible

Rate limiting step regulated by ratio of NAPPH/NADP

Glucose-6-phosphate

NADP → NADPH

Glucose-6-phosphate dehydrogenase (G6PD)

↑ Insulin upregulates expression of gene of G6PD

6-Phosphogluconolactone

6-phosphogluconolactone-hydrolase

6-phosphogluconate

NADP → NADPH + CO_2

6-phosphogluconate-dehydrogenase

Reversible

Ribulose-5-phosphate

Xylulose-5-phosphate

Ribose-5-phosphate

Glyceraldehyde-3-phosphate

Purine

Glycolysis

NADPH Uses:

1. Reductive Biosynthesis (by donating its electron)
2. H_2O_2 Reduction
3. Monooxygenase System
4. Phagocytosis
5. NO production

* Reductive Biosynthesis

NADPH $\xrightarrow{H^+}$ NADP

→ used in fatty acid synthesis, cholesterol synthesis

* H_2O_2 Reduction

→ H_2O_2 is reactive oxygen specie

→ toxic

H_2O_2

↓ Glutathione Reductase

$OH^- + H_2O$

NADH reactivates Glutathione to be used as Glutathione Reductase

* Monooxygenase System

$$R\text{-}H + O_2 + NADPH^{+H} \longrightarrow R\text{-}OH + H_2O + \underset{NADPH}{}$$

1- Mitochondrial System (CYP-P450)

2- Microsomal system (CYP-3A4)