GLYCOLYSIS (also known as: EMBDEN-MEYERHOFF PATHWAY)

•Topics include:

•main reactions leading to the formation of pyruvate

•control mechanisms

•terminal reactions for the regeneration of NAD

•energetics and energy coupling

•ancillary reactions feeding into the glycolytic pathway

INTRO

•glycolysis is the major metabolic route responsible for the breakdown of glucose to pyruvate

present in all eukaryotes and prokaryotes

•conversion of glucose to pyruvate is exergonic

coupled to the synthesis of a limited amount of ATP

•it is an anaerobic process

in obligate anaerobes it is the main source of ATP

•some facultative anaerobies, such as yeast, grow "normally" solely on ATP produced from glycolysis

•pyruvate can be transformed anaerobically into EtOH (yeast) or lactate (muscle)

•in aerobic organisms, pyruvate can enter the mitochondria and be completely oxidized to CO_2 and H_2O

HISTORICAL BACKGROUND

•essential features of the pathway were worked out from early studies of yeast and muscle metabolism

•key observations:

It is 1897. The Buchner Brothers…

•were making "yeast juice" for therapeutic use

tried sucrose as a preservative and found it was fermented into alcohol…Voila! fermentation did not require living cells!

AND SO METABOLISM BECAME CHEMISTRY…

In 1905 Harden and Young:

•found that alcohol fermentation by yeast juice was dependent on P_i and that hexose diphosphate was an intermediate in the utilization of glucose

the P_i was incorporated into a sugar phosphate

the hexose di-P was later shown to be fructose 1,6-bisP

•also fractionated the yeast extract into a heat stable and a heat labile fraction

heat labile = enzymes

heat stable = cofactors and coenzymes

ATP

ADP

NAD

Meyerhoff

•found that minced muscle was capable of promoting the conversion of glucose to lactate by a process which shared many features with the yeast fermentation system

•detailed reactions worked out by 1940 by Embden, Meyerhoff, Warburg, Neuberg, Parnas, and Gerty and Carl Cori

OVERALL REACTION

pyruvate formation:

$C_6H_{12}O_6$ (glucose) + $2P_i$ +2ADP + $2NAD^+$ ---->$2CH_3COCOOH$ (pyruvate)+ 2ATP + 2NADH + $2H^+$ + $2H_2O$

regeneration of NAD^+ (muscle):

$2CH_3COCOOH$ (pyruvate) + 2NADH + $2H^+$---->$2CH_3CHOHCOOH$ (lactate) + $2NAD^+$

sum:

$C_6H_{12}O_6 + 2P_i + 2ADP \text{----}> 2CH_3CHOHCOOH + 2ATP + 2H_2O$

Note that the forms above retain the proton, so would correctly be called "pyruvic acid, lactic acid…however at physiological pH they are no doubt ionized (pKs?) and correctly identified with the "ate" suffix (lactate, pyruvate)

INDIVIDUAL REACTIONS OF GLYCOLYSIS

•the formation of pyruvate from glucose involves 10 reactions, each catalyzed by a different enzyme

•all reactions take place in the cytosol

•all the intermediates are phosphorylated compounds

•the negative charges due to the phosphate prevents diffusion of the intermediates out of the cell

•Note that all the reactions except HEX, and the control point reactions PFK and PK, have a $\Delta G'$ near equilibrium ($\Delta G \sim 0$) and are therefore revesible. The reversible reactions are catalyzed by the same enzymes in glycolysis and gluconeogenesis (glucose synthesis).

•1 Joule = 4.184 cal

Stage 1: conversion of glucose into fructose 1,6-bisP

1. formation of glucose-6-P

uses 1 ATP

•**hexokinase (HEX)**

has broad specificity; also phosphorylates fructose, mannose and a number of other 6-C sugars

$\Delta G°' = -4$ kcal/mol

$\Delta G' = -8$

not reversible

•reaction also catalyzed by **glucokinase (GK)**

channels glucose into glycogen storage pathway

has high K_M, and a low affinity for glucose, so it only functions when [glucose] is high

•what does this mean??

don't make glycogen unless there's a lot of glucose around

let brain and muscle have the glucose first

•GK and glycogen pathway active in liver

2. formation of fructose-6-P

isomerization of aldose to ketose

•glucose phosphate isomerase

$\Delta G^{\circ\prime}$ = 0.4 kcal/mol

$\Delta G'$ = - 0.6

reversible

3. formation of fructose 1,6-bisP

uses another ATP (the 2nd one)

•PFK -phosphofructokinase

major control point in glycolysis

committed step; controls inflow (forward flux) to the glycolytic pathway

allosteric tetrameric enzyme

activated by ADP or AMP

inhibited by citrate, fatty acids, ATP, H^+ (prevents metabolic acidosis)

$\Delta G^{\circ\prime}$ = - 3.4 kcal/mol

$\Delta G'$ = - 5.3

not reversible

Stage 2: formation of 3-phosphoglycerate

4. fructose 1,6-bisP (F1,6-bisP) is split into two 3-C units:

dihydroxyacetone P (DHAP) and glyceraldehyde 3-P (G3-P)

•aldolase

$\Delta G^{\circ\prime}$ = + 5.7 kcal/mol

$\Delta G'$ = - 0.3

reaction favors formation of hexose

products are removed very efficiently so reaction proceeds in forward direction

mechanism involves fromation of a Schiff base between the keto group of dihydroxyacetone P and the NH_2 group of a specific lys in the active site of aldolase in most eukaryotes

5. DHAP (ketose) is isomerized to G3-P (aldose)

only G3-P can go through the rest of the pathway

•triose phosphate isomerase

although the equilibrium mixture consists of 96% DHAP, 4% G3-P

the reaction proceeds readily from DHAP to G3-P

•why?

efficient removal of products!!

•thus two molecules of G3-P are formed from 1 molecule of glucose

$\Delta G^{\circ\prime}$ = + 1.8 kcal/mol

$\Delta G'$ = + 0.6

reversible

6. G3-P is converted into 1,3-BPG

remember there are two from each glucose

•glyceraldehyde 3-phosphate dehydrogenase (G3PD)

oxidation/reduction reaction

aldehyde (G3-P) is oxidized to an acid (1,3-BPG)

NAD^+ is reduced to NADH

•it is a coupled process in which a high energy phosphate is formed using the energy of oxidation of the aldehyde function

•substrate (G3-P) is phosphorylated by P_i ;called substrate level phosphorylation

$\Delta G^{\circ\prime}$ = + 1.5 kcal/mol

$\Delta G'$ = - 0.4

reversible

7. 1,3-BPG is converted to 3-phosphoglycerate

ATP is formed at this step (2 from each entering glucose)

•phosphoglycerate kinase

transfers the phosphate from position 1 to ADP

$\Delta G^{\circ\prime}$ = - 4.5 kcal/mol

$\Delta G'$ = + 0.3

reversible

Stage 3: formation of pyruvate

8. 3-phosphoglycerate (3-PG) is converted into 2-phosphoglycerate (2-PG)

•phosphoglyceromutase

mutases generally "rearrange" molecules

phosphoryl group moves from position 3 to 2

$\Delta G^{\circ\prime}$ = + 1.1 kcal/mol

$\Delta G'$ = + 0.2

reversible

9. phosphoenolpyruvate (PEP) is formed from 2-PG

•enolase

inhibited by flouride

dehydration reaction

elimination of water leads to an increase in the free energy of hydrolysis of the phosphate ester

•enol phosphates (like PEP) have a high Phosphate Group-Transfer Potential

PGTP of PEP is 14.8 kcal/mol

$\Delta G^{\circ\prime}$ = + 0.4 kcal/mol

$\Delta G'$ = - 0.8

reversible

10. pyruvate is formed from PEP

PGTP is so large for PEP because the enol intermediate (enol pyruvate) that is initially formed from PEP is converted into a ketone: pyruvate

•**pyruvate kinase**

ATP is formed (2)

another regulatory point in the pathway: controls outflow

inhibited by ATP and fatty acids

activated by fructose 1,6-bisP

$\Delta G^{\circ\prime}$ = - 7.5 kcal/mol

$\Delta G'$ = - 4.0

not reversible

CONTROL OF GLYCOLYSIS

1. the enzymes that catalyze the essentially irreversible steps in a pathway are the potential sites of control

•in glycolysis these steps are cayalyzed by:

hexokinase (HEX), PFK, and pyruvate kinase (PK)

2. PFK is the key inflow control enzyme and therefore catalyzes the committed step for glycolysis

why not HEX?

•consider the dual role of the pathway:

generates ATP but also provides building blocks for biosynthesis, for example for fatty acid biosynthesis, glycogen biosynthesis, synthesis of the phospholipid precursor inositol, pentose phosphate pathway (NADPH, ribose) and more…

G6-P is the precursor for synthesis of glycogen and is also used in pentose phosphate pathway to form NADPH

•thus the HEX step is not the committed step

because product of the reaction goes other places…committed means it only goes in that one pathway

•inhibition of PFK (by ATP, citrate, fatty acids) does lead to inhibition of HEX, since G6-P builds up and this inhibits HEX

•PFK responds to metabolic signal that biosynthetic precursors are abundant by its sensitivity to inhibition by citrate and fatty acids

citrate is a citric acid cycle intermediate

many biosynthetic precursors are generated in the citric acid cycle (TCA cycle)

•PFK is allosterically activated by fructose 2,6-bisP

formed by PFK2 when [F6-P] is high, and you need to metabolize it to F1,6-bisP

hydrolyzed to F6-P (fructose 6-P) when [F6-P] is low by FBPase2

→both enzymes on same 53kd pp chain

•PFK catalyzes the committed step in glycolysis

3. PK controls the outflow from glycolysis

•3 forms, or isozymes

all are tetramers w/ subunit MW of 55K

L in liver

M in muscle and brain

A in other tissues

•the isozymes differ in how they are regulated

•L form most highly regulated--binds PEP cooperatively

is inhibited by high [ATP], alanine

activated by fructose 1,6-bisP

•L is also controled by phosphorylation through action of the hormone glucagon

blood glucose low, glucagon triggers phosphorylation of PK which makes it inactive

so blood glucose doesn't get too low, for brain and muscle

•M isozyme not regulated by phosphorylation, A form intermediate between L and M

4. 2,3-BPG formed from 1,3-BPG when [1,3-BPG] is high

•activates phosphoglycerolmutase (as well as stabilizing the deoxy (T) form of Hb), which converts 3-PG to 2-PG

REGENERATION OF NAD^+

•since NAD^+ is present only in catalytic amounts, and is used in other pathways as well, the continual functioning of the glycolytic reactions (and the rest of the cell) depends on the reoxidation of NADH formed at the G3PD step (G3-P to 1,3-BPG)

1. anaerobic metabolism in muscle tissue:

•during periods of vigorous excerise, muscle tissue is functioning essentially under anaerobic conditions, and the ATP is derived almost exclusively from glycolysis

under these conditions, pyruvate is reduced to lactate

→reaction requires NADH and yields NAD^+

•catalyzed by **lactate dehydrogenase**

$CH_3COCOOH$ (pyruvate) + NADH + H^+---->$CH_3CHOHCOOH$ (lactate) + NAD^+ + H^+

the lactate formed diffuses from the muscle and is transported through the circulatory system to the liver where it is slavaged by being converted to glucose (gluconeogenesis)

lactate formation from pyruvate also occurs in certain microorganisms (lactobacilli) that carry out lactic acid fermentation

2. alcoholic fermentation is another anaerobic process that regenerates NAD^+ :

•pyruvate is first decarboxylated to acetaldehyde by **pyruvate decarboxylase** requires cofactor thiamine pyrophosphate (TPP)

$CH_3COCOOH$---->CH_3CHO (acetaldehyde) + CO_2

•the reducing equivalents of NADH generated in glycolysis are then used to reduce acetaldehyde to ethanol by **alcohol dehydrogenase**

$CH_3CHO + NADH + H^+$---->CH_3CH_2OH (EtOH, ethanol) + NAD^+

3. under aerobic conditions all eukaryotic cells and many bacteria oxidize NADH by a series of oxidation/reduction reactions in which the terminal oxidant is molecular oxygen

this pathway is known as the respiratory chain

CATABOLISM OF OTHER CARBOHYDRATES

•storage compounds (glycogen in animals, starch in plants) and sugars other than glucose can be converted to intermediates of glycolysis and then enter the pathway

1. polysaccharides

•both glycogen and starch are polymers of glucose linked primarily through 1 - 4 glycosidic linkages

•glycogen is cleaved by **glycogen phosphorylase** to yield glucose 1-P

$(C_6H_{12}O_6)_n + P_i$ ----> $(C_6H_{12}O_6)_{n-1}$ + glucose 1-P

•**phosphoglucomutase** then converts glucose 1-P to glucose 6-P which can then enter glycolysis

glucose 1-P----> glucose 6-P----> glycolysis

2. disaccharides

•sucrose, maltose, and lactose are the 3 common disaccharides that occur in the diets of higher animals

these sugars are hydrolyzed to the monosaccharides by specific enzymes:

•**invertase (sucrase)**

sucrose→ glucose + fructose

•**maltase**

maltose → 2 glucose

•**lactase (β – galactosidase)**

lactose → glucose + galactose

3. **monosaccharides**

•fructose is phosphorylated to fructose 1-P by **fructokinase** in the liver

fructose 1-P is cleaved by **fructose 1-P aldolase** to glyceraldehyde and DHAP

glyceraldehyde can then be phos. to G3-P by **triose kinase**

•fructose is also phosphorylated by hexokinase to fructose 6-P, but affinity for glucose is 20x higher

little formed this way in liver because of high [glucose]

more formed this way in adipose tissue where]fructose] is high and [glucose] low

•galactose is first phosphorylated by **galactokinase** to galactose 1-P (gal 1-P)

gal 1-P reacts w/ UDP-glucose to form UDP-gal and glucose 1-P: catalyzed by a **transferase**

phosphoglucomutase converts glu 1-P to glu 6-P to enter glycolysis

UDP-gal is epimerized to regenerate UDP-glucose by an **epimerase**

NAD^+ is transiently reduced and then reoxidized

•galactosemia

patients lack the transferase

high levels of gal cause toxic substances such as galactitol to accumulate (galactitol forms in the lens of the eye and causes cataracts)

vomiting, diarrhea, when milk is consumed

enlarged liver and jaundice

infants fail to thrive and become mentally retarded

all except mental retardation is reversible by elimination of milk

ENERGETICS OF GLYCOLYSIS

1. anaerobic glycolysis with glucose as substrate:

ATP input = 2 mol /mol glucose

ATP output = 4 mol /mol of glucose

net yield of ATP = 2 mol /mol of glucose

•the synthesis of 2 mol ATP is equivalent to a conservation of energy of 2 x 7.3 kcal = 14.6 kcal

•$\Delta G^{\circ\prime}$ = - 47 kcal/mol

•efficiency under standard conditions (1M reactants. and products.) = $\frac{14.6}{47}$ = 31%

the actual efficiency is higher because the $\frac{ADP}{ATP}$ ratio is low and the $\Delta G'$ > than 7.3 kcal/mol

2. anaerobic glycolysis with glycogen as substrate:

ATP input = 1 mol /mol of glucose 1-P formed

ATP output = 4 mol /mol of glucose

net yield of ATP = 3 mol /mol of glucose

• $\Delta G^{\circ\prime}$ for the reaction:

$(C_6H12O_6)_n + H_2O$----> $(C_6H12O_6)_{n-1}$ + 2 lactate

is - 52 kcal under standard conditions

•the efficiency is therefore $\frac{3 \times 7.3}{52}$ = 42%

3. the coupling of the energy of oxidation of G-3P to ATP synthesis

•energy coupling is accomplished by two enzymes

G3PD and phosphoglycerate kinase

G3P to 1,3-BPG and 1,3-BPG to 3PG

•G3PD is a tetrtamer

each subunit has MW of 33,000

each binds one NAD^+ and has four essential SH groups

acyl enzyme forms during the reaction

prevented by SH blocking reagents such as iodoacetamide

•absolutely dependent on inorganic phosphate (P_i) but also proceeds with arsenate

arsenate structurally looks a lot like phosphate but compounds it forms are not stable

no ATP formed at next step with arsenate

•$\Delta G°'$ for formation of the high energy acyl phosphate G3P = + 1.5 kcal

•second part of the coupling is a transfer of the high energy phosphate of 1,3-BPG to ADP

catalyzed by PGK (phosphoglycerokinase)

$\Delta G°'$ = - 4.5 kcal

formation of 3PG and ATP highly favored

GLYCOGEN METABOLISM

Glycogen Catabolism

1. glycogen is digested from food by α -amylase, beginning in the mouth (saliva)

2. glycogen is mobilized (or catabolized) as follows:

(glycogen breakdown called **glycogenolysis**)

•glycogen is a polymer of glucose linked primarily through α1-4 glycosidic linkages

"branches" at α1-6 linkages

•α1-4 glycosidic linkages cleaved by **glycogen phosphorylase** to yield glucose 1-P

$(C_6H_{12}O_6)_n + P_i$ ----> $(C_6H_{12}O_6)_{n-1}$ + glucose 1-P

thermodynamically reversible: ΔG = + 0.7 kcal/mol

proceeds in degradative direction because of high intracellular [P_i]

•"debranched" by oligo (α1,4→α1,4) glucantransferase **(glycogen debranching enzyme)**

-why are there branches? more ends for glycogen phosphorylase to attack= faster mobilization of glycogen

•**phosphoglucomutase** then converts glucose 1-P to glucose 6-P which can then enter glycolysis or be converted to glucose

glucose 1-P----> glucose 6-P----> glycolysis

3. glucose 6-P turned into glucose by **glucose-6-phosphatase**

•gluconeogenesis and glycogen breakdown both occur largely in liver

•glucose-6-phosphatase found only in liver, kidney and intestine

-phosphorylated glucose can't get out of liver cell to enter bloodstream and get to other tissues

-so often converted to glucose

•no glucose-6-phosphatase in muscle or brain

-glucose-6-P from glycogen breakdown in muscle all enters glycolysis immediately

Regulation Of Glycogen Breakdown

•hormonal and non hormonal

•must be able to mobilize glycogen stores very rapidly

-for fight or flight response; instantaneous requirement for increased energy generation and utilization

A. glycogen phosphorylase

1. 2 identical 97K polypeptide chains

-binds PLP cofactor via Schiff base (PLP a vitamin B6 derivative)

-only the phosphate of PLP participates in catalysis: acts as a general acid-base catalyst

•phosphorylase ***a*** is active (phosphorylated)

-activation (of phos-b) is catalyzed by **phosphorylase kinase**

-ser at position 14 in both chains is phosphorylated

•phosphorylase ***b*** is inactive (not phosphorylated)

-deactivation (of phos-a) is catalyzed by **phosphoprotein phosphatase-1**

2. phosphorylase kinase is also activated by phosphorylation of α and β subunits

-a complex multi subunit protein with 4 nonidentical subunits, α β γ δ

-γ has catalytic site

•catalyzed by **cyclic AMP-dependent protein kinase (cAPK)**

-catalyzes phosphorylation. of a number of proteins

•activity of cyclic AMP-dependent protein kinase controlled by:

-intracellular [cyclic AMP]

-cAMP synthesized by adenylate cyclase, which is stimulated by certain hormones

-cAMP broken down by cAMP phosphodiesterase

-activation is rapid and efficient in response to hormone signals

B. hormonal control

1. cyclic AMP produced in response to hormonal stimulation

•epinephrine or glucagon

•second messenger

-receives messages from outside cell (in form of hormonal stimulation); transmits them within cell

-transmission involves activation of some processes and inhibition of some processes

2. primary hormone for glycogenolysis in muscle is **epinephrine** (also called **adrenaline**)

•secreted from adrenal medulla

•binds to receptors in muscle cell membrane

•stimulates **adenylylate cyclase**

-catalyzes synthesis of cyclic AMP from ATP

•cAMP stimulates the cyclic AMP-dependent protein kinase (cAPK)

•cAPK catalyzes phosphorylation (activation) of phosphorylase kinase

•phosphorylase kinase phosphorylates phosphorylase ***b*** to form phosphorylase ***a***

*rapid response to fight or flight thus possible at muscle level

•epinephrine also triggers other physiological responses, such as increased depth and frequency of heart beat

C. calmodulin

1. phosphorylase kinase contains a **calmodulin** subunit (**cal**cium-**modul**ating prote**in**)

•calcium is important. physiological regulator, especially of muscle and nerve processes

-mediated through calmodulin

•MW = 17K

•4 calcium binding sites

•very sensitive to Ca^{++} ; can respond to 1μM

• without Ca++, the active site of phosphorylase kinase is blocked

•Ca^{++} binding to calmodulin causes a conformational change is calmodulin that results in "unblocking" of the phos kinase active site so it can now bind its substrate phosphorylase ***b***

-so CaM is required for activity

•so through this mechanism glycogenolysis is also regulated by calcium

*contraction in muscle stimulated by Ca release which also stimulates glycogenolysis

D. non hormonal control

1. phosphorylase ***b*** also can be activated by AMP (not cyclic AMP)

•usually doesn't occur in cell because ATP competes for binding with AMP

-ATP usually much more abundant than AMP

•under energy starvation, AMP can accumulate and signal glycogen breakdown

Glycogen Biosynthesis

*for years, thought that glycogen. synthesis was reversal of breakdown

A. early evidence that pathways for glycogen synthesis and breakdown are different:

1. epinephrine only activated breakdown

2. high levels of intracellular P***i*** would make it unlikely on equilibrium grounds for phosphorylase to work in direction of synthesis

3. although phosphorylase can synthesize glycogen ***in vitro*** product is very different from natural glycogen (much smaller)

B. glycogen is synthesized from UDP-glucose (UDP-glc)

1. UDP-glc discovered in 1950s by Luis Leloir

2. synthesized from glucose-1-P

*comes from glu-6-P by phosphoglucomutase

•catalyzed by **UDP-Glc pyrophosphorylase**

UTP + glucose-1-P ----> UDP-glc + PP***i***

reaction is driven by rapid hydrolysis of pyrophosphate:

PP***i*** + H_2O ----> 2P***i***

yields about 7.2 kcal/mol

catalyzed by **pyrophosphatase**

3. glucose is added to glycogen chain via UDP-glc in reaction catalyzed by **glycogen synthase**

•1-4 addition

4. 1-6 branches are formed by the **branching enzyme (amylo-(1,4--->1,6)-transglycosylase**

Reciprocal Regulation of Glycogen Synthesis and Breakdown

•when breakdown is activated, synthesis is inhibited

A. phosphorylation of glycogen synthase

•tetramer MW = 350K

1. like phosphorylase, has 2 forms:

-glycogen synthase ***b*** = phosphorylated (inactive)

-glycogen synthase ***a*** = not phosphorylated (active)

•phosphorylation increases K_M for UDP-glucose

•cAMP dependent phosphorylation catalyzed by same enzyme as in breakdown: **phosphorylase kinase** (other kinases also involved)

2. b form is dependent on presence of glucose-6-P: if the concentration is high enough, it will be active even without phosphorylation

•because glucose-6-P is an allosteric effector

•**but no effect** if glucose-6-P < than 1mM

•"a" form independent of glucose-6-P

3.

•"b" form in resting muscle

•"a" form during contraction

B. glucose-6-P facilitates non hormonal regulation

•activator

•also, if high, the b form is active

•makes metabolic sense: if high, want to make glycogen

C. hormonal regulation

*complicated; lots of kinases

1. epinephrine or glucagon >>> adenylylate cyclase

• adenylylate cyclase >>>cAMP >>>active cAMP dependent protein kinase

2. cAMP dep. kinase can P a to b itself and can also P phosphorylase kinase which then Ps a to form b

•reg. of breakdown more sensitive because of extra required step

•maximum rate of breakdown 330x that of synthesis

-physiologically important for rapid response

3. 3 additional kinases also P glycogen synthase a

-not well understood

•each kinase Ps a different ser

-so really >> than 2 forms of synthase

-graded series of responses

4. progressive changes:

•decreased affinity for substrate (UDP-glc)

•decreased affinity for allosteric activator (glucose-6-P)

•increased affinity for ATP and P***i*** (antagonizes activation by glucose-6-P)

5. dephosphorylation of glycogen synthase ***b***

•catalyzed by **phosphoprotein phosphatase (PP-1)**

•PP-1 activity inhibited by **phosphoprotein phosphatase inhibitor (PI-1)**

•phosphorylated form of PI-1 is active

-carried out by cAMP dep. kinase

•so cAMP inactivates synthase by:

-phosphorylation of synthase

-inhibition of phosphatase

•insulin stimulates PP-1 (opposite effect to glucagon and epinephrine)

D. functions of glycogen stores in muscle and liver

•muscle glycogen = major energy source in muscle

•liver glycogen = main source for blood glucose

-liver get most of its metabolic energy from fatty acid oxidation

•liver is a "glucostat"

-senses blood glucose levels and adjusts glycogen synthesis and breakdown accordingly

-glycogen is 2-8% of liver weight

•rates of synthesis and breakdown in liver are about =, whereas in muscle breakdown 300x >> than synthesis

•enzymology of synthesis and breakdown similar in liver and muscle, but endocrine control very different

-enzymes differ structurally (isozymes)

E. congenital defects of glycogen metabolism in humans

•glycogen storage diseases

•accumulation of abnormal forms or quantities of glycogen or both

•liver enlarged-can be 40% glycogen

•defects in glucose-6-phosphatase, branching enzyme and debranching enzyme, or muscle glycogen phosphorylase