Glycolysis

Glycolysis ÷ — 1-5 : Energy-Investment
— 6-10 : Energy-Generation (sub.-level)

Net products: 1 Glucose → 2 Pyruvate
2 ADP → 2 ATP
2 NAD+ → 2 NADH

Glycerol-P : 2+4 = 6
Malate-Aspartate : 2+6 = 8

Glycogen ⇄ (Glycogenolysis / Glycogenesis) Glucose ⇄ (Glycolysis / Gluconeogenesis) Pyruvate

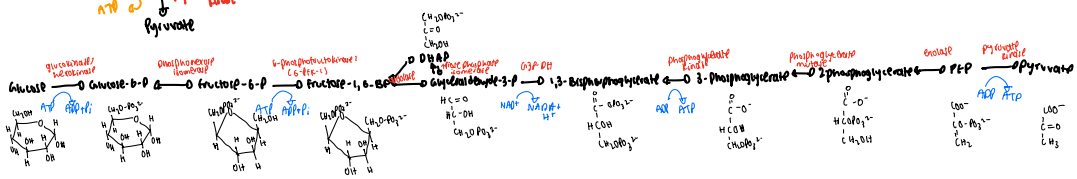
GLUT TRANSPORTERS

I- BBB — B- Blood (RBCs - Erythrocytes), B- Baby (fetus), B- Blood-brain barrier
II- KIDS LIPS — K- Kidney, L- Liver, P- Pancreas
III- PINK — P- Placenta, N- Neurons, K- Kidney
} insulin-independent

IV- MOTHER / FATHER — M- Muscle (skeletal + cardiac), F- Fat (adipose tissue) } insulin-dependent

Glycolysis:
- Occurs in cytoplasm
- S.S: glucose
- E.P: 2 Pyruvates
- NET ATP: 2 ATP
- 2 NADH

Glucose
↓ (Liver) glucokinase / hexokinase (muscles & other tissues) — ATP, ADP+Pi
Glucose-6-P
↓ phosphohexose isomerase
Fructose-6-P
↓ phosphofructokinase 1 — ATP, ADP+Pi — late-limiting & committed step of glycolysis
Fructose-1,6-BP
↓ aldolase
DHAP ⇄ (triose-P. isomerase) Glyceraldehyde-3-P — 2 NAD+ → 2 NADH
↓ GAZP DH
1,3-bisphosphoglycerate
↓ phosphoglycerate kinase — 2 ADP, 2 ATP
3-phosphoglycerate
↓ phosphoglycerate mutase
2-phosphoglycerate
↓ enolase
Phosphoenol Pyruvate
↓ pyruvate kinase — ADP, ATP
Pyruvate



pyruvate kinase deficiency → hemolytic anemia

Regulatory key enzymes: (3)

1) Glucokinase / hexokinase : Glucose + ATP → Glucose-6-Phosphate + ADP+Pi

2) 6-Phosphofructokinase-1 : Fructose-6-Phosphate + ATP → Fructose-1,6-BP + ADP+Pi • MAIN REG. ENZYME

3) Pyruvate kinase : PEP → Pyruvate (ADP, ATP)

	Activation	Inhibition
hex:	• insulin	Glc-6-P
Glu:	• Fru-1-P	Fru-6-P
	• ↓ ATP/AMP	• ↑ ATP/AMP
	• Fru-2,6-BP	• citrate
	• Insulin	• acidic pH
	• insulin	• Glucagon
	• Fru-1,6-BP	• ↑ ATP/AMP
		• acetyl-CoA

Pyruvate → PEP ⇌ 2-phospho-glycerate ⇌ 3-phospho-glycerate ⇌ 1,3-BP glycerate ⇌ Glyceraldehyde-3-P ⇌ fructose-1,6-BP

↓

fructose-6-phosphate

↓

glucose-6-phosphate

↓

glucose

Gluconeogenesis

"reversed glycolysis"

w/ exception of

3 reactions

Breakdown of lipids, ketone bodies

energetically important lipids → TAGs
(we're not discussing phospholipids ...)

ox. of 1g of
- fatty acids = 38 kJ
- carb. / protein } 17 kJ

TAG supply sufficient for weeks

healthy person has 15% of body weight = TAGs

MAIN SITE OF TAG ACCUMULATION = adipocytes (fat cells)

Lipid breakdown:
Lipids as E source

homosensitive lipase (HSL) → releases FAs from stores, performs complete lipolysis
1 TAG → 3 FA + 1 glycerol

inhibited by: insulin
activated by: counter-reg. hormones → glucagon, adrenaline, noradrenaline

insulin wants less fats & stuff → doesn't want to release FAs & glycerol & opposite for glucagon, adrenaline, noradrenaline

utilizing lipids → 3 steps
1) lipid mobilization : TAG → DFA + glycerol transported by blood
2) activation of FA : transp. from cytosol (where they've activated) to HIT matrix
3) β-oxidation : FA → acetyl-CoA → KC
reduced cofactors produced, used directly in resp. chain

1) lipid mobilization
TAG → FA + glycerol
released from cell into blood

FA longer than 12C → carrier in plasma membr. (lipoprotein)
(arrives → albumin)

glycerol → in liver (glycolysis / glucose gener.)
glycerol $\xrightarrow[\text{ATP}]{\text{glycerol kinase}}$ glycerol-3-P $\xrightarrow[\text{glycerol-3-P DH}]{\text{NAD}^+, \text{NADH+H}^+}$ DH-AP

Lipolysis regulation	Activation	Inhibition
Hormone sensitive lipase (adipocytes)	• catecholamines • glucagon • ACTH (phosphorylation)	• insulin • prostaglandins
Lipoprotein Lipase (endothelium surface)	• insulin • apolipoprotein C-II	

Metabolism of ketone bodies

3 ketone compounds

acetoacetate, β-hydroxybutyrate, acetone

(acetoacetate, β-hydroxybutyrate: essential; acetone: waste product, excreted)

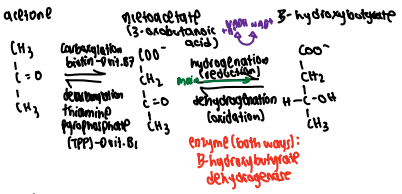
- completely degraded to CO_2 & water

Ketones essentially blood-transportable version of acetyl (they're derived from acetyl-CoA)

ONLY formed in liver mitochondria

so ketogenesis (ketone body synthesis) → organ: liver ONLY → cellular location: mitochondria ONLY

ketone bodies:



glucose runs out (starvation) → ketones produced by liver

ketones used by all body except liver (no enzyme)

& erythrocytes (RBCs) → no mito. → no ketone body breakdown (degradation)

carboxylase deficiency → OAA deficiency → TCC slows down → more convert acetyl-CoA → ketogenesis

& low glycemia → glucagon activated → TAG breakdown bec. HSL activated by glucagon → high FA → β-oxidation → high acetyl-CoA → ketogenesis

Energy Storage in cells

After meal → insulin / glucagon ratio ↑ → nutrients converted to E storage molecules

excess of glucose → stored as glycogen
or → converted to pyruvate (glycolysis) then acetyl-CoA (used for FA synthesis).

excess of FA (from diet or formed from excess glucose & AA) → synthesized into TAGs
main energy reserve form in body

fat storage → TAG
saccharide storage → glycogen
protein storage → none

Glycogen → carb. storage in animal cytoplasm (violet color) in almost all cells

women → more glycogen → vaginal mucosa

Glycogen in
- liver → used to maintain glycemia
- muscle → used during short-term stenous muscle work
- vaginal mucosa → defense against microorganisms → acidic environment (glycogen → lactate → pH + production).

PAS → stains glycogen brightly, violet.

Glycogen:
branched homopolymer
α-1,4-glycosidic bonds
branching: α-1,6 glycosidic bonds
2 groups of enzymes to cleave α1,4 & α1,6

glycogen → 2 ends
elongation & shortening → non-reducing ends (w/o OH)

reducing end has semi-acetyl hydroxyl bound by protein glycogenin

Glycogen branched on every 8th - 10th glucose
only 1 reducing end, all rest non-reducing (branches)

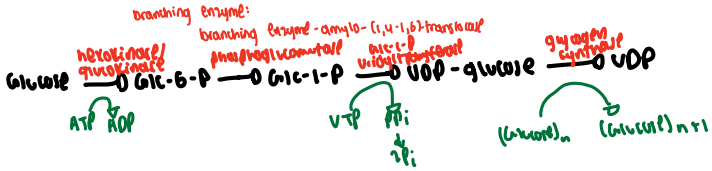
Glycogenesis → glycogen synthesis
- in cytosol
- 4 steps

1) phosphorylation: in liver: glucokinase; in muscle: hexokinase — glucose + ATP → Glc-6-P + ADP
2) isomerization: glucose phosphate isomerase — Glc-6-P → Glc-1-P (= coriester)
3) coupling of UDP: UDP-glucose pyrophosphorylase — Glc-1-P + UTP → UDP-Glc (monoergic compound formed)
4) connection of UDP-Glc to non-reducing end of glycogen: glycogen synthase
UDP released, α-1,4 bond formed
8-10 glucoses then branch

branching enzyme:
branching enzyme - amylo-(1,4-1,6)-transferase

Glucose —(hexokinase/glucokinase)→ Glc-6-P —(phosphoglucomutase)→ Glc-1-P —(Glc-1-P uridyltransferase)→ UDP-glucose —(glycogen synthase)→ UDP

ATP, ADP; UTP, PPi → 2Pi; $(Glucose)_n$, $(Glucose)_{n+1}$



Glycogen synthesis:
- primer required: remaining glycogen or glycogenin enzyme

Regulation of glycogen synthesis: glycogenesis:

glycogen synthase:
[active in dephosphorylated form
[inactive in phosphorylated form

to phosphorylate glycogen synthase (inactive) → protein kinase
to dephosphorylate glycogen synthase (active) → phosphoprotein phosphatase

- insulin → wants to ↓ free glucose levels in blood → activates glycogen synthase
glucagon inhibits it
adrenaline inhibits it

protein kinase A (PKA) → cAMP dependent
CAMK (calmodulin dependent protein kinase) - active when protein calmodulin binds
↓ Ca^{2+} → bind to calmodulin → active calmodulin can now bind to CAMK

glucagon → activates adenylate cyclase → forms cAMP → activates PKA → phosphorylates glycogen synthase
muscle contraction → Ca^{2+} ↑ intracellularly → binds to calmodulin → active calmodulin → activates CAMK → inactivates it
→ activates PKA → phosp. glyc. syn. → inactivates it

insulin → activates phosphodiesterase → cleaves cAMP to AMP → inactivates PKA

↳ also activates, phosphoprotein phosphatases → dephosp. → activates glyc synth.

Glycogenolysis (hydrolysis): degradation of glycogen molecule (breakdown)

- also in cytosol
- 3 steps

1) phosphorolytic cleavage

α1,4 bond cleaved → Glc-1-P (Cori ester) formed

free P$_i$ used linked to C$_1$ glucose

Enzyme: glycogen phosphorylase

ends 4 glc molecs. before branching

2) isomerization:

Glc-1-P ⟶ Glc-6-P
(phosphoglucomutase / glucose phosphate isomerase)

3) cleavage of branch → removal of α-1,6 bond

glucanotransferase (+ debranching enzyme)

Regulation of glycogen degradation (glycogenolysis):

glycogen phosphorylase → active: phosphorylated by phosphorylase kinase
→ inactive: dephosphorylated

phosphorylase kinase: inhibited by insulin, activated by counter regulatory hormones

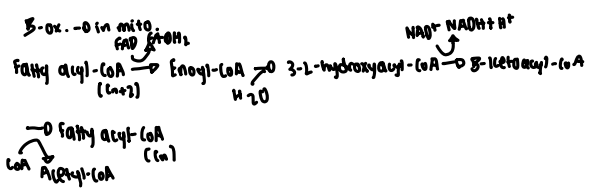
Signaling via PKA & CAMK

in food (meal) → glycogen present → free glucose absorbed by blood (α-amylase (hydrolase))

Regulation	Activators	Inhibitors
Synthesis: Glycogen synthase	: Insulin, Glc-6-P	: calcium, Adrenaline
Degradation: Glycogen phosphorylase	• Glucagon, Adrenaline, ↓ATP, AMP, • Ca^{2+} (in muscle)	• ↑ATP, AMP • Glc-6-P • Glucose

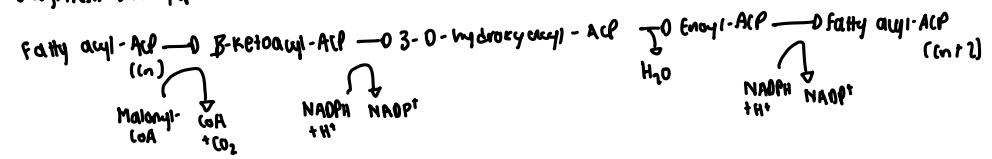
Synthesis of fatty acids

FA degradation vs. synthesis



- FAD & NAD^+ e⁻ acceptors
- CoA is acyl group carrier

Biosynthesis - O in cytoplasm



- NADPH is e⁻ donor
- ACP is acyl carrier

Malonyl-CoA formation:

- it's the initial substrate for FA-acetyl-CoA synthesis

acetyl-CoA + ATP + HCO_3 → malonyl-CoA + ADP + Pi + H^+

carboxylation
enzyme: acetyl-CoA carboxylase
cofactor: biotin (vit. H1B7)

acetyl-CoA carboxylase → reg. enzyme of whole pathway → also affects FA β-oxidation

CO_2 removed during condensation w/ growing FA

Individual steps of FA synthesis:
(uses NADPH from pentose cycle)

- 1) malonyl-CoA synthesis w/ enzyme acetyl-CoA carboxylase

acetyl-CoA + ATP + HCO_3^- → malonyl-CoA + ADP + Pi + H^+

- 2) binding of acetyl to cond. enzyme (CE) w/ enzyme acetyltransacylase

acetyl-CoA + CE → acetyl-CE + CoA

- 3) malonyl-CoA binding to ACP (acyl carrier protein) w/ enzyme malonyltransacylase

malonyl-CoA + ACP → malonyl-ACP + CoA

- 4) condensation reaction: connecting malonyl ACP & acetyl-CE w/ enzyme β(3)-ketoacyl-ACP synthase

acetyl-CE + malonyl-ACP → acetoacetyl-ACP + CE + CO_2

- 5) reduction w/ enzyme β-ketoacyl reductase

acetoacetyl-ACP + NADPH → 3-hydroxybutyryl-ACP + H_2O

- 6) dehydration w/ enzyme 3-hydroxyacyl dehydratase

D-3-hydroxybutyryl-ACP → crotonyl-ACP + H_2O

- 7) reduction w/ enzyme enoyl reductase

crotonyl-ACP + NADPH → butyryl-ACP + NADP

end product: palmitate (16c)

thioesterase cleaves ACP from palmitate by hydrolyzing thioester bond

requirements for palmitate formation

8 acetyl-CoA
14 NADPH
7 ATP

acetyl-CoA transp. to mito using citrate

8 NADPH obtained by transp. citrate to cyto. & remaining 6 in pentose cycle

TAG synthesis:

TAG - final form of FA storage

- starting w/ DHAP

  reduction: DHAP OH

  DHAP + NADH → glycerol-3-P + NAD^+

- adding first 2 FAs

  enzyme: acyltransferase

  glycerol-3-P + acyl-CoA → monoacylglycerol-3-P + CoA

  monoacylglycerol-3-P + acyl-CoA → diacylglycerol phosphate (phosphatidic acid)

- remove P_i from phosphatidic acid hydrolytically

  enzyme: phosphatidic acid phosphatase

  phosphatidic acid + H_2O → 1,2-diacylglycerol + P_i

- connection of last FA

  enzyme: acyltransferase

  1,2-diacylglycerol + acyl-CoA → TAG + CoA

Metabolism of amino acids

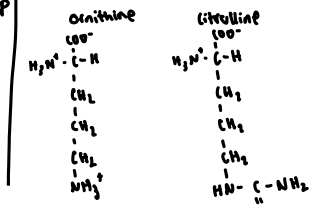
Proteinogenic AAs:

biosynthesis: Essential - not made in body, get from diet
Non essential - made in body

degradation: Glucogenic: C skeleton makes Glc
Ketogenic: C skeleton makes Acetyl-CoA

Essential AAs: Val, Leu, Ile
PVT TIM HALL — Phe, (Tyr), Trp
His, Lys, Arg
Met (Cys)
Thr

Other important AAs in body:



AAs used for:
proteosynthesis
N-compound synthesis
degradation (E, glucose, fat)

AA degradation: 1) $-NH_2$ group removal
2) deaminization of amino group
3) C skeleton metabolism
→ 7 products

cofactor for amino transferases:
pyridoxal phosphate (PLP) derived from vit. B_6 (pyridoxine)

transamination:
$AA_1 + \alpha\text{-}KA_2 \rightarrow \alpha\text{-}KA_1 + AA_2$

alanine + glutamate ⟷ α-KG + pyruvate

OAA
Asp
AST or GOT
alanine aminotransferase (ALT) or GPT
α-KG

Metabolism of lipoproteins

Absorbed fat (diet) & lipids synthesized in liver & adipose tissue → must be transported between various tissues & organs to use & store.

Lipids → insoluble in water
associate (TAGs & CE) w/ amphipathic lipids (phospholipids & cholesterol) & proteins to make water-miscible lipoproteins
nonpolar lipids

Lipoprotein = lipid + apoprotein

Cholesterol → Good - HDL
Bad - LDL

Lipoproteins classified based on density

Chylomicrons
VLDL
IDL
LDL
HDL
FFA / NEFA

Lipoproteins are classified according to proportion of individual components that affect their density

TAGs - lowest density
proteins - highest density

Surface of lipoproteins has monolayer of phospholipids w/ free cholesterol and Apolipoproteins (Apo)
inside: TAG & CE

Chylomicrons:
lowest density
most TAG, least proteins

Chylomicrons
B-48
C-II
E
produced in intestine
principal lipid: TAG
transport TAG from diet → tissues

CHM remnants
B-48
E
source: CHM (chylomicrons)
principal lipids: TAG, cholesterol, phospholipids
transport remnants of chylomicrons to liver

VLDL
C-II
B-100
source: liver
principal lipids: TAG
transport newly synthesized TAG to other tissues

IDL
B-100
source: VLDL
principal lipids: cholesterol, phospholipids, TAG
transport VLDL remnants to other tissues

LDL
B-100
source: VLDL
principal lipids: cholesterol
transport cholesterol to extrahepatic tissues

HDL:
A-I
F-II
source: liver
main lipids: cholesterol, lipoproteins
apoproteins supply
transport cholesterol from tissues

back to liver

Type	Source	Principal Lipids	Important apoproteins	they transport:
chylo-microns	intestine	TAG	B-48 C-II E	TAG from diet to tissues
CHM remnants	CHM (chylomicron)	TAG Phospholipid Cholesterol	B-48 E	CHM remnants to liver
VLDL	liver	TAG	B-100, C-II	newly synthesized TAG to other tissues
IDL	VLDL	TAG phospholipids cholesterol	B-100	VLDL remnants to other tissues
LDL	VLDL	cholesterol	B-100	cholesterol to extrahepatic tissues
HDL	liver	cholesterol phospholipids Apoproteins supply	A-I C-II E	cholesterol from tissues back to liver

HDL involved in cholesterol esterification
enzyme LCAT

HDL gets TAG from VLDL
VLDL gets cholesterol ester from HDL
} CETP