IV. Lipid Biosynthesis

1. INTRODUCTION

A. Biological functions of lipids

A.1 Principal form of stored energy in most organisms

A.2 Major constituents of cell membranes

A.3 Pigments : retinal, carotene

A.4 Cofactors : vitamin K

A.5 Detergents : bile salts

A.6 Transporters : dolichols

A.7 Hormones : vitamin D derivatives, sex hormones, adrenal cortical hormones

A.8 Extracellular and intracellular messengers : eicosanoids and derivatives of phosphatidyl inositol

A.9 Anchors for membrane proteins : covalently attached fatty acids, prenyl groups and phosphatidyl inositol

B. Biosynthesis of lipids

B.1 The ability to synthesize a variety of lipids is essential to all organisms.

B.2 The strategies for assembling the water-insoluble products from water-soluble precursors such as acetate.

B.3 The biosynthetic reactions require ATP and NADPH.

2. BIOSYNTHESIS OF FATTY ACIDS AND EICOSANOIDS

A. Introduction

A.1 Fatty acid biosynthesis and breakdown occur by different pathways, are catalyzed by different sets of enzymes and take place in different parts of the cell.

A.2 Malonyl-CoA participates in the biosynthesis of fatty acids.

B. Malonyl-CoA is formed from acetyl-CoA and bicarbonate.

B.1 Acetyl-CoA carboxylase (biotin-containing enzyme)

a. Acetyl-CoA carboxylase reaction :

Acetyl-CoA + HCO_3^- + ATP $\rightarrow$ malonyl-CoA + ADP + Pi

b. Biotin carboxylase, biotin carrier protein and transcarboxylase

c. The enzyme contains a biotin prosthetic group covalently bound in amide linkage to the ε–amino group of a Lys residue.

d. Bacteria enzyme : three separate polypeptide subunits

e. Animal enzyme : three activities are part of a single multifunction polypeptide

f. Plant enzyme : both forms

B.2 Mammalian enzyme :

a. 230 kD polypeptide

b. Allosteric and hormonal control

c. Citrate as stimulator and increases Vmax

d. Long chain fatty acyl-CoA as feedback inhibitor

e. Ser 79 is phosphorylated by AMP-dependent kinase. Enzyme is inactivated. Glucagon and epinephrine promote the phosphorylation. Insulin stimulates dephosphorylation.

B.3 One of rate-controlling steps for fatty acid biosynthesis

C. Fatty acids are synthesized by a repeating reaction sequence.

C.1 Fatty acids are assembled in a repeating four-step sequence.

C.2 The four-step sequence lengths a growing fatty acyl chain by two carbons.

C.3 The overall process of palmitate synthesis.

a. The chain length reaches 16 carbons, the product palmitate leaves the cycle.

b. The reducing agent in the synthetic sequence is NADPH.

C.4 Fatty acid synthase

a. The details of enzyme structure differ in prokaryotes and in eukaryotes.

b. Biosynthetic four-step process is the same in all organisms.

D. The fatty acid synthase complex has seven different active sites.

D.1 Proteins of the fatty acid synthase complex of *E. coli*.

D.2 These proteins act together to catalyze the formation of fatty acids.

D.3 During the process, the intermediates remain covalently attached to one of two thiol groups of the complex.

D.4 Acyl carrier protein (ACP)

a. 4'-Phosphopantetheine group forms a thioester with an acyl group and is esterified with a hydroxyl of serine 36 of ACP.

b. *E. coli* ACP (77 amino acid residues, Mr : 8860)

c. The Mr of the ACP lie between 8600 (*Clostridium butyricum*) and 16,000 (yeast)

d. In animals, ACP is part of the multifunctional fatty acid synthase.

E. Fatty acid synthase receives the acetyl and malonyl groups

E.1 Acetyl-CoA-ACP transacetylase and malonyl-CoA-ACP transferase

E.2 Step 1 condensation

a. β–Ketoacyl-ACP synthase catalyzes the condensation of activated acetyl and malonyl groups to form acetoacetyl-ACP.

b. The function of HCO_3^- and CO_2 release

E.3 Step 2 reduction of the carbonyl group

a. β–Ketoacyl-ACP reductase catalyzes acetoacetyl-ACP to D-β-hydroxybutyryl-ACP

(L-β-hydroxyacyl intermediate in fatty acid oxidation).

b. NADPH as electron donor.

E.4 Step 3 dehydration

a. β-Hydroxyacyl-ACP dehydratase

b. D-β-Hydroxybutyryl-ACP $\rightarrow$ trans-Δ^2-butenoyl-ACP

E.5 Step 4 reduction of the double bond

a. Enoyl-ACP reductase catalyzes trans-Δ^2-butenoyl-ACP to butyryl-ACP

b. NADPH as electron donor.

F. The fatty acid synthase reactions are repeated to form palmitate

F.1 Beginning of the second round of the fatty acid synthesis cycle

F.2 Seven cycles of condensation and reduction produce the 16-carbon saturated palmitoyl group still bound to ACP.

F.3 Free palmitate and small amounts of longer fatty acid such as stearate are formed.

F.4 In certain plants (coconut and palm) up to 90 % of the fatty acids are between 8 and 14 carbons long.

F.5 The overall reaction for the palmitate synthesis

a. Acetyl CoA + 7 malonyl-CoA + 14 NADPH + 14 H^+ $\rightarrow$ palmitate + 7 CO_2 + 8 CoA + 14 $NADP^+$ + 6 H_2O

b. 8 Acetyl CoA + 7 ATP + 14 NADPH + 14 H^+ $\rightarrow$ palmitate + 8 CoA + 6 H_2O + 7 ADP + 7 Pi + 14 $NADP^+$

G. The fatty acid synthase of some organisms is composed of multifunctional proteins

G.1 *E. coli* and some plants : seven active sites (six enzymes and ACP) in seven separate polypeptides. In these complexes, each enzyme is positioned with its site near that of preceding and succeeding enzymes of the sequence.

G.2 Yeast : seven distinct active sites reside in two large, multifunctional polypeptides, with three activities on the α–subunit and four on the β subunit.

G.3 Vertebrates :

a. Seven biosynthesis enzymatic activities and hydrolytic activity in one large polypeptide (240 kD).

b. The enzyme from vertebrates functions as a dimer (480 kD) in which the two identical subunits lie head-to-tail, forming two active sites at their interface.

H. Fatty acid synthesis occurs in the cytosol of many organisms but in the chloroplasts of plants.

H.1 In higher eukaryotes, the fatty acid synthase complex is found exclusively in the cytosol, and many of degradative reactions take place in the mitochondrial matrix.

H.2 NADPH is the electron carrier for anabolic reactions, and NAD^+ serves in catabolic reactions.

H.3 In hepatocytes, [NADPH]/[NADP$^+$] ratio is very high (about 75) in the cytosol for reductive synthesis of fatty acids and other molecules.

H.4 [NADH]/[NAD$^+$] ratio in the cytosol and within the mitochondria is different.

H.5 Production of NADPH :

a. In hepatocytes and adipocytes : pentose phosphate pathway and malic enzyme.

b. In the photosynthetic cells of plants (chloroplast stroma) : light reactions of photosynthesis.

H.6 Subcellular localization of lipid metabolism :

Yeast and vertebrate animal cells differ from higher plant cells in the compartmentation of lipid metabolism.

I. Acetate is shuttled out of mitochondria as citrate.

I.1 In nonphotosynthetic eukaryotes, acetyl-CoA, the starting material for fatty acid synthesis (in the cytosol) is generated in the mitochondria.

I.2 Acetyl-CoA enters the cytosol in the form of citrate via the tricarboxylate transport system.

I.3 Citrate synthase and ATP-citrate lyase

I.4 Citrate transporter

J. Fatty acid biosynthesis is tightly regulated

J.1 When a cell or organism has more than enough metabolic fuel available to meet its energy needs, the excess is generally converted to fatty acids and stored as lipids.

J.2 Acetyl-CoA carboxylase

a. The rate-limiting step

b. Palmitoyl-CoA as a feedback inhibitor

c. Citrate is an allosteric activator and increasing Vmax.

d. The function of citrate

- Precursor of cytosolic acetyl-CoA
- , Allosteric signal for the activation of acetyl-CoA carboxylase
- *ƒ* Inhibitor for phosphofructokinase-I

e. Covalent modification

- Phosphorylation triggered by glucagon and epinephrine inactivates the enzyme and slowing fatty acid synthesis.
- , Active (dephosphorylation) form; the enzyme polymerizes into long filaments.

f. The enzyme from plants and bacteria is not regulated by citrate or by a phosphorylation-dephosphorylation cycle.

g. Plant enzyme is activated by an increase in stromal pH and Mg^{2+} concentration (upon illumination).

J.3 Gene expression

J.4 During fatty acid synthesis, the production of the first intermediate malonyl-CoA, shuts down β–oxidation at the level of a transport system in the mitochondrial inner membrane.

K. Long-chain saturated fatty acids are synthesized from palmitate.

K.1 Palmitate is the precursor of other long-chain fatty acids.

K.2 Elongases are present in mitochondria and endoplasmic reticulum, the mechanisms are different.

- **a.** Mitochondrial fatty acid elongation : the process is the reverse of fatty acid oxidation and NADPH as redox coenzyme.
- **b.** Elongation in the endoplasmic reticulum : successive condensations of malonyl-CoA with acyl-CoA (not ACP derivative).

L. Some fatty acids are desaturated.

L.1 Palmitate and stearate serve as precursors of the biosynthesis of the unsaturated fatty acids.

L.2 Mammalian hepatocytes can introduce double bonds at the Δ^9 position of fatty acids but can not introduce additional double bonds in the fatty acid chain between C-10 and the methyl-terminal end.

L.3 Fatty acyl-CoA desaturase in animal tissues

- **a.** Saturated fatty acyl-CoA → monounsaturated fatty acyl-CoA
- **b.** Desaturase, cytochrome b_5 and flavoprotein (cytochrome b_5 reductase) are present in the smooth endoplasmic reticulum.

L.4 Essential fatty acids for mammals : linoleate and linolenate

- **a.** Linoleate → γ-linoleate → eicosatrienoate → arachidonate
- **b.** Linolenate → other polyunsaturated fatty acids

L.5 Plant system :

- **a.** Stearoyl-ACP desaturase produced oleate in the chloroplast stroma and reduced ferredoxin as electron donor.
- **b.** Plant desaturases introduce double bonds at Δ^{12} and Δ^{15} positions are located in the endoplasmic reticulum and chloroplast.
- **c.** The endoplasmic reticulum enzymes act not on free fatty acids but on a phospholipid : phosphatidylcholine.

L-6 Plants and bacteria synthesize polyunsaturated fatty acids to ensure membrane fluidity at reduced temperatures.

※ Mixed-function oxidases, oxygenases and cytochrome P-450

A. Molecular oxygen is a participant in several enzymes that carry out oxidation-reduction reactions.

B. Oxidases : enzymes catalyze oxidations in which molecular oxygen is the electron acceptor but oxygen atoms do not appear in the oxidized product.

B.1 Many, but not all, oxidases are flavoproteins.

B.2 Fatty acyl-CoA oxidation in peroxisomes : H_2O_2

B.3 Cytochrome oxidase of mitochondrial ETC : H_2O

C. Oxygenases

C.1 The enzymes catalyze oxidative reactions in which oxygen atoms are directly incorporated into the substrate molecule forming a new hydroxyl or carboxyl group.

C.2 Dioxygenases

- **a.** The enzymes catalyze reactions in which both of the oxygen atoms of O_2 are incorporated into the organic substrate molecule.
- **b.** Tryptophan 2,3-dioxygenase
- **c.** Cyclooxygenase

C.3 Monooxygenases (hydroxylases, mixed-function oxidases, mixed-function oxygenases)

- **a.** The enzymes are more abundant and more complex in their action.
- **b.** The enzymes catalyze reactions in which only one of the two oxygen atoms of O_2 is incorporated into the organic substrate, the other being reduced to H_2O.
- **c.** $AH + BH_2 + O_2 \rightarrow A\text{-}OH + B + H_2O$
  - • AH : main substrate
  - , BH_2 : cosubstrate
- **d.** Different classes of monooxygenases : nature of the cosubstrate
  - • NADPH (NADH) + H^+
  - , Reduced flavin nucleotides : $FMNH_2$ or $FADH_2$
  - *ƒ* α-Ketoglutarate
  - „ Tetrahydrobiopterin

D. Cytochrome P-450

D.1 A heme protein is present in the smooth endoplasmic reticulum.

D.2 It can react with O_2 and binds CO. The CO complex of reduced form absorbs light strongly at 450 nm : P-450.

D.3 The action of cytochrome P-450

D.4 Cytochrome P-450 is actually a family of closely similar proteins with different substrate specificity.

- **a.** Hydroxylation of steroids to yield the adrenocortical hormones
- **b.** Hydroxylation of many different drugs : barbiturates and xenobiotics (hydrophobic and relatively insoluble)
- **c.** Detoxification and toxification

M. Eicosanoids are formed from 20-carbon polyunsaturated fatty acids.

M.1 Eicosanoids are a family of very potent biological signaling molecules that act as short-range messengers, affect tissues near the cells.

M.2 Phospholipase A_2

- **a.** Present in most types of mammalian cells
- **b.** Response to hormonal or other stimuli
- **c.** Attacks membrane phospholipids and releases arachidonate

M.3 Cyclooxygenase (COX, prostaglandin H_2 synthase)

- **a.** The enzyme is present in smooth endoplasmic reticulum and converts arachidonate to PGH_2.
- **b.** PGH_2 : immediate precursor of many other prostaglandins and thromboxanes
- **c.** COX : bifunctional enzyme
  - • Cyclooxygenase activity : arachidonate $\rightarrow PGG_2$; introduce 2 oxygen molecules
  - ‚ Peroxidase activity : $PGG_2 \rightarrow PGH_2$
  - ƒ Aspirin (acetylsalicylate) irreversibly inactivates the cyclooxygenase activity by acetylating a Ser residue and inhibits the synthesis of PGs and thromboxanes.
  - „ Ibuprofen (nonsteroidal antiinflamatory drug, NSAIDs)
  - … Isozymes of COX
- **d.** Cyclooxygenase isozymes and the search for a better aspirin : relief is in the active site
  - • Aspirin consumption and history
  - ‚ Aspirin inhibits platelet aggregation and blood clotting (at low doses to treat patients at risk of heart attacks).
  - ƒ NSAIDs : aspirin, acetaminophen, Ibuprofen and naproxen
  - „ Aspirin has serious side effects.
  - … New NSAIDs
  - † Two isozymes, COX-1 and COX-2, in mammals have different functions but closely similar amino acid sequences (60 ~ 65 %) and reaction mechanisms.
  - ‡ COX-1 is responsible for the synthesis of PGs that regulate the secretion of gastric mucin.
  - ˆ COX-2 for the PGs that mediate inflammation, pain and fever.
  - ‰ Aspirin inhibits both isozymes about equally.
  - Š New NSAIDs inhibit COX-2 specifically.

M.4 Thromboxane synthase

- **a.** The enzyme is present in blood platelets (thrombocytes) and converts PGH_2 to thromboxane A_2.
- **b.** Cyclic pathway : arachidonate $\rightarrow$ PGs and thromboxanes (contain a ring of five or six atoms)
- **c.** Linear pathway : arachidonate $\rightarrow$ leukotrienes

M.5 The linear pathway from arachidonate to leukotrienes

- **a.** Lipoxygenases are present in leukocytes and in heart, brain, lung and spleen.
- **b.** Mixed-function oxidases use cytochrome P-450 and are not inhibited by aspirin or other NSAIDs.

M.6 Jasmonate as plant signaling molecule

- **a.** Phospholipase releases linolenate.
- **b.** Lipoxygenase catalyzes linolenate to jasmonate.
- **c.** Specific signaling roles for jasmonate.

3. BIOSYNTHESIS OF TRIACYLGLYCEROLS

A. Introduction

A.1 The fates of most of the fatty acids : triacylglycerols (storage of metabolic energy) and phospholipids (components of membranes)

A.2 The partitioning between these alternative fates depends on the needs of the organism.

A.3 Both pathways begin at the same point, the formation of fatty acyl esters of glycerol.

B. Triacylglycerols and glycerophospholipids are synthesized from the same precursors.

B.1 Animals can synthesize and store large quantities of triacylglycerols.

B.2 Humans store a few hundred grams of glycogen in liver and muscle cells, and store about 15 kg triacylglycerol in a 70 kg man (adipose tissue).

B.3 Triacylglycerols have the highest energy content : 38 kJ/g.

B.4 Plants manufacture triacylglycerols and mainly stored in fruits, roots and seeds.

B.5 The biosynthetic pathway to phosphatidic acid (diacylglycerol 3-phosphate) : a central intermediate in lipid biosynthesis.

B.6 Phosphatidic acid is the precursor of both triacylglycerols and glycerophospholipids, commonly but not invariably, the fatty acid at C-1 is saturated and that C-2 is unsaturated.

C. Triacylglycerol biosynthesis in animals is regulated by hormones.

C.1 In humans, the amount of body fat stays relatively constant over long periods.

C.2 Biosynthesis and degradation of triacylglycerols are regulated reciprocally : metabolic resources and requirements of the moment.

C.3 The rate of triacylglycerol biosynthesis is altered by the action of several hormones.

C.4 Insulin promotes the conversion of carbohydrate into triacylglycerols.

C.5 Triacylglycerol metabolism is influenced by glucagon, pituitary growth hormone and adrenal cortical hormones.

4. BIOSYNTHESIS OF MEMBRANE PHOSPHOLIPIDS

A. Introduction

A.1 Membrane phospholipids : glycerophospholipids and sphingolipids

A.2 The assembly of phospholipids from simple precursors :

- **a.** Synthesis of the backbone molecule (glycerol or sphingosine)
- **b.** Attachment of fatty acid(s) to the backbone in ester or amide linkage
- **c.** Addition of a hydrophilic head group joined to the backbone through a phosphodiester linkage
- **d.** Alteration or exchange of the head group to yield the final phospholipid product

A.3 In eukaryotic cells, phospholipid synthesis occurs primarily at the surface of the smooth endoplasmic reticulum and the inner membrane of mitochondria. Some remains there, most are destined for other cellular locations.

B. There are two strategies for attaching head groups.

B.1 Phosphatidic acid

- **a.** Two fatty acid groups are esterified to C-1 and C-2 of L-glycerol 3-phosphate.
- **b.** Phosphorylation of a diacylglycerol by a specific kinase

B.2 Phospholipid head group is attached to a diacylglycerol by a phosphodiester bond.

B.3 Two general strategies for forming the phosphodiester bond of phospholipids.

- **a.** CDP-diacylglycerol : eukaryotic and prokaryotic cells
- **b.** CDP-head group : eukaryotic cells

C. Phospholipid synthesis in *E. coli* employs CDP-diacylglycerol

C.1 Phosphatidylserine and phosphatidylethanolamine

C.2 Phosphatidylglycerol and cardiolipin

D. Eukaryotes synthesize anionic phospholipids from CDP-diacylglycerol

D.1 Phosphatidylglycerol

D.2 Cardiolipin : CDP-diacylglycerol + phosphatidylglycerol

D.3 Phosphatidylinositol : CDP-diacylglycerol + inositol

D.4 Phosphatidylinositol kinases convert phosphatidylinositol to its phosphorylated derivatives.

E. Eukaryotic pathways to phosphatidylserine, phosphatidylethanolamine and phosphatidylcholine are interrelated.

E.1 In yeast

- **a.** CDP-diacylglycerol + serine → phosphatidylserine → phosphatidylethanolamine
- **b.** Phosphatidylethanolamine → phosphatidylcholine : methyltransferase and 3 adoMet.

E.2 In mammalian cells

a. Phosphatidylserine + ethanolamine ⇆ phosphatidylethanolamine + serine

b. Choline → phosphocholine → CDP-choline → phosphatidylcholine

c. Ethanolamine → phosphoethanolamine → CDP-ethanolamine → phosphatidylethanolamine

d. Phosphatidylethanolamine → phosphatidylcholine (in liver only)

E.3 Summary of the pathways to phosphatidylcholine and phosphatidylethanolamine

F. Plasmalogen synthesis requires formation of an ether-linked fatty alcohol

F.1 The peroxisome is a major site of plasmalogen synthesis.

F.2 Synthesis of ether lipids and plasmalogens

Dihydroxyacetone phosphate as the starting material

G. Sphingolipid and glycerophospholipid synthesis share precursors and some mechanisms

G.1 Sphinganine (18-carbon amine) : palmitoyl-CoA + serine

G.2 N-acylsphinganine : fatty acid in amide linkage

G.3 N-acylsphingosine (ceramide) : desaturation

G.4 Cerebroside : ceramide + UDPGlc

G.5 Sphingomyelin : ceramide + phosphatidylcholine

H. Polar lipids are targeted to specific cell membranes

H.1 Polar lipids are synthesized on the smooth endoplasmic reticulum, and inserted into different cell membranes in different proportions.

H.2 Transport of polar lipids

a. Membrane vesicles

b. Cytosolic proteins

5. BIOSYNTHESIS OF CHOLESTEROL, STEROIDS AND ISOPRENOIDS

A. Introduction

A.1 The roles of cholesterol : as structure component of many membranes, as a precursor of steroid hormones and bile acids

A.2 Cholesterol is an essential molecule in many animals, cells can synthesize it from simple precursor-acetate.

A.3 The origin of the carbon atoms of cholesterol (27-carbon) : acetate

A.4 Isoprene units

B. Cholesterol is made from acetyl-CoA in four stages

B.1 A summary of cholesterol biosynthesis

B.2 Synthesis of mevalonate from acetate

a. Acetyl-CoA → acetoacetyl-CoA → β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) → mevalonate

b. Cytosolic HMG-CoA synthase is distinct from the mitochondrial isozyme (ketone body formation)

c. HMG-CoA reductase

- an integral membrane protein of the smooth endoplasmic reticulum
- a major regulation point of cholesterol biosynthesis

B.3 Conversion of mevalonate to two activated isoprenes

a. Three ATP molecules activate mevalonate.

b. Δ^3-isopentenyl pyrophosphate

c. dimethylallyl pyrophosphate

B.4 Condensation of six activated isoprene units to form squalene.

a. Head to tail condensation

Dimethylallyl pyrophosphate + isopentenyl pyrophosphate → geranyl pyrophosphate → farnesyl pyrophosphate

b. Head to head condensation

2 farnesyl pyrophosphate → squalene (first isolated from the liver of sharks)

c. Geraniol, farnesol and many natural scents of plant origin are synthesized from isoprene units.

B.5 Conversion of squalene to the four-ring steroid nucleus

a. All of the sterols have four fused rings (the steroid nucleus) and all are alcohols with a hydroxyl group at C-3.

b. Squalene monooxygenase catalyzes squalene to squalene 2,3-epoxide.

c. Animals : squalene 2,3-epoxide → lanosterol → cholesterol

d. Plants : stigmasterol

e. Fungi : ergosterol

C. Cholesterol has several fates.

C.1 Cholesterol synthesis in vertebrates takes place in the liver.

C.2 The functions : membrane component of hepatocytes, biliary cholesterol, bile acids and cholesteryl esters.

C.3 Bile acids and salts are synthesized in the liver and aid in lipid digestion.

C.4 Cholesteryl esters are formed in the liver.

a. Acyl-CoA-cholesterol acyl transferase (ACAT)

b. More hydrophobic form

C.5 Steroid hormones : adrenal gland and gonads

C.6 Vitamin D

D. Cholesterol and other lipids are carried on plasma lipoproteins.

D.1 Lipids are carried in the blood plasma from one tissue to another as plasma lipoproteins : macromolecular complexes.

D.2 Apolipoproteins combine with lipids to form several classes of lipoprotein particles, spherical complexes with hydrophobic lipids in the core and hydrophilic amino acid side chains at the surface.

D.3 Major classes of human plasma lipoproteins :

- **a.** Some properties
- **b.** Each has a specific function : synthesis point, lipid composition and apolipoprotein content.
- **c.** Apolipoproteins of the human plasma lipoproteins

D.4 Chylomicrons

- **a.** Largest of the lipoproteins, the least dense and high proportion of triacylglycerols
- **b.** Synthesis in the endoplasmic reticulum of epithelial cells that line the small intestine
- **c.** Apolipoproteins : apoB-48, apoE, apoC-II (activates lipoprotein lipase)
- **d.** Chylomicron remnants

D.5 Very-low-density lipoprotein (VLDL)

- **a.** Apolipoproteins : apoB-100, apoC-I, apoC-II, apoC-III and apoE
- **b.** VLDL remnants (intermediate density lipoproteins, IDL)

D.6 Low-density lipoprotein (LDL)

- **a.** Very rich in cholesterol and cholesteryl esters
- **b.** ApoB-100 as major apolipoprotein

D.7 High-density lipoprotein (HDL)

- **a.** Small protein-rich particle from the liver and small intestine
- **b.** Relatively little cholesterol and triacylglycerols
- **c.** ApoA-1, apoC-I, apoC-II and other apolipoproteins
- **d.** Lecithin-cholesterol acyl transferase (LCAT) : present on the surface of HDL and is stimulated by the HDL component apoA-1.
- **e.** Reverse cholesterol transport pathways
- **f.** ABC1 protein
  - A member of a large family of multidrug transporters
  - , ABC transporters : ATP-binding cassettes
  - *ƒ* Actively transport a variety of ions, amino acids, vitamins, steroid hormones and bile salts across plasma membranes.

E. Cholesteryl esters enter cells by receptor-mediated endocytosis

E.1 LDL receptors : apoB-100

E.2 Receptor-mediated endocytosis

E.3 Cholesterol enters cells : incorporated into membranes or converted into cholesteryl esters by ACAT.

E.4 LDL receptor binds to apoE : hepatic uptake of chylomicrons and VLDL remnants.

F. Cholesterol biosynthesis is regulated by several factors.

F.1 Cholesterol synthesis is a complex and energy-expensive process.

F.2 In mammals, cholesterol production is regulated by intracellular cholesterol concentration and by glucagon and insulin.

F.3 The rate-limiting step is the conversion of HMG-CoA into mevalonate (HMG-CoA reductase) : the pathway's main regulatory site.

F.4 HMG-CoA reductase

- **a.** 887 Amino acid residues
- **b.** Endoplasmic reticulum membrane-bound enzyme
- **c.** A complex regulatory enzyme : activity is modulated over a 100-fold range.
- **d.** Unidentified metabolites of cholesterol stimulate proteolysis of enzyme and inhibit transcription of its gene.
- **e.** Phosphorylated (at Ser 871, AMP-dependent protein kinase, inactive) and unphosphorylated (active) forms
- **f.** Glucagon stimulates phosphorylation (inactivation) and insulin promotes dephosphorylation, activating the enzyme and favoring cholesterol synthesis.

F.5 High intracellular concentrations of cholesterol activate ACAT : cholesteryl esters for storage.

F.6 High cellular cholesterol diminishes transcription of the gene that encodes the LDL receptor : reduce the uptake of cholesterol from the blood.

F.7 Unregulated cholesterol production-high cholesterol level

- **a.** Atherosclerosis
- **b.** Familial hypercholesterolemia (LDL receptor is defective)
- **c.** Two strategies are used to counteract hypercholesterolemia besides following a low-cholesterol diet.
  - Ingestion of resins that bind bile acids and preventing their intestinal absorption
  - Treatment with competitive inhibitors of HMG-CoA reductase : compactin, simvastatin, pravastatin and lovastatin

G. Bile acids

G.1 Biosynthesis of bile acids represents the major metabolic fate of cholesterol, accounting for more than half of the 800 mg/day that is metabolized in the normal human adult.

G.2 Steroid hormone synthesis accounts for only about 50 mg of cholesterol metabolized per day.

G.3 Glycocholate and taurocholate

H. Steroid hormones are formed by side chain cleavage and oxidation of cholesterol

H.1 All steroid hormones are derived from cholesterol

H.2 Steroid hormones in the cortex of the adrenal gland

- **a.** Mineralocorticoids (aldosterone) : control the reabsorption of the organic ions by the kidney.
- **b.** Glucocorticoids (cortisol) : regulate gluconeogenesis and reduce the inflammatory response

H.3 Sex hormones are produced in male or female gonads and the placenta.

- **a.** Progesterone regulates the female reproduction cycle.
- **b.** Androgens (testosterone) and estrogens (estradiol)

I. Intermediates in cholesterol biosynthesis have many alternative fates.

I.1 Isopentenyl pyrophosphate is the activated precursor of a huge array of biomolecules with diverse biological roles.

I.2 An overview of isoprenoid biosynthesis

I.3 Prenylation (covalent attachment of an isoprenoid) is a common mechanism by which proteins are anchored to the inner surface of mammalian cell membranes.

- **a.** Farnesyl or geranylgeranyl group on carboxyl-terminus cysteine
- **b.** Prenylation reactions target proteins to different membranes, depending upon which lipid is attached.
- **c.** Prenylation of certain proteins is essential for their biological activity.