

12 Nov. 2003

Lipid Review.

INSTRUCTOR: Daniel R. TerBush, Ph.D., Rm. #B4021 or B4024. E-mail: danter1@aol.com. Phone: 295-3587

Lipid Review

This material is intended to provide an overview and review of selected topics presented in the previous lipid lectures.

See the other lecture's learning objectives for what you need to know about lipid biochemistry.

I thought it would be convenient to have a condensed summary of most of the lipid lecture content as a study aid. So this is it. Note that this summary is NOT complete as it ignores (mostly) lipoprotein metabolism. Refer to the lipoprotein "cheat sheet" and its accompanying figure for a condensed overview of lipoproteins.

This review is divided into three basic parts:

Part I is designed to follow the fate of a fatty acid obtained from synthesis or the diet to its incorporation into a TG (or a phospholipid), its transport to a fat cell where it is deposited for storage and its return back to the liver for degradation.

Part II is designed to follow a molecule of cholesterol obtained from synthesis or the diet, to its transport to and then from the peripheral tissues and then back to the liver where it is converted into a bile acid and eventually excreted.

Part III is composed of some added sections covering steroid hormones and eicosanoids.

PART I--Fatty Acid Fates.

Synthesis of a Fatty Acid in the LIVER

Fatty acids are synthesized *de novo* by the liver in response to a high carbohydrate, low fat diet.

Glucose is converted into pyruvate in the cytoplasm by **glycolysis**.

Pyruvate is transported into the mitochondria and is converted into acetyl-CoA and CO₂ by the **pyruvate dehydrogenase complex**.

The acetyl CoA subunits are shuttled to the cytoplasm by the **Citrate-Pyruvate Cycle (CPC)**.

The Citrate-Pyruvate Cycle not only moves acetyl-CoA into the cytoplasm for fatty acid synthesis it also provides 8 of the 14 NADPH molecules necessary to synthesis palmitate.

Palmitoyl-CoA inhibits the citrate-phosphate antiporter.

Acetyl CoA is converted into Malonyl CoA by **acetyl CoA carboxylase (ACC)**.

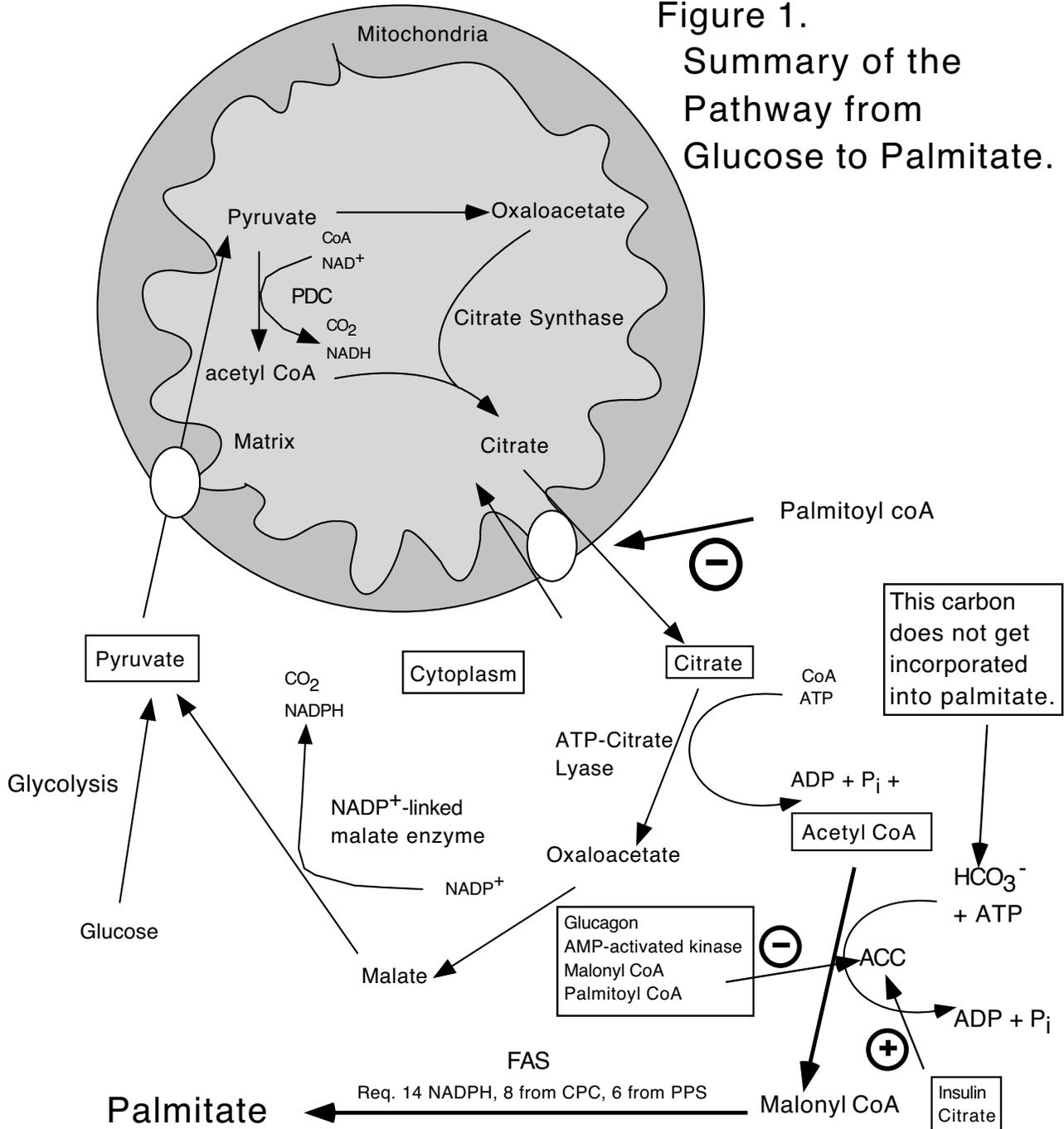
ACC is inhibited by glucagon and epinephrine by PKA activation and phosphorylation, by phosphorylation with AMP-activated kinase, by palmitoyl CoA and by malonyl CoA.

ACC is activated by insulin and citrate.

Fatty acid synthase (FAS) converts one molecule of acetyl CoA, 7 malonyl CoA, 14 NADPH and 20 protons into one molecule of palmitate, 7 CO₂, 14 NADP⁺, 6 H₂O, and 8 CoA

8 NADPH come from the **CPC** and 6 come from the **Pentose Phosphate Shunt (PPS)**

Figure 1.
Summary of the
Pathway from
Glucose to Palmitate.



Charging reaction requiring CoA, transfer to the reactive cysteine, followed by 7 cycles of 1) Incorporation of 2-carbon units from malonyl CoA, 2) C3 reduction, 3) C3 dehydration, 4) C2=C3 double bond reduction, 5) Transfer to reactive cysteine. After 7th cycle, cleavage by thioesterase.

Once a Fatty Acid (FA) has been synthesized it has several possible fates. It can be incorporated into a glycerolipid or sphingolipid after modification, including desaturation and/or elongation. It can be incorporated into a triacylglycerol (TG) for export in a VLDL lipoprotein particle for eventual deposit in adipose or it could be burned by fatty acid oxidation.

Regulation Basics:

1) Under conditions where you are synthesizing FAs (high carbohydrate, low fat diet), malonyl CoA levels are high and they inhibit FA oxidation by inhibiting the carnitine- palmitoyl transferase I (CPTI) enzyme found in the outer mitochondrial membrane. This prevents FA import of 12-carbon atom and longer FAs into the mitochondria and this prevents their β -oxidation. Most FAs will end up as TGs under these conditions in the liver.

2) All cells, including the liver, need to continuously synthesize glycerolipids and sphingolipids. All cells need an intact plasma membrane to survive more than a cell needs to synthesize TGs for export or storage. When fatty acids become limiting, such as during a prolonged fast (starvation), the glycerolipid and sphingolipid pathways get preference for fatty acids.

3) Under conditions when one is fasting, FAs are not synthesized *de novo* to any significant extent (look at the regulation of ACC), but the liver still needs to synthesize VLDL to try and maintain circulating levels of lipoproteins. Under these circumstances, FAs are recruited from adipose tissue (lipolysis, see regulation of hormone sensitive lipase) and FAs and glycerol are exported from adipose and transported to the liver. There, most FAs will be converted into ketone bodies and the glycerol will be used for gluconeogenesis, but some of each will be used to make TGs for VLDL synthesis. However, FA incorporation into VLDL will not occur to any significant extent during prolonged starvation (see 2 above).

Incorporation of a Fatty Acid into PC--Membrane Biosynthesis

1) Insertion of palmitate or another long chain fatty acid obtained from the diet into the ER membrane bilayer.

2) Activation of the fatty acid by acyl CoA synthetase. In this reaction ATP is hydrolyzed to AMP + PP_i and it is the hydrolysis of PP_i by pyrophosphatase that drives the reaction to completion.

3) The fatty acid is elongated and a double bond is added.

4) The fatty acid is esterified to glycerol 3-phosphate at position-1 and then a second fatty acid is then esterified to position-2 in reactions catalyzed by glycerol phosphate acyltransferase to form phosphatidate. Glycerol 3-phosphate synthesis will be described in 11) and 12) below.

5) Phosphatidate phosphatase removes the phosphate to form diacylglycerol.

6) CDP-choline: 1, 2-diacylglycerol phosphocholine transferase transfers phosphocholine to DG to form phosphatidylcholine (PC). The CDP-choline synthesis will now be described.

7) Meanwhile, choline obtained from the diet enters the cell. Choline can be synthesized *de novo* but normally all we need is obtained from the diet.

8) Choline is phosphorylated by choline kinase in the cytosol.

9) CTP:PC cytidyltransferase is recruited to the ER membrane and activated in response to:

- Decreased PC
- Decreased phosphorylation
- Increased ER membrane DG content
- Increased ER membrane FA content

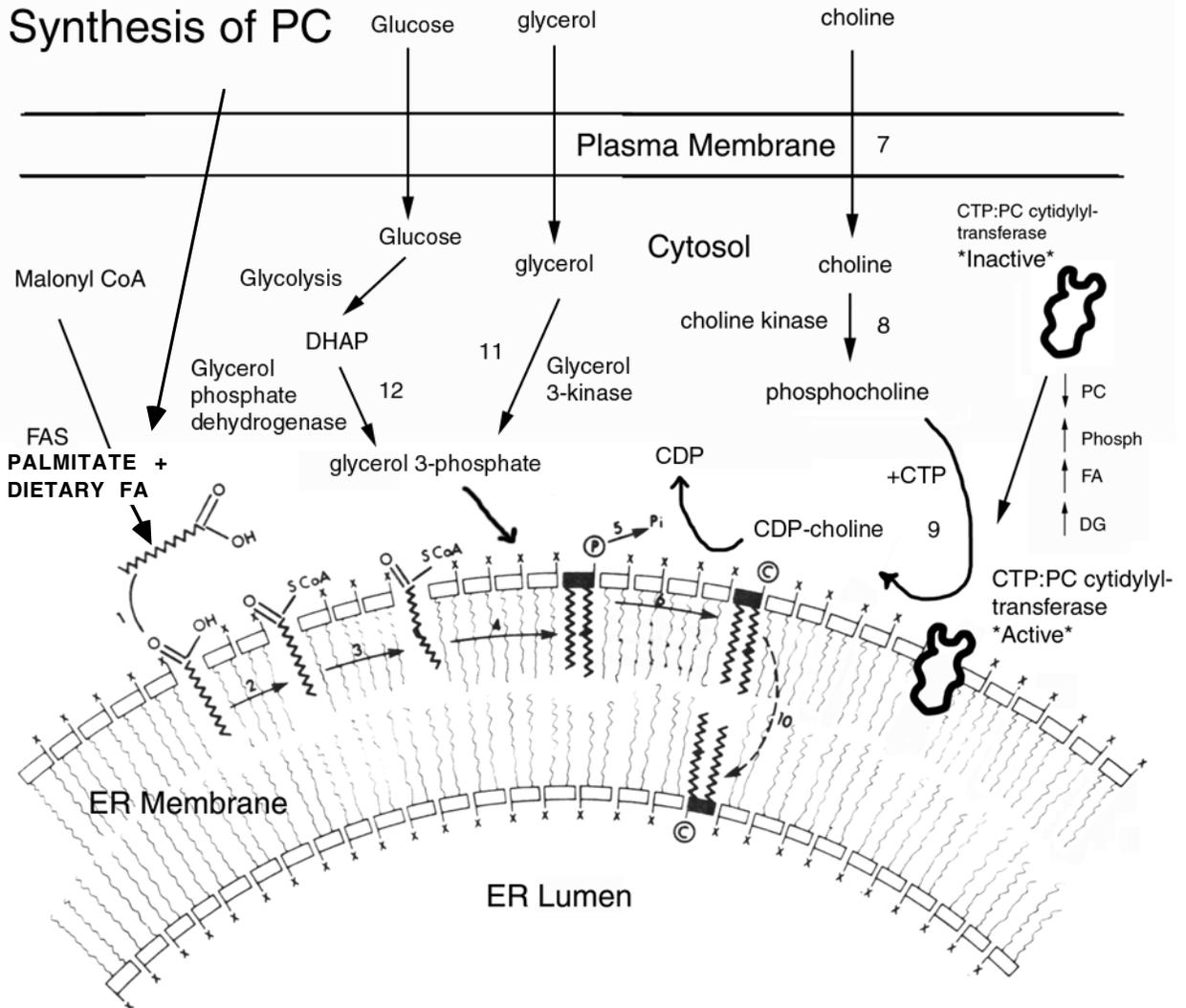
CTP:PC cytidyltransferase then activates phosphocholine by conjugating it to CDP.

10) After PC is synthesized it is flipped to the luminal side of the ER membrane bilayer by a flipase. PC is concentrated in the outer leaflet of the plasma membrane. The luminal face of the ER membrane is topologically the same as the outer surface of the plasma membrane (see Protein Trafficking lecture of 13 Oct.)

11) Glycerol obtained from the diet or from lipolysis in adipose is transported to the liver and activated by glycerol 3-kinase. Glycerol 3-kinase is lacking in adipose tissue but abundant in the liver.

12) Glycerol 3-phosphate can also be obtained from DHAP, a glycolysis intermediate, by the action of glycerol phosphate dehydrogenase.

Synthesis of PC



Membrane Synthesis Notes

PE synthesis occurs by the same pathway as PC synthesis with a couple of PE specific enzymes that do the same reactions as the PC-specific enzymes.

PS is made from PE by head group exchange.

PC can be made from PE by transfer of three methyl groups using SAM as a methyl donor.

PI is made by activating DG by conjugating it to CDP and then PA is transferred to inositol to make PI.

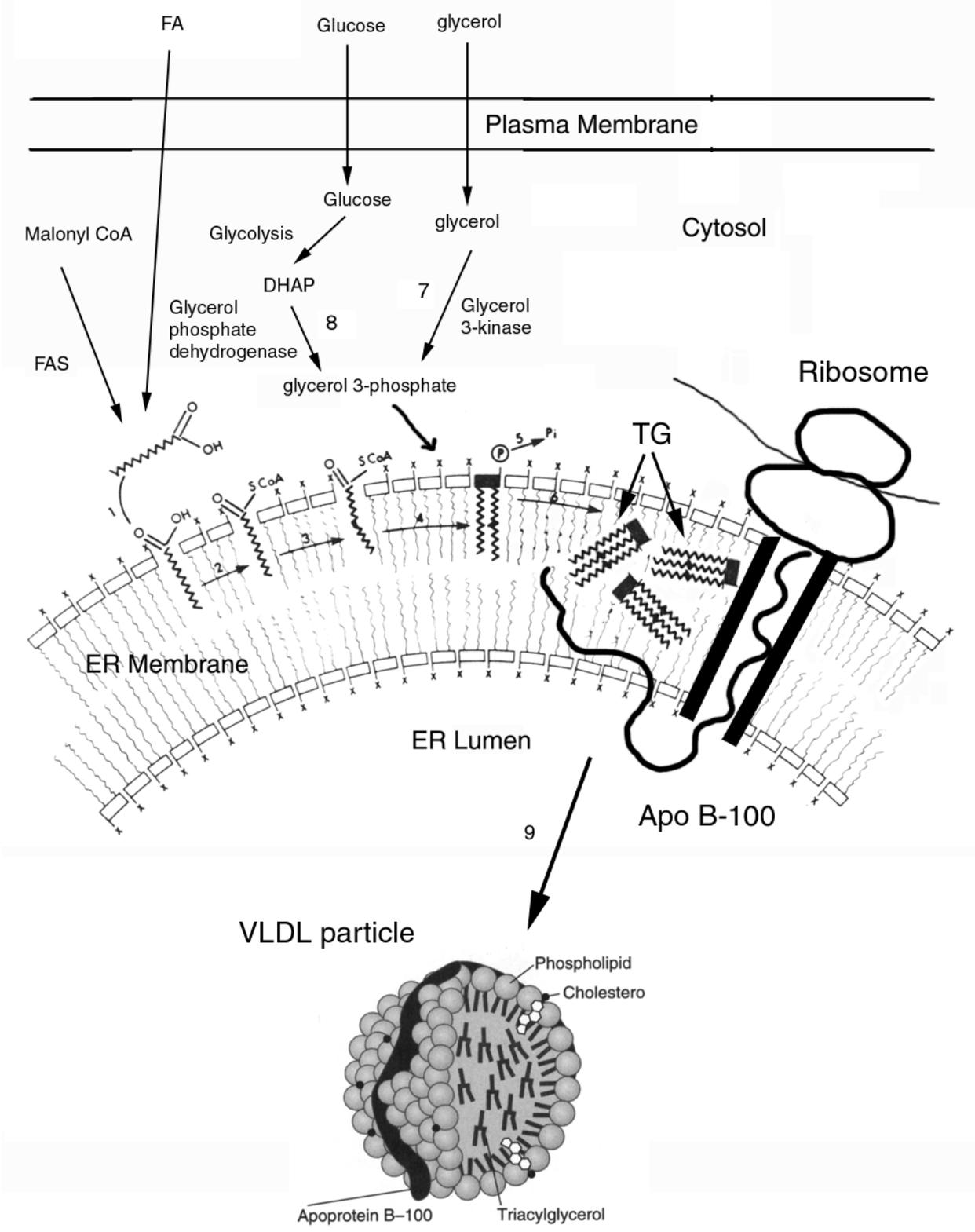
PC, sphingomyelin and glycolipids are in the outer leaflet and PE, PI, and PS are in the

inner leaflet of the plasma membrane lipid bilayer.

Incorporation of a Fatty Acid into TG and Transport to Adipose by VLDL

- 1) Insertion of palmitate or another long chain fatty acid obtained from the diet into the ER membrane bilayer.
- 2) Activation of the fatty acid by acyl CoA synthetase. In this reaction ATP is hydrolyzed to AMP + PP_i and it is the hydrolysis of PP_i by pyrophosphatase that drives the reaction to completion.
- 3) The fatty acid is elongated and a double bond is added.
- 4) The fatty acid is esterified to glycerol 3-phosphate at position-1 and then a second fatty acid is then esterified to position-2 in reactions catalyzed by glycerol phosphate acyltransferase to form phosphatidate. Glycerol 3-phosphate synthesis will be described in 11) and 12) below.
- 5) Phosphatidate phosphatase removes the phosphate to form diacylglycerol.
- 6) Diglyceride acyltransferase esterifies the third position of DG and forms TG. TG is very non-polar and moves into the inner portion of the ER membrane lipid bilayer.
- 7) Glycerol, obtained from the diet or from lipolysis in adipose, is transported to the liver and activated by glycerol 3-kinase. Glycerol 3-kinase is lacking in adipose tissue but abundant in the liver.
- 8) Glycerol 3-phosphate can also be obtained from DHAP, a glycolysis intermediate, by the action of glycerol phosphate dehydrogenase.

TG and VLDL Synthesis

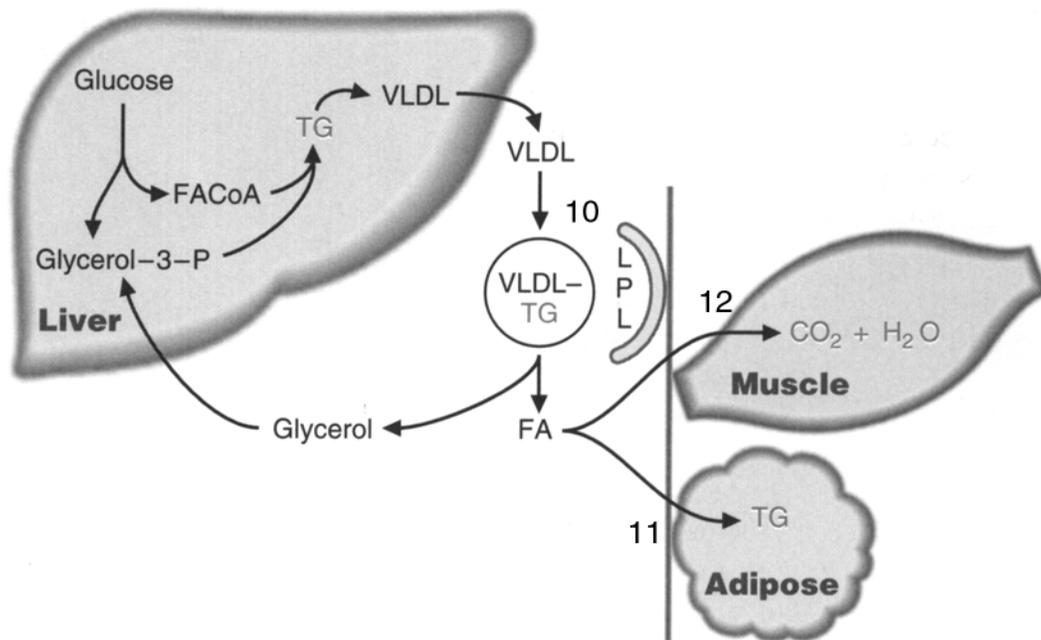


9) The VLDL particle forms as Apo B-100 is synthesized in response to the TG accumulating in the ER membrane. Apo B-100 helps to pinch off the bulging “lens” of ER membrane (phospholipid/cholesterol monolayer filled with TGs and a small amount of cholesterol esters) and moves it into the ER lumen forming a VLDL lipoprotein particle. The VLDL particle is then transported through the secretory pathway and secreted by exocytosis into the space of Disse and enters the blood stream through discontinuities in the hepatic capillaries.

10) The VLDL secreted into the blood travels through muscle and adipose tissue capillaries and the TGs are hydrolyzed by LPL (lipoprotein lipase) to FAs and glycerol.

11) FAs in adipose can be resynthesized into TGs for deposition but carbohydrate must be available since adipose cells can only make glycerol 3-phosphate from DHAP, a glycolytic intermediate.

12) FAs in muscle are oxidized for energy production.



TGs and VLDL Synthesis Notes

The synthesis of TGs (steps 1-5 and 7-8 above) are the same steps in PC biosynthesis (steps 1-5 and 11-12)

Recruitment of FA from Adipose and Transport Back to the Liver

Up to this point, our synthesized FA has either been deposited in TG in adipose or synthesized into a membrane phospholipid, PC. Let's consider the fate of the FA deposited in adipose as fat when fasting.

1) Receptors on the cell surface sense the amount of insulin or glucagon present in the blood (the insulin/glucagon ratio). If this falls i.e. there is an increase in glucagon and/or a decrease in insulin, then lipolysis is activated.

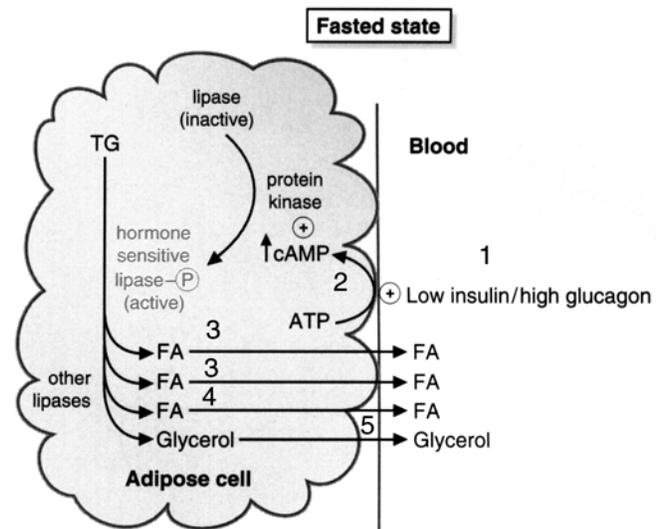
2) At the simplest level, the regulation of lipolysis is due to changes in the phosphorylation state of hormone sensitive lipase (HSL). Glucagon increases phosphorylation of HSL by increasing cAMP and activating cAMP-dependent protein kinase. Insulin decreases phosphorylation of HSL both by activating processes that decrease cAMP in the cell and by activating phosphatases that directly remove phosphates from HSL and inactivate it.

3) Active HSL cleaves the first two FAs from the glycerol backbone.

4) Monoacylglycerol lipase cleaves off the last FA and also produces glycerol.

5) The free FAs and glycerol are released into the blood. FAs bind to serum albumin and some are transported to the liver for ketone body production, β -oxidation, and also for a small amount of resynthesis of TGs for VLDL production. A large proportion of the FAs released from adipose will be β -oxidized by muscle for energy. The glycerol will also be transported to the liver. Adipose lacks the glycerol 3-kinase enzyme and cannot convert released glycerol into intermediates in the gluconeogenic or glycolytic pathways. Glycerol in the liver will be mostly used for gluconeogenesis, but a small amount will be used for TG synthesis for VLDL production.

Recruitment of Fat by Lipolysis



β -oxidation of the Fatty Acid

Most of the released FAs will be directly used by muscle for β -oxidation and some will be transported to the liver for β -oxidation and ketone body production. Next, let's follow the FA through β -oxidation to CO_2 and H_2O to produce ATP.

A) FA must be activated by conjugation to CoA primarily on the outer mitochondrial membrane. Acyl CoA synthetase catalyzes this reaction. The reaction is driven to the right by hydrolyzing ATP to AMP + PP_i and then subsequently hydrolyzing PP_i to 2 P_i by pyrophosphatase.

B) CTP1 catalyzes the transfer of the acyl group from CoA to carnitine at the inner surface of the outer mitochondrial membrane.

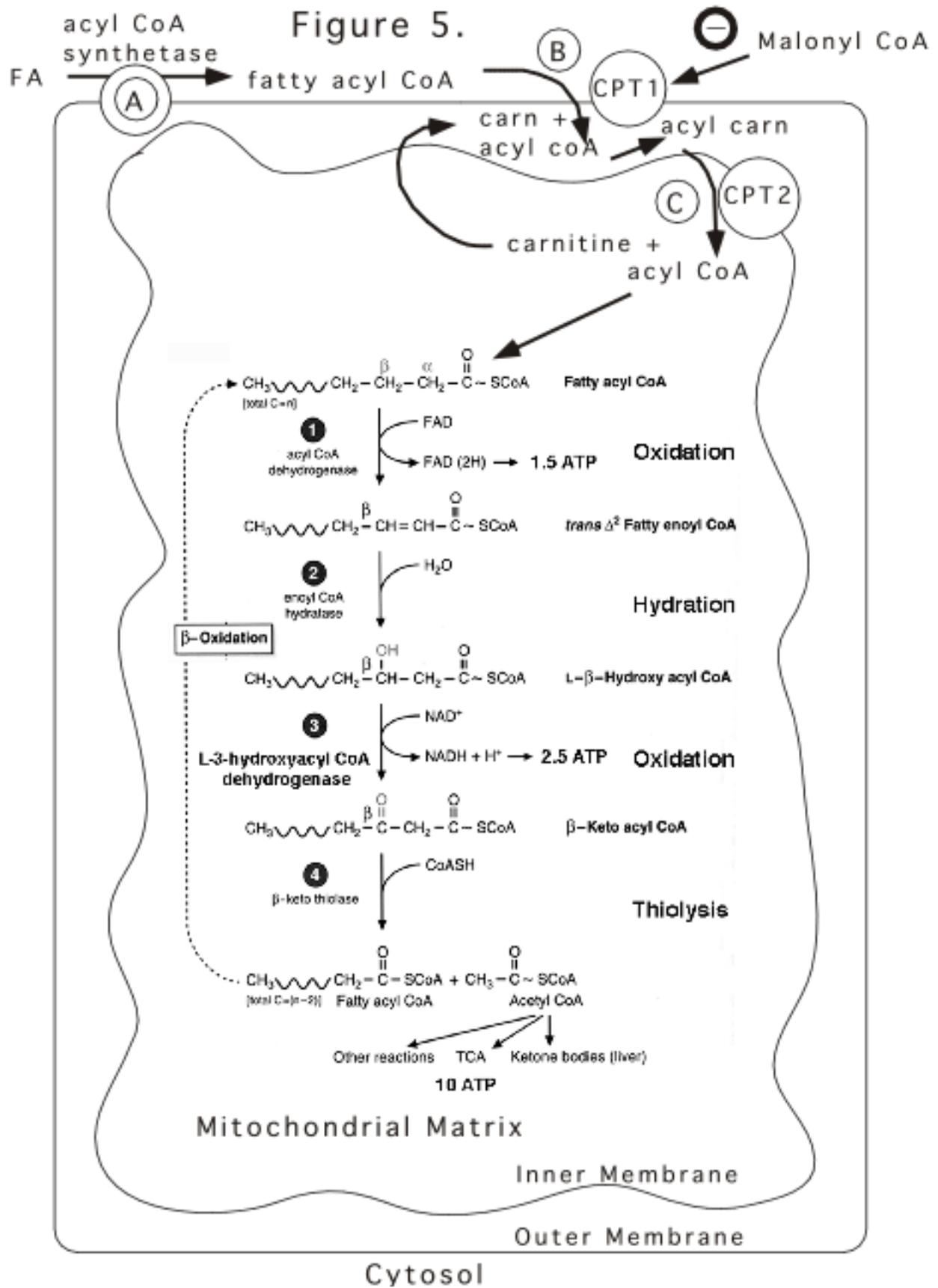
C) Acyl carnitine is transported into the mit. matrix in exchange for carnitine and CPT2 then transfers the acyl group back to CoA to reform a fatty acyl CoA and liberate carnitine.

1) Acyl CoA dehydrogenase oxidizes the acyl chain to form a C2=C3 double bond and generate FADH₂ which yields 1.5 ATP in the electron transport chain (ETC).

2) Enoyl CoA hydratase add a hydroxyl group to the C3 carbon.

3) The C3 carbon is then oxidized to a ketone by L-3-hydroxyacyl CoA dehydrogenase to yield NADH which produces 2.5 ATP in the ETC.

4) CoA then attacks the b-carbon in a reaction catalyzed by b-ketothiolase which results in the cleavage of an acetyl group from the b-keto acyl CoA yielding an acyl CoA shortened by 2 carbons and acetyl CoA. Acetyl CoA then produces 10 ATP in the TCA cycle and ETC.



Conversion of Acetyl CoA into Ketone Bodies in the Liver

- 1) 2 molecules of acetyl CoA in the mitochondrial matrix are converted into acetoacetate by 3-ketothiolase (thiolase). This occurs more during fasting when β -oxidation is going full bore and a lot of acetyl CoA is being produced.
- 2) Production of β -hydroxybutyrate by D-3-hydroxybutyrate dehydrogenase also occurs in the mitochondria when NADH is being produced in excess by STEP 3 of β -oxidation shown above.
- 3) The ketone bodies are released to the outside of the cell and are transported to the muscle tissue for oxidation as an energy source.
- 4) β -hydroxybutyrate can be converted back into acetoacetate by muscle cells by the D-3-hydroxybutyrate dehydrogenase enzyme running in the reverse direction.
- 5) Acetoacetate is converted back into acetyl CoA by several enzymatic steps. Acetyl CoA is then run through the TCA cycle and ETC to produce 10 ATP per acetyl CoA molecule. The key thing here is that one enzyme in the conversion pathway, Succinyl CoA: acetoacetate CoA transferase is absent from the liver but present in the muscle. Therefore, liver can produce ketone bodies but can't consume them.

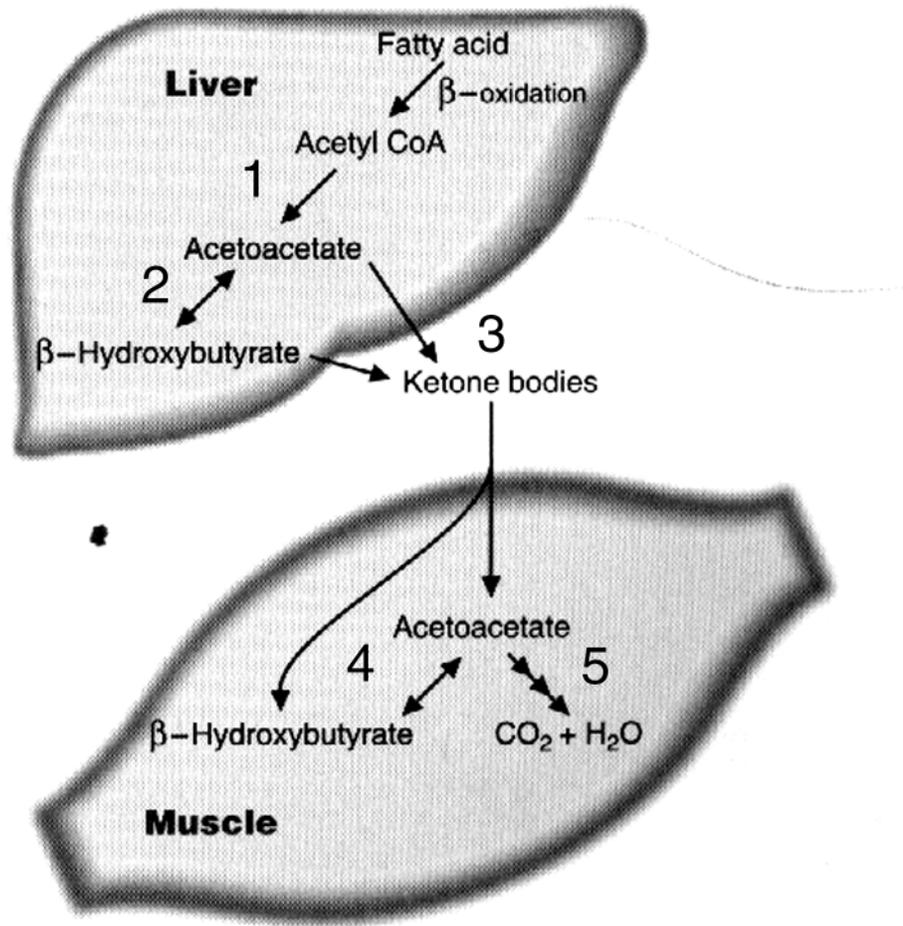


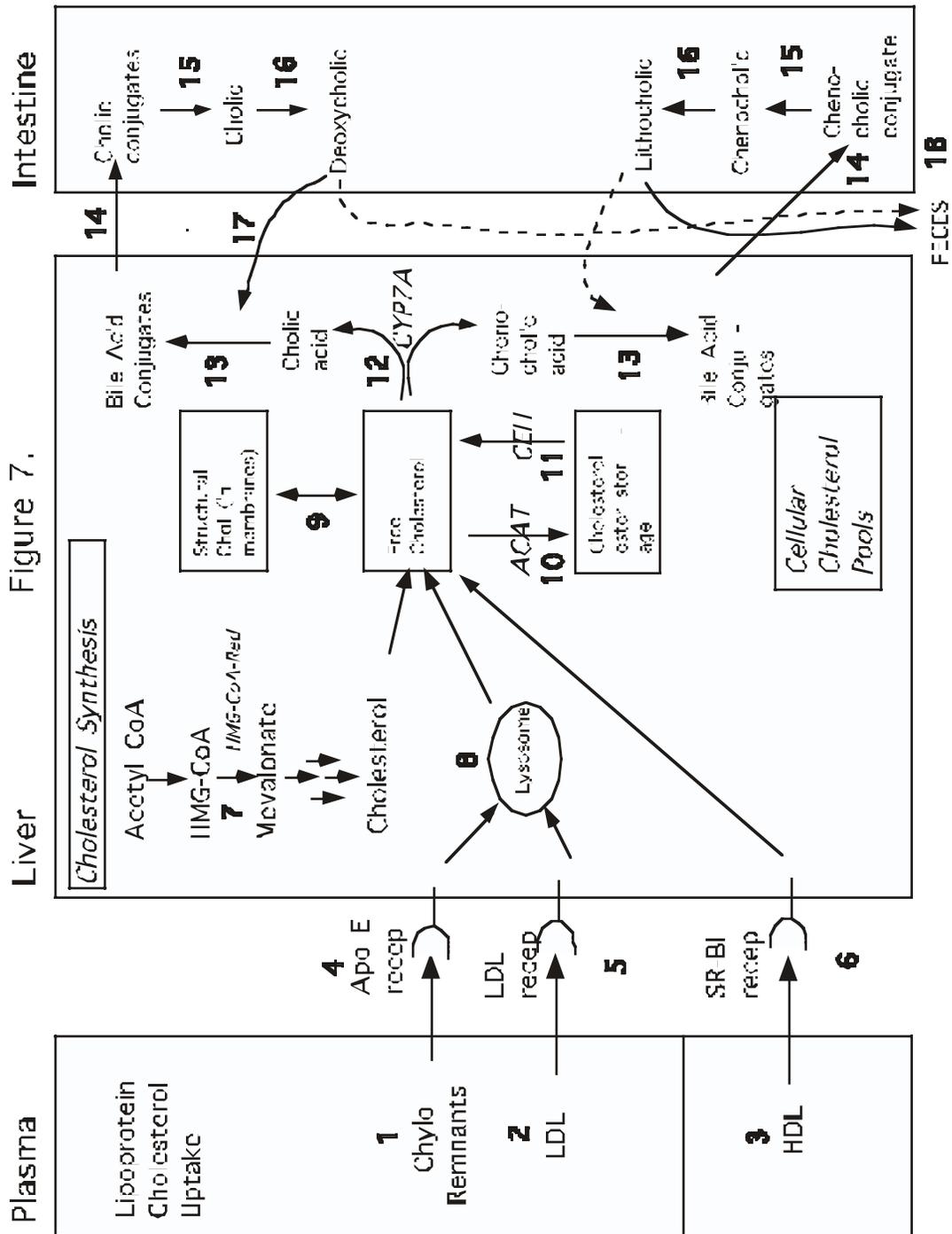
Fig. 23.17. Transfer of ketone bodies from liver to other tissues.

Ketone Body Notes

During starvation, the brain can adapt to use ketone bodies as fuel. As much as 75% of the ATP needs of the brain can be met by ketone bodies.

PART II: Cholesterol/Bile Acids

II. cholesterol Metabolism



Adapted from Gastroenterology Clinics, 28, 1999

1 Chylomicron remnants are created from chylomicrons by the action of LPL (lipoprotein

lipase) in muscle and adipose tissue capillaries.

2 LDL (low density lipoprotein) is made by conversion of VLDL to IDL to LDL by the action of LPL and CETP (cholesterol ester transfer protein). CETP concentrates cholesterol esters in IDL to make LDL.

3 HDL (high density lipoprotein) is made by the liver in lipid poor form and secreted into the lymph (space of Disse). There ABC1 transfers phospholipid and cholesterol to lipid poor HDL to make nascent discoidal HDL. Nascent discoidal HDL also acquires LCAT, Apo A-2, Apo C-II and Apo E both from the free plasma pool. In the space of Disse, there is probably a fairly high concentration of these proteins in the free pool because they are released from larger spherical forms of HDL during their catabolism at the liver by SR-BI and HL. Nascent discoidal HDL then enters into the hepatic capillaries through discontinuities.

4 Chylos are cleared from the plasma by the ApoE/remnant receptor found on the liver.

5 LDL is cleared from the plasma by LDL receptors found on the liver and peripheral tissues. Only the fate of LDL cholesterol taken up by the liver is shown here.

6 HDL is unloaded of cholesterol esters by the hepatic scavenger receptor, type B, class I (SR-BI) and of triglycerides by hepatic lipase (HL) and is converted into smaller spherical or the discoidal forms of HDL.

7 Cholesterol is also synthesized by the liver. About 1/2 of the body cholesterol is obtained from the diet and the rest is synthesized. The liver is the major site of chol synthesis. HMG-CoA reductase is the rate-limiting enzyme and changes in its transcription, translational efficiency, mRNA stability and degradation rate in response to changing concentrations of bile acids, mevalonate metabolites and sterols accounts for its regulation.

8 LDL and Chylo remnant cholesterol esters are transported to the lysosome by endocytosis and the ester is hydrolyzed and free cholesterol is released into the cytosol.

9 Some of the free cholesterol serves a structural role in the hepatic cell plasma membrane and some this can be recruited back into the intracellular free pool.

10 Some of the free cholesterol is converted into cholesterol ester for storage by the action of ACAT, acyl CoA: cholesterol acyltransferase.

11 The esterified cholesterol can be brought back into the free pool by the action of cholesterol ester hydrolase (CEH).

12 Large amounts of cholesterol in the liver are converted into bile acids. A cytochrome P₄₅₀ monooxygenase enzyme, CYP7A, is the rate-limiting enzyme in bile acid synthesis and it is feed-back inhibited by high levels of bile acids.

13 Cholic acid and chenocholic acid and their taurine and glycine conjugates are the primary bile acids. Conjugation of cholic and chenocholic results in products with lower pKa values and makes them better detergents.

14 Bile acids are stored in the gall bladder and are secreted into the duodenum in response to ingesting a meal. Bile acids main role is to emulsify fat, that is, break it up into tiny droplets to increase the surface area for pancreatic lipase to break down the TGs found in a fatty meal.

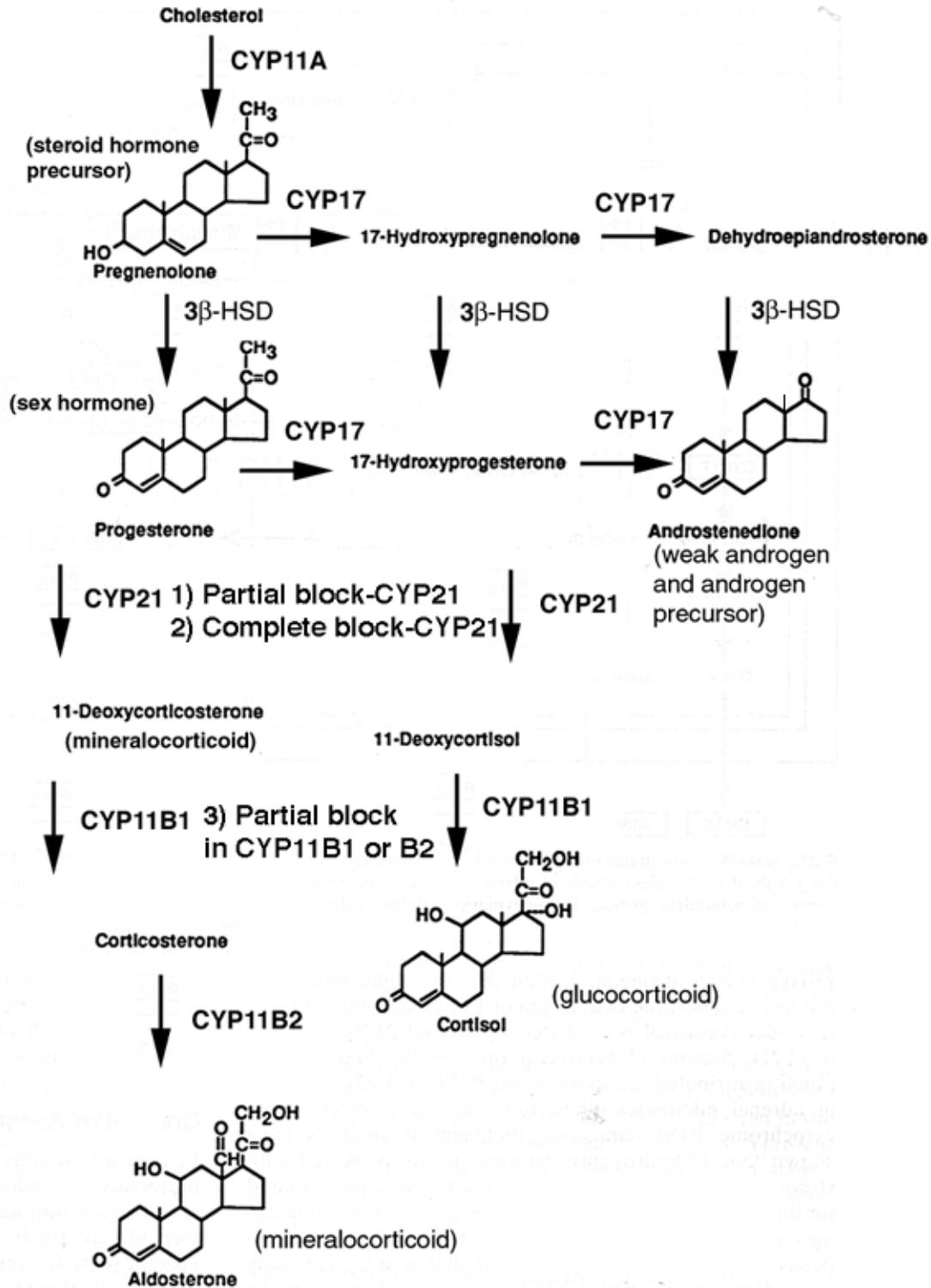
15 Bacteria deconjugate cholic and chenocholic-based bile acids.

16 Bacteria remove the 7-OH group from the primary bile acids. Bile acids that have the 7-OH group removed by bacteria in the ileum are now called secondary bile acids.

17 Most of the bile acids are reabsorbed from the ileum into the hepatic portal vein which transports them back to the liver where they are reabsorbed. The cycle of bile acids from the liver to the gall bladder to the ileum to the hepatic portal vein and back to the liver is called the enterohepatic circulation.

18 Some of the bile acids are lost in the feces. Lithocholic acid, the least soluble and most hydrophobic of the secondary bile acids accounts for a lot of this loss. About 5% of the bile acids are lost in the feces each day. About 95% is efficiently recycled. The loss of bile acids and secreted cholesterol (which is also a component of bile) in the feces is the only way to remove the sterols from the body and this is very important to overall cholesterol homeostasis.

PART III: Steroids and Eicosanoids



I. Glucocorticoids and Mineralocorticoids.

Aldosterone regulates salt absorption in the renal tubule cells. Increased aldosterone from normal will increase retention of NaCl and HCO₃ in the plasma and promote increased K⁺ excretion in the urine. Decreased levels from normal cause the opposite effects.

Cortisol is involved in regulating normal levels of the enzymes in the carbohydrate synthesis and breakdown pathways and in regulating proper immune, inflammation and allergic responses.

Congenital Adrenal Hyperplasia (CAH)--basic cause is a block in CYP21, CYP11B1 or CYP11B2 that blocks the production of aldosterone and/or cortisol and the decreased levels are sensed at the pituitary and the hypothalamus with the net result being release of ACTH (adrenocorticotropin hormone) from the pituitary which acts on the adrenal cortex to increase its SIZE (hyperplasia) and the AMOUNT of enzymes in the synthesis pathways.

1) Partial CYP21 block (autosomal recessive): decreased levels of cortisol and aldosterone causes CAH. The CAH compensates for the decreased levels of hormones so there will not be any obvious defect in a newborn to regulate stress responses or electrolytes. But, the combination of the CYP21 partial block and the upregulation of all the enzymes results in overproduction of androstenedione--a weak androgen. This results in masculinization of female genitalia in XX genetic newborns and premature virilization in male newborns (XY). CYP21 deficiencies (combination of both types) are the most common cause of CAH in newborns (90% of CAH) and occurs about 1:10000 births.

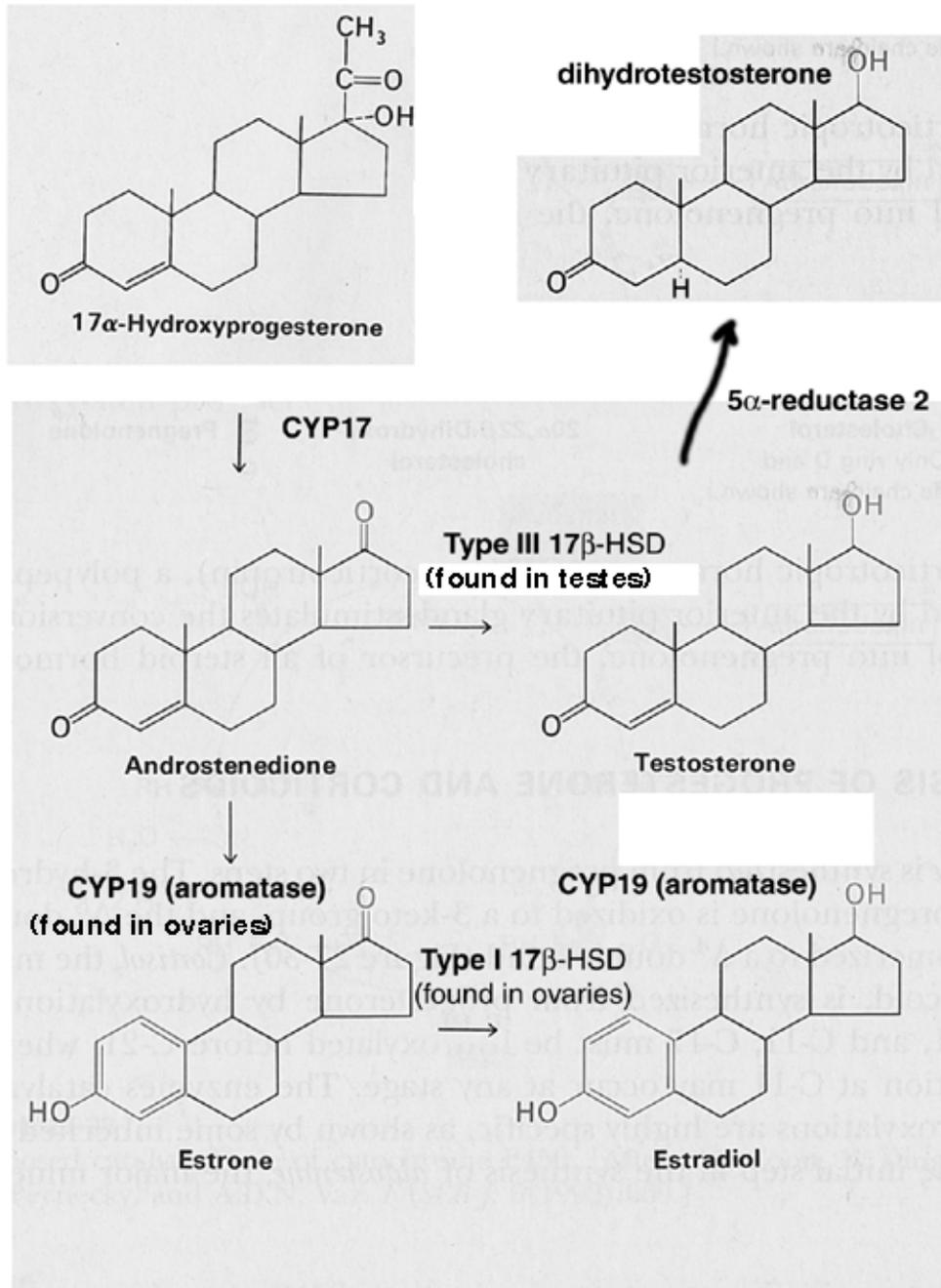
2) Complete CYP21 block (autosomal recessive): decreased levels of cortisol and aldosterone causes CAH. The CAH CANNOT compensate for the decreased levels of hormones so there will be immediate adrenal crisis upon birth as the newborn cannot regulate electrolytes and has no stress response. Also, the complete block in CYP21 results in overproduction of androstenedione--a weak androgen. This results in masculinization of female genitalia in XX genetic newborns and premature virilization in male newborns (XY).

3) Partial CYP11B1 or B2 block (autosomal recessive): decreased synthesis of cortisol and aldosterone (B1 only) or of only aldosterone (B2 only) cause CAH and can be compensated for. Will also cause masculinization of female genitalia and premature virilization in males. But key difference compared to CYP21-deficiencies is that 11-deoxycorticosterone levels are very high. 11-deoxycorticosterone is a weak mineralocorticoid, but high levels will cause increased salt retention (causing hypertension) and loss of K⁺ in the urine (hypokalemia) in the newborn.

Apparent Mineralocorticoid Excess (AME) results from loss of renal tubule 11-βHSD. 11-βHSD normally converts cortisol into cortisone in tubule cells thus inactivating

cortisol and preventing it from binding to and activating the mineralocorticoid receptor which is non-selective between gluco- and mineralocorticoids. Loss of 11- β HSD results in excess salt retention (hypertension) and excess loss of K^+ (hypokalemia), but adrenal cortex size is normal and levels of cortisol and aldosterone in plasma are normal, and genitalia are normal.

II. Estrogens and Androgens



General notes: the default pathway in embryonic development is a female urogenital tract. Testosterone/dihydrotestosterone interacting with the androgen receptors in the correct target tissues is required for development of a normal male urogenital tract.

A. Estrogens are synthesized in premenopausal women in ovaries. Key enzyme is aromatase (CYP19) as the formation of a benzene ring structure is the key structural feature that generates estrogen receptor binding activity. Estrone is a weak estrogen, but conversion of the ketone group at C-17 into a hydroxyl group makes estradiol, the most potent estrogen. In postmenopausal women, a peripheral tissue aromatase can convert some testosterone (yes, normally all women have a tiny amount of this male hormone and men have a tiny amount of estrogen too) into estradiol as the ovarian CYP19 activity is lost during menopause.

Aromatase can be inhibited by a drug called anastrozole (Arimidex).

B. Testosterone is synthesized in testes by Type III 17 β -HSD from androstenedione. Testosterone is not the most potent androgen though, dihydrotestosterone is more potent and it is made from testosterone by a peripheral tissue 5 α -reductase 2 enzyme. Testosterone is responsible for the development of essentially all the "internal" features of the male urogenital-tract, but to have full external, normal male genitalia synthesis of dihydrotestosterone must occur. Absence of dihydrotestosterone (5 α reductase 2 deficiency) results in a type of pseudohermaphroditism.

Complete loss of the androgen receptor is associated with complete loss of the male urogenital tract and external presentation of a completely normal female, even though the individual is XY. This is called complete testicular feminization. Individuals with this will have a "blunt-ended" vagina with no uterus, fallopian tubes or ovaries and may not discover that they are genetically XY until they have their first pelvic exam/pap smear or are tested as a result of being unable to conceive.

5 α -reductase activity can be inhibited by finasteride (Rogaine) and is used to treat hair loss in men and women by topically applying it to the hair as a gel or cream once per week. Finasteride may not be selective between the different types of 5 α -reductases.

IV. Eicosanoids
A. Family

Essential Fatty Acid (EFA) Family

Omega-3

|

**Linolenic acid
(linolenate)**

|

**Docosahexanoic acid
and
Eicosapentanoic acid**

|

**Less proinflammatory
mediators**

**Prostacyclin (PGI₃)
Leukotriene B₅
Interleukin 2
Endothelial-derived
relaxing factor**

**They tend to inhibit
platelet aggregation,
intimal hyperplasia, vaso-
constriction, monocyte/
macrophage function**

Omega-6

|

**Linoleic acid
(linoleate)**

|

Arachidonic Acid

|

|

|

**More proinflammatory
mediators**

**Leukotrienes A₄-E₄
Thromboxane A₂
Prostaglandins D₂-H₂**

**They tend to promote
platelet aggregation
vasoconstriction
chemotaxis
vascular permeability
bronchospasm
and activate monocyte/
macrophage function**

B. “Key” Structural Features

1) Prostaglandins--5-membered, cyclic ring. Two types: PGF--soluble in phosphate buffers (more hydrophilic) and PGE--soluble in ether (more lipophilic). Made in a variety of tissues from linoleate--> arachidonic acid as precursors, except prostacyclin that is made from linolenate as a precursor.

2) Thromboxanes--6-membered ring containing an ether made in platelets from arachidonate. Promotes platelet aggregation.

3) Leukotrienes--contain 3 conjugated C=C double bonds and no cyclic ring structure. Made from both linoleate--> arachidonate and linolenate depending on the specific subtype. Potent vasoconstrictors especially if oversynthesized in bronchial muscle. This can result in asthma in some individuals from taking aspirin that inhibits COX1/COX2 and floods the lipoxygenase pathway with arachidonate resulting in too much leukotriene A4/C4/D4 synthesis and bronchial constriction.

C. Aspirin inhibits non-selectively COX1 and COX2 isoforms--the key enzymes in the synthesis of prostaglandins and thromboxanes. It acetylates (covalently modifies) the active site serine which irreversibly inhibits the enzymes. There are now “selective” COX2 inhibitors for patients with rheumatoid arthritis that may spare the GI track and cause fewer ulcers. Examples: celecoxib and rofecoxib.