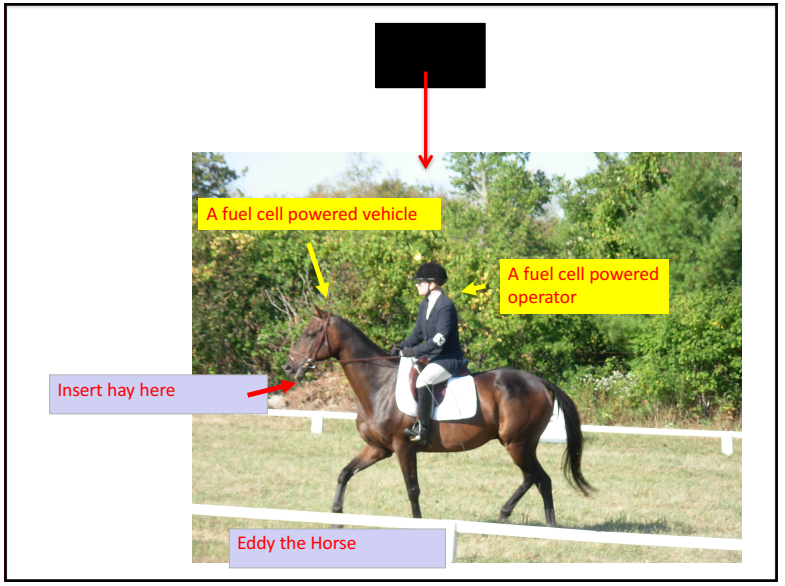
Biochemistry

4. Bio-Energetics

4.3 Carbohydrates & Glycogen

4.3a) Carbohydrates

Prof. Dr. Klaus Heese

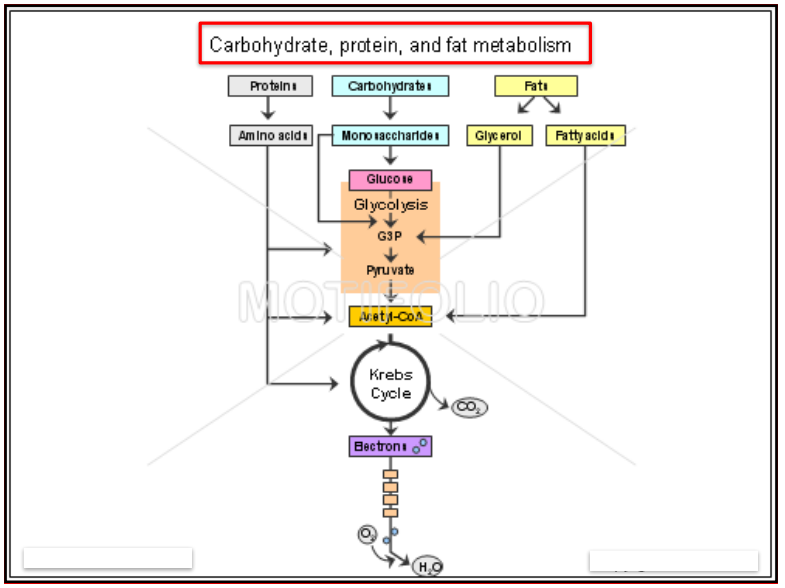


Key words

- energy sources: carbohydrates, proteins, fats, ATP, aerobic-anaerobic systems
- types of energy: mechanical energy, heat energy, chemical energy, electromagnetic energy, nuclear energy, kinetic energy, potential energy, gravitational potential energy, energy conversion
- Law of Conservation of Energy (photosynthesis)

Fuel Summary

- **CHO:** used anaerobically and aerobically, low amount stored in body
- **Fats:** used only aerobically: large amounts stored in body, can only be used if CHO is available
- **Protein:** only used in starvation states

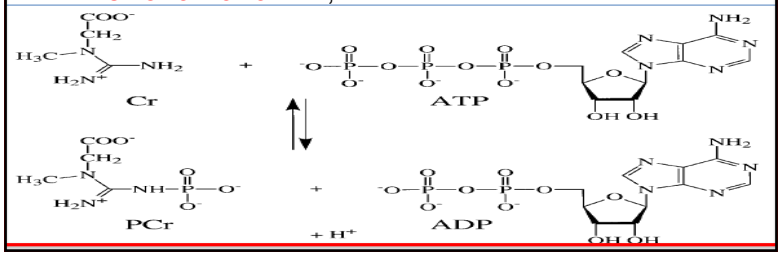


Forms of Energy Transfer

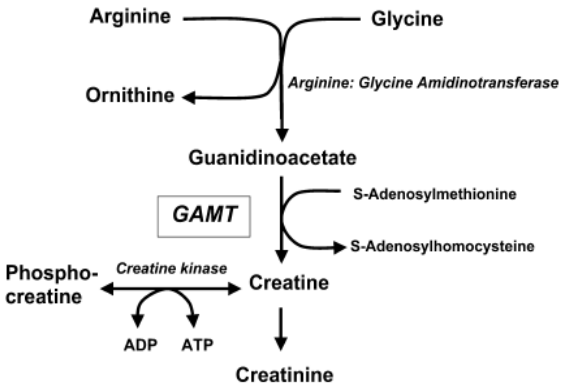
- The ATP-CP system relying on the "Phosphogens".
  - anaerobic
- The glycolytic (lactic acid) system relying on
  - anaerobic breakdown of CHO.
- The oxidative system relying on the
  - aerobic breakdown of CHO, Fat, and Protein depends *on oxygen supply/availability.*

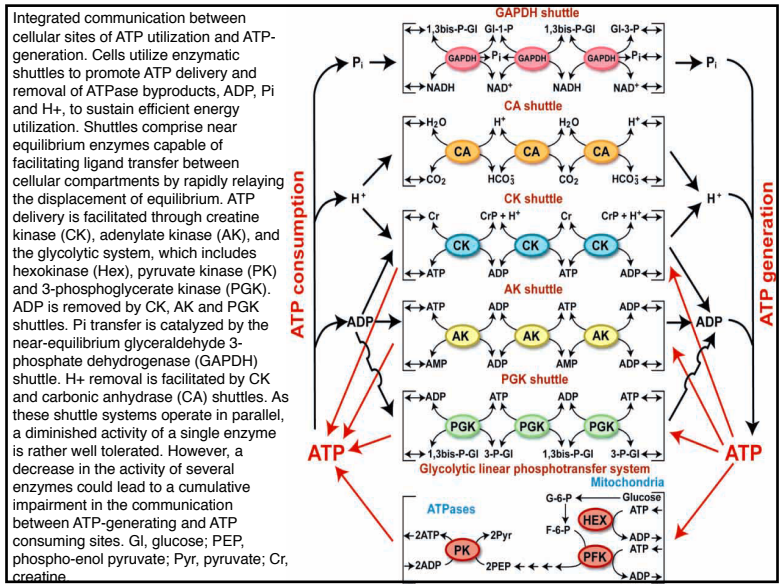
Creatine Phosphate (CP or PC system)

- In the ATP-CP system, P_i is separated from CP through the action of creatine kinase (enzyme that adds P).
- Energy yield is 1 mole of ATP per 1 mole of CP.
- The P_i can then combine with ADP to reform ATP.
- the change in free energy ($\Delta G\,^{\circ\prime}$) (pH 7.0) for the hydrolysis of PCr is -45.0 kJ/mol compared with -31.8 kJ/mol for ATP,



Creatine synthesis – a 2-step process



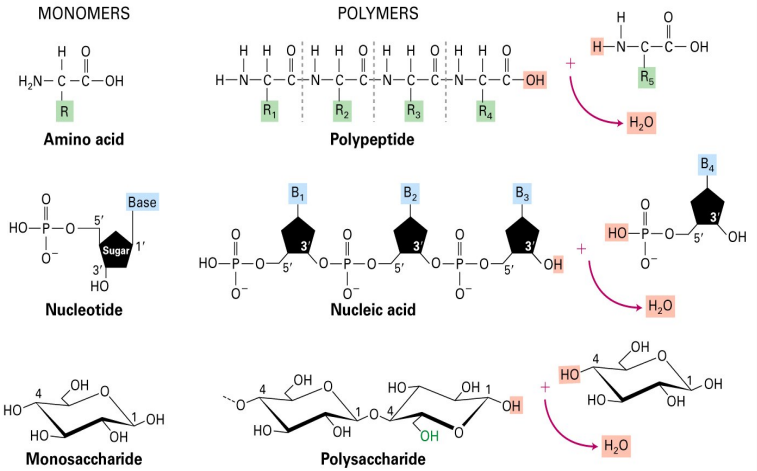


Integrated communication between cellular sites of ATP utilization and ATP-generation. Cells utilize enzymatic shuttles to promote ATP delivery and removal of ATPase byproducts, ADP, Pi and H+, to sustain efficient energy utilization. Shuttles comprise near equilibrium enzymes capable of facilitating ligand transfer between cellular compartments by rapidly relaying the displacement of equilibrium. ATP delivery is facilitated through creatine kinase (CK), adenylate kinase (AK), and the glycolytic system, which includes hexokinase (Hex), pyruvate kinase (PK) and 3-phosphoglycerate kinase (PGK). ADP is removed by CK, AK and PGK shuttles. Pi transfer is catalyzed by the near-equilibrium glyceraldehyde 3-phosphate dehydrogenase (GAPDH) shuttle. H+ removal is facilitated by CK and carbonic anhydrase (CA) shuttles. As these shuttle systems operate in parallel, a diminished activity of a single enzyme is rather well tolerated. However, a decrease in the activity of several enzymes could lead to a cumulative impairment in the communication between ATP-generating and ATP consuming sites. Gl, glucose; PEP, phospho-enol pyruvate; Pyr, pyruvate; Cr, creatine

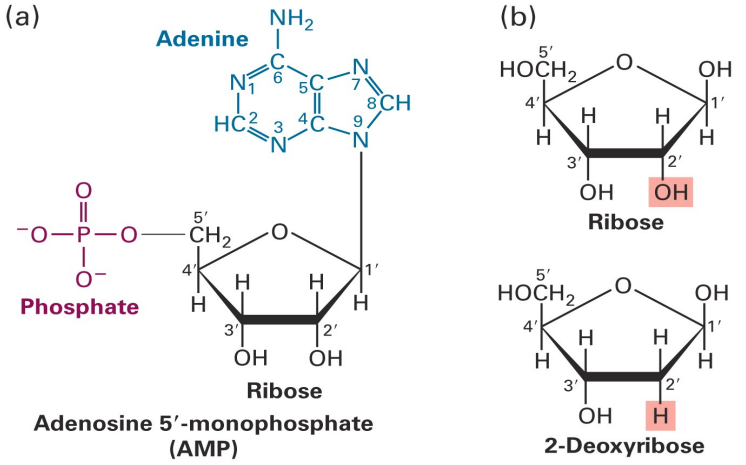
Glycolysis

- The glycolytic system involves the process of glycolysis, through which glucose is broken down to pyruvic acid via glycolytic enzymes.
- When conducted without oxygen, the pyruvic acid is converted to lactic acid. (→ Kreb's cycle)
- 1 mole of glucose yields 2 moles of ATP, but 1 mole of glycogen yields 3 moles of ATP.
- **Key processes:**
- Gluconeogenesis: the process by which protein or fat is converted into glucose.
- Glycogenesis: the process by which glycogen is synthesized from glucose.
- Glycogenolysis: **breakdown of glycogen for ATP production.**

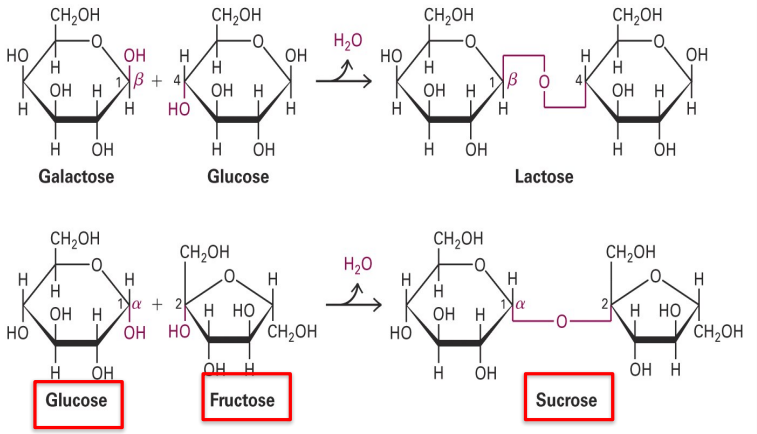
Essential Bio-Energy-related Bio-Molecules



Common Structure of Nucleotides



Di-Saccharides Lactose and Sucrose



As for all parts of this lecture:
It's not about human physiology – but, to know the systems in order to be able to make use of it ('translate' and apply) from the bioengineering point of view !

Without its knowledge, no innovative and creative ideas for its potential bioengineering applications !

Carbohydrates

Carbohydrates

- **glucose** provides energy for the brain and ½ of energy for muscles and tissues
- **glycogen** is stored glucose
- **glucose** is immediate energy
- **glycogen** is reserve energy

Carbohydrates

- all plant food
- milk

- carbohydrates are not equal
  - simple carbohydrates
  - complex carbohydrates

Simple Carbohydrates

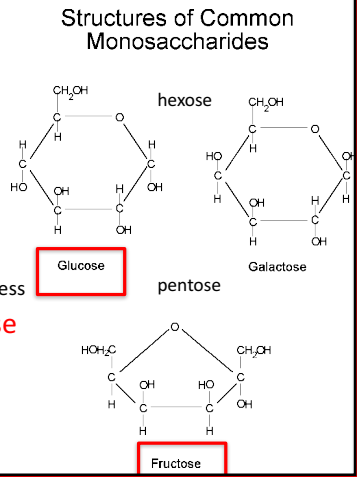
- **sugars**
  - monosaccharides – single sugars
  - disaccharides – 2 monosaccharides

Complex Carbohydrates

- starches and fibers
- polysaccharides
  - chains of monosaccharides

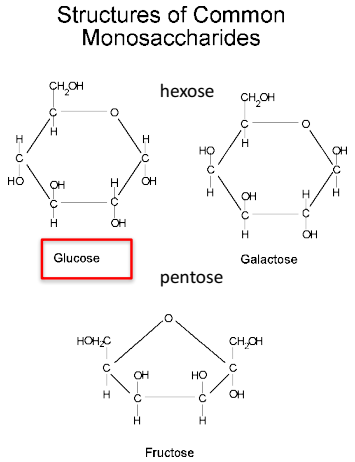
Simple Carbohydrates

- monosaccharides
  - all are 6 carbon hexes
    - 6 carbons
    - 12 hydrogens
    - 6 oxygens
    - arrangement differs
      - accounts for varying sweetness
  - glucose, fructose, galactose



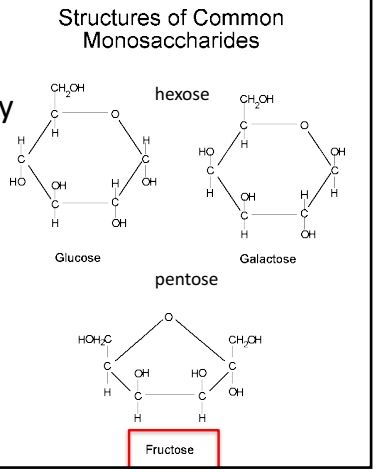
Glucose

- mild sweet flavor
- known as blood sugar
- essential energy source
- found in every disaccharide and polysaccharide



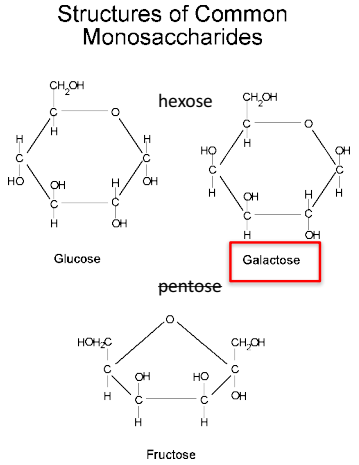
Fructose

- sweetest sugar
- found in fruits and honey
- added to soft drinks, cereals, deserts



Galactose

- hardly tastes sweet
- rarely found naturally as a single sugar

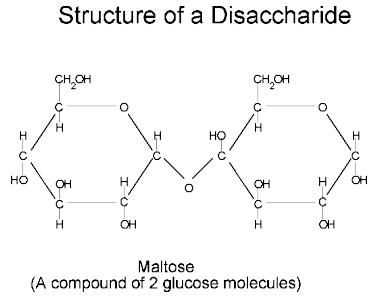


Disaccharides

- **= pairs of the monosaccharides**
  - **glucose is always present**
  - 2nd of the pair could be fructose, galactose or another glucose
  - taken apart by hydrolysis
  - put together by condensation
  - hydrolysis and condensation occur with all energy nutrients
  - maltose, **sucrose**, lactose

Condensation

- making a disaccharide
  - chemical reaction linking 2 monosaccharides



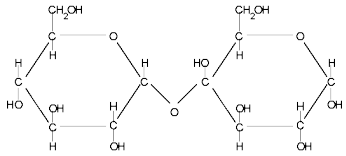
Hydrolysis

- breaking a disaccharide
  - water molecule splits
  - occurs during digestion

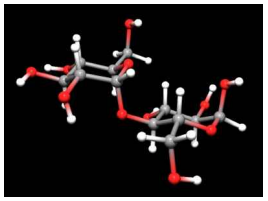
Maltose

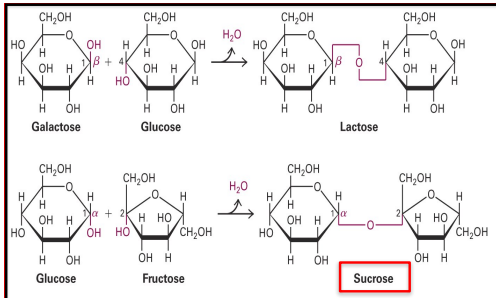
- 2 glucose units
- produced when starch breaks down
- not abundant

Structure of a Disaccharide



Maltose
(A compound of 2 glucose molecules)



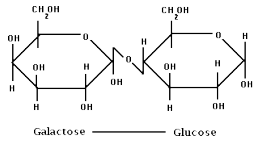


Sucrose

- **fructose and glucose**
- tastes sweet
  - fruit, vegetables, grains
- table sugar is refined sugarcane and sugar beets
- brown, white, powdered

Lactose

- **glucose and galactose**
- main carbohydrate in milk
  - known as milk sugar

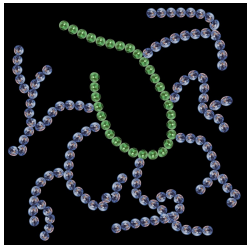


Complex (larger/longer) Carbohydrates

- **polysaccharides**
  - **glycogen** and **starch** (amylose (linear) and amylopectin (branch))
    - built entirely of glucose
  - fiber
    - variety of monosaccharides and other carbohydrate derivatives

Glycogen

- limited in meat and not found in plants
  - not an important dietary source of carbohydrate
- BUT
  - all glucose is stored as glycogen
  - long chains allow for hydrolysis and release of energy



Starches

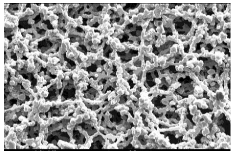
(amylose (linear, α(1-4)-D-Glucose) and amylopectin (branch, α(1-4)-D-Glucose and α(1-6)-D-Glucose))

- **stored in plant cells**
- body hydrolyzes plant starch to glucose

Fiber

- structural parts of plants
  - found in all plant-derived food
- bonds of fibers cannot be broken down during the digestive process
  - minimal or no energy available

Fiber types



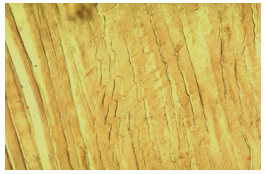
- cellulose
- pectins
- lignins
- resistant starches
  - classified as fibers
  - escape digestion and absorption

(**almost no energy supply to human, but**…)

But eventually used by other organisms --->

Fiber Characteristics

- **soluble fibers**, viscous, **fermentable**
  - easily digested by bacteria in colon
  - associated with protection against heart disease and diabetes
    - lower cholesterol and glucose levels
  - found in legumes and fruits



Fiber

- **insoluble** and **not easily fermented**
  - promote bowel movements
  - alleviate / promotes constipation ---> have in food
  - found in grains and vegetables

Carbohydrate Digestion

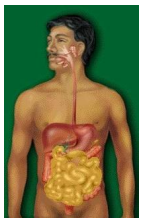
- **break down into glucose**
  - body is able to absorb and use
- large starch molecules
  - extensive breakdown
- disaccharides
  - broken once
- monosaccharides
  - don't need to be broken down

Carbohydrate Digestion

- begins in mouth
  - chewing releases saliva
  - enzyme amylase hydrolyzes starch to polysaccharides and maltose
- stomach
  - no enzymes available to break down starch
  - acid does some breakdown
  - fibers in starch provide feeling of fullness

Enzymes involved in CHO digestion / break down

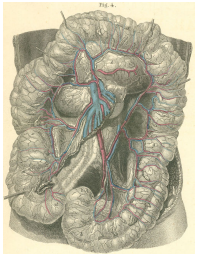
- small intestine
  - majority of carbohydrate digestion takes place here
  - pancreatic amylase reduces carbs to glucose chains or disaccharides
  - specific enzymes finish the job
    - maltase
      - maltose into 2 glucose
    - sucrase
      - sucrose into glucose and fructose
    - lactase
      - lactose into glucose and galactose



Biotechnological applications

CHO digestion

- large intestine
  - 1-4 hours for sugars and starches to be digested
  - only fibers remain
    - attract water, which softens stool
  - bacteria ferment some fibers
    - water, gas, short-chain fatty acids (used for energy)

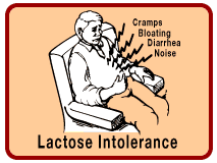


Carbohydrate Absorption

- glucose can be absorbed in the mouth
- majority absorbed in small intestine
  - active transport
    - glucose
  - facilitated diffusion
    - fructose
    - smaller rise in blood glucose

Lactose Intolerance

- more lactose is consumed than can be digested
  - lactose molecules attract water
    - cause floating, abdominal discomfort, diarrhea
  - intestinal bacteria feed on undigested lactose
    - produce acid and gas



Lactose Intolerance

- age, damage, medication, diarrhea, malnutrition
- management requires dietary change
  - 6 grams (1/2 cup) usually tolerable
  - take in gradually
  - hard cheeses & cottage cheese
  - enzyme drops or tablets
- lactose free diet is extremely difficult to accomplish

Carbohydrate Metabolism

- 1/3 of body's glycogen is stored in liver
  - released as glucose to bloodstream

1. eat – intake glucose
2. liver condenses extra glucose to glycogen
3. blood glucose falls
4. liver hydrolyzes glycogen to glucose

Glycogen is bulky, so we store only so much: short term energy supply

Fat is the long term energy supply.

Glucose for Energy

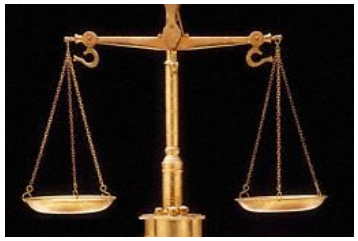
- enzymes break apart glucose – yielding energy
- inadequate supply of carbohydrates
  - ketone bodies (fat fragments) are an alternate energy source during starvation
  - excess ketones can lead to ketosis: imbalance of acids in body
- minimum of 50 – 100 grams of carbs/day are needed to avoid ketosis

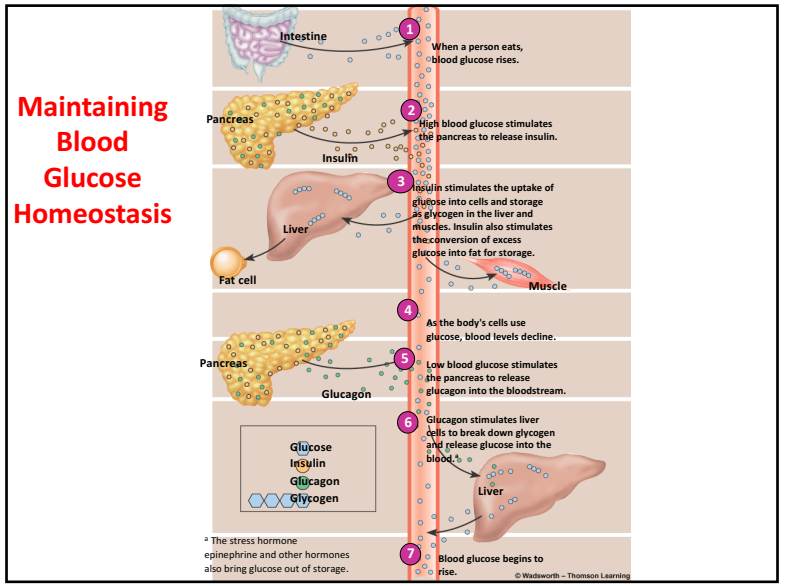
Glucose Homeostasis

- maintaining an even balance of glucose is controlled by insulin and glucagon
  - **insulin**
    - moves glucose into the blood (ensures proper usage/uptake of glucose by the various cells/tissues/organs – if ---> diabetes)
  - **glucagon**
    - brings glucose out of storage

- maintaining balance
  - balanced meals at regular intervals
    - fiber and some fat slow the digestive process down
    - glucose gets into the blood slow and steady

3 or 5, doesn't matter --- but energy input ~ energy output





Imbalance

- diabetes
  - after food intake, blood glucose rises and is not regulated because insulin is inadequate (---> use of ketobodies)
- hypoglycemia
  - blood glucose drops dramatically
    - too much insulin, activity, inadequate food intake, illness
    - diet adjustment includes fiber-rich carbs and protein

Sugar

- ½ comes from natural sources, ½ from refined and added
  - sucrose, corn syrup, honey
- excess can lead to nutrient deficiencies and tooth decay
  - empty calories
  - sugar and starch break down in the mouth

Starch and Fiber

- diet that includes starch, fiber and natural sugars
  - whole grains, vegetables, legumes, fruits
    - may protect against heart disease and stroke
    - reduces the risk of type 2 diabetes
    - enhances the health of the large intestine
    - can promote weight loss

Starch and Fiber

- starch intake
  - 45-65%
  - 225 – 325 grams (DV (daily value) is 300 grams)
  - 900-1300 kcal/2000 kcal
  - RDA (Recommended Daily Allowance) is 130 grams
- fiber intake
  - Daily Value (DV) is 25 grams/2000 kcal

TABLE 4-2 Fibers: Their Characteristics, Food Sources, and Health Effects in the Body

Fiber Characteristics	Major Food Sources	Actions in the Body	Health Benefits
Viscous, soluble, more fermentable • Gums and mucilages • Pectins • Psyllium[a] • Some hemicelluloses	Whole-grain products (barley, oats, oat bran, rye), fruits (apples, citrus), legumes, seeds and husks, vegetables; also extracted and used as food additives.	• Lower blood cholesterol by binding bile. • Slow glucose absorption. • Slow transit of food through upper GI tract. • Hold moisture in stools, softening them. • Yield small fat molecules after fermentation that the colon can use for energy.	• Lower risk of heart disease. • Lower risk of diabetes.
Nonviscous, insoluble, less fermentable • Cellulose • Lignins • Psyllium[a] • Resistant starch • Many hemicelluloses	Brown rice, fruits, legumes, seeds, vegetables (cabbage, carrots, brussels sprouts), wheat bran, whole grains; also extracted and used as food additives.	• Increase fecal weight and speed fecal passage through colon. • Provide bulk and feelings of fullness.	• Alleviate constipation. • Lower risks of diverticulosis, hemorrhoids, and appendicitis. • May help with weight management.

[a]Psyllium, a fiber laxative and cereal additive, has both soluble and insoluble properties.

TABLE 4-3 Fiber in Selected Foods

Bread, Cereal, Rice, and Pasta Group

Whole-grain products provide about 1 to 2 grams (or more) of fiber per serving:

- 1 slice whole-wheat, pumpernickel, rye bread.
- 1 oz ready-to-eat cereal (100% bran cereals contain 10 grams or more).
- ½ c cooked barley, bulgur, grits, oatmeal.

Vegetable Group

Most vegetables contain about 2 to 3 grams of fiber per serving:

- 1 c raw bean sprouts.
- ½ c cooked broccoli, brussels sprouts, cabbage, carrots, cauliflower, collards, corn, eggplant, green beans, green peas, kale, mushrooms, okra, parsnips, potatoes, pumpkin, spinach, sweet potatoes, swiss chard, winter squash.
- ½ c chopped raw carrots, peppers.

Fruit Group

Fresh, frozen, and dried fruits have about 2 grams of fiber per serving:

- 1 medium apple, banana, kiwi, nectarine, orange, pear.
- ½ c applesauce, blackberries, blueberries, raspberries, strawberries.
- Fruit juices contain very little fiber.

Legumes

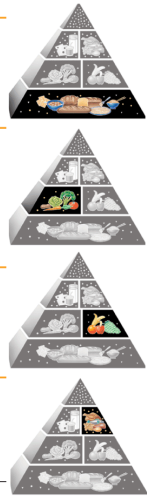
Many legumes provide about 6 to 8 grams of fiber per serving:

- ½ c cooked baked beans, black beans, black-eyed peas, kidney beans, navy beans, pinto beans.

Some legumes provide about 5 grams of fiber per serving:

- ½ c cooked garbanzo beans, great northern beans, lentils, lima beans, split peas.

NOTE: Appendix H provides fiber grams for over 2000 foods.



Groceries

- grains: 1 serving = 15 grams
- vegetables
  - ½ cup starchy = 15 grams
  - ½ cup nonstarchy = 5 grams
- fruit: 1 serving = 15 grams
- milk: 1 cup = 12 grams
- meat: none or little
- legumes: ½ cup = 15 grams

Artificial Sweeteners

- help keep sugar and energy intake down
- anything we eat has FDA (food and drug administration) approval
  - saccharin
  - aspartame
  - acesulfame potassium
  - sucralose
  - neotame

TABLE H4-1 Sweeteners

Sweeteners	Relative Sweetness[a]	Energy (kcal/g)	Acceptable Daily Intake	Average Amount to Replace 1 tsp Sugar	Approved Uses
Approved Sweeteners					
Saccharin	450	0	5 mg/kg body weight	12 mg	Tabletop sweeteners, wide range of foods, beverages, cosmetics, and pharmaceutical products
Aspartame	200	4[b]	50 mg/kg body weight[c] Warning to people with PKU: Contains phenylalanine	18 mg	General purpose sweetener in all foods and beverages
Acesulfame-K	200	0	15 mg/kg body weight[d]	25 mg	Tabletop sweeteners, puddings, gelatins, chewing gum, candies, baked goods, desserts, alcoholic beverages
Sucralose	600	0	5 mg/kg body weight	6 mg	Carbonated beverages, dairy products, baked goods, coffee and tea, fruit spreads, syrups, tabletop sweeteners, chewing gum, frozen desserts, salad dressing
Neotame	8000	0	18 mg/day	0.5µg	Baked goods, nonalcoholic beverages, chewing gum, candies, frostings, frozen desserts, gelatins, puddings, jams and jellies, syrups
Tagatose	0.8	1.5	7.5 g/day	1 tsp	Baked goods, beverages, cereals, chewing gum, confections, dairy products, dietary supplements, health bars, tabletop sweetener
Sweeteners with Approval Pending					**Proposed Uses**
Alitame	2000	4[e]	—		Beverages, baked goods, tabletop sweeteners, frozen desserts
Cyclamate	30	0	—		Tabletop sweeteners, baked goods

[a] Relative sweetness is determined by comparing the approximate sweetness of a sugar substitute with the sweetness of pure sucrose, which has been defined as 1.0. Chemical structure, temperature, acidity, and other flavors of the foods in which the substance occurs all influence relative sweetness.
[b] Aspartame provides 4 kcalories per gram, as does protein, but because so little is used, its energy contribution is negligible. In powdered form it is sometimes mixed with lactose, however, so a 1-gram packet may provide 4 kcalories.
[c] Recommendations from the World Health Organization and in Europe and Canada limit aspartame intake to 40 milligrams per kilogram of body weight.
[d] Recommendations from the World Health Organization limit acesulfame-K intake to 9 milligrams per kilogram of body weight.
[e] Alitame provides 4 kcalories per gram, as does protein, but because so little is used, its energy contribution is negligible.

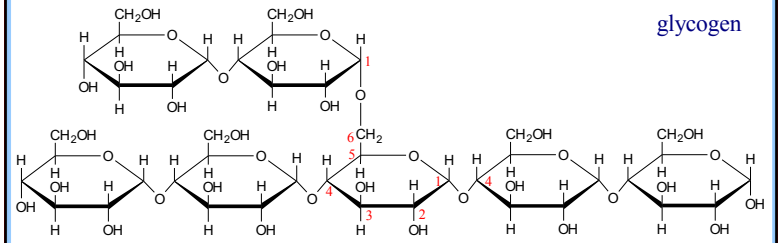
Sugar Replacers

- sugar alcohols
  - provide bulk and sweetness
    - cookies, gum, candy, jelly
  - do not cause dental caries
  - low glycemic response
    - absorbed slowly
  - do not cause dental caries

Biochemistry

4.3b) Glycogen Metabolism

Prof. Dr. Klaus Heese



Glycogen is a polymer of **glucose** residues linked by

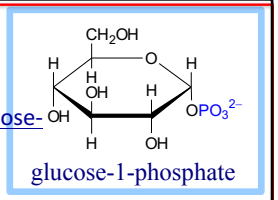
- α(1→4) glycosidic bonds, mainly
- α(1→6) glycosidic bonds, at **branch points**.

Glycogen chains & branches are longer than shown.

Glucose is stored as glycogen predominantly in **liver** and **muscle** cells.

Glycogen catabolism
(breakdown):

The major product of glycogen breakdown is glucose-1-phosphate, from Phosphorylase activity.



Glycogen Phosphorylase catalyzes phosphorolytic cleavage of the **α(1→4)** glycosidic linkages of glycogen, releasing glucose-1-phosphate as reaction product.

glycogen$_{(n\ residues)}$ + P_i →

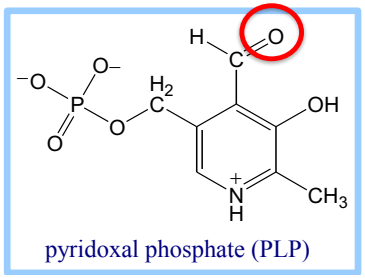
glycogen $_{(n-1\ residues)}$ + glucose-1-phosphate

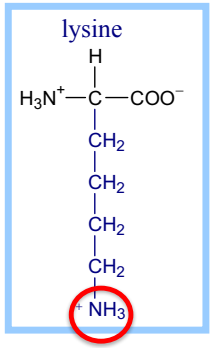
This **phosphorolysis** may be compared to hydrolysis:

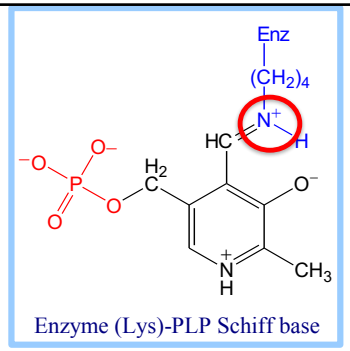
Hydrolysis: **R-O-R' + HOH → R-OH + R'-OH**

Phosphorolysis: **R-O-R' + HO-PO_3^{2-} → R-OH + R'-O-PO_3^{2-}**

Pyridoxal phosphate (**PLP**), a derivative of vitamin B_6, serves as prosthetic group for Glycogen Phosphorylase.



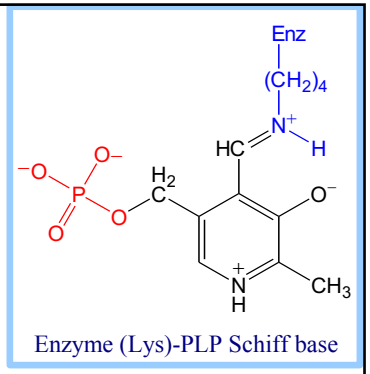




Pyridoxal phosphate (PLP) is held at the active site by a **Schiff base** linkage, formed by reaction of the aldehyde of PLP with the ε-amino group of a **lysine** residue.

In contrast to its role in other enzymes, the **phosphate** of PLP is involved in acid/base catalysis by Phosphorylase.

The **P_i substrate** binds between the phosphate of PLP and the glycosidic O linking the terminal glucose residue of the glycogen.



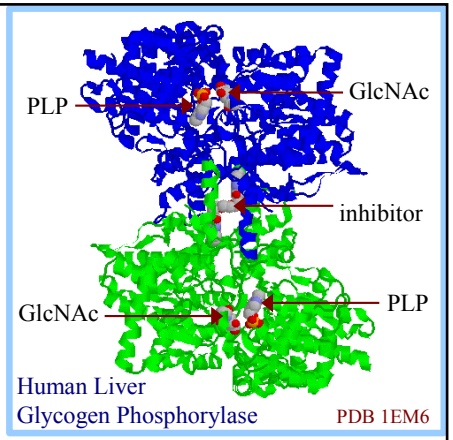
After the P_i phosphate substrate donates **H^+** during cleavage of the glycosidic bond, it receives H^+ from the phosphate moiety of PLP.

PLP then takes back the H^+ as the phosphate O attacks C1 of the cleaved glucose to yield glucose-1-phosphate.

Glycogen Phosphorylase:

a **homodimeric** enzyme, subject to allosteric control.

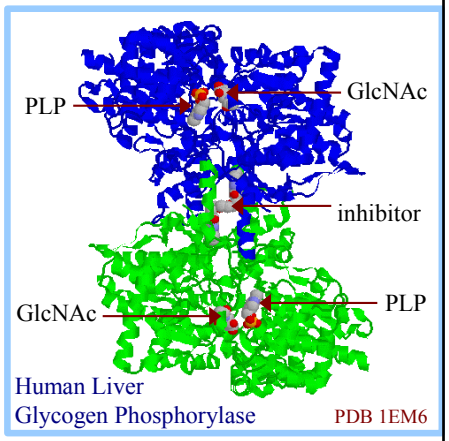
It transitions between "**relaxed**" (active) & "**tense**" (inhibited) conformations.



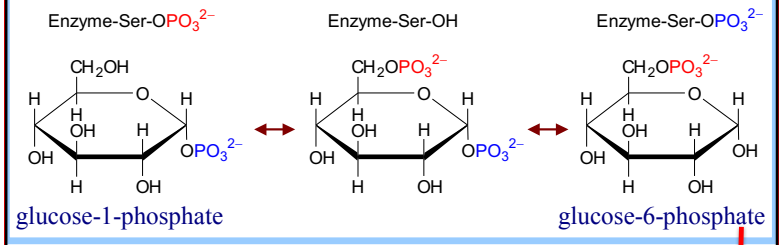
A **glucose analog**, *N*-acetylglucosamine (GlcNAc), is adjacent to pyridoxal phosphate at the **active site** in the crystal structure shown.

A class of drugs developed for treating the hyperglycemia of diabetes (chloroindole-carboxamides), inhibit liver Phosphorylase allosterically.

These **inhibitors** bind at the dimer interface, stabilizing the inactive (tense) conformation.



Question: Why would an inhibitor of Glycogen Phosphorylase be a suitable treatment for diabetes?



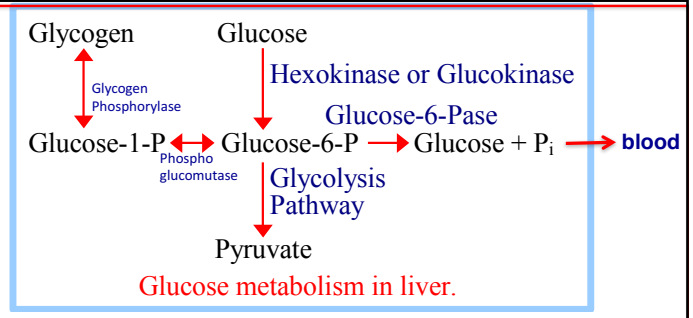
Phosphoglucomutase catalyzes the reversible reaction:

glucose-1-phosphate ⟷ glucose-6-phosphate glycolysis

A **serine OH** at the active site donates & accepts P_i.

The bisphosphate is not released.

Phosphoglycerate Mutase has a similar mechanism, but instead uses His for P_i transfer.



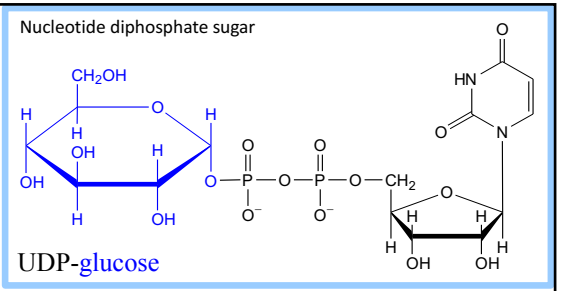
Glucose-6-phosphate may enter Glycolysis or (mainly in liver) be dephosphorylated for release to the blood.

Liver **Glucose-6-phosphatase** catalyzes the following, essential to the liver's role in maintaining blood glucose:

glucose-6-phosphate + H_2O → glucose + P_i

Most other tissues lack this enzyme.

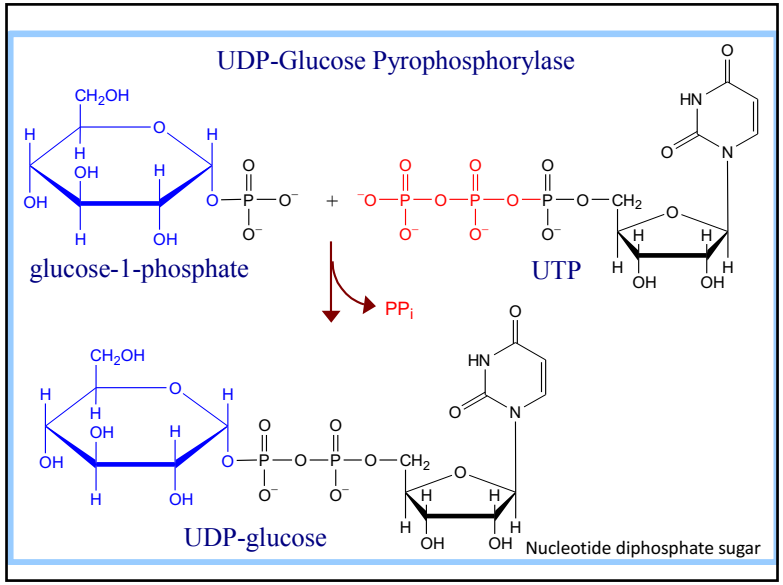
Glycogen synthesis



Uridine diphosphate glucose (UDP-glucose) is the immediate precursor for **glycogen synthesis**.

As glucose residues are added to glycogen, UDP-glucose is the substrate and UDP is released as a reaction product.

Nucleotide diphosphate sugars are precursors also for synthesis of other complex carbohydrates, including oligosaccharide chains of glycoproteins, etc.



UDP-glucose is formed from glucose-1-phosphate:

- **glucose-1-phosphate + UTP → UDP-glucose + PP_i**
- **PP_i + H_2O → 2 P_i**

Overall:

- **glucose-1-phosphate + UTP → UDP-glucose + 2 P_i**

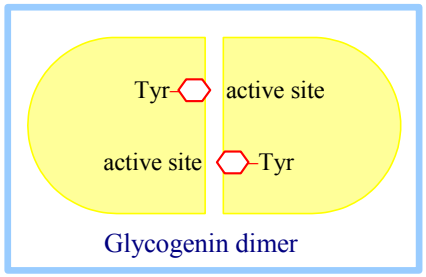
Spontaneous hydrolysis of the ~P bond in PP_i (P~P) drives the overall reaction.

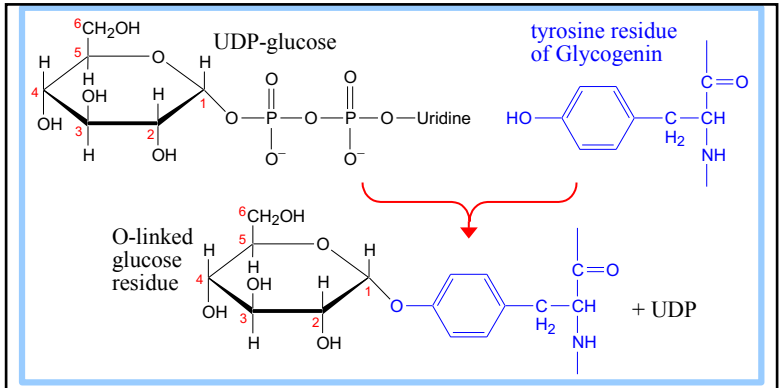
Cleavage of PP_i is the only energy cost for glycogen synthesis (<u>one</u> ~P bond per glucose residue).

Glycogenin, the enzyme that initiates glycogen synthesis.

Glycogenin is an enzyme that catalyzes the attachment of a **glucose** molecule to one of its own **tyrosine** residues.

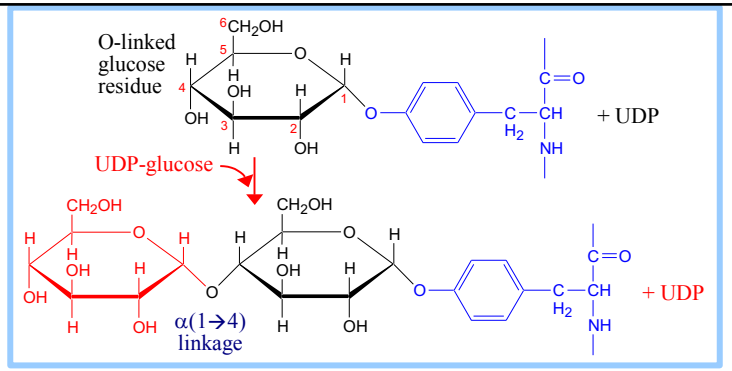
Glycogenin is a **dimer**, and evidence indicates that the 2 copies of the enzyme glucosylate one another.





A **glycosidic bond** is formed between the anomeric C1 of the glucose moiety derived from UDP-glucose and the hydroxyl oxygen of a **tyrosine** side-chain of **Glycogenin**.

UDP is released as a product.



Glycogenin then catalyzes glucosylation at C4 of the attached glucose (UDP-glucose again the donor), to yield an O-linked disaccharide with α(1→4) glycosidic linkage.

This is repeated until a **short linear glucose polymer** with α(1→4) glycosidic linkages is built up on Glycogenin.

Glycogen Synthase then catalyzes **elongation** of glycogen chains initiated by Glycogenin.

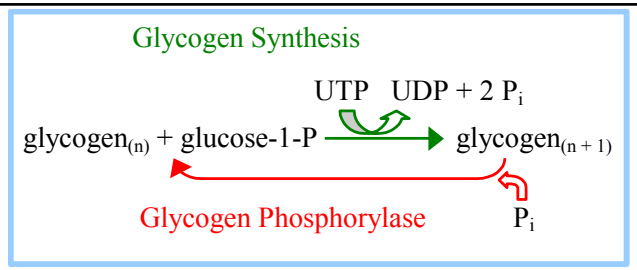
Question: Where would you expect to find Glycogenin within a cell?

Answer: Most of the Glycogenin is found associated with **glycogen particles** (branched glycogen chains) in the cytoplasm.

Glycogen Synthase catalyzes transfer of the glucose moiety of UDP-glucose to the hydroxyl at C4 of the terminal residue of a glycogen chain to form an **α(1→ 4)** glycosidic linkage:

glycogen$_{(n\ residues)}$ + UDP-glucose →
glycogen$_{(n+1\ residues)}$ + UDP

A **branching enzyme** transfers a segment from the end of a glycogen chain to the C6 hydroxyl of a glucose residue of glycogen to yield a branch with an **α(1→6)** linkage.



Both synthesis & breakdown of glycogen are spontaneous.

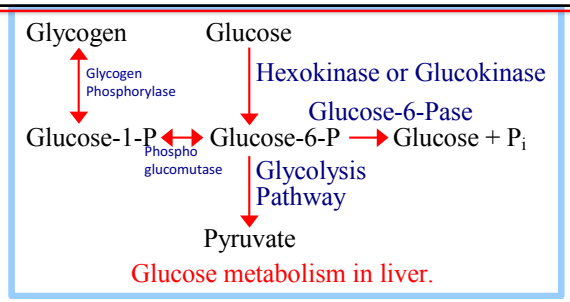
If both pathways were active simultaneously in a cell, there would be a "**futile cycle**" with cleavage of **one ~P bond per cycle** (in forming UDP-glucose).

To prevent such a futile cycle, Glycogen Synthase and Glycogen Phosphorylase are **reciprocally regulated**, by allosteric effectors and by phosphorylation.

Glycogen Phosphorylase in **muscle** is subject to allosteric regulation by AMP, ATP, and glucose-6-phosphate.

A separate isozyme of Phosphorylase expressed in liver is less sensitive to these allosteric controls.

- **AMP** (present significantly when ATP is depleted) **activates** Phosphorylase, promoting the relaxed conformation.
- **ATP** & **glucose-6-phosphate**, which both have binding sites that overlap that of AMP, **inhibit** Phosphorylase, promoting the tense conformation.
- Thus glycogen breakdown is inhibited when ATP and glucose-6-phosphate are plentiful.



Glycogen Synthase is allosterically **activated** by **glucose-6-P** (opposite of effect on Phosphorylase).

Thus Glycogen Synthase is active when high blood glucose leads to elevated intracellular glucose-6-P.

It is useful to a cell to store glucose as glycogen when the input to Glycolysis (glucose-6-P), and the main product of Glycolysis (ATP), are adequate.

Regulation by covalent modification (phosphorylation):

The hormones **glucagon** and **epinephrine** activate G-protein coupled receptors to trigger **cAMP cascades**.

- Both hormones are produced in response to **low blood sugar**.
- Glucagon, which is synthesized by α-cells of the pancreas, activates cAMP formation in liver.
- Epinephrine activates cAMP formation in muscle.

The cAMP cascade results in **phosphorylation** of a serine hydroxyl of **Glycogen Phosphorylase**, which promotes transition to the **active** (relaxed) state.

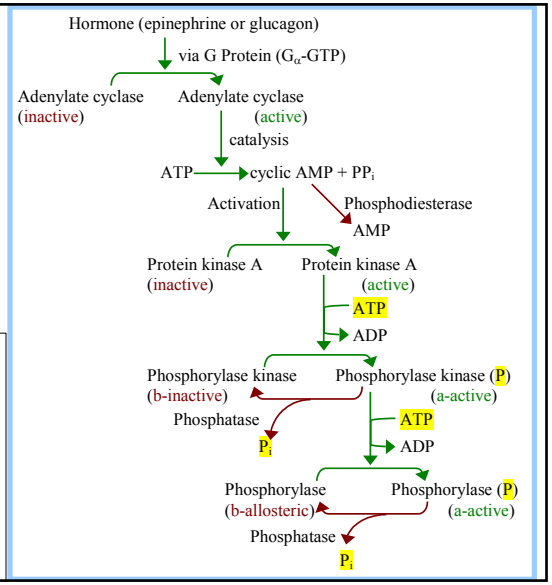
The phosphorylated enzyme is **less sensitive to allosteric inhibitors**.

Thus, even if cellular ATP & glucose-6-phosphate are high, Phosphorylase will be active.

The glucose-1-phosphate produced from glycogen in liver may be converted to free **glucose** for release to the blood.

With this hormone-activated regulation, the needs of the organism take precedence over needs of the cell.

Signal cascade by which Glycogen Phosphorylase is activated.



Commonly used terminology:

- **"a"** is the form of the enzyme that tends to be **active**, and **independent** of allosteric regulators (in the case of Glycogen Phosphorylase, when phosphorylated).
- **"b"** is the form of the enzyme that is **dependent** on local allosteric controls (in the case of Glycogen Phosphorylase when dephosphorylated).

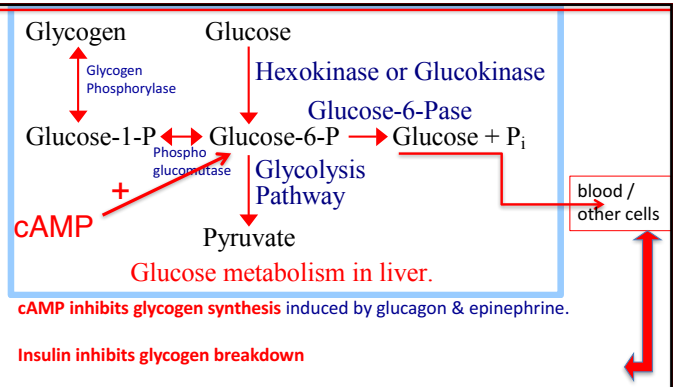
The **cAMP cascade** induced in liver by glucagon or epinephrine has the **opposite effect on glycogen synthesis**, it promotes the breakdown of glucogen to glucose by Glycogen Phosphorylase

Glycogen Synthase is **phosphorylated** by Protein Kinase A as well as by Phosphorylase Kinase.

Phosphorylation of Glycogen Synthase promotes the "**b**" (less active) conformation.

The cAMP cascade thus **inhibits glycogen synthesis**.

Instead of being converted to glycogen, glucose-1-P in liver may be converted to glucose-6-P, and dephosphorylated for release to the blood.



cAMP inhibits glycogen synthesis induced by glucagon & epinephrine.

Insulin inhibits glycogen breakdown

High cytosolic glucose-6-phosphate, which would result when blood glucose is high, turns off the signal with regard to glycogen synthesis.

The conformation of Glycogen Synthase induced by the allosteric activator glucose-6-phosphate is susceptible to dephosphorylation by Protein Phosphatase.

Insulin, produced in response to **high blood glucose**, triggers a separate signal cascade that leads to **activation of Phosphoprotein Phosphatase**.

This phosphatase catalyzes removal of regulatory phosphate residues from Phosphorylase, Phosphorylase Kinase enzymes.

Thus **insulin antagonizes** effects of the **cAMP** cascade induced by **glucagon** & **epinephrine**.

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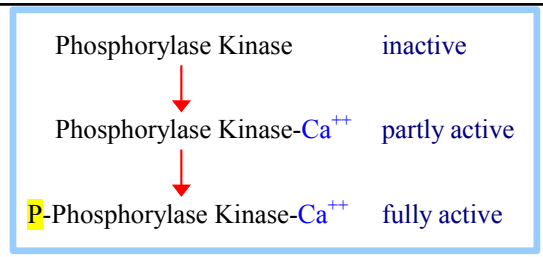
Insulin, inhibits glycogen breakdown.

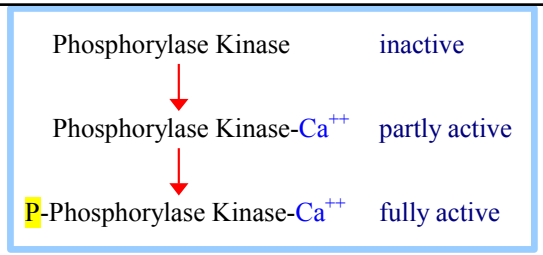


Ca^{++} also regulates glycogen breakdown in **muscle**.

During activation of contraction in skeletal muscle, **Ca^{++}** is released from the sarcoplasmic reticulum to promote actin/myosin interactions.

The released **Ca^{++}** also **activates Phosphorylase Kinase**, which in muscle includes **calmodulin** as its **δ subunit**.

Phosphorylase Kinase is partly activated by binding of **Ca^{++}** to this subunit.



Phosphorylation of the enzyme, via a cAMP cascade induced by epinephrine, results in further activation.

These regulatory processes ensure release of phosphorylated glucose from glycogen, for entry into **Glycolysis** to provide **ATP** needed for muscle contraction.

During **extended exercise**, as glycogen stores become depleted, muscle cells rely more on glucose uptake from the blood, and on fatty acid catabolism as a source of ATP.

A **genetic defect** in the isoform of an enzyme expressed in **liver** causes the following **symptoms**:

- **After eating** a **CHO** meal, **elevated** blood levels of **glucose**, **lactate**, & lipids.
- **During fasting**, **low blood glucose** & high ketone bodies.

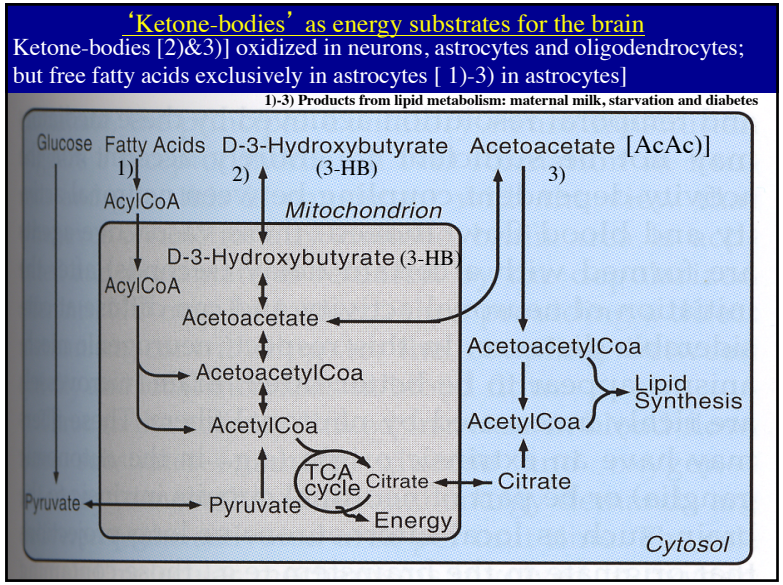
Which liver enzyme is defective? **Glycogen Synthase**

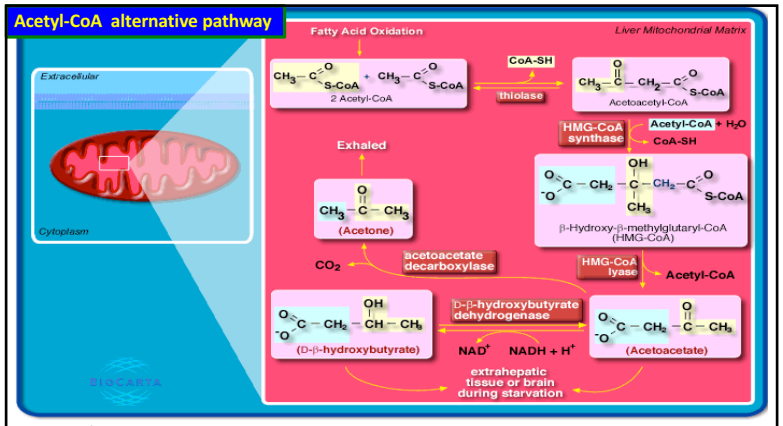
Explain Symptoms:

- **After eating**, blood **glucose** is high because liver cannot store it as glycogen. Some excess glucose is processed via **Glycolysis** to produce **lactate** & fatty acid precursors.
- **During fasting**, **glucose** is low because the liver lacks glycogen stores for generation of glucose.
  Ketone bodies are produced as an **alternative fuel**.

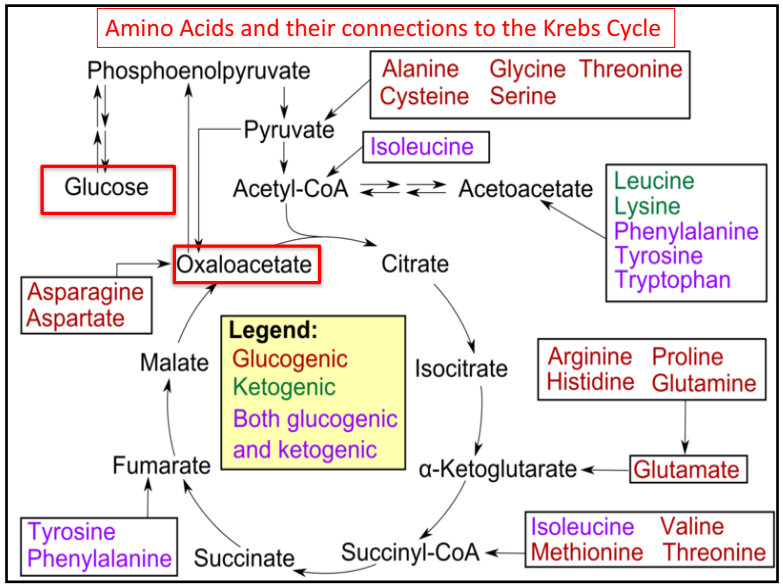
Ketone Bodies

- Use of fatty acids in the citric acid (Kreb's) cycle requires carbohydrates (CHO) for the production of oxaloacetate (OAA) – 'fat burns in CHO flame'.
- During starvation or diabetes, OAA is used to make glucose
  - Fatty acids are then used to make ketone bodies (acetoacetate and D–3–hydroxybutarate)





The acetyl-CoA produced by mitochondrial beta-oxidation of fatty acids enters the Kreb's cycle to produce energy, but that is not the only fate of acetyl-CoA. In liver mitochondria, some acetyl-CoA is converted to acetoacetate, beta-hydroxybutyrate, and acetone, collectively called ketone bodies. Ketone bodies are transported to other tissues such as brain, muscle or heart where they are converted back to acetyl-CoA to serve as an energy source. The brain normally uses only glucose for energy, but during starvation ketone bodies can become the main energy source for the brain. In the metabolic condition called ketosis, ketone bodies are produced faster than they are consumed by tissues and the smell of acetone can be detected on a person's breath. The smell of acetone is one indication that a person may have diabetes. The consumption of high-fat/low carbohydrate diets has been used as a weight loss program by many, intentionally inducing ketosis to consume fat stores, but these ketogenic diets can cause unwanted side effects related to increased urea production resulting from protein intake and risk of heart disease from increased cholesterol and fat intake.

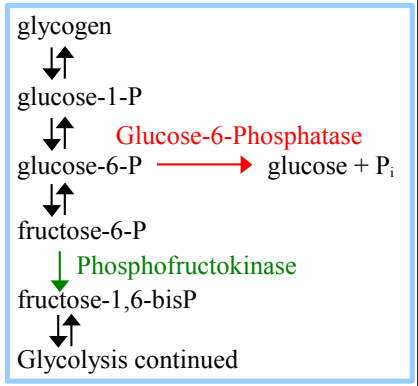


Question: How would you nutritionally treat deficiency of liver Glycogen Synthase?

- Frequent meals of **complex carbohydrates** (avoiding simple sugars that would lead to a rapid rise in blood glucose)
- Meals high in **protein** to provide substrates for **gluconeogenesis**.

Glycogen Storage Diseases are genetic enzyme deficiencies associated with **excessive glycogen accumulation** within cells.

Some enzymes whose deficiency leads to glycogen accumulation are part of the inter-connected pathways shown here.



Symptoms in addition to excess glycogen storage:

- When a genetic defect affects mainly an isoform of an enzyme expressed in **liver**, a common symptom is **hypoglycemia**, relating to impaired mobilization of glucose for release to the blood during fasting.
- When the defect is in **muscle** tissue, **weakness** & **difficulty with exercise** result from inability to increase glucose entry into Glycolysis during exercise.
- Additional symptoms depend on the particular enzyme that is deficient.

Glycogen Storage Disease	Symptoms, in addition to glycogen accumulation
Type I, liver deficiency of **Glucose-6-phosphatase** (von Gierke's disease)	**hypoglycemia** (low blood glucose) when fasting, liver enlargement.
Type IV, deficiency of **branching enzyme** in various organs, including liver (Andersen's disease)	**liver dysfunction** and early death.
Type V, muscle deficiency of **Glycogen Phosphorylase** (McArdle's disease)	**muscle cramps** with exercise.
Type VII, muscle deficiency of **Phosphofructokinase**.	**inability to exercise**.

Maintaining Blood Glucose Homeostasis