Metabolic Biochemistry Notes - 2

Metabolic Biochemistry (University of Technology Sydney)

http://www.youtube.com/watch?v=J8PAPK2h39w
http://www.flashcardmachine.com/biochemistry-523.html
http://voh.chem.ucla.edu/vohtar/spring04/classes/153A-2/pdf/Problem_set_5_solutions.pdf

Metabolic Biochemistry Notes (91320)

by Andrew Severino

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Metabolism Overview

Metabolism: (Greek: metabolē – "change")

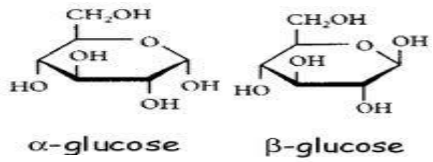
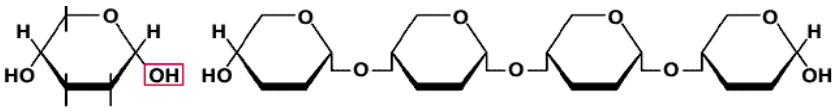
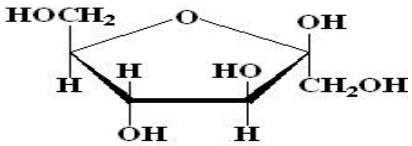
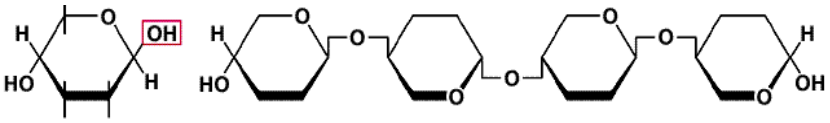
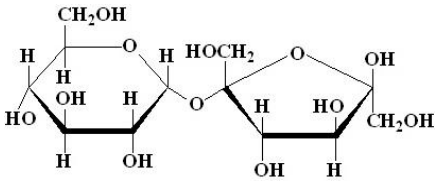
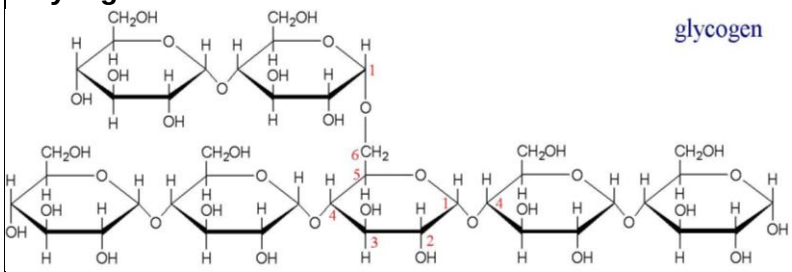
- Has a coherent design with common motifs.
- ***Catabolism:*** energy being created from the breakdown of large molecules to smaller ones.
- ***Anabolism:*** compounds being synthesised by small molecules for cell functioning.
- ***Metabolites:*** substrates, intermediates and products of metabolism.

Summary of Reaction Pathway

CATABOLIC ⟶ ANABOLIC ⟶ METABOLIC

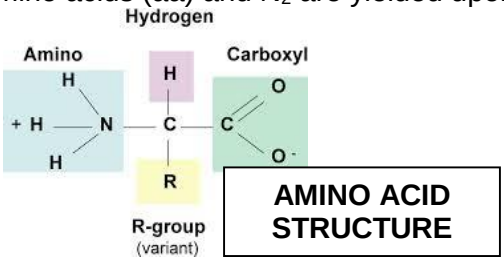
Sources of Energy

- The 3 ways that humans obtain energy:
  1. Carbohydrates
     - 3 forms: simple sugars (glucose, fructose, sucrose), cellulose and starch.

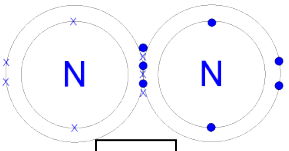
Simple	***Complex***
Glucose  α-glucose β-glucose	**Starch**  **Alpha-glucose** **Amylose**
Fructose 	**Cellulose**  **Beta-glucose** **Cellulose**
Sucrose 	**Glycogen**  glycogen

- Glucose ($C_6H_{12}O_6$) is yielded upon digestion.
- Energy is made by glucose being further digested.
- Found in food such as rice, bread, corn and cereals.

2. Proteins
   - Major building blocks for cells and tissues.
   - Also have enzymatic properties.
   - Amino acids (aa) and N_2 are yielded upon digestion.



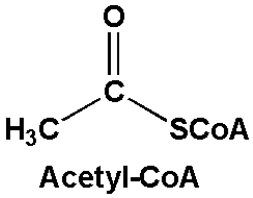
AMINO ACID STRUCTURE



N_2

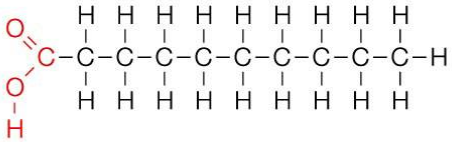
   - AA ⟶ Proteins through translation process.
   - Found in foods such as meat, poultry, fish, nuts and dairy products.

3. Lipids and Fats
   - Concentrated sources of energy with different functions.
   - Fatty acids and Acetyl-CoA (a coenzyme) is yielded upon digestion.
   - Acetyl-CoA ⟶ Energy (ATP) through Citric Acid Cycle.
   - Saturated fatty acids have single bonds, polyunsaturated have double or triple bonds.

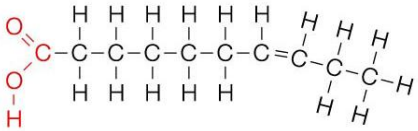


Acetyl-CoA

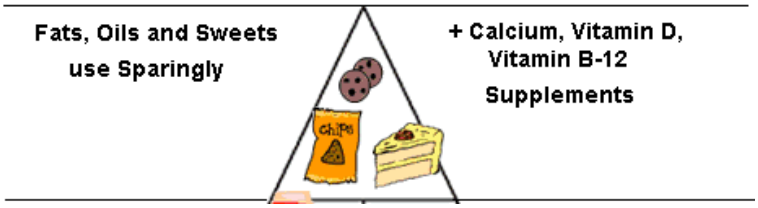
Saturated



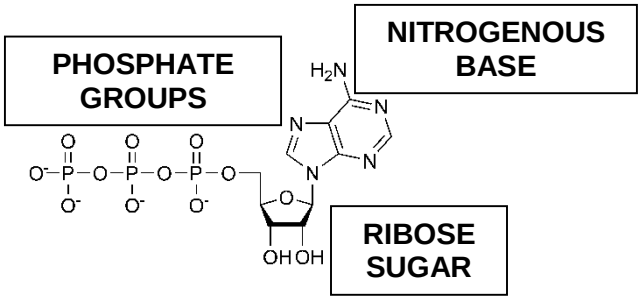
Unsaturated



   - Found in foods such as sweets, butters, oils and fast foods.



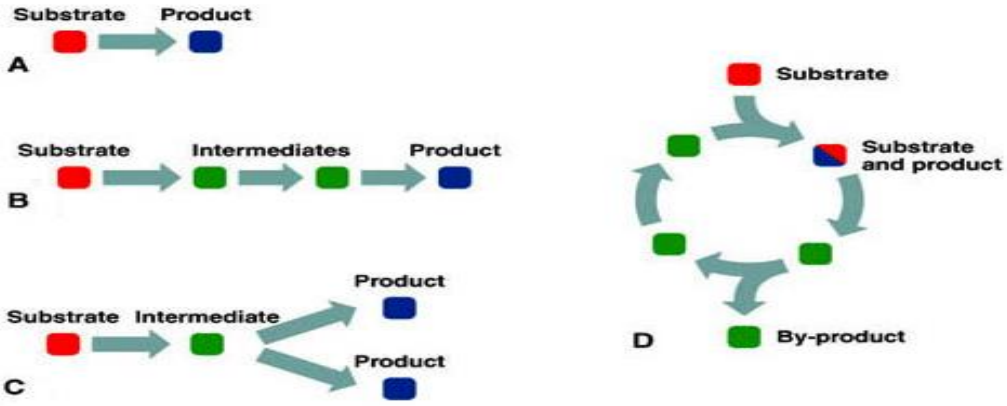
Adenosine Triphosphate (ATP)



- Energy currency of cells.
- Phosphate groups have high energy bonds due to their covalence.
- **ATP** ⟶ **ADP** ⟶ **AMP**
- Carrier of chemical energy.
- Nicotinamide Adenine Dinucleotide (NAD^+) carry H^+ and e^-.

Metabolic Pathways

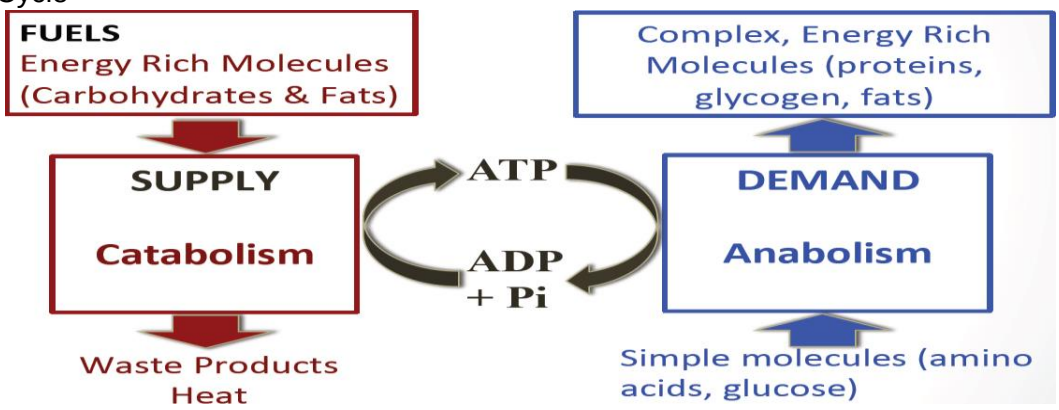
- Series of reactions catalysed by enzymes.
- They share intermediates and products.
- Catabolic reactions are exergonic (ones that yield free energy from metabolites).
- Energy released by catabolic reactions is utilised to synthesise ATP.
- A few intermediates are shared in catabolism process.
- Products can be re-used as substrates for other reactions.
- Reactions abide to cellular demand by being continuously regulated and coordinated.



What is the difference between oxidised and reduced molecules?

- Reduced molecules have accepted e- which can be passed on to release free energy (more H^+).
- Oxidised molecules are donors of e- and can pass less free energy (more O_2).
- Fatty acids are highly reduced whereas glucose is highly oxidised.

ATP Cycle



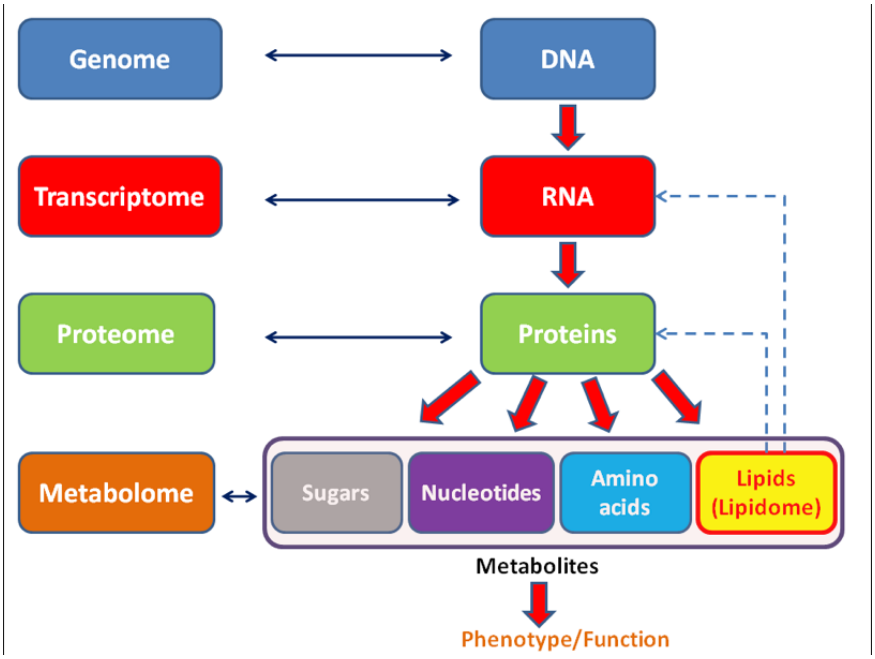
Inherited Metabolic Diseases

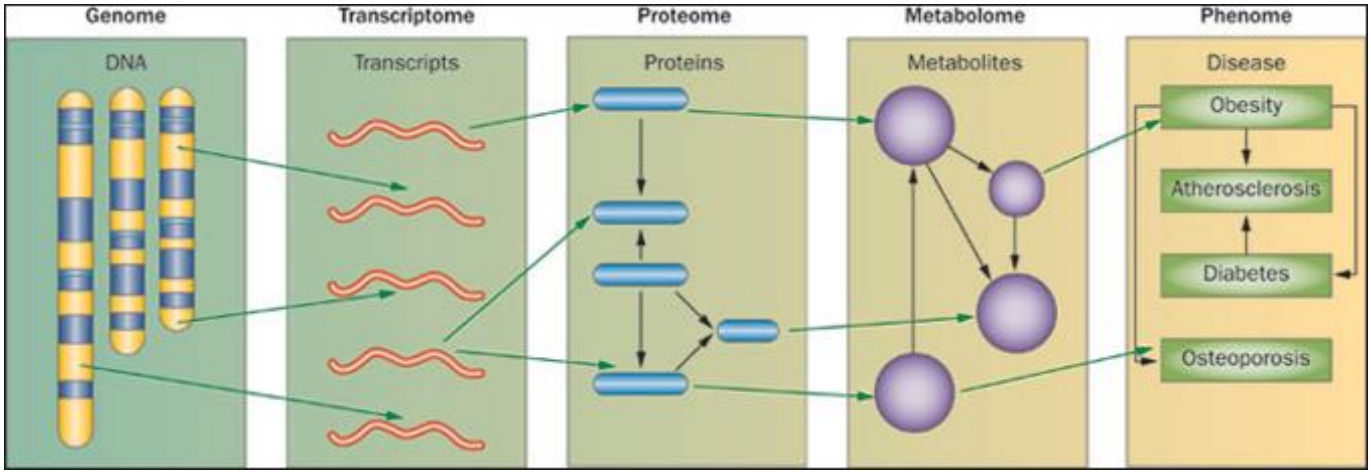
- Large class of genetic disease which involves disorders of metabolic.
- Can be caused by a single defective genes in the enzymatic process, substrates⟶ products.
- Mainly includes carbohydrate and AA diseases.

Metabolomics

Systematic study of unique chemical fingerprints that are left behind by specific cellular processes.

- Metabolomes represent a collection of all metabolites in an organism's biological cells, tissues and organs.
- Metabolic profiling = instantaneous snapshot of a cells' physiology.





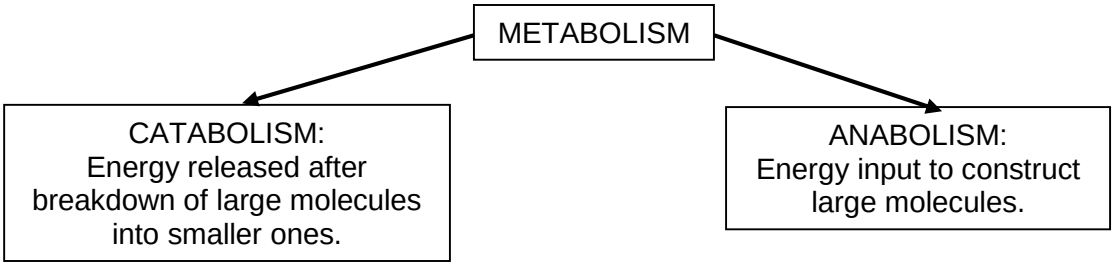
Bioenergetics and Enzyme Catalysis

What is Life?

- Breathing Energy and Respiration
- Energy of organic molecules used for respiration.

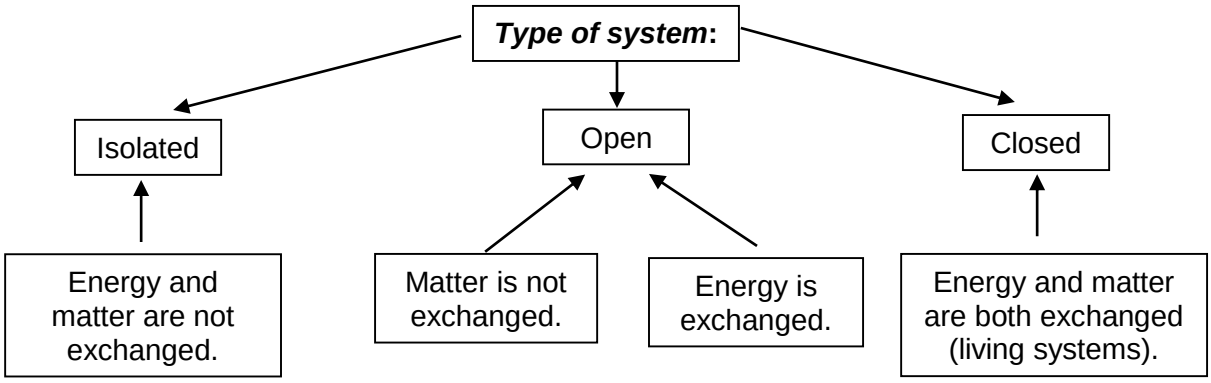
Bioenergetics

- Antoine Lavoisier discovered that chemical reactions needed O_2.
- Metals became heavier when reacted with O_2 and lighter when react with carbon.
- How does a cell?... Extract energy and reduce power from environment, and synthesize macromolecules.



Thermodynamics

- Flow of energy, heat and matter.
- Systems must be at equilibrium.
- Determines the stability of a system or the spontaneity of a reaction.



Equilibrium Constant

$$A + B \longleftrightarrow C + D$$

$$K_{eq} = \frac{[C][D]}{[A][B]}$$

$K_{eq} = equilibrum\ constant$
$[\,] = concentration\ of\ substituent.$
$A\ \&\ B = reactants$
$C\ \&\ D = products$

Thermodynamic laws

1. **Conservation of Energy**
    - "Energy is neither created nor destroyed, but transformed and transferred.
2. **Universe tends towards increasing disorder**
    - "In all natural processes the universe's entropy increases.
    - > Entropy = Randomness.
    - Entropy also increases when heat is given off.

Free Energy (Gibbs's Free Energy)

- "Energy that can be harnessed to do work".
- Chemical bonds also contain energy that can do work.
- Carbon-Hydrogen bonds are reduced (contains e^-) meaning that they contain vast amounts of energy.

$$+\boldsymbol{\Delta G}$$

$= Unfavourable\ reaction\ that\ does\ not\ occur\ spontaneously\ because\ an\ energy\ input\ is\ needed.$

$-\boldsymbol{\Delta G} = favourable\ reaction\ that\ does\ occur\ spontaneously\ because\ energy\ is\ released.$

- Glycogen degradation is a favourable reaction whereas the synthesis of peptidoglycan is an unfavorable reaction.
- Free energy (ΔG) is used to do Work.
- Non-useable energy is lost to disorder (entropy:ΔS).

$$\boldsymbol{Total\ Energy = \Delta G + \Delta S}$$

$$\boldsymbol{Exergonic\ Reaction: \Delta G < 0}$$
$$\boldsymbol{Endergonic\ Reaction: \Delta G > 0}$$

Thermodynamic Parameters

- Change in ΔG:
    - Negative, exergonic, loss of energy from system and favourable.
    - Positive, endergonic, system gains energy and unfavourable.
- Change in Enthalpy (ΔH):
    - Negative, exothermic, loss of heat from system.
    - Positive, endothermic, system gains heat.
- Change in ΔS:
    - Negative, order increases, entropy loss.
    - Positive, order decreases, entropy gain.

$$\boldsymbol{\Delta G = \Delta H - T\Delta S}$$
$$\Delta G = Gibbs's\ Free\ Energy$$
$$\Delta H = Change\ in\ Enthalpy$$
$$T = Temperature\ (Kelvin: K)$$
$$\Delta S = Change\ in\ Entropy$$

Favourable Reaction	***Unfavourable Reaction***
$\Delta H < 0$	$\Delta H > 0$
$\Delta S > 0$	$\Delta S < 0$
$\Delta G < 0$	$\Delta G > 0$

Quantifying thermodynamic Parameters

- ΔG is used to express the magnitude of the force driving a system to equilibrium when the system is not at this point.
- $\Delta G'°$ = difference between a product's free energy content and reactants free energy content.
- $\Delta G'°$ is used for:
  - Standard transformed constants.
  - Standard biological condition (buffered solutions): $[H^+] = 10^{-7}M$, $[H_2O] = 55.5M$

$$\boldsymbol{\Delta G'° = -RTInK'_{eq}}$$

$$R = 8.31447 \frac{J}{mol.K}\ (Universal\ Gas\ Constant)$$

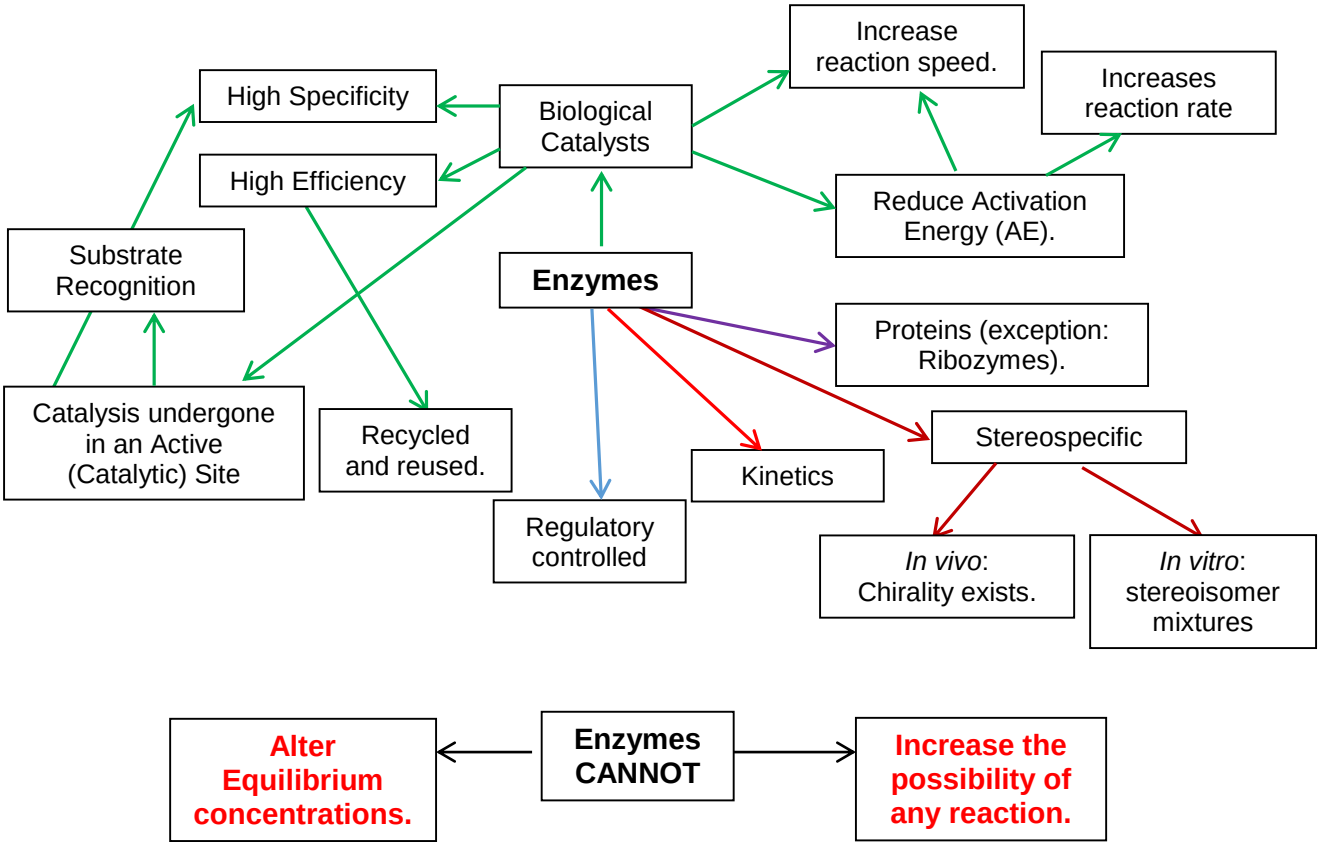
$$T = temperature\ (K)$$

$$In\ is\ the\ natural\ log$$

Rules:		
$K'_{eq} > 1.0$	$\Delta G'° = -ive$	▪ Reaction proceeds forward spontaneously. ▪ Products less free energy than reactants.
$K'_{eq} = 1.0$	$\Delta G'° = 0$	▪ Reaction at equilibrium.
$K'_{eq} < 1.0$	$\Delta G'° = +ive$	▪ Reaction tends to proceed in reverse. ▪ Products more free energy than reactants.

- Creatine contributes as an energy source to muscle contractions.
- Two forms:
  Free creatine
  Creatine phosphate
- Quickly replenishes ATP.
- Energy is released when chemical bonds are broken.
- Reduced compounds carry energy.

Chapter 6 – Enzymes (pp.



Activation Energy

- Energy required for a reaction to take place (to start).
- Determines reaction speed.
- A path of least resistance is followed.
- Always positive.

Enzyme Kinetics as an approach to understanding the mechanism (pp. 200-

- A reaction rate the amount of time that a reactant takes to be converted into a products.
- Rate constants (k) and [chemicals] determine the rate.

Reaction	***Rate of reaction***
A ⟶ C	$-[\boldsymbol{A}] = \boldsymbol{k}[\boldsymbol{C}];\ \ \boldsymbol{decrease\ in}\ [\boldsymbol{A}]$ $[\boldsymbol{C}] = \boldsymbol{k}[\boldsymbol{A}];\ \ \boldsymbol{increase\ in}\ [\boldsymbol{C}]$

NOTE: Enzyme kinetics is used to determine the rate of a reaction and how experimental parameters change this reaction rate.

Equilibrium Simple Reaction

$$V_{forward} \underset{K_{-1}}{\overset{K_{+1}}{\rightleftharpoons}} V_{reverse}$$

E + S ⟷ ES ⟷ EP ⟷ E + P

NOTE: Enzyme is Recycled and Product can be used for other reactions.

Rate Equation:

$$V = k[S]$$

Equilibrium Constants:

$$V_{forward} = k_{+1}\,[A]$$
$$V_{reverse} = k_{-1}\,[C]$$
$$k_{+1}[A] = k_{-1}[C](At\ Equilibrium)$$

- Therefore Equilibrium constant for a reaction is equal to:
  I. Equilibrium ratio of product and reactant concentrations.
  II. Ratio of characteristic rate constants of reaction.

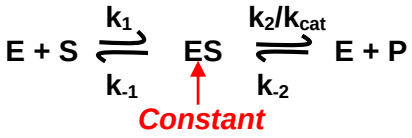
$$k_{eq} = \frac{k_{+1}}{k_{-1}} = \frac{[C]}{[A]}$$

- Rate of reaction by enzymatic catalysis can be affected by substrate concentration [S].
- Initial velocity (V_0) is a function of [S] and [S] itself is a constant.

$$V_0\ increases\ linearly\ with\ [S]\ when\ low$$
$$increase\ in\ [S]\ slows\ increase\ in\ V_0$$
$$V_0 \approx [S]\ increase$$

Maximum velocity (V_{max}) is this plateau-like region where [S] and V_0 remain the same because the enzyme has reached saturation point.

Assumptions



- *No reverse reaction ($k_{-2} = 0$).*
- *k_2 is rate limiting (k_{cat}).*
- *[ES] is constant.*

K_{cat} = # substrate molecules converted to product over a specified time on one enzyme molecule that is always saturated.

- Pre-steady state of a catalytic reaction is when [ES] builds up.
- Steady state is where [ES] remains constant over time.

Michaelis-Menten Equation:

$$V_0 = \frac{V_{max}\,[S]}{K_m + [S]}$$

$$V_0 = initial\ velocity$$

$$V_{max} = \max velocity$$

$$[S] = concentration\ of\ substrate$$

$$K_m = Michaelis\ Constant$$

Maximal Velocity

- Rate of reaction WILL NOT increase indefinitely if [S] is increased indefinitely.
- Saturation point is where the rate of reaction slows due to all catalytic sites being occupied by substrate.
- The equation reflects the velocity of which an enzyme catalyses a reaction.

Michaelis Constant

- Measures the binding affinity of enzyme for substrate.
- Low K_m there is tighter binding and high K_m means weaker binding.
- If the constant is higher, a much larger [S] is needed to achieve half maximum velocity of reaction velocity.

$$K_m = \frac{(k_{-1} + k_2)}{k_1}$$

Mitochondria has low K_m
Cytosol has high K_m.

Double-Reciprocal Plot (Lineweaver-Burk Plot)

$$\frac{1}{V_0} = \left(\frac{K_m}{V_{max}}\right)\frac{1}{[S]} + \frac{1}{V_{max}}$$

$$x - intercept = \frac{-1}{K_m}$$

$$y - intercept = \frac{1}{K_m}$$

Enzyme Inhibitors

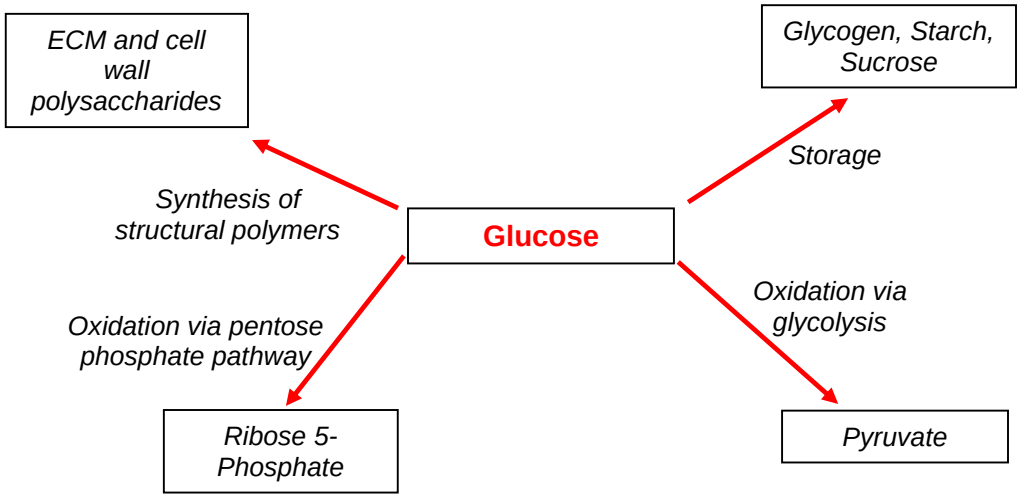
- Irreversible inhibitors take long to dissociate from target enzyme due to covalent bonding (i.e. drugs and toxins).
- Reversible inhibitors rapidly dissociate from enzyme and can be competitive, uncompetitive or mixed.

Competitive Inhibitor ▪ Resembles substrate. ▪ Binds at catalytic site of free enzyme. ▪ Causes catalysis of substrate to stop, therefore no product is made.	***Uncompetitive Inhibitor*** ▪ Binds to another site that is not the active site. ▪ Binds to ES complex.	***Mixed Inhibitor*** ▪ Inhibitor site can be in the enzyme or ES complex. ▪ Noncompetitive inhibitors can bind enzyme even if substrate is bounded or not.

Regulatory Enzymes

- When the product from a particular enzymatic reaction binds to an allosteric site, the conformation of that enzyme's catalytic site is altered.
- This alteration of the catalytic site is known as allosteric modulation.
- In any reaction, allosteric enzymes are at the initial steps or branch points.

Chapter 14 – Glycolysis, Gluconeogenesis, and the Pentose Phosphate Pathway (pp. 543-580)



Glycolysis (pp. 544-558)

Greek: glykys = "sugar" and lysis = splitting

- This process involves several enzyme-catalysed reactions that reduce glucose to make 2 pyruvate molecules.
- Throughout the process, free energy is stored as ATP and NADH.
- **Fermentation** is the anaerobic reduction of organic nutrients to obtain energy.

Overview of Glycolytic phases

- Glycolysis has a preparatory phase and payoff phase.

Preparatory Stage (5 steps)

- *Involves the phosphorylation of glucose and its conversion to glyceraldehyde 3-phosphate*.

1) Glucose *phosphorylated* at hydroxyl (OH) group on C-6 to make **glucose 6-phosphate**.
2) **Glucose 6-phosphatase** is then *converted* into **fructose 6-phosphate**.
3) **Fructose 6-phosphate** is then *phosphorylated* on C-1 to make **fructose 1, 6-bisphosphate**.

In the first 3 steps, ATP is the phosphoryl group donor.

4) **Fructose 1, 6-bisphosphate** is then cleaved to yield **Dihydroxyacetone phosphate** and **Glyceraldehyde 3-phosphate**.
5) Isomerisation of Dihydroxyacetone phosphate to a second Glyceraldehyde 3-phosphate.

Payoff Stage (Steps 6-10)

6) *Oxidation* and *phosphorylation* by PO_4^{3-} of both **Glyceraldehyde 3-phosphate** molecules occurs to yield two molecules of **1, 3-Biophosphoglycerate**.
This also produces 2 NADH and ADP molecules.

7) Two ATP are formed by *phosphorylation of ADP*. This causes both **1, 3-bisphosphoglycerate** molecules to become **3-phosphoglycerates**.

8) **3-phosphoglycerate** molecules *converted* to **2-phosphoglycerate** molecules.

9) **2-phosphoglycerate** then undergoes a *dehydration reaction* to form **phosphoenolpyruvate (PEP)** and two *ADP* molecules.

10) *Phosphoryl group is transferred* from **PE**P to ADP and the end products are 2 ATP molecules and 2 **pyruvate molecules**.

The Preparatory Phase of Glycolysis in Detail

1) Phosphorylation of glucose through hexokinase trapping it in cells

- **Hexokinase** activates glucose through the *phosphorylation* of C-6.
- This *phosphorylation* occurs through ATP being a phosphoryl (PO_3^{2-}) donor and **hexokinase** transferring PO_3^{2-} to C-6 of glucose.

NOTE: Mg^{2+} is needed to activate hexokinase because it shields the negative charges that the ATP PO_3^{2-} group possesses.

- This forms ADP and yields **glucose 6-phosphate (G-6-P).**

NOTE: This is an irreversible reaction and phosphorylation of glucose must occur to destabilise it and because G-6-P cannot diffuse out of cell.

2) Isomerisation: Converting G-6-P to Fructose 6-phosphate

- **Phosphohexose isomerase (phosphoglucose isomerase)** catalyses the *reversible isomerisation* of the aldose G6P to the ketose **fructose 6-phosphate (F6-P**).
- This promotes the formation of a fructose 5C ring.
- Small$\Delta G'° = 1.7\ kJ/mol$.

3) Phosphorylation of F6-P to fructose 1,6-bisphosphate

- **Phosphofructokinase-1 (PFK-1)** catalyses the transfer of a PO_3^{2-} from ATP to 1-C of F6-P and yields **fructose 1, 6-bisphosphate**.

Mg^{2+} is again used for this step.

- ***PFK-1*** *is an allosteric enzyme that has its activity regulated when ATP is diminished or if there is an excess of ADP and AMP*.

4) Cleavage of 1, 6-bisphosphate

- **Aldolase** catalyses a reversible *aldol reaction* of **1,6-bisphosphate** to yield *two* **triose phosphates**:
  - **Dihydroxyacetone phosphate (DHP) – an aldose.**
  - **Glyceraldehyde 3-phosphate (GAP) – a ketose**.

These triose phosphate compounds are isomers of each other.

5) Interconversion of DHP and GAP

- **Triose phosphate isomerase** rapidly and reversibly converts **DHP** into **GAP** two form a second **glyceraldehyde 3-phophate** molecule.

The formation of two glyceraldehyde molecules ends the preparatory stage!!

The Payoff phase of Glycolysis in Detail

6) **Oxidising GAP yields 1, 3-bisphosphoglycerate.**
   - **Glyceraldehyde 3-phosphate dehydrogenase** *oxidises* **GAP** to yield **1, 3-bisphosphoglycerate (1, 3-BPG)**.
   - *Aldehyde (H-C=O) group* on **GAP** is *oxidised* to a *carboxylic acid anhydride*, an *acyl phosphate* with a high standard free energy.
   - Energy is conserved by the *acyl phosphate group* being formed at C-1 of **1, 3-BPG**.
   - NADH is formed by the reduction of NAD^+ and is continuously reoxidised.to NADH.
   - *Reduction* of NAD^+ also yields H^+ ions

1, 3-bisphosphoglycerate has high PO_3^{2-} transfer potential.

7) **1, 3-BPG phosphoryl transfer to ADP**
   - The high-energy PO_3^{2-} group from carboxyl group (C-1) of **1, 3-BPG** is transferred to ADP via the enzyme **phosphoglycerate kinase (PGK)**.

Mg^{2+} is used in the reaction and PGK does the reverse reaction.

   - This phosphorylation yields **3-phosphoglycerate** and ATP.
   - With ATP being formed by phosphorylation of **1, 3-bisphosphoglycerate** it is referred to as substrate-level phosphorylation.

Net ATP = 0

NOTE: Steps 6 and 7 constitute an enzyme-coupling reaction where 1, 3-BPG is the product of step 6 and the reactant of step 7.

8) **Isomerising 3-phosphoglycerate to make 2-phosphoglycerate**
   - **Phosphoglycerate mutase** catalyses a *reversible shift of the PO_3^{2-} group* between C-2 and C-3 of **glycerate**.

NOTE: Mg^{2+} is vital for this step to proceed.

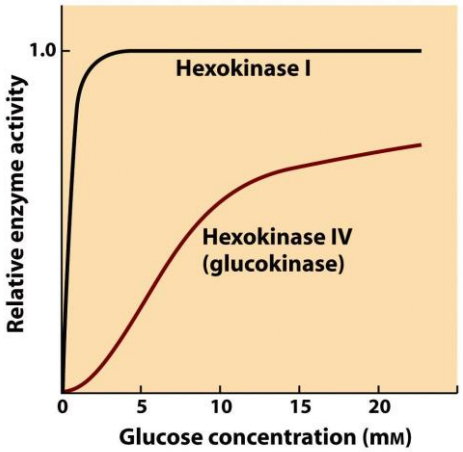
   - This reaction occurs in two steps to yield **2-phosphoglycerate**.

9) **2-phosphoglycerate dehydrated to phosphoenolpyruvate**
   - **Phosphenolpyruvate (PEP)** is yielded from **enolase** promoting *reversible removal* of water from **2-phosphoglycerate**.
   - Mechanism of **enolase reaction** involves an *enolic intermediate* stabilised by Mg^{2+}.

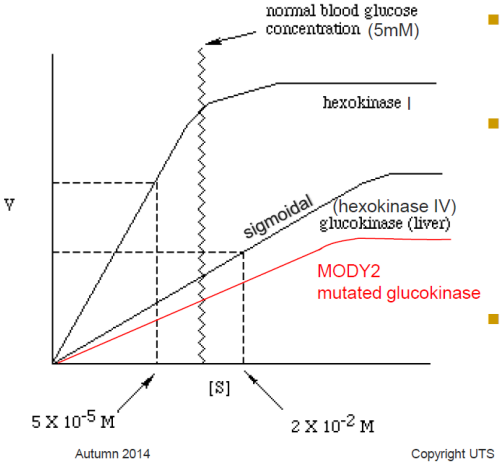
10) **PO_3^{2-} group transfer from phosphoenolpyruvate to ADP**
   - A PO_3^{2-} group is transferred from **PEP** to ADP is catalysed by **pyruvate kinase**.
   - For **pyruvate kinase** to carry out catalysis K^+, Mn^{2+} or Mg^{2+} is needed.
   - **Pyruvate** first appears in its **enol** form and then undergoes *tautomerisation rapidly* and *nonenzymatically* to its keto form.
   - Large*, negative standard free-energy change*.

Isoenzymes

- Different enzymes that catalyse the same reaction
- **Hexokinase** and **Hexokinase IV (glucokinase)** catalyse the reaction of glucose and ATP.
- Hexokinase IV is found in the liver and pancreas.



Glucokinase & MODY2



- Normal glucokinase: insulin secretion as the glucose >5 mM.
- MODY2: loss-of-function mutations → glucokinase molecule that is less sensitive or less responsive to rising levels of glucose.
- β-cells have a normal ability to make and secrete insulin, but do so only above an abnormally high threshold (7-8 mM).

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Gluconeogenesis (pp. 570-580)

- Process in which glucose is made.
- Mainly occurs in the liver.
- Glucose is sythesised from pyruvate.
- Glycolytic reactions involving **hexokinase**, **PFK-1** and **pyruvate kinase** must be bypassed due their large negative ΔG.

1. Bypass 1: Conversion of pyruvate to PEP

- This involves two exergonic reactions:
  - *i. Reaction where pyruvate is the glucogenic precursor*
    - ***Alanine*** *transanimated* from ***pyruvate***.
    - **Pyruvate carboxylase** *(only in mitochondria)* converts ***pyruvate*** to ***oxaloacetate***.
      Coenzyme Biotin is needed for this conversion to take place.
    - **Mitochondrial malate dehydrogenase** *reduces* ***oxaloacetate to malate*** in order for it to be transported across the membrane.
    - ***Malate*** is reoxidised to oxaloacetate by **cytosolic malate dehydrogenase**.
    - The final product, ***PEP*** is made by **phosphoenolpyruvate carboxykinase** converting oxaloacetate.
      Reaction is dependent on Mg^{2+}, and a PO_3^{2-} group from GTP.

ii. *Reaction where lactate is the glucogenic precursor*.
   - **Lactate** is transformed to **pyruvate** by **lactase dehydrogenase**, which also yields NADH and H^+ ion.
   - Once in the mitochondria, **oxaloacetate** is made by **pyruvate** being converted by **pyruvate carboxylase**.
   - **Oxaloacetate** is then quickly converted to **PEP** by the **isozyme mitochondrial PEP carboxykinase** and transported out of the mitochondria

2. Bypass 2: Phosphofructokinase

- **Fructose 6-phophate** is made by Mg^{2+}-dependent fructose **1, 6-bisphosphatase (FBPase-1)** *hydrolysing* the C-1 of **fructose 1, 6-bisphosphatase**.

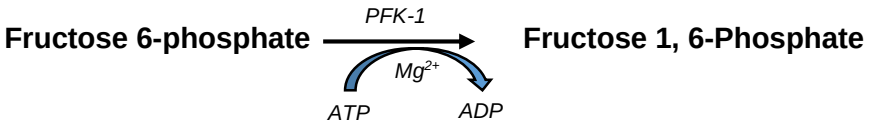
3. Bypass 3: Hexokinase

- *Dephosphorylation* of **glucose 6-phosphate** to **glucose**.
- **Glucose 6-phosphotase** catalyses the *hydrolysis reaction* to yield **glucose**.

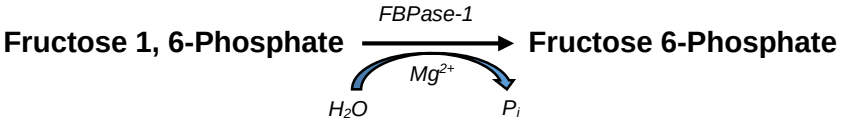
Regulation of Glycolysis and Gluconeogenesis (page 574)

- Regulated by **allosteric phosphorylation**.

GLYCOLYSIS



GLUCONEOGENESIS



Regulation by Transcription

- Increase hexokinase gene transcription activates glycolysis.
- Increase in glucose 6-phosphatase gene transcription activates gluconeogenesis.

Regulation: Fructose 2, 6-bisphosphatase

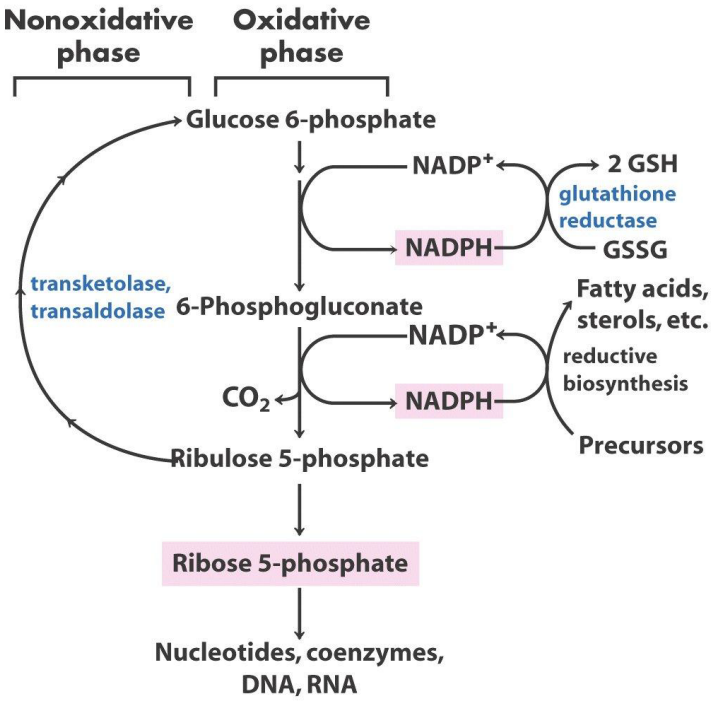
- Stimulates PFK-1 in glycolysis.
- Inhibits FBPase-1 in gluconeogenesis.

Regulation: Pyruvate kinase

- Glycolysis is inhibited by ATP, acetyl-coA and fatty acids.
- Glycolysis is activated by stimulation of pyruvate kinase by F1, 6BP.

Pentoses and NADPH

- Rapidly dividing cells: bone marrow, skin and intestinal mucosa.
- Free radical exposed cells: RBCS and cornea.
- Cells synthesising fatty acids: liver, adipocytes and lactating mammary glands.
- Cells synthesising cholesterol and steroid hormones.



Chapter 16 – The Citric Acid Cycle (pp. 633-666)

The Mitochondria

- Matrix contains: pyruvate dehydrogenase (PDH), enzymes of the Citric Acid Cycle (CAC) and enzymes of other pathways.
- Outer membrane: large ion channels.
- Inner membrane: cristae, ATP synthase, a major permeability barrier.

How is pyruvate transported into the mitochondria?

- Pyruvate is transported in a symport with H^+ by pyruvate translocase.

Pyruvate preparation via oxidative decarboxylation (page 634)

- **Oxidative decarboxylation** is an irreversible oxidative reaction which sees a carboxyl group ($O=C-O^-$) removed from pyruvate as CO_2.

  OXIDATION of the carboxyl group yields a 2C pyruvate molecule.
- This process generates NADH which then gives up a hydride (H^-) ion to the respiratory chain.

  Reaction is catalysed by pyruvate dehydrogenase.
- In anaerobic conditions, **pyruvate** is *oxidised* to **lactate** or **ethanol**.

Pyruvate dehydrogenase (PDH) Complex coenzymes (pp. 634-635)

I. **Coenzyme A (CoA-SH)**
   - Reactive *thiol (-SH)* group vital for **CoA** as and *acyl carrier*.
   - *Thioesters* formed by acyl groups covalently binding to the –SH group.
   - Thioesters have a high acyl group transfer potential, allowing donation to several acceptor molecules.

II. **Nictotinamide adenine dinucleotide (NAD^+)**
   - Reversible reduction of nicotinamide ring.
   - Soluble e^- carries.

III. **Flavin adenine dinucleotide (FAD)**
   - Derived from riboflavin.
   - *Dimethylisoalloxazine ring* system can underdo *oxidation* and *reduction*.
   - ***Permanently bound*** to E_3 of **PDH complex**, acting as a temporary e^- holder.

     $$FAD + 2e^- + 2H^+ \longrightarrow FADH_2$$

     PERMANTELY BOUND TO E_3.

IV. **Lipoate**
   - Has *two thiol groups* that can undergo *oxidation* to form a disulphide bond (-S-S-).
   - **Can be an e^- carrier and an acyl carrier**.
   - Carboxyl end of *lipoic acid* chain forms an *amide bond* with *sidechain of lysine residue* of E_2 to yield *lipoamide*.
   - Long flexible arm links each *dithiol* of lipoamide to *one of two lipoate-binding domains* of E_2.
   - This flexible arm extends from core of multienzyme complex and exchange reducing equivalents to E_3.

     PEMANENTLY BOUND TO E_2.

V. **Thiamine pyrophosphate (TPP)**
   - Derivative of *thiamine* (vitamin B_1).
   - H^+ readily disassociates from the carbon (N=C-S) of *thiazole ring*.

- This results in a *carbanion* that can attack the e⁻deficient *keto carbon* of **pyruvate**.

PERMANTELY BOUND TO E_1.

Three enzymes of the PDH Complex (page 635)

1. **Pyruvate dehydrogenase (E_1)**: 20-30 copies.
2. **Dihydrolipoyl transacetylase (E_2)**: 60 copies.
3. **Dihydrolipoyl dehydrogenase (E_3)**: 6 copies.

PDH reaction

i. *Keto carbon (C-1)* of **pyruvate** reacts with *carbanion (C-2)* of **TPP** on E_1 yields addition compound. *Thiazole ring* promotes loss of CO_2 and left is a **hydroxylethyl-TPP**.
ii. *Hydroxylethyl carbanion* on TPP of E_1 reacts with –S-S- of lipoamide on E_2. Keto carbon oxidised to acetate and –S-S- of lipoamide reduced to two –SH groups
iii. Acetate transferred from –SH of lipoamide to –SH of CoA to form acetyl-CoA.
iv. *Reduced lipoamide* swings to E_3 active site. Dihydroylipoamide is reoxidised to the –S-S-, as $2e^- + 2H^+$ are transferred to E_3 –S-S-.
v. Dithiol on E_3 is reoxidised as $2e^- + 2H^+ \rightarrow$ FAD. $FADH_2$ is then reoxidised,

$2e^- + NAD \rightarrow NADH + H^+$.

http://www.wiley.com/college/boyer/0470003790/animations/pdc/pdc.htm

Citric Acid Cycle (pp. 638-655)

1) **Formation of Citrate**
   - **Citrate synthase** catalyses the *condensation* of **acetyl-CoA** and **oxaloacetate** to **citrate**.
   - *Methyl carbon* of *acetyl group* on **pyruvate** is attached to the *C-2* of **oxaloacetate**.
   - On the catalytic site of citrate synthase, a temporary high-energy *thioester intermediate*, **citroyl-CoA** is formed.
   - **Cytroyl-CoA** undergoes a rapid *hydrolysis reaction* to free **citrate** and **CoA** which then are released from catalytic site.
   - *Hydrolysing* the **citroyl-CoA** causes the reaction to be *highly exergonic* $\Delta G'^{\circ} = -32.2\ kJ/mol$.

     NOTE: CoA is released to convert the second pyruvate to citrate.

2) **Cis-Aconitate forms Isocitrate**
   - **Aconitase** catalyses the *reversible transformation* of **citrate** to **isocitrate**.
   - Transformation occurs through the intermediary formation of **cis-aconitate** that **cannot** disassociate from the **aconitase active site**.
   - *Reversible addition* of H_2O to the double bond of **cis-Aconitate** is promoted by **aconitase**.
   - Iron-sulphur centre of **aconitate** binds substrate at active site and catalytic addition/removal of H_2O.

3) **α-Ketoglutarate and CO_2 are products formed by Oxidation of Isocitrate**
   - *Oxidative decarboxylation* of **isocitrate** forms **α-Ketoglutarate** and CO_2 which is released.
   - Reaction is catalysed by **isocitrate dehydrogenase**.
   - Found in the enzyme's catalytic site is Mn^{2+} which interacts with the C=O group of **oxalosuccinate intermediate** and stabilises the **enol** formed by *decarboxylation*.

NOTE: Oxalosuccinate intermediate DOES NOT leave the binding site until it is decarboxylated into α-Ketoglutarate.
Both the intermediate and enol are formed temporarily.

4) **Oxidation of α-Ketoglutarate to Succinyl-CoA and CO_2**
   - **Succinyl-CoA** and CO_2 are formed by the *oxidative decarboxylation* of **α-Ketoglutarate**.
   - This *decarboxylation* is catalysed by the **α-Ketoglutarate dehydrogenase complex**, where NAD^+ acts as an e^- acceptor and CoA as a **succinyl group carrier**.
   - Energy of oxidation of **α-Ketoglutarate** is convsered in the *succinyl-CoA thioester bond*.

5) **Conversion of Succinyl-CoA to Succinate**
   - **Succinate** is made by energy from breaking the *thioester bond* of **succinyl-CoA** being used to synthesise a *phosphoanhydride bond* in GTP.
   - Reaction is catalysed by **succinyl-CoA synthetase**.
   - **Intermediate step: enzyme molecule being phosphorylated as a His residue found in its active site.**
   - PO_3^{2-} is transferred to ADP (GDP) to form ATP (GTP).
   - **Nucleoside diphosphate kinase** catalyses the *reversible reaction* of the PO_3^{2-} transfer from GTP (formed by succinyl CoA) to ADP to make ATP.

6) **Oxidation of Succinate → Fumarate**
   - **Succinate** is *oxidised* by **flavoprotein succinate dehydrogenase** to **fumarate**.
   - Electrons pass from **succinate** through FAD to form $FADH_2$.
   - E^- Are then passed from $FADH_2$ to O_2, the terminal e^- acceptor in the Electron Transport Chain (ETC).

NOTE: Succinate dehydrogenase is tightly bound to the mitochondrial inner membrane of eukaryotic cells.

7) **Malate → Fumarate via hydration**
   - **Fumerase** catalyses the *reversible hydration* of **fumarate** to **L-malate**.
   - *Carbanion* is a transition state of this reaction.
   - *Highly stereospecific*; trans double bond of **fumerate** is hydrolytically catalysed.

8) **Oxidation of L-Malate → Oxaloacetate**
   - *Oxidation* of **L-malate → oxaloacetate** is catalysed by NAD-linked **L-malate dehydrogenase**.
   - *Endergonic reaction* with a very large standard *free energy*.
   - **Citrate synthase** continually removes **oxaloacetate**.

http://www.wiley.com/college/boyer/0470003790/animations/tca/tca.htm

Energy of oxidations in Cycle is Efficiently Conserved (pp. 647-648)

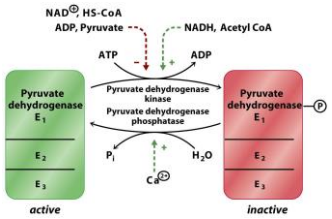
- Energy released in *oxidations* of **isocitrate** and **α-ketoglutrate** was conserved with 3x NAD^+ and 1x FAD being reduced and ATP being produced.
- **Oxaloacetate** is regenerated at the end of cycle.
- Although the cycle only produces 1x ATP (**succinyl-CoA→succinate**), the *four oxidation steps* provide a large flow of e^- to the respiratory chain via NADH and $FADH_2$.

Citric Acid Cycle Regulation (pp.653-655)

PDH complex is regulated by allosteric regulation and covalent modification

- **PDH complex** is inhibited by ATP, NADH and acetyl-CoA.
- Greatly enhanced from *allosteric inhibition* by fatty acids (FA).
- AMP, CoA and NAD^+ (fuels) *allosterically activate* the **PDH complex** when acetate levels are very low.
- NADH competes with NAD^+ for binding to $\mathbf{E_3}$.
- Acetyl-CoA competes with CoA for binding to $\mathbf{E_2}$.
- **Citrate synthase** is *inhibited* by NADH, succinyl-CoA, citrate and ATP but is *allosterically activated* by ADP.
- **Isocitrate dehydrogenase** is inhibited by ATP and allosterically activated by Ca^{2+} and ADP.
- Succinyl-CoA and NADH *deactivate* the **α-ketoglutarate dehydrogenase complex**, but Ca^{2+} *allosterically activates* it.

Regulation of the mammalian PDH Complex via covalent modification



Chapter 19 – Oxidative Phosphorylation (pp. 731-

Overview

- Transference of e^- from NADH and $FADH_2$ to membrane bound proteins in **ETC**.
- This transference creates a protein gradient across the inner mitochondrial membrane.
- **Ubiquinone (Coenzyme Q or Q)** and **Cytochrome C (Cyt *c*)** are mobile e^- carriers that transport e^- from protein to protein.
- $FADH_2$ e^- → Q → Cyt c → ½ O_2 + $2H^+$ → $2H_2O$.
- Electrochemical gradient is used to produce ATP through the **ATP synthase rotary motor**.
- Iron-sulfur (Fe-S) proteins is iron being associated with either inorganic sulfur or S atoms of Cys residues (Cys-SH) in the protein.
- These Fe-S centres can range from a single Fe atom to 4Cys-SH or Fe-S centres with two or four iron atoms.

RIESKE iron-sulphur proteins are single Fe atoms being coordinated to two His-residues.

Electrons are funneled to universal e^- acceptors (page 734)

- When e^- enter the respiratory chain, oxidative phosphorylation commences.
- They arise from dehydrogenases which collect them from catabolic pathways and funnel them to universal e^- acceptors, NAD^+ and FMN or FAD^+.

Nicotinamide nucleotide-linked dehydrogenase

NAD^+ ⇌ oxidised substrate + NADH + H^+

E^- pass through a series of membrane bound carriers (page 735)

- **Q** and **Cyt c** are mobile electron carriers.

Ubiquinone (Co enzyme $Q_{(10)}$/Q)

- Lipid-soluble benzoquinone ring with long isoprenoid side chain.
- Can diffuse across the lipid bilayer of the inner mitochondrial membrane and is able to transport reducing equivalents between other, less mobile e^- carriers.
- Central role in coupling e^- flow and H^+ movement.

Cytochrome c

- Heme C centre.
- Soluble protein associated with outer surface of inner membrane by electrostatic forces.

Multienzyme Complex (737-

Complex I: NADH → Ubiquinone

- Known as **NADH dehydrogenase** and made of 42 different peptide chains.
- These peptide chains include an *FMN-containing protein* and at least six *Fe-S centres*.
- Catalyses two simultaneous and obligatory coupled processes:
  1) **Exergonic transfer of H^- from NADH → ubiquinone and H^+ from the matrix**.
     $$NADH + H^- + Q \rightarrow NAD^+ + QH_2$$
  2) **Endergonic transfer of $4H^+$ from matrix → intermembrane space**.
     $$NADH + 5H_N^+ + Q \rightarrow NAD^+ + QH_2 + 4H_P^+$$
- This makes **Complex I** a *proton pump* that is driven by the energy of e^- transfer.
- **QH_2 diffuses from Complex I → Complex III**.

Complex II: Succinate → Ubiquinone

- It is **succinate dehydrogenase**.
- E^- transfer: **succinate-binding site → FAD → $FADH_2$ → Fe-S → Q-binding site**.
- **Heme *b* IS NOT** in the direct path of e^- transfer, and serves to prevent leakage of e^- from succinate → O_2 to produce H_2O_2 and $\cdot O_2^-$.

Complex III: Ubiquinone to Cytochrome *c*

- **Ubiquinone: cytochrome c oxidoreductase or cytochrome bc_1 complex**.
- This complex *couples e^- transfer* from **ubiquinol (QH_2)** to **Cyt *c*** with vectorial transport of H^+ from matrix to intermembrane space.
- The **Q cycle** is a model used to describe the passage of e^- and H^+ through **Complex III**.
  $$\mathbf{QH_2 + 2cyt\ c_1\ (oxidised) + 2H_N^+ \rightarrow Q + 2cyt\ c_1\ (reduced) + 2H_P^+}$$
- **Q cycle** accommodates the switch between $2e^-$ carrier **ubiquinol** and $1e^-$ carriers (cytochromes *b*, *c* and c_1).
- **Cyt *c*** is a soluble protein of intermembrane space.
- After heme accepts e^- from **Complex III**, **Cyt *c*** transverses to donate it to the binuclear copper centre in **Complex IV**.

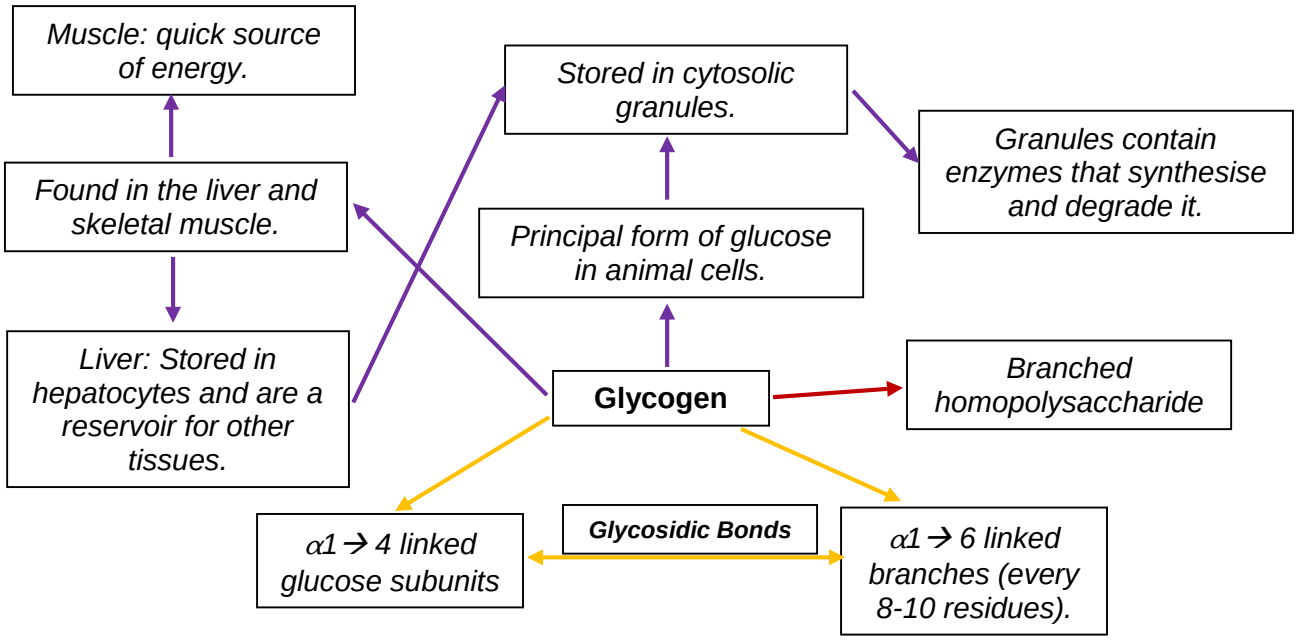
Complex IV: Cytochrome *c* → O_2

- Known as **cytochrome oxidase** which carries electrons from **Cyt *c* → O_2 to form H_2O**.
- Cytochrome oxidase has three subunits that are vital for its function.
- ***Subunit II*** contains two Cu ions complexed with –SH groups of two Cys residues in a *binuclear centre (Cu_A)*, resembling 2Fe-2S centres.
- **Subunit I** has two heme groups; *heme a* and *a_3*, and another Cu ion (*Cu_B*).
- *Second binuclear centre, Heme a_3 and Cu_B* accepts e^- from *heme a*, transferring them to O_2 which is bound to a_3.
  E^- transfer: Cyt *c* → Cu_A → heme a → heme a_3-Cu_B centre → O_2.
- $4H^+$ from *N-side* are consumed by enzyme in converting O_2 → $2H_2O$ after $4e^-$ have passed through complex.
- Energy from this reaction is used to pump $1e^-$ into *P-side* for each e^- that has passed through, adding to the electrochemical potential.
  $$\mathbf{4\ cyt\ c\ (reduced) + 8H_N^+ + O_2 \rightarrow 4\ cyt\ c\ (oxidised) + 4H_P^+ + 2H_2O}$$

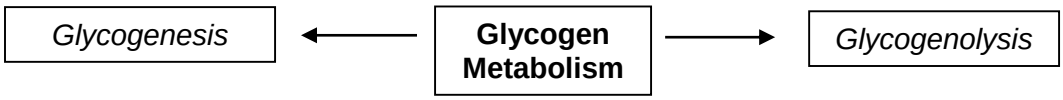
NOTE:

- **Reaction involves redox centres that can carry only ONE e^- at a time and incompletely reduced intermediates MUST NOT be released.**
- **Intermediates TIGHTLY bound to complex until FULL conversion to water.**

Overview of Glycogen (pp. 255-



Glycogen Metabolism (pp. 612-619)



Enzymes in the Glycogenolysis Pathway

A. Glycogen Phosphorylase

- Cleaves the $\alpha 1 \rightarrow 4$ glycosidic linkage from the non-reducing end of glycogen.
- Forms **Glucose-1-phosphate** by adding a phosphoryl (PO_3^{2-}) on C1.
- Cleavage is continuous but stops when it is 4 residues away from the $\alpha 1 \rightarrow 6$ glycosidic linkage.

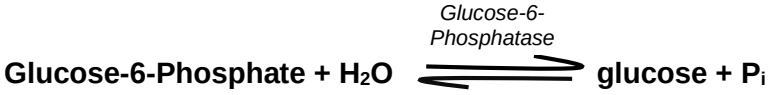
B. Glycogen Debranching Enzyme

- Has two independent active sites that catalyses 2 successive reactions:
  1. **Transferase Activity**
     - Transers 3 glucose residues to the non-reducing end of the glycogen chain.
  2. **$\alpha 1 \rightarrow 6$ Glucosidase Activity**
     - Cleaves $\alpha 1 \rightarrow 6$ glycosidic linkage and yields a free glucose residue.
     - Creates a non-branched portion of glycogen chain in which glycogen phosphorylase can begin catalysing.

C. Phosphoglucomutase

Glucose-1-Phosphate $\rightleftharpoons$ glucose-6-phosphate

- G-6-P can enter glycolysis in skeletal muscle.
- G-6-P is catalysed by glucose-6 phosphatase in liver and the glucose is released into blood stream.

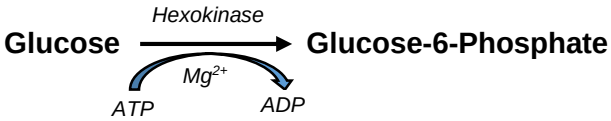


http://www.youtube.com/watch?v=Eovh2X4sLLA
http://oregonstate.edu/instruct/bb450/summer09/lecture/glycogennotes.html

Glycogenesis

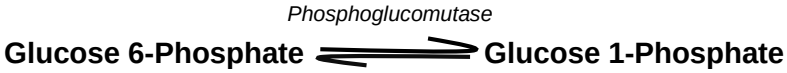
- Occurs in skeletal muscle and liver.

1. Production of Glucose-6-Phosphate.

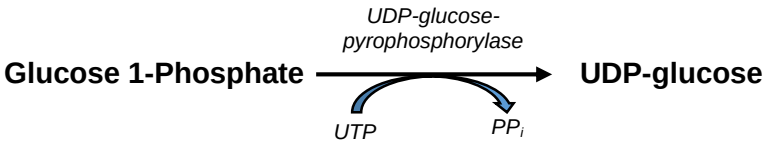


- **Hexokinase I** and **Hexokinase II** catalyse this reaction in skeletal muscle.
- **Hexokinase IV** catalyses this reaction in liver.

2. **Conversion of G-6-P to G-1-P.**

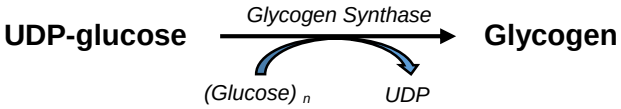


3. **Synthesis of UDP-glucose from G-1-P and UTP**.



- UDP-glucose pyrophosphorylase catalyses the reaction of G-1-P to UDP-glucose.
- Nucleotide UTP being used in reaction and two inorganic phosphates are lost.
- UDP is made and is attached to C1 of the glucose residue.

4. **Glycogen is made by glycogen synthase catalysing the reaction of UDP-glucose.**



- **UDP-glucose** immediately donates glucose residues.
- **Glycogen synthase** then transfers the glucose residue from UDP-glucose to α1→ 4 glycosidic linkage of the branched glycogen molecule.
- By glycogen synthase elongating glycogen chains, the solubility of it increases.

Glycogen Synthase CANNOT initiate new glycogen chains.

http://www.youtube.com/watch?v=RKUPqmCO6TQ

Glycogen Branching Enzyme

- Transfers a segment (7 residues) from non-reducing end of glycogen chain to C6 of a glucose residue of a different chain, yielding a branch with α1→ 6 linkage.

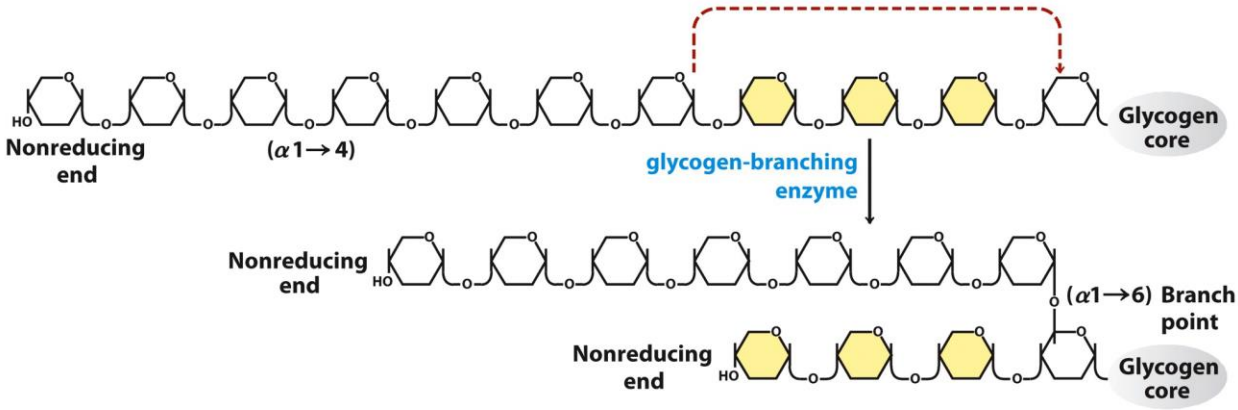


Figure 15-33
Lehninger Principles of Biochemistry, Sixth Edition

Glycogenin Primes the initial sugar residues in Glycogen (page 619)

Primer *which assembles new chains.*	← **Glycogenin** →	***Enzyme*** *that catalyses the assembly.*

- A glucose residue from UDP-glucose is transferred to the hydroxyl (-OH) of tyrosine^{194} (Tyr^{194}) of **glycogenin**.
- This reaction is catalysed by the protein's intrinsic **glucosyl-transferase activity**.

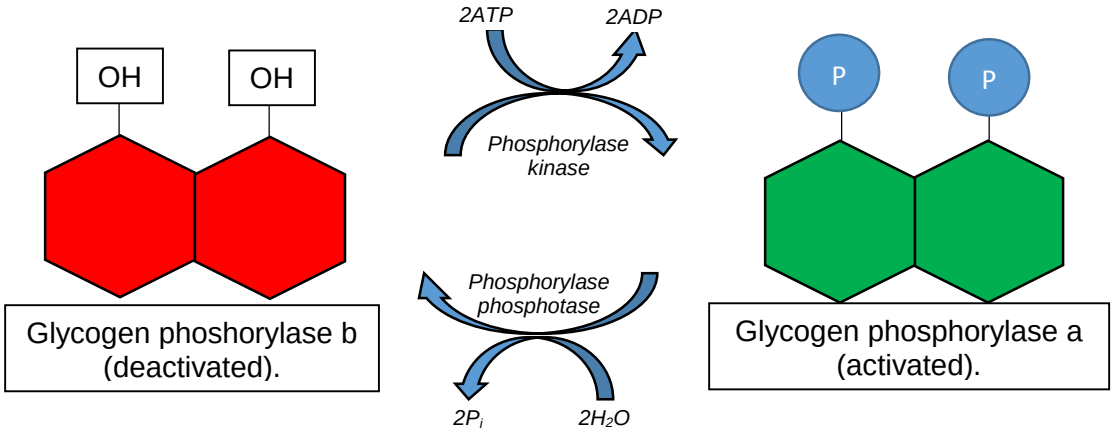
The Allosteric and Hormonal control of glycogen phosphorylase and glycogen synthase (pp. 621-)

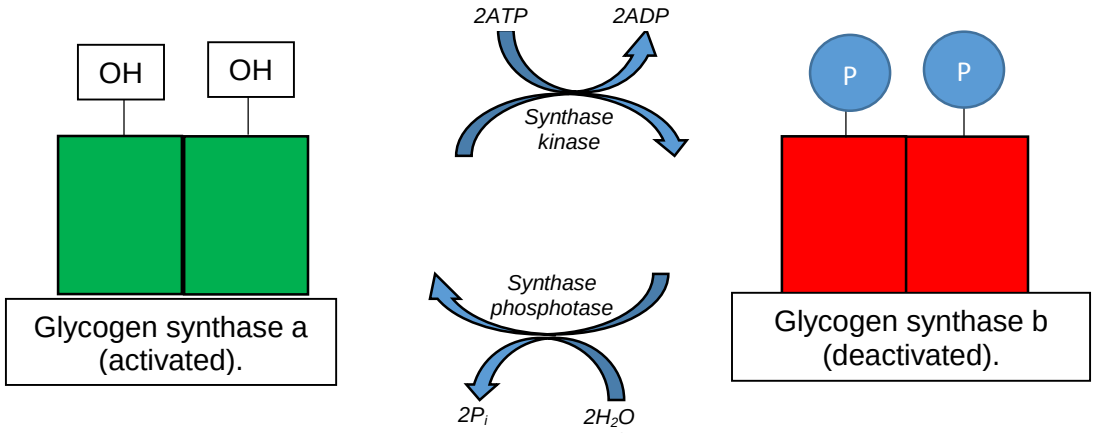
Allosteric Regulation of Glycogen synthase and Glycogen phosphorylase

- **Glycogen synthase** is activated by high intracellular level of G6P.
- **Glycogen phosphorylase** transitions between the relaxed (R) and tense (T) conformations.
- Transition between these two states is due to the allosteric regulation by AMP, ATP and glucose-6-phosphate.
- AMP activates **glycogen phosphorylase** and the R confirmation is enhanced (**glycogenolysis**).
- ATP and **G-6-P** inhibit **glycogen phosphorylase** activity, enhancing the T confirmation.

Regulation via Phosphorylation and Dephosphorylation

- Catalytic properties of enzymes can be altered by covalent attachment of a PO_3^{2-}.
- PO_3^{2-} is usually attached to specific amino acid residues (i.e. serine, threonine and tyrosine.
- Phosphorylation can activate or deactivate enzymes.

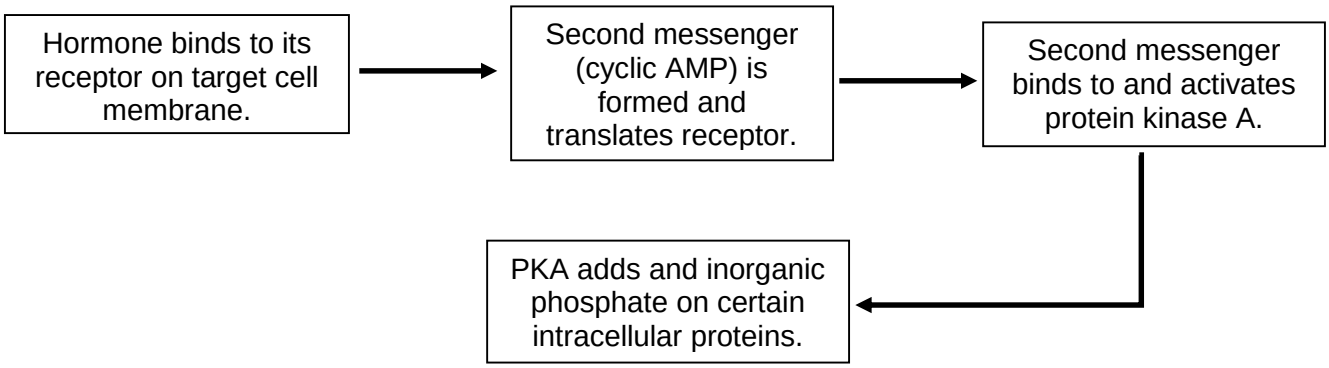




Hormonal control of glycogenolysis and glycogenesis

- Insulin, glucagon and epinephrine (adrenaline) regulate glycogen metabolism.
- Insulin promotes glycogenesis.
- Glucagon and epinephrine promotes glycogenolysis.

Glucagon and Epinephrine Cascade



Insulin Cascade

- The insulin signal cascade activates **phosphorylase phosphatase**.
- This phosphatase catalyses the removal of phosphate residues from glycogen phosphorylase and glycogen synthase.
- This inactivates glycogen phosphorylase, but activates glycogen synthase from glycogenesis.

Chapter 10 – Lipids (pp. 357-

Overview (page 357)

- Lipids are biomolecules characterised by low solubility in water.
- Two major classes include: storage and structural/functional lipids.
- Ubiquitous constituents of all cells.
- Are exogenous (dietary) as well as endogenous.
- Functions: Storage of energy, insulation (prevents heat loss), water repellent, membrane structure, buoyancy in marine mammals, cofactors (Vit K), signalling molecules (paracrine and steroid hormones) and antioxidants (Vit E).

Nomenclature

- Carbons numbered 1-n from carboxyl end or,
- Greek lettering system (ω carbon is the methyl carbon, C-2 = α, C-3 = β, C-4 = γ).
- Notation of saturated FA (N:0), unsaturated FA (N:=)

Storage Lipids

- Triacylglycerol's, fats or neutral fats.
- Ester linkage of 3 FA chains joined with glycerol.
- Constitute 95% of fat stored in tissue, serving as an energy source.
- Exist as fat droplets in adipocytes, serving as insulation.
- Sources of acylglycerols include: dietary fat and fat stored in adipose tissue.
- Adipose cells: synthesis, storage and mobilisation.

Processing of TAGs

Intestinal Lumen

- Incorporated into micelles.
- Pancreatic lipases digest TAGs to monoglycerols and free FA.
- FA then transported to intestinal lumen.

Intestinal mucosa

- TAGs resynthesised.
- Packaged into chylomicrons which are then released into blood..

Sterols - Lipids that do not contain FA

- Component of the cell membrane and have a steroid nucleus.
- Cholesterol found in animal tissue.
- Precursors to steroid hormones.

Phospholipids – Structural Lipids

- Contain a PO_4^{3-} group and a nitrogenous base or –OH.
- Essential components of cell membranes.

Eicosanoids – signalling lipids

- Paracrine hormones that are FA derivatives (Arachidonic acid 20:4($\Delta^{5, 8, 11, 14}$)).
- Involved in immune response, coagulation process and inflammation.
- 3 classes:
  1) Prostaglandins (PGs)
     - First isolated in pancreas.
     - Two groups: PGE (ether soluble) and PGF (lipid buffer soluble).
     - Mediate inflammation, pain and fever.

  2) Thromboxanes (TXs)
     - Produced by platlets.
     - Enhance coagulation and vasoconstriction near coagulation sites.
- Hormonal stimuli causes phospholipase A_2 to attach membrane phospholipids releasing arachidonate.
- Arachidonate → PGH_2.
- PGH_2 is a precursor to other prostaglandins and thromboxanes.
- Cyclooxygenase (COX) synthesises reactions that produce PGH_2.
- Thromboxane synthase converts PGH_2 to thromboxane A_2.

  3) Leukotrienes (LTs)
     - Location: leukocytes.
     - Contain 3 conjugated double bonds.
     - Mediate airway constriction.
- Syhtesis begins with lipoxygenases.

Isozymeric forms of COX

COX-1
- Synthesises PGs that regulate gastric mucin secretion.

COX-2
- Synthesis PGs that mediate inflammation, pain and fever.

NOTE: Both isoenzymes are irreversibly inhibited by aspirin. It acelyates a Serine residue that is a competitive inhibitor, which ultimately prevents synthesis of PGs and TXs.

Utilisation of Fatty Acids (FA)

- Occurs in three stages:

1. Mobilisation
   - Triacylglycerol lipase degrades TAGs to FA and glycerol through lipolysis.
   - Phosphorylation actives TAG lipase.
   - Adipose tissue releases FA which are then bound to albumin and transported to other tissue.
   - Lipolysis stimulated by epinephrine and glucagon but inhibited by insulin.
   - Glycerol is stored in liver where it is converted to GAP and used an intermediate for either glycolysis or gluconeogenesis.

2. Activation and Transportation
   - FA + CoA → fatty-acyl CoA = activation.
   - Catalysed by Acyl CoA synthetase.
   - Once active, long FA chains are transported to mitochondrial matrix for degradation.
   - Carnitine transports these chains across mitochondrial membrane.
   - Translocase moves carnitine across inner mitochondrial membrane.

3. Degradation
   - Saturated Acyl-CoA undergoes a sequence of 4 recurring reactions:
     a. *1st Oxidation (FAD)*
        - Acyl-CoA → Enoyl CoA, catalysed by Acyl CoA dehydrogenase.
        - H^+ from acyl-CoA is given to FAD to form $FADH_2$.
     b. *Hydration*
        - Enoyl CoA Hydratase catalyses the hydration of C2=C3 double bond.
        - Hydration of Enoyl CoA is stereospecific, only L-isomer of 3-hydroxyacyl CoA.
     c. *2nd Oxidation (NAD^+)*
        - Oxidation of L-3-Hydroxyacyl CoA → 3-ketoacyl CoA catalysed by hydroxyacyl CoA dehydrogenase.
        - Oxidation of L-3-Hydroxyacyl CoA sees 2H loss at C2 and transmitted to NAD^+ to form H^+ + NADH.
     d. *Thiolysis*
        - Thiolysis of 3-Ketoacyl CoA → Acyl CoA + Acetyl CoA by β-ketothiolase.

β-oxidation of Fatty Acids

- C16 saturated FA is degraded in seven rounds of β-oxidation to form 8 Acetyl-CoA.
- These 8 Aceytl CoA are then used in the CAC/Krebs Cycle and produce NADH and $FADH_2$.
- These high energy molecules along with those made from FA degradation are used in ETC to from ATP.
- FA chains even number of carbons: n/2 acetyl-CoA
- Odd numbered carbon chains: [n/3)/2] acetyl-CoA + 1 propionyl-CoA (3C unit).
- Peropionyl CoA nand Acetyl CoA are final products of degradation.
- Propionyl CoA converted to succinyl CoA which enters CAC.

FA Synthesis

- FA synthesis occurs in two stages:
  1) Formation of malonyl CoA
     - An irreversible reaction that is a committed step and also a major point of regulation. Enzyme = ACC

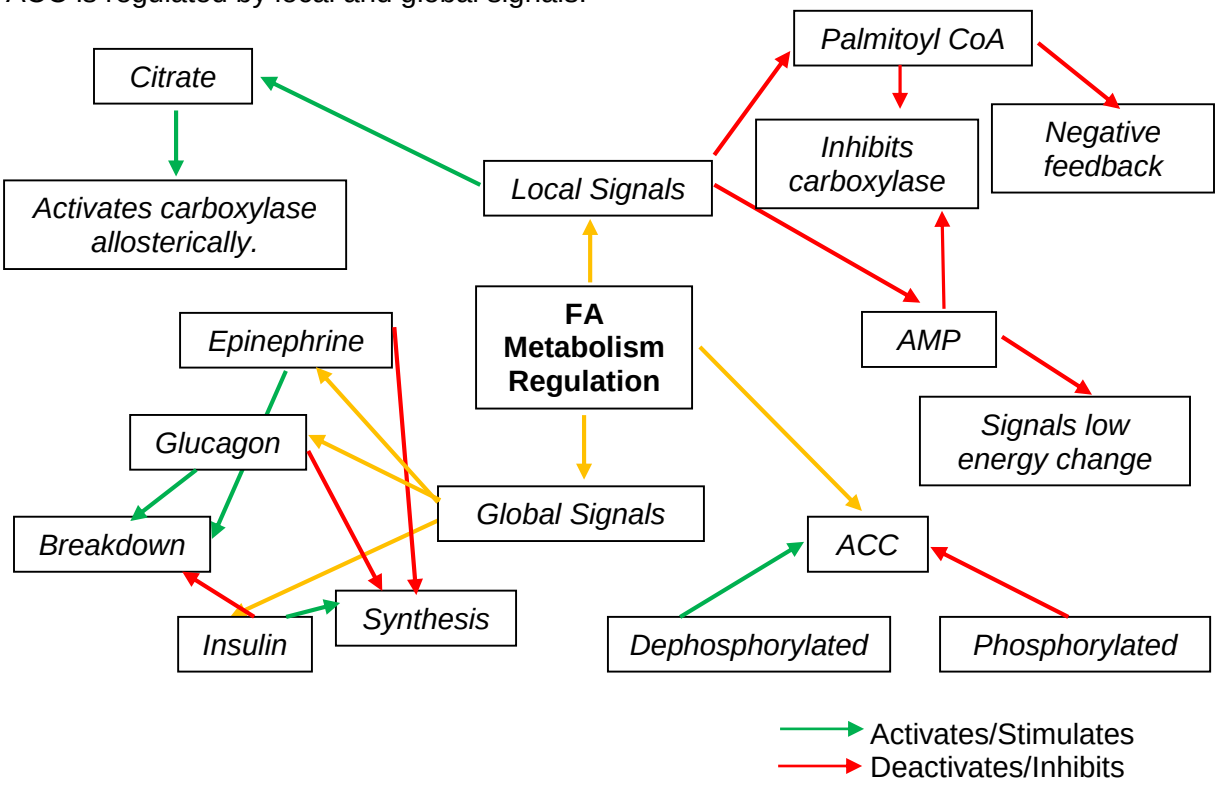
       Acetyl CoA + ATP + HCO_3^- → Malonyl CoA + ADP + P_i + H^+
     - The malonyl CoA intermediate that is formed links to the –SH terminus of a phosphopantetheine group.
     - This phosphpantetheine group is attached to a Ser residue of ACP.

  2) Elongation of the carbon chain
     - Occurs in four reoccurring reactions catalysed by Fatty Acid Synthase:
       i. Condensation
          - Acetoacetyl ACP (C4) is formed by the acyl-malonyl ACP condensing enzyme catalysing the condensation reaction between Acetyl ACP and Malyonyl ACP.
       ii. Reduction
          - Acetoaceytl ACP reduced by β-ketoacyl ACP to form D-3-Hyroxybutyryl ACP.
       iii. Dehydration
          - D-3-Hyroxybutyryl dehydrated to form Crotonyl ACP.
       iv. 2nd Reduction
          - Reduction of crotonyl ACP by Enoyl ACP reductase sees the formation of Butyryl ACP.
          - After final reduction, FA chain is lengthened by 2C.

- After this 2C addition to the chain, the first cycle of elongation is complete.
- Commencement of second elongation is when Butyryl ACP (C4) and malonyl ACP undergo condensation to form C6-acyl ACP.
- Formation of C16-acyl ACP sees the end of FA synthesis.
- A thioesterase hydrolyses this C16-acyl ACP and yields Palmitate + ACP
- Unsaturated FA and longer chained FA require more synthesis steps.

Regulation of FA metabolism

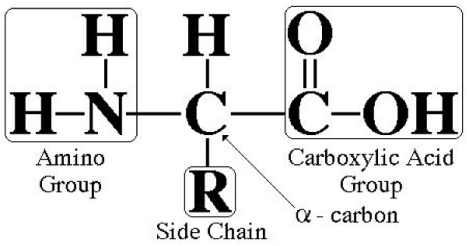
- Synthesis is at its peak when carbohydrates and energy are plentiful.
- Acetyl CoA carboxylase (ACC) lays a central role in the synthesis due to it catalysing the committed step of producing malonyl CoA.
- ACC is regulated by local and global signals.



Amino Acid Metabolism

Biological Molecules containing Nitrogen

- Amino acids and Nucleotides.



- There are 20 known amino acids in biological systems.
- Joined by a peptide bond.
- Have an N-terminus and C-terminus