Chapter 25
LIPID METABOLISM

1) Lipid digestion, absorption and transport
2) Fatty acid oxidation
3) Keton bodies
4) Fatty acid biosynthesis
5) Regulation of fatty acid metabolism
6) Cholesterol metabolism
7) Eicasonoid metabolism
8) Phospholipid and glycolipid metabolism
Lipid Digestion, Absorption and Transport

**Major form of energy: triacylglycerol/fat/triglycerides**

- 90% of dietary lipid
- Oxidized to CO$_2$ and H$_2$O
- 6 times more energy/weight of glycogen
- Water insoluble
- Digestion at lipid/water interface
- Emulsified by bile salts/bile acids in small intestine
- Cut at pos 1 and 3 by lipase (triacylglycerol lipase)
  
 \[
  \text{TAG} \rightarrow \text{1,2-diacylglycerol} \rightarrow 2 \text{ acylglycerol}
  \]

- + Na$^+$, K$^+$ salts -> fatty acid salts/soap bind to I-FABP

![1-Palmitoyl-2,3-dioleoyl-glycerol](image)
### Energy Content of Food Constituents

<table>
<thead>
<tr>
<th>Constituent</th>
<th>$\Delta H$ (kJ \cdot g$^{-1}$ dry weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>16</td>
</tr>
<tr>
<td>Fat</td>
<td>37</td>
</tr>
<tr>
<td>Protein</td>
<td>17</td>
</tr>
</tbody>
</table>


**Fat storage: anhydrous!**
Mechanism of interfacial activation of triacylglycerol lipase in complex with procolipase

- **Pancreas Lipase** = TAG lipase
- Lipase activation by colipase
- Interfacial activation
- Activity depends on surface area
- Alpha/beta hydrolase fold
- 25 AS lid structure
- Catalytic triad, asp ser his
- Hydrolysis similar to peptidase
Catalytic action of phospholipase $A_2$

- Generates a lysophospholipid! Which are detergents
- Cobra and bee venom
- Interfacial activation without conformational change ≠ TAG lipase, but hydrophobic channel

\[
\begin{align*}
\text{Phospholipid} & \xrightarrow{\text{phospholipase } A_1} \quad \text{Lysophospholipid} \\
\text{Phospholipid} & \xrightarrow{\text{phospholipase } C} \quad \text{Lysophospholipid} \\
\text{Phospholipid} & \xrightarrow{\text{phospholipase } D} \quad \text{Lysophospholipid}
\end{align*}
\]
Substrate binding to phospholipase $A_2$

No conformational change
Upon interfacial binding
The X-ray structure of porcine phospholipase $A_2$

- Catalytic diad, His, Asp
- $Ca^{2+} / 2x H_2O$ instead of Ser
- no acyl-enzyme intermediate, as in TAG lipases
LIPID ABSORPTION by enterocytes

As micelles with bile salts and PC (lecithin)
Or lipid-protein complexes also for Vit A, D, E, K

Inside the cell:
- I-FABP, increases solubility of FAs in the cytosol of enterocytes
- Protect cells from their detergent effect
- β-clam structure (Muschel)
Lipid transport

- Hydrolyzed lipids are absorbed by the intestinal mucosa
- Converted back to triglycerides!
- Packed into lipoprotein particles, chylomicrons
- Released into lymph/blood -> delivered to tissue
- Triglyceride made by liver is packaged into VLDL part. -> Released into blood
- TAG hydrolyzed in periphery by lipoprotein lipase ->
- FA uptake but glycerol back transport to liver and kidney
- TAG in adipose tissue is mobilized by hormone-sensitive lipase -> free FA enter blood, bound to serum albumin
Conversion of glycerol to the glycolytic intermediate dihydroxyacetone phosphate

- Glycerol release by lipoprotein lipase
- Taken up by liver and kidney
- Converted into glycolytic intermediate, DAHP
X-Ray structure of human serum albumin in complex with 7 molecules of palmitic acid

- Increased solubility of free FAs in blood from \( \mu M \) to \( mM \)
- FAs would form micelles, \( \rightarrow \) detergents, toxic!
- **Analbuminemia**, low levels of albumin but no severe phenotype \( \rightarrow \) other FA-binding proteins
- Albumins comprise 50% of serum proteins!
Lipases overview

1) Pancreas lipase, TAG
2) Phospholipase A2, A1, C, D
3) Lipoprotein lipase
4) Hormone-sensitive, adipocytes
Fatty acid oxidation

- degradation of fatty acid through oxidation of $C_\beta = \beta$-oxidation
- mitochondria
- FA need to cross 2 membranes to reach matrix
- not as CoAs but as acyl-carnitine
- CPT-I, cytosol; CPT-II, matrix
- separate pools of mitoch/cytosol.
  - CoAs
  - ATPs
  - NAD$^+$
Franz Knoop’s classic experiment indicating that fatty acids are metabolically oxidized at their \( \beta \)-carbon atom

- Phenyl-labelled even- or odd-numbered fatty acids
- Feed to dogs -> what product appears in urine?

**Fatty acid fed**

- **Odd-chain fatty acid**
  - (n + 1) C\(_2\)

**Breakdown product**

- **Benzoic acid**

**Excretion product**

- **Hippuric acid**
  - Glycine residue

**Fatty acid fed**

- **Even-chain fatty acid**
  - (n + 1) C\(_2\)

**Breakdown product**

- **Phenylacetic acid**

**Excretion product**

- **Phenylaceturic acid**
  - Glycine residue
Mechanism of fatty acid activation catalyzed by acyl-CoA synthetase

1) Activation of acyl chains to acyl-CoAs in cytosol
2) Requires ATP $\rightarrow$ acyl-adenylate intermediated
3) Transesterification to CoA
4) Driven by inorganic pyrophosphatase $\text{PP}_i \rightarrow \text{H}_2\text{O}+2\text{P}_i$
5) $^{18}\text{O}$-labels AMP and Acyl-CoA
Acylation of carnitine catalyzed by carnitine palmitoyltransferase

2nd step: preparation for mitochondrial import
- Transesterification of acyl-CoA to carnitine (no AMP intermediate !)
- Catalyzed by CPTI (equilibrium close to 1)
Transport of fatty acids into the mitochondrion

as: acyl-carnitine, through carnitine carrier protein IMM
• Chemically resembles the cytric acid cycle: Decarboxylation of succinate via fumarate and malate to oxaloacetate
β-oxidation, 4 steps

1. Formation of **trans-α,β double bond**, by FAD-dependent **acyl-CoA dehydrogenase (AD)**
2. Hydration of the double bonds by **enoyl-CoA hydratase (EH)** to form 3-L-hydroxyacyl-CoA
3. **NAD⁺-dependent dehydrogenation** by **3-L-hydroxyacyl-CoA dehydrogenase (HAD)** to form β-ketoacyl-CoA
4. **Cα-Cβ cleavage** by **β-ketoacyl-CoA thiolase (KT, thiolase)** -> acetyl-CoA and C2 shortened acyl-CoA
The β-oxidation pathway of fatty acyl-CoA

Long chain versions of EH, HAD and KTs in α₄β₄ octameric protein, mitochondrial trifunctional protein -> chanelling, no detectable intermediates
acyl-CoA dehydrogenases

- **1st step**: acyl-CoA dehydrogenases (AD)
  - mitos contain 4 such dehydrogenases with different chain length specificities

- VLCAD (C12-C18), LCAD (C8-C12)
- MCAD (C6-C10)
- SCAD (C4-C6)
- MCAD deficiency linked to sudden infant death syndrome
- Jamaican vomiting sickness, ackee fruit with hypoglycin A
- FADH2 is reoxidized via the electron transport chain
- generates acetyl-CoA and C2 shortened acyl-CoA

[Image: MCAD, homo-tetramer FAD green]
Metabolic conversions of hypoglycin A to yield a product that inactivates acyl-CoA dehydrogenase

Jamaican vomiting sickness, lethal!
Ingestion of unripe ackee fruits -> mechanism based inhibition of MCAD -> covalent modification of FAD

\[
\text{Hypoglycin A} \quad \overset{\text{metabolism}}{\rightarrow} \quad \text{Methylenecyclopropylacetyl-CoA (MCPA-CoA)}
\]

Possible reactive intermediate that reacts with the FAD of acyl-CoA dehydrogenase
Mitochondrial trifunctional protein

2-enoyl-CoA are further processed by chain length-specific:

- Enoyl-CoA hydratase (EHs)
- Hydroxyacyl-CoA dehydrogenase (HADs)
- $\beta$-ketoacyl-CoA thiolase (KTs)

- Long chain version contained $\alpha_4\beta_4$ octameric protein = mitochondrial trifunctional protein
  - $\alpha$ chain contains LCEH and LCHAD
  - $\beta$ chain LCKT
  (multifunctional protein, more than one enzyme on pp)

Multienzyme complex
Channeling of intermediates
Mechanism of action of $\beta$-ketoacyl-CoA thiolase

- Final step in $\beta$-oxidation
- Via an enzyme thioester bound intermediate to the substrates oxidized $\beta$ carbon, displaced by CoA
Energy balance of $\beta$-oxidation

- for C16 palmitic acid: 7 rounds of $\beta$-oxidation $\rightarrow$ 8 x acetyl-CoA

- Each round of $\beta$-oxidation produces:
  - 1 NADH $\rightarrow$ 3 ATP
  - 1 FADH$_2$ $\rightarrow$ 2 ATP
  - 1 acetyl-CoA $\rightarrow$ TCA (1 GTP, 3 NADH, 1 FADH$_2$) (respiration only !)

**OVERALL:**
- 129 ATP per C16
Oxidation of unsaturated fatty acids

Structures of two common unsaturated fatty acids,
Usually, cis double bond at C9
Additional double bond in C3 intervals, i.e. next at C12
-> odd, even numbered C atoms

Problems for $\beta$-oxidation

**Oleic acid**
(9-cis-Octadecenoic acid)

**Linoleic acid**
(9,12-cis-Octadecadienoic acid)
Problems for $\beta$-oxidation of unsaturated fatty acids

1) Generation of a $\beta, \gamma$ double bond
2) A $\Delta 4$ double bond inhibits hydratase action
3) Isomerization of 2,5-enoyl-CoA by 3,2-enoyl-CoA isomerase
Problem 1: Generation of a $\beta, \gamma$ double bond

No substrate for hydroxylase
No substrate for hydroxylase

Stability of DB
Oxidation of odd chain fatty acids

- Most naturally FA are even numbered
- Odd numbered FA are rare, some plants and marine organisms
- Final round of b-oxidation yields propionyl-CoA
- Propionyl-CoA is converted to succinyl-CoA → TCA
- Propionate is also produced by oxidation of Ile, Val, Met
- Ruminant animals, most caloric intake from acetate and propionate produced by microbial fermentation of carbohydrates in their stomach
**Propionyl-CoA**

- \( \text{Propionyl-CoA} \rightarrow \text{succinyl-CoA} \)

**3-step reaction:**
1. **Propionyl-CoA carboxylase**, tetrameric enzyme with biotin as prosthetic group, C3→C4
2. **Methylmalonyl-CoA racemase**
3. **Methylmalonyl-CoA mutase**, B12 containing

Direct conversion would involve an extremely unstable carbanion at C3
The propionyl-CoA carboxylase reaction

See also pyruvate carboxylase

1) Carboxylation of biotin by bicarbonate, ATP req.
2) Stereospecific transfer of carboxyl group
The rearrangement catalyzed by methylmalonyl-CoA mutase

Vit B12-dependent
Highly stereospecific (R-methylmalonyl-CoA) -> racemase
1. Heme-like corrin ring
2. 4 pyrrol N coordinate 6 fold coordinated Co
3. 5,6 coordination by dimethylbenzimidazole and deoxyadenosyl (C-Co bond!)
4. In carbon-carbon rearrangements
5. Methyl group transfer
6. About 12 known B12-dependent enzymes
7. Only 2 in mammals
   a. Methylmalonyl mutase, homolytic cleavage, free radical mechanism
   b. Methionine synthase
8. B12 acts as a reversible free radical generator, hydrogen rearrangement or methyl group transfer by homolytic cleavage
X-Ray structure of *P. shermanii* methylmalonyl-CoA mutase in complex with 2-carboxypropyl-CoA and AdoCbl

\(\alpha/\beta\)-barrel class of enzymes
Proposed mechanism of methylmalonyl-CoA mutase
Vit B12 deficiency

Pernicious anemia
- in elderly
- decreased number of red blood cells
- treated by daily consumption of raw liver (1926) -> (1948)
- only few bacteria synthesize B12, plants and mammals not
- human obtain it from meat
- Vit. B12 is specifically bound in intestine by **intrinsic factor**
- complex absorbed in intestinal mucosa -> blood
- bound to **transcobalamins** in blood for uptake by tissue
- not usually a dietary disease but result from insufficient secretion of **intrinsic factor**
The fate of Succinyl-CoA

• Succinyl-CoA is not consumed in TCA cycle but has a catalytic function
• To consume it, it must first be converted to pyruvate or acetyl-CoA
  • Conversion to malate (TCA)
  • Export of malate to cytosol, if conc. are high
  • Conversion to pyruvate by malic enzyme

![Chemical structures of malate and pyruvate]
Peroxisomal $\beta$ oxidation

- $\beta$-oxidation occurs both in mitochondria and in peroxisomes
- Peroxisomes: Shortening of very-long chain fatty acids (VLCFA) for subsequent transport and oxidation in mitochondria
- **ALD protein** to transport VLCFA into peroxisomes, no carnitine required, VLCFA-CoA synthetase
- X-adrenoleukodystrophy caused by defects in ALD, lethal in young boys, 13% reduced efficiency of lignoceric acid (C24:0) to lignoceryl-CoA conversion
- first step in perox. oxid. Acyl-CoA oxidase generates $\text{H}_2\text{O}_2 \rightarrow$ name! Catalase
- carnitine for transport of chain shortened FAs out of perox. and into mito.
Peroxisomal $\beta$-oxidation

First step:
Fatty acyl-CoA + $O_2$ $\rightarrow$ enoyl-CoA + $H_2O_2$

FAD dependent but direct transfer of electrons to $O_2$
Pathway of $\alpha$ oxidation of branched chain fatty acids

- $\beta$-oxidation is blocked by methyl group at C$\beta$
- Phytanic acid, breakdown product of Chlorophyll’s phytanyl side chain
- Degraded by $\alpha$-oxidation
- Generates formyl-CoA
- and propionyl-CoA
- C-end will give 2-methyl-propionyl-CoA
- Refsum disease/phytanic acid storage d.
- Omega oxidation in the ER, Cyt P450
Ketone bodies

- Fate of acetyl-CoA generated by β-oxidation:
  1. TCA cycle
  2. Ketogenesis in liver mitochondria.
- Ketone bodies, fuel for peripheral tissue (brain !)
- Where they are again converted into acetyl-CoA
- Water soluble equivalent of fatty acids
Ketogenesis

3 step reaction:
1. Condensation of 2 acetyl-CoA -> acetoacetyl-CoA (reversal of thiolase rxt)
2. Addition of third acetyl-CoA
3. Cleavage by HMG-CoA lyase

Ketosis:
spontaneous decarboxylation of acetoacetate to $CO_2$ and acetone breath (more fuel than used)
The metabolic conversion of ketone bodies to acetyl-CoA in the periphery.

**Liver lacks ketoacyl-CoA transferase -> export of acetoacetyl/hydroxybutyrate**
Proposed mechanism of 3-ketoacyl-CoA transferase involving an enzyme-CoA thioester intermediate
Fatty acid Synthesis

Synthesis of FA through condensation of C2 units -> reversal of β-oxidation
Cytosolic, NADPH <-> mitochondrial, FAD, NAD
Difference in stereochemistry
C3 unit for growth (malonyl-CoA) <-> C2 for oxidation (acetyl-CoA)

Growing chain esterified to acyl-carrier protein (ACP)
Esterified to phosphopantetheine group as in CoA which itself is bound to a Ser on ACP
ACP synthase transfers phosphopantetheine to apo-ACP to form a holo-ACP
A comparison of fatty acid β oxidation and fatty acid biosynthesis

β Oxidation
- Occurs in mitochondrion
- CoA is acyl group carrier
- FAD is electron acceptor
- FADH₂
- Enoyl-CoA
- 3-L-Hydroxyacyl-CoA
- NAD⁺ is electron acceptor
- NADH + H⁺
- β-Ketoacyl-CoA
- CoA
- Acetyl-CoA
- C₂ unit product is acetyl-CoA
- Fatty acyl-CoA (Cₙ)

Biosynthesis
- Occurs in cytoplasm
- ACP is acyl group carrier
- NADPH is electron donor
- Fatty acyl-ACP (Cₙ+2)
- Enoyl-ACP
- 3-D-Hydroxyacyl-ACP
- β-Ketoacyl-ACP
- NAD⁺
- NADPH + H⁺
- Fatty acyl-ACP (Cₙ)
The phosphopantetheine group in acyl-carrier protein (ACP) and in CoA

Phosphopantetheine prosthetic group of ACP

Phosphopantetheine group of CoA
Acetyl-CoA carboxylase

- Catalyzes first and committed step of FA synthesis
- Biotin-dependent (see propionyl-CoA carboxylase)
- Hormonally regulated
- Glucagon -> cAMP up -> PKA -> ACC is phosphorylated -> inactive, inhibited by palmitate
- AMPK, AMP-dependent kinase activates ACC
- ACC undergoes polymerization during activation
- Mammals two isoforms:
  - α-ACC, adipose tissue
  - β-ACC, tissue that oxidize FA, heart muscle, regulates β-ox. as malonyl-CoA inhibits CPT-I
Association of acetyl-CoA carboxylase protomers

- Multifunctional protein in eukaryotes (1 polypeptide chain)
- Composed of 3 proteins in bacteria:
  - Biotin carboxylase
  - Transcarboxylase
  - Biotin carboxyl-carrier
- Polymerizes upon activation
Fatty acid synthase

- Synthesis of FA from acetyl-CoA (starter) and malonyl-CoA (elongation) requires 7 enzymatic reactions
- 7 proteins in E. coli + ACP
- $\alpha_6\beta_6$ complex in yeast
- Homodimer in mammals, 272 kD

EM-based image of the human FAS dimer as viewed along its 2-fold axis, each monomer has 4 50 Å diameter lobs -> functional domains antiparallel orientation

Courtesy of Salih Wakil and Wei Chiu, Baylor College of Medicine
Schematic diagram of the order of the enzymatic activities along the polypeptide chain of a monomer of fatty acid synthase (FAS)

Multifunctional protein with 7 catalytic activities
Head to tail interaction of monomer in the dimer (KS close to ACP)
Acetoacetyl-ACP

\[ \text{H}^+ + \text{NADPH} \rightarrow \beta\text{-ketoacyl-ACP reductase (KR)} \]

\[ \text{NADP}^+ \rightarrow \begin{array}{c} \text{OH} \\ \text{H} \end{array} \rightarrow \text{d-\beta-Hydroxybutyryl-ACP} \]

\[ \text{H}_2\text{O} \rightarrow \beta\text{-hydroxyacyl-ACP dehydrase (DH)} \]

\[ \begin{array}{c} \text{CH}_3 \\ \text{H} \end{array} \rightarrow \alpha,\beta\text{-trans-Butenoyl-ACP} \]

\[ \text{H}^+ + \text{NADPH} \rightarrow \text{enoyl-ACP reductase (ER)} \]

\[ \text{NADP}^+ \rightarrow \begin{array}{c} \text{O} \\ \text{H} \end{array} \rightarrow \text{Butyryl-ACP} \]

Recycle Reactions 2a–5 six more times

After 7 reaction cycles

\[ \begin{array}{c} \text{CH}_3\text{CH}_2-(\text{CH}_2)_{15} \rightarrow \text{SACP} \\ \text{H}_2\text{O} \rightarrow \text{palmitoyl thioesterase (TE)} \]

\[ \begin{array}{c} \text{CH}_3\text{CH}_2-(\text{CH}_2)_{15} \rightarrow \text{C-O}^- + \text{H} \rightarrow \text{SACP} \]

Palmitate
\[
CH_3-CH_2-CH_2-C-\text{SACP}
\]

**Butyryl-ACP**

recycle Reactions 2a-5 six more times

after 7 reaction cycles

\[
CH_3CH_2-(CH_2)_3-C-\text{SACP}
\]

**Palmitoyl-ACP**

\[
H_2O \xrightarrow{6} \text{palmitoyl thioesterase (TE)}
\]

\[
CH_3CH_2-(CH_2)_3-C-O^- + H-SACP
\]

**Palmitate**
The mechanism of carbon–carbon bond formation in fatty acid biosynthesis

$CO_2$ that has been incorporated into malonyl-CoA is not found in the final FA
An example of polyketide biosynthesis: the synthesis of erythromycin A

- 2000kD
- $\alpha_2\beta_2\gamma_2$ complex

DEBS: Deoxyerythronolide B synthase
KS: Ketosynthase
AT: Acyltransferase
ACP: Acyl carrier protein
KR: Keto reductase
ER: Enoyl reductase
DH: Dehydratase
TE: Thioesterase

Erythromycin A

6-Deoxyerythronolide B (6dEB)
Transfer of acetyl-CoA from mitochondrion to cytosol via the tricarboxylate transport system

- Acetyl-CoA: produced by pyruvate dehydrogenase, beta-oxidation in mito
- Acetyl-CoA enters the cytosol in form of citrate via the tricarboxylate transporter
- In the cytosol:
  - Citrate + CoA + ATP \leftrightarrow acetyl-CoA + OXA + ADP + Pi (cytrate lyase)
  - citrate export balanced by anion import (malate, pyruvate, or Pi)
Fatty acid elongation and desaturation

Elongation at carboxy terminus:
- mitochondria (reversal of $\beta$-ox)
- ER (malonyl-CoA)

Mitochondrial fatty acid elongation
FA desaturation

Properties:
- Cis, $\Delta^9$ first, not conjugated
- Membrane-bound, nonheme iron enzymes, cyt $b_5$-dependent
- Mammals front end desaturation ($\Delta^9, 6, 5/4$)
- Essential FA, linoleic ($C18:2n-6, \Delta^{9,12}$), linolenic ($C18:3n-3, \Delta^{9,12,15}$)
- Some made by combination of desaturation and elongation
- PUFAs, fish oil, n-3, n-6 (omega)
- Vision, cognitive functions

The electron-transfer reactions mediated by the $\Delta^9$-fatty acyl-CoA desaturase complex
The reactions of triacylglycerol biosynthesis

TAG are synthesized from fatty acyl-CoAs and glycerol-3-phosphate or dihydroxyacetone phosphate

- Glycerol-3-phosphate acyltransferase in ER and mitochondria
- DHP acyltransferase in ER and peroxisomes

Glyceroneogenesis in liver
Partial gluconeogenesis from oxalacetate
Phosphatidic acid

Phosphatidic acid phosphatase

\[ \text{Phosphatidic acid} \xrightarrow{\text{phosphatidic acid phosphatase}} P_i \]

1-acylglycerol-3-phosphate acyltransferase

\[ R' - C - SCoA \xrightarrow{\text{1-acylglycerol-3-phosphate acyltransferase}} H - SCoA \]

Phospholipids

2-Monoacylglycerol

2-monoacylglycerol acyltransferase

\[ R' - C - O - C - H - \xrightarrow{\text{2-monoacylglycerol acyltransferase}} R' - C - O - C - H \]

1,2-Diacylglycerol (DAG)

\[ \text{2-Monoacylglycerol (from intestinal digestion)} \]

\[ \text{1,2-Diacylglycerol (DAG)} \]

\[ \text{Triacylglycerol} \]
Metabolic control

Differences in energy needs:
- between resting and activated muscle 100x
- feed <-> fasting

- Breakdown of glycogen and fatty acids concern the whole organism
- organs and tissues connected by blood stream

- Blood glucose levels sensed by pancreatic α cells, glucose down -> secrete glucagon
- β cells, glucose up -> insulin

- These hormones also control fatty acid synthesis <-> β oxidation
**Short term regulation**
regulates catalytic activities of key enzymes in minutes or less:
- substrate availability
- allosteric interactions
- Covalent modification

$\rightarrow$ ACC

**Long term regulation**
amount of enzyme present, within hours or days

$\rightarrow$ ACC
Sites of regulation of fatty acid metabolism

Synthesis or oxidation of FA?
Short-term, hormonal
Long-term
Cholesterol metabolism

- Vital constituent of cell membranes
- Precursor to:
  - Steroids
  - Bile salts
- Cardiovascular disease, delicate balance!

All of cholesterol’s carbon atoms are derived from acetate
Cholesterol is made by cyclization of squalene

Squalene from 6 isopren units (C30), polyisopren
Part of a branched pathway that uses isoprenes
The branched pathway of isoprenoid metabolism in mammalian cells.

Acetyl-CoA ➔ HMG-CoA ➔ HMG-CoA reductase ➔ Mevalonate ➔ Mevalonate pyrophosphate ➔ Isopentenyl pyrophosphate ➔ Dimethylallyl pyrophosphate ➔ Isopentenyl adenosine (tRNA) ➔ Geranyl pyrophosphate ➔ Farnesyl pyrophosphate ➔ trans-Prenyl transferase ➔ Geranyl-geranyl phosphate ➔ Ubiquinone ➔ Squalene synthase ➔ Squalene ➔ cis-Prenyl transferase ➔ Cholesterol ➔ Dolichol ➔ Protein prenyl transferase ➔ Farnesylated proteins.
Formation of isopentenyl pyrophosphate from HMG-CoA

HMG-CoA is rate-limiting ER membrane enzyme, 888 Aa
1. Reduction to OH
2. Phosphorylation
3. Pyrophosphate
4. Decarboxylation/Dehydration
Action of pyrophosphomevalonate decarboxylase
Mechanism of isopentenyl pyrophosphate isomerase
Formation of squalene from isopentenyl pyrophosphate and dimethylallyl pyrophosphate
Two possible mechanisms for the prenyltransferase reaction
Action of squalene synthase

\[
\begin{align*}
&\text{Farnesyl pyrophosphate} \\
&\text{Farnesyl pyrophosphate} \\
&\text{Presqualene pyrophosphate} \\
&\text{Squalene}
\end{align*}
\]
Proposed mechanism for the formation of presqualene pyrophosphate from two farnesyl pyrophosphate molecules by squalene synthase

Via cyclopropyl intermediate
Mechanism of rearrangement and reduction of presqualene pyrophosphate to squalene as catalyzed by squalene synthase.
Squalene synthase

- ER anchored
- Monomer single domain
The squalene epoxidase reaction

- Preparation for cyclization
- Oxygen required for cholesterol synthesis

Squalene $+ O_2 \xrightarrow{\text{squalene epoxidase}}$ 2,3-Oxidosqualene

\[ \text{NADPH} \rightarrow \text{NADP}^+ \]
The oxidosqualene cyclase reaction

**Lanosterol synthase**
Folding of oxidosqualene on the enzyme!

**Related reaction in bacteria:**
$O_2$-independent
Squalene-hopene cyclase
Squalene-hopene cyclase

α/α barrel

monotopic
membrane protein
Active as homodimer
Squalene-hopene cyclase with its membrane-bound region yellow

Hydrophobic channel from active site to membrane

Courtesy of Georg Schulz, Institut für Organische Chemie and Biochemie, Freiburg im Breisgau, Germany
The 19-reaction conversion of lanosterol to cholesterol

- 19 steps
- Loss of 3 methyl groups
- C30 -> C27
- One oxidation
- 9 O₂ dependent
- ER localized enzymes

Lanosterol -> cholesterol
Cholesterol

Liver synthesized cholesterol is:
- converted to bile salts
- esterified to cholesteryl ester, ACAT
which are then packaged into lipoprotein complexes, VLDL
and taken up by the tissue by LDL receptor mediated endocytosis

Mammalian cells thus have 2 ways to acquire cholesterol:
de novo synthesis or via LDL uptake

Dietary sterols are absorbed in small intestine and
transported as chylomicrons in lymph to tissue/liver

HDL transports cholesterol from the peripheral tissue to the liver
LDL receptor-mediated endocytosis in mammalian cells
Regulation of cholesterol levels

Sterol Homeostasis:
1. HMG-CoA reductase, i.e. de novo synthesis
   short-term: competitive inhib., allosteric, cov. mod.
   long-term, rate of enzyme synthesis and degradation
   => SREBP PATHWAY !!
2. Regulation of LDL Receptor
3. Regulating esterification, ACAT
Model for the cholesterol-mediated proteolytic activation of SREBP
The SREBP Pathway

SREBP, membrane anchored transcription factor (1160 Aa)
480 Aa N-term, basic helix-loop-helix/leucine zipper
dom. => binds SRE element
central 2 TMD, loop
590 Aa C-term regulatory domain

SCAP, integral membrane protein, ER, 1276 Aa
N-term 8 TMDs (730 Aa), Sterol-sensing domain
C-term, WD40 repeat => protein interaction (546 Aa)

1) Long term regulation of HMG-CoA reductase
2) Short term by phosphorylation via AMPK (see ACC1),
   P-form less active
3) LDL receptor
Control of plasma LDL production and uptake by liver LDL receptors. (a) Normal human subjects
Control of plasma LDL production and uptake by liver LDL receptors

(b) Familial hypercholesterolemia
(c) High cholesterol diet

VLDL

Genetically defective LDL receptor synthesis

LDL

VLDL

IDL

Free fatty acids

VLDL

IDL

Free fatty acids

Dietary cholesterol

Cholesterol repression of LDL receptor synthesis

lipoprotein lipase

lipoprotein lipase

(d) Overexpression of LDL receptor prevents diet-induced hypercholesterolemia
Competitive inhibitors of HMG-CoA reductase used for the treatment of hypercholesterolemia

\[ \text{Lovastatin (Mevacor)} \]
\[ \text{Atorvastatin (Lipitor)} \]
\[ \text{Pravastatin (Pravachol)} \]
\[ \text{Simvastatin (Zocor)} \]

\[ \text{HMG-CoA} \]
\[ \text{Mevalonate} \]
COMBINATORIAL THERAPY

1) Anion exchanger, cholestyramine, reduced uptake of dietary cholesterol => 15-20% drop
2) HMG-CoA inhibitor statins

Combined => 50-60% reduction of blood cholesterol levels
Simplified scheme of steroid biosynthesis

- Progestins
- Glucocorticoids
- Mineralocorticoids
- Androgens
- Estrogens

Side-chain cleavage in mitochondria!!
Bile acids and their glycine and taurine conjugates

- Only route for cholesterol excretion, < 1 g/day
- Cholesterol 7α-hydroxylase is rate-limiting, ER
- Detergent properties

\[ R_1 = \text{OH} \quad \text{Cholic acid} \quad R_1 = \text{H} \quad \text{Chenodeoxycholic acid} \n\]
\[ R_2 = \text{OH} \quad \text{Glycocholic acid} \quad R_2 = \text{NH} - \text{CH}_2 - \text{COOH} \quad \text{Glycochenodeoxycholic acid} \n\]
\[ R_2 = \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{SO}_3\text{H} \quad \text{Taurocholic acid} \quad R_2 = \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{SO}_3\text{H} \quad \text{Taurochenodeoxycholic acid} \]
Prostaglandins (PGs)

- 1930, Ulf von Euler: human semen extract stimulates uterus contraction and lower blood pressure
- Thought to originate in prostatica -> name
- Mid 50s, isolated from body fluids in ether extract (PGE)
- Made by all cells except RBC
Eicosanoid metabolism:
Prostaglandins, prostacyclins, thromboxanes, leukotriens, and lipoxins

Collectively: eicosanoids, C20 compounds
- profound physiological effects at very low conc.
- hormone-like but paracrine
- bind to G-coupled receptors, affect cAMP
- signal as hormones do
- arachidonic acid C20:4

What you inhibit by aspirin !!
NSAIDs, nonsteroidal anti-inflammatory drugs

What you inhibit by cortisol !!
Eicosanoids

Mediate:

1) inflammation
2) production of pain and fever
3) regulate blood pressure
4) induction of blood clotting
5) reproductive functions
6) sleep/wake cycle
Prostaglandin structures. (a) The carbon skeleton of prostanoic acid, the prostaglandin parent compound

Cyclopentane ring
Synthesized from arachidonic acid, $C_{20}:4$, $\Delta5,8,11,14$ ($\omega-6$ FA)
Prostaglandin structures. (b) Structures of prostaglandins A through I.
Prostaglandin structures. (c) Structures of prostaglandins $E_1$, $E_2$, and $F_{2\alpha}$ (the first prostaglandins to be identified)
Synthesis of prostaglandin precursors, arachidonic acid

Linoleic acid (9,12-octadecadienoic acid)

-2H  \( \Delta^6 \)-desaturase

γ-Linolenic acid (GLA; 6,9,12-octadecatrienoic acid)

+2C  \( \Delta^6 \)-desaturase (plants only)

DihomoGLA (DGLA; 8,11,14-eicosatrienoic acid)

-2H  \( \Delta^5 \)-desaturase

Arachidonic acid (5,8,11,14-eicosatetraenoic acid)

-2H  PGH synthase

\( \Delta^5 \)-desaturase

\( \Delta^5 \)-desaturase

α-Linolenic acid (ALA; 9-12-15-octadecatrienoic acid)

-2H

5,8,11,14,17-Eicosapentaenoic acid (EPA)
Arachidonic acid is the precursor to PGs

- Arachidonic acid: C20:4, n-6, Δ5,8,11,14

- AA is synthesized from the essential linoleic acid, C18:3, Δ6,9,12 by elongation and desaturation

- AA is phospholipid bound (sn2, PI) and released upon stimuli by:
  1) phospholipase A2
  2) phospholipase C \( \rightarrow \) DAG + P-Ins \( \rightarrow \) PA (DAG kinase) \( \rightarrow \) AA (PLA2)
  3) DAG hydrolysis by DAG lipase

- Corticosteroids inhibit PLA2 and thus act through PGs !! anti-inflammatory
Release of arachidonic acid by phospholipid hydrolysis

phospholipase A_2

\[
\begin{align*}
\text{Arachidonoyl group} & \quad \text{phospholipase C}
\end{align*}
\]

\[
\begin{array}{c}
\text{H}_{31}\text{C}_{19} \quad \text{C} \\
\text{O} \\
\text{CH} \\
\text{CH}_2 \quad \text{O} \quad \text{C} \quad \text{R}_1 \\
\text{O} \\
\text{CH} \\
\text{CH}_2 \quad \text{O} \quad \text{P} \quad \text{X} \\
\text{O} \\
\end{array}
\]

X = Inositol
Pathways of arachidonic acid liberation from phospholipids

Phospholipid (phosphatidylinositol)

- Phospholipase A$_2$
- Phospholipase C

Phosphoinositol

- 1,2-Diacylglycerol (DAG)

- Diacylglycerol kinase
- Diacylglycerol lipase

Phosphatidic acid

- Phospholipase A$_2$

Lysophosphatidic acid

- + Arachidonic acid

Monoacylglycerol

- + Arachidonic acid

Lysophospholipid + Arachidonic acid
The cyclic and linear pathways of arachidonic acid metabolism

[Diagram showing the pathways of arachidonic acid metabolism, including Prostaglandins, 5-Hydroperoxyeicosatetraenoic acid (5-HPETE), Leukotrienes, Hepoxilins, and Lipoxins.]
The cyclic pathway of arachidonic acid metabolism
The reactions catalyzed by PGH synthase (PGHS)

- PGHS catalyzes first step in the cyclic pathway
- cyclooxygenase (COX) + peroxidase activity
- heme activates Tyr radical
- Target of aspirin
- Monotopic membrane protein (see squalene-hopene cyclase)
X-Ray structure of PGH synthase (PGHS) from sheep seminal vesicles in complex with the NSAID flurbiprofen

Homodimeric monotopic ER membrane protein

Heme
Flurbiprofen
Active side Tyr

Courtesy of Michael Gerwit, Michigan State University
X-Ray structure of PGH synthase (PGHS) from sheep seminal vesicles in complex with the NSAID flurbiprofen. 

(b) A $C_\alpha$ diagram of a PGHS subunit (green)
ASPIRIN

- Acetylsalicylic acid
- Inhibits cyclooxygenase activity of PGHS
- Acetylates Ser 530
- Flurbiprofen blocks channel
- Low dose of aspirin reduce heart-attack risk, inhibits platelet aggregation (enucleated cells, 10 days lifetime, cannot resynthesize enzyme)
Inactivation of PGH synthase by aspirin

Aspirin + PGH synthase (active) → Salicylic acid + PGH synthase (inactive)
Some nonsteroidal anti-inflammatory drugs (NSAIDs)

Aspirin (acetylsalicylic acid)

Indomethacin

Ibuprofen

Flurbiprofen

Acetaminophen

Naproxen

Phenylbutazone
2 PGH synthase isoforms, **COX1**, **COX-2**
- **COX-1** is constitutively expressed in most tissues, including the gastrointestinal mucosa
- **COX-2** only in certain tissues expressed in response to inflammatory stimuli

**Aspirin can induce gastrointestinal ulceration**

⇒ Search for selective **COX-2** inhibitors (coxibs) for long-term treatment, i.e. arthritis

**COX-3** may be the target of acetaminophen, widely used analgesic/antipyretic drug → treat pain & fever
COX-2 inhibitors

Rofecoxib (Vioxx)

Celecoxib (Celebrex)
The linear pathway: Leukotrienes and Lipoxinds

- Conversion of arachidonic acid to different hydroperoxyeicosatetraenoic acids (HPETEs) by lipoxygenase
- Hepoxilins, hydroxy epoxy derivatives of 12-HEPTE, anti-inflammatory

The 5-LO-catalyzed oxidation of arachidonic acid to LTA₄ via the intermediate 5-HPETE
15-lipoxygenase (15-LO) in complex with its competitive inhibitor RS75091

- N-term β-barrel
- Fe
Formation of the leukotrienes from LTA₄
Lipoxin biosynthesis

Arachidonic acid

15-LO + glutathione peroxidase → O₂

Endothelial and epithelial cells → aspirin-acetylated COX-2

(15S)-HETE

H₂O → 5-LO

Leukocytes

(15R)-HETE

H₂O → 5-LO

hydrolase

15-LXA₄

15-epi-LXA₄
ESKIMOS

- Low risk of cardiovascular disease despite the fact that they eat a lot of fat, why?
- Are healthy because they eat fish, PUFAs, n-3, n-6
- Reduce cholesterol, leukotriene and PG levels
Phospholipid and glycerolipid metabolism:
The glycerolipids and sphingolipids

\[
\begin{align*}
\text{Glycerolipid} & : \\
& \overset{\text{O}}{\text{R}_2-\text{C}-\overset{\text{CH}_2-\text{O}}{\overset{\text{O}}{\text{C}}}-\overset{\text{R}_1}{\text{C}}-\overset{\text{H}}{\text{C}}-\text{H} \\
& \text{CH}_2-\text{O}-\text{X} \\
\text{Sphingolipid} & : \\
& \overset{\text{O}}{\text{R}_2-\text{C}}-\overset{\text{NH}}{\overset{\text{CH}}{\text{C}}}-\overset{\text{H}}{\overset{\text{(CH}_2)_12}{\text{(CH}_2)_{12}}}-\overset{\text{CH}_3}{\text{CH}}-\text{H} \\
& \text{CH}_2-\text{O}-\text{X}
\end{align*}
\]

- \( X = \text{H} \) : 1,2-Diacylglycerol, \( N \)-Acylsphingosine (ceramide)
- \( X = \text{Carbohydrate} \) : Glyceroglycolipid, Sphingoglycolipid (glycosphingolipid)
- \( X = \text{Phosphate ester} \) : Glycerophospholipid, Sphingophospholipid
Membrane lipids

Amphipathic: hydrophobic tail / hydrophilic head
- glycerol, 1,2-diacyl-sn-glycerol
- N-acylsphingosine (ceramide)
- Head:
  - phosphate ester
  - carbohydrate

- 2 categories of phospholipids:
  - Glycerophospholipids, sphingophospholipids

- 2 categories of glycolipids
  - Glyceroglycolipids, sphingoglycolipids/glycosphingolipids
Glycerophospholipid biosynthesis

- sn-1: saturated FA
- sn-2: unsaturated FA

Biosynthesis of diacylglycerophospholipids
  - from DAG and PA as TAG synthesis

Head group addition:
  - PC/PE
    - P-activated Etn or Cho
    - -> CDP-activated Etn or Chol
    - -> transfer on DAG
  - PS, head-group exchange with PE
  - PI/PG, CDP-DAG
The biosynthesis of phosphatidylethanolamine and phosphatidylcholine

- DAG and CDP-ethn or CDP-chol
- Methylation pathway in the liver
  PE -> PC, SAM-dependent

\[
\text{Ethanolamine} \quad \text{Choline}
\]

\[
\begin{align*}
\text{ethanolamine kinase or choline kinase} & \quad \uparrow \\
\text{ATP} & \quad \rightarrow \quad \text{ADP}
\end{align*}
\]

\[
\begin{align*}
\text{R'} = \text{H} & \quad \text{Phosphoethanolamine} \\
\text{R'} = \text{CH}_3 & \quad \text{Phosphocholine}
\end{align*}
\]


CTP:phosphoethanolamine cytidyltransferase

or CTP:phosphocholine cytidyltransferase

\[
\text{Cytidine} \quad \text{P} \quad \text{O} \quad \text{O} \quad \text{P} \quad \text{O} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{NR}_3^+ \quad \text{O} \quad \text{O}^{-}
\]

\[ \text{R}' = \text{H} \quad \text{CDP-ethanolamine} \]
\[ \text{R}' = \text{CH}_3 \quad \text{CDP-choline} \]

CDP-ethanolamine:1,2-diacylglycerol phosphoethanolamine transferase

or CDP-choline:1,2-diacylglycerol phosphocholine transferase

\[
\quad \text{1,2-Diacylglycerol} \quad \text{O} \quad \text{O} \quad \text{CH}_2 \quad \text{O} \quad \text{C} \quad \text{R}_1
\]
\[ \quad \text{R}_2 \quad \text{C} \quad \text{O} \quad \text{C} \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{R}' = \text{H} \quad \text{Phosphatidylethanolamine} \]
\[ \quad \text{R}' = \text{CH}_3 \quad \text{Phosphatidylcholine (lecithin)} \]

\[ \quad \text{CMP} \]

\[ \quad \text{2} \quad \text{PP}_i \]
Phosphatidylserine synthesis

Head group exchange with PE
The biosynthesis of phosphatidylinositol and phosphatidylglycerol

\[ \text{CDP-DAG} \text{ activated DAG} \]
\[ + \text{inositol or glycerol-3P} \]
\[ = \text{PI or PG} \]
The formation of cardiolipin

Mitochondrial phospholipid

\[ 2 \times PG = CL + \text{Glycerol} \]
Tissue and cell-type specific introduction of defined FA into lipids

Examples:
- 80% of brain PI contains C18:0 in sn-1 and C20:4 in sn-2
- 40% of lung PC has C16:0 in both positions, surfactant
Plasmalogens

Around 20% of mammalian PLs are plasmalogens
  o Nervous tissue
  o Mainly PEs

1. Plasmalogens: vinyl ether linkage in C1
2. Alkylacylglycerophospholipids: ether linkage
The biosynthesis of ethanolamine plasmalogen via a pathway in which 1-alkyl-2-acyl-sn-glycerolphosphoethanolamine is an intermediate.
1-Alkyl-2-acyl-sn-glycerol-3-phosphate $\xrightarrow{\text{CoASH}}$ 1-Alkyl-sn-glycerol-3-phosphate

$R'' - \text{C} - \text{O} - \text{C} - \text{H}$

$\text{CH}_2\text{OH}$

1-Alkyl-2-acyl-sn-glycerol

$\xrightarrow{\text{CDP-ethanolamine}}$ 1-Alkyl-2-acyl-sn-glycerophosphoethanolamine

$O_2 + \text{NADH} + H^+ \xrightarrow{\text{cytochrome } b_5} 2\text{H}_2\text{O}$

$\text{Ethanolamine plasmalogen}$
Sphingolipids

1. Cover the external surface of the plasma membrane, biosynthesis in ER/Golgi lumen

2. Sphingomyelin is major phosphophingolipid, phosphocholine head group, not from CDP-choline but from PC

3. Sphingoglycolipids
   1. Cerebrosides, ceramide monosaccharides
   2. Sulfatides, ceramide monosaccharides sulfates
   3. Globosides, neutral ceramide oligosaccharides
   4. Gangliosides, acidic, sialic acid-containing ceramide oligosaccharides
The biosynthesis of ceramide

1) Serine + palmitoyl-CoA = KS
2) Reduction of KS to sphinganine (LCB)
3) LCB + Acyl-CoA = ceramide (DHC)
4) Oxidation of DHC to Cer
The synthesis of sphingomyelin from \( \text{N-acylsphingosine} \) and \( \text{phosphatidylcholine} \)

\[ \text{Ceramide (N-acylsphingosine)} + \text{Phosphatidylcholine} \rightarrow \text{Diacylglycerol} \]

- \( \text{PC} \) is head-group donor to convert \( \text{Cer} \) to SM

\[ \text{Sphingomyelin} \]
Principal classes of sphingoglycolipids

**Cerebrosides**
- Glucocerebroside
- Galactocerebroside
- Sulfatide

**Globosides**
- Lactosyl ceramide
- Trihexosyl ceramide
- Globoside

**Gangliosides**
- $G_M^3$
- $G_M^2$
- $G_M^1$

**Molecules**
- Red = glucose
- Blue = N-acetylgalactosamine
- Green = galactose
- Yellow = ceramide
- $NANA = N$-acetylneuraminic acid (sialic acid)
The biosynthesis of cerebrosides

Most common:
- galactosylceramide
- glucosylceramide

Ceramide + UDP-hexose
The biosynthesis of sulfatides

Account for 15% of lipids in white matter in the brain
Transfer of activated sulfate group from PAPS to C3 OH of galactose on galactosylcerebroside

\[ \text{3’-Phosphoadenosine-5’-phosphosulfate (PAPS)} \]

\[ \text{Galactocerebroside} \rightarrow \text{3’-Phosphoadenosine-5’-phosphate} \]

\[ \text{Sulfatide (galactocerebroside-3-sulfate)} \]
The biosynthesis of globosides and gangliosides

- **Globosides**: neutral ceramide oligosaccharides
- **Gangliosides**: acidic, sialic-acid containing ceramide oligosaccharides

- Made by a series of glycosyltransferases
  1) galactosyl transfer to glucocerebroside
     -> lactosyl ceramide, precursor to globosides and gangliosides (over 60 different gangliosides known)
  2) UDP activated sugar
The biosynthesis of globosides and $G_M$ gangliosides

\[
\text{Glc} \beta (1 \rightarrow 1') \text{ceramide} \\
\text{Glucocerebroside} \\
\text{UDP-Gal} \leftarrow \text{UDP} \\
\text{Gal} \beta (1 \rightarrow 4) \text{Glc} \beta (1 \rightarrow 1') \text{ceramide} \\
\text{CMP-NANA} \quad \text{Lactosyl ceramide} \quad \text{UDP-Gal}
\]
Sphingoglycolipid degradation and lipid storage disease

- Degraded in lysosomes by series of enzyme-mediated hydrolytic steps
- Catalyzed at lipid-water interface by soluble enzymes
- Aid of SAPS, sphingolipid activator proteins
- $GM_2$-activator-$GM_2$ complex binds hexosaminidase $A$ that hydrolyzes N-acetylgalactosamine from $GM_2$

- Enzymatic defect leads to sphingolipid storage disease, e.g., **Tay-Sachs disease**, deficiency in hexosaminidase $A$, neuronal accumulation of $GM_2$ as shell-like inclusions, In utero diagnosis possible with fluorescent substrate

- Substrate deprivation therapy, inhibition of glucosylceramide synthase
Cytoplasmic membranous body in a neuron affected by Tay-Sachs disease

Most common SL storage disease
Hexosaminidase deficiency
Cytoplasmic membrane bodies in neurons
Model for $G_{M2}$-activator protein-stimulated hydrolysis of ganglioside $G_{M2}$ by hexosaminidase
The breakdown of sphingolipids by lysosomal enzymes
**Sphingolipid Storage Diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Enzyme Deficiency</th>
<th>Principal Storage Substance</th>
<th>Major Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G&lt;sub&gt;Mr&lt;/sub&gt; Gangliosidosis</td>
<td>G&lt;sub&gt;Mr&lt;/sub&gt; β-galactosidase</td>
<td>Ganglioside G&lt;sub&gt;Mr&lt;/sub&gt;</td>
<td>Mental retardation, liver enlargement, skeletal involvement, death by age 2</td>
</tr>
<tr>
<td>Tay–Sachs disease</td>
<td>Hexosaminidase A</td>
<td>Ganglioside G&lt;sub&gt;M2&lt;/sub&gt;</td>
<td>Mental retardation, blindness, death by age 3</td>
</tr>
<tr>
<td>Fabry’s disease</td>
<td>α-Galactosidase A</td>
<td>Trihexosylercamide</td>
<td>Skin rash, kidney failure, pain in lower extremities</td>
</tr>
<tr>
<td>Sandhoff’s disease</td>
<td>Hexosaminidases A and B</td>
<td>Ganglioside G&lt;sub&gt;M2&lt;/sub&gt; and globoside</td>
<td>Similar to Tay–Sachs disease but more rapidly progressing</td>
</tr>
<tr>
<td>Gaucher’s disease</td>
<td>Glucocerebrosidase</td>
<td>Glucocerebroside</td>
<td>Liver and spleen enlargement, erosion of long bones, mental retardation in infantile form only</td>
</tr>
<tr>
<td>Niemann–Pick disease</td>
<td>Sphingomyelinase</td>
<td>Sphingomyelin</td>
<td>Liver and spleen enlargement, mental retardation</td>
</tr>
<tr>
<td>Farber’s lipogranulomatosis</td>
<td>Ceramidase</td>
<td>Ceramide</td>
<td>Painful and progressively deformed joints, skin nodules, death within a few years</td>
</tr>
<tr>
<td>Krabbe’s disease</td>
<td>Galactocerebrosidase</td>
<td>Deacetylated galactocerebroside</td>
<td>Loss of myelin, mental retardation, death by age 2</td>
</tr>
<tr>
<td>Metachromatic leukodistrophy</td>
<td>Arylsulfatase A</td>
<td>Sulfatide</td>
<td>Mental retardation, death in first decade</td>
</tr>
<tr>
<td>(Sulfatide lipidosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>