SUMMARY

Tuesday, December 9, 2014
12:45 AM

Homeostasis

⁺many cells prefer to use FAs over Glucose
⁺Always Need Glucose: RBC, B

			Carbs	Proteins	Fats	Energy
Fed	I	Builds up	↓Glucose/↑Glycogen	↓AA/↑Protein	↓KBs↕FA/↑TG	↑ATP
Fasting	G/E	Breaks down	↑Glucose/↓Glycogen	↑AA/↓Protein	↑KBs↑FA/↓TG	↓ATP

Carb Transport

- Indigestible Carbs:
  - Lactose (some)
  - Sorbitol
  - Lactulose *(used for hyperammonemia)*
  - Stachiose/Raffinose *(Beans = α-galactosidase)*
- Glucose Transporters:

- Na⁺ SENSITIVE (SGLP)	- I *(2 Na⁺)* - K *(1,2 Na⁺)*
- INSULIN-SENSITIVE (GLUT4)	- A *(fed)* - M *(fed+exercise)*
- INDEPENDENT	- L, RBC, B

Glucose

Glycolysis (PFK) *(backup when ↓O_2)*	All L	Glucose → G6P → F6P → F16BP → DHAP/G3P → PEP → Pyruvate	AMP F26BP, I	ATP G/E
GNG	L, K	Glucose ← G6P ← F6P ← F16BP ← DHAP/G3P ← PEP ← Pyruvate	G/E	I
Glycogenolysis *(24 hrs)*	L M	Glycogen → Glucose	G/E cAMP, Ca^{+2}	I
Glycogenesis	L, M	Glycogen ← Glucose	I	G/E

NADH --> NAD^+ *(1 cell will not have both)*

GP-Shuttle	Mito	DHAP + NADH → G3P
MA-Shuttle	Mito	OAA + NADH → Malate

CAC = (A-CoA → NADH/$FADH_2$)

PD	Mito	Pyruvate → Acetyl-CoA + NADH		NADH/$FADH_2$ A-CoA
PC	Mito	Pyruvate → OAA	Biotin A-CoA	
CAC	Mito	A-CoA → Citrate → αKG → Succinate → OAA → NADH/$FADH_2$		NADH/$FADH_2$

OxPhos = (NADH/$FADH_2$ → → ATP)

ETC	Mito	e⁻ from NADH/$FADH_2$ → O_2 (→ H_2O)	
H^+ PUMPS (I,III,IV)	Mito	H^+ (Matrix → Intermembrane), electrochem gradient	
ATP SYNTHASE	Mito	uses H^+ gradient for ADP → ATP	ATP

PPP

Oxidative Branch (G6PD)	All	G6P → Pentoses + NADPH *(only way to make NADPH in RBC)*		
Sugar Branch	All	F6P, GAP → Pentoses		

NADPH = reduces GSSG (GSSG → GSH)
GSH = reduces radicals (•)
G6PD Deficiency = anemia with oxidizing drugs
Me-Blue = Methemoglobinemia tx (DO NOT USE w/ G6PD Deficiency)
(Me-Blue + NADPH --> Leuko-Me-Blue)

FA Uptake

Uptake	lumen → I	TG → FA + MG (→ TG)		
Uptake (LPL)	blood → A	TG → FA + Glycerol/G3P (→ TG)	I	G/E
LDLR	All	TG → FA + Glycerol/G3P		

Cholesterol Synth

HMG-CoAR	L	A-CoA → Mevalonate (→ Cholesterol)	I	G/E, Statins

FA Synth

FA Synth *De Novo* (ACoAC)	L, (others)	Citrate → A-CoA → Malonyl-CoA	I *(high) (L)*	AMP *(other cells)*
DESATURASE/ELONGASE	L	Malonyl-CoA + NADPH → FA	NADPH	

FA Metabolism

Lipolysis (HSL)	A → blood	TG → FA	G/E	I
FA into Mito	blood → Mito	FA → FA-CoA → FA-Carnitine → FA-CoA		Malonyl-CoA
FA β-Ox	*not:* B	FA-CoA → A-CoA + NADH/$FADH_2$	PPARα, Fibrates	NADH/$FADH_2$

KBs

KB Synth	L	A-CoA → KB	A-CoA
KB Ox	*not:* L, RBC	KB → A-CoA	

AAs

Mitochondria

With	Without
L, K, M, B	RBC

Insulin Secretion:

↑I	↓I
Glucose* GLP-1/GIP KBs FAs AAs	G/E

Glucagon Secretion:

↑G	↓G
AAs* E	Glucose

GLYCOGEN - poly-glucose
GLUCAGON - pancreas α-cell hormone

GNG

Carbon Skeleton	1) Lactate* 2) Alanine 3) Glycerol 4) AAs
ATP	β-Oxidation > CAC > OxPhos

GLYCEROL + 3FAs = TG

If the Cell Doesn't Use ATP
(↓AMP/ADP, ↑ATP, ↑H+ gradient)
- ETC stops
- CAC stops
- PD stops
- PFK stops

Radical (•) Removal:
- GSH
- C/E
- Urate
- BR

Protein Synth *(most)*		AA → Protein	I	G/E
NH_3 Production (G,GD)		Gln (-NH_3) → Glu (-NH_3) → aKG		
Urea *(Liver)*	L *(Mito/cyt)*	NH_3 → CP (+ O) → C (+Asp) → AS (-F) → Arg → Urea	G/E	I
Alternate Excretions (Drugs) *(Liver)*		Gly → Benzoyl Glycine Gln → Phenylacetyl Glutamine		

Necessary for Urea Cycle = *Glu, Arg, ACoA*
Sources of N = *Gly, Gln, Glu, Asp*

Loss of N:
- Urea*
- Ammonium (NH_4^+)
- Creatinine
- Uric Acid

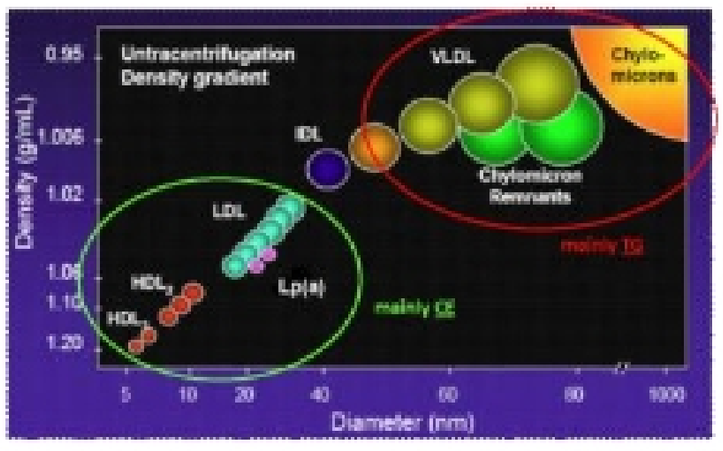
Diabetes Meds

α-Glucosidase Inhibitors	prevents carb uptake
K_{ATP} Inhibitors *(sulfonylurea, glinides)*	↑ Insulin
GLP1 Agonists	↑ Insulin *(glucose-dependent)*
DPP4 Inhibitors	↑ GLP1
SGLT Inhibitors	↓ Glucose
Insulin	

Lipoproteins

Lipoprotein	Apo	Main Lipids	Present in Fasting Blood
Chylo	B-48, C, E	TG	NO
VLDL	B-100, C, E	TG	YES
IDL	B-100, C, E		YES
LDL	B-100	Cholesterol	YES
HDL	A, C, E	Cholesterol	YES

**C,E: acquired in circulation*
**B-48 is part of B-100.. B-48 doesn't contain LDLR binding site*



Apoproteins

Apo	Receptor	Function
A-I	LCAT	Cholesterol --> CE
A-I	SR-B1	load/unload Cholesterol from HDL into cell
C-II	LPL	hydrolyzes TG (lipolysis)
E	LDLR, LRP	removal from blood
B-100	LDLR	removal from blood

Removal of Lipoproteins:

LDLR	E, B-100
LRP *(major in brain)*	E
HSPG	non-specific
SR-B1	A
Macrophages (other SRs)	non-specific

**LDL Removal = LDLR only*

**cells that need Cholesterol will express LDLR*

REVERSE CHOLESTEROL TRANSPORT - macrophage donates Cholesterol to HDL (which takes it back to Liver)
ABC TRANSPORT (EFFLUX) PROTEINS - transfer cholesterol out of macrophages into A-I/HDL

Intestinal Absorption

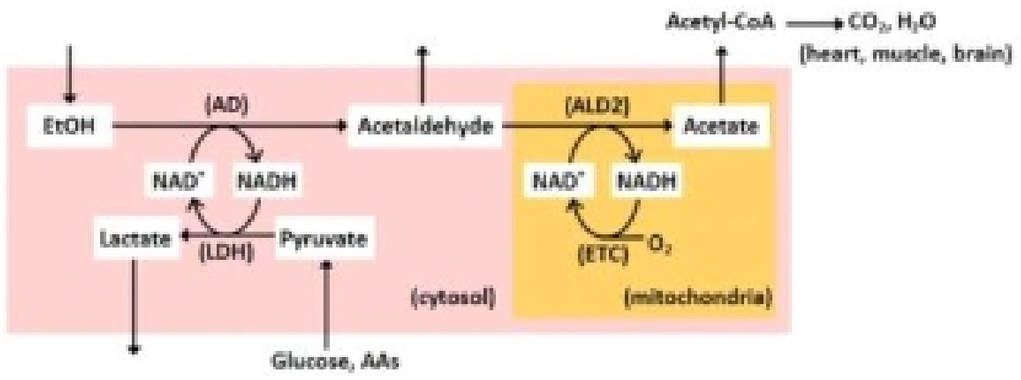
Bile Acids	Lumen → BILE ACID TRANSPORT PROTEIN → Enterocyte → Portal Vein → Liver → Bile Acids (Chylo) → Blood
Cholesterol	Lumen → NPC1-L1 → Enterocyte → ACAT (ER) → Chylomicron → Lymph → Liver → Bile Acids (Chylo) → Blood
Phytosterol	Lumen → NPC1-L1 → Enterocyte → ABCG5/8 → Lumen *(never really get into the blood)*

NPC1-L1 - Cholesterol transporter (Lumen → Enterocyte)
EXETIMIBE - NPC1-L1 Inhibitor

HYPERGLYCEMIA - not enough Insulin
HYPOGLYCEMIA - too much Insulin

KETOSIS - healthy patients + Atkins diet
KETOACIDOSIS - DM patients

Ethanol Metabolism



*NAD+ → NADH: ↓CAC, β-Ox, GNG (↓Pyruvate)…HYPOGLYCEMIA

ALD2*2 - inactive ALD2; Asian; causes flushing due to ↑Acetaldehyde

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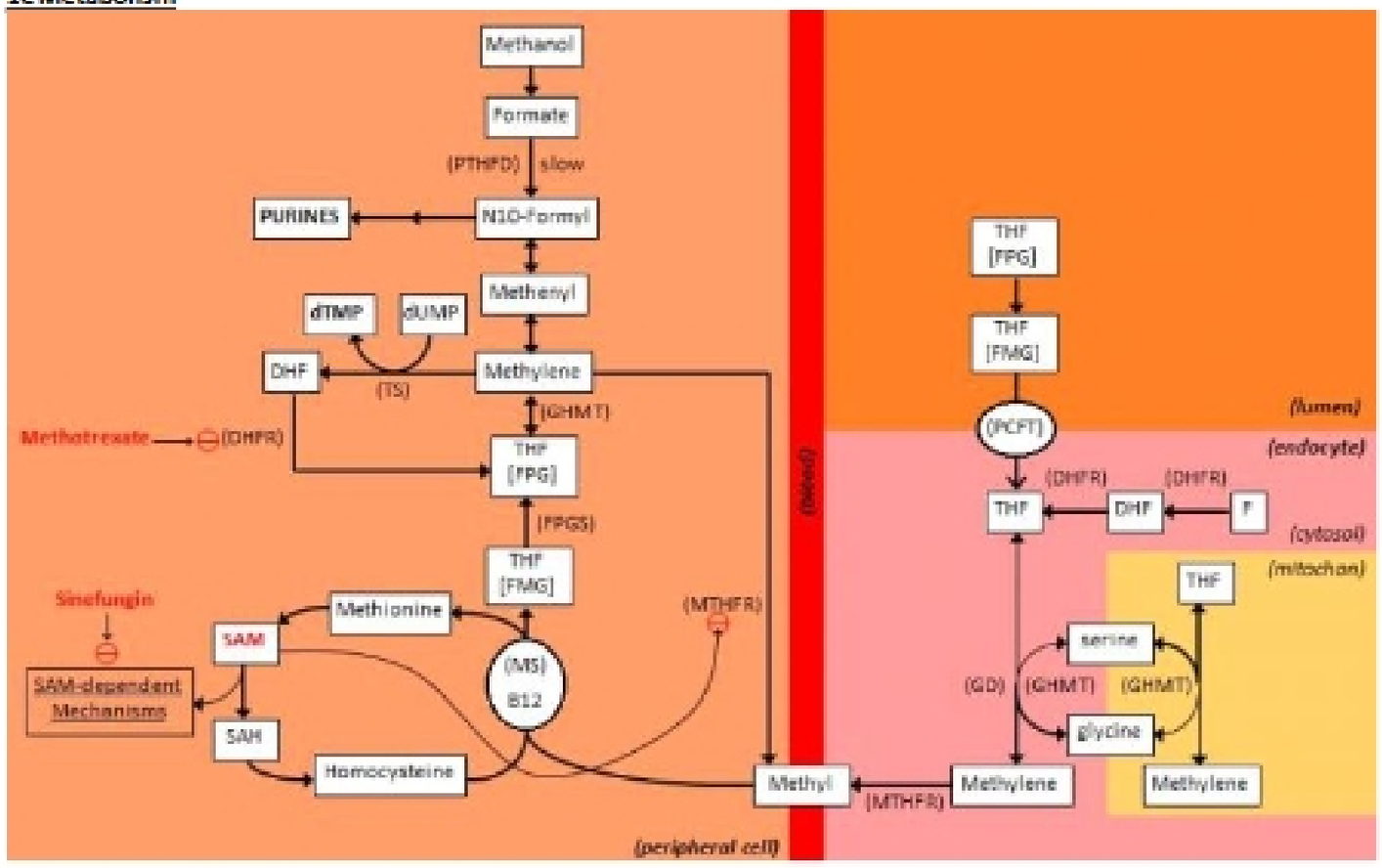
Methanol (MeOH)

MeOH → Formate (+THF) → N10FormylTHF + CO_2

FORMATE (HCO_2^-) - ox-Methanol; can combine with THF to form N10FormylTHF, but is SLOW = BAD! (toxic: acidosis & blindness)

Tx: EtOH, Fomepizole

1C Metabolism



FOLATES (B9) - any form of THF

THF - carries 1C for synthesis of nucleotides (Purines + Thymidine)

Folate Deficiency: Macrocytic Anemia, Diarrhea

COBALAMIN (B12) - cofactor for MS (Homocysteine → Methionine → SAM)… &… MethylMalonylCoA Mutase (AA Debranching Enzyme for CAC) (MethylMalonyl-CoA→Succinyl-CoA)

B12 Deficiency (2° Folate Deficiency): anemia (↑ MethylMalonyl-CoA)

SAM-Dependent Methylations:
- DNA
- RNA
- Protein
- Phospholipids
- Epinephrine
- **Creatine**
- (many more!)