Chapter 10. Lipid Metabolism

* 소화, 흡수, 운반 : Micelle, lipase, chylomicron
* 지방산의 산화 : Carnitine, β-oxidation, acetyl-CoA
* 케톤체 생성 : β-hydroxybutyrate, acetoactate, acetone
* 지질대사 호르몬 : Epinephrine, glucagon, insulin
* 지질대사는 탄수화물과 달리 ATP를 형성하기 위하여 산소분자를 요구한다

1. Digestion, mobilization and transport of fatty acid

(지방산의 소화, 이동 및 운반)

1) Dietary fats are absorbed in the small intestine

(식이지방은 작은창자에서 흡수된다)

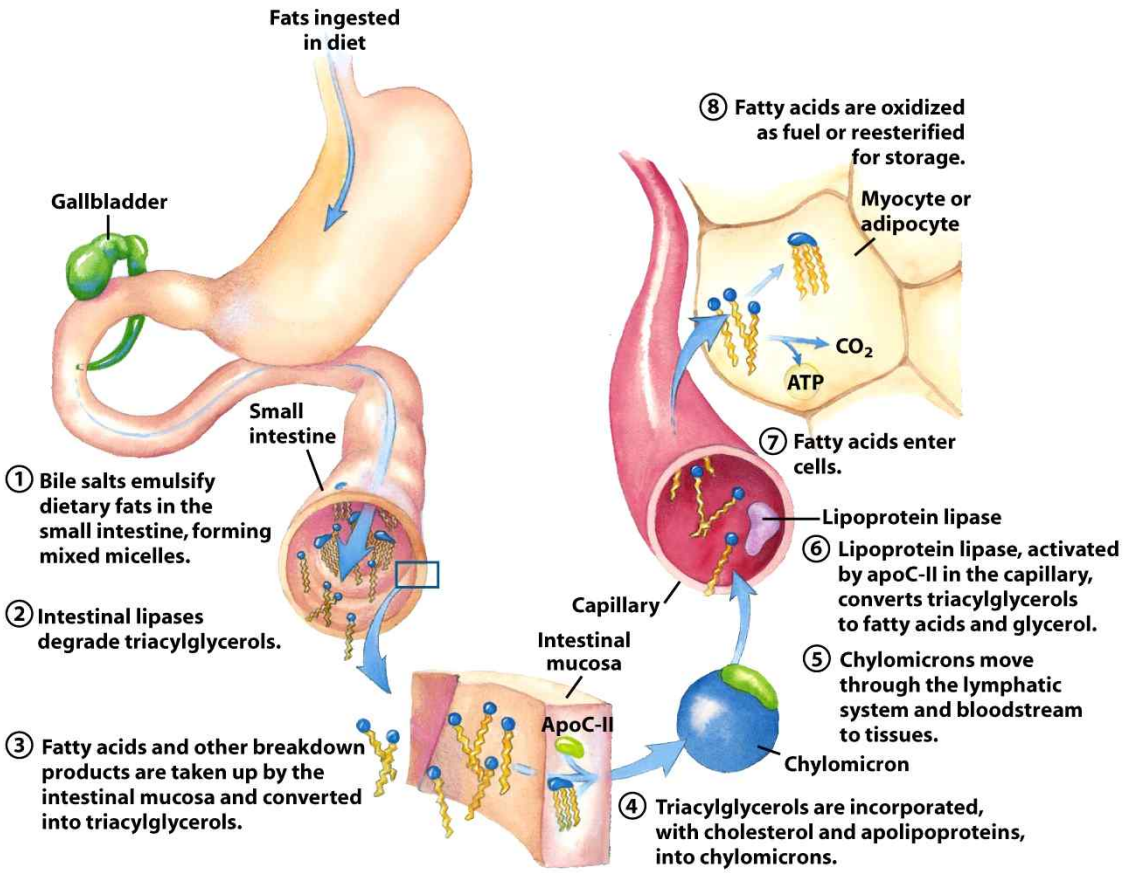


Fig. Processing of dietary lipid in vertebrates. The fatty acids released from tracylglycerols are packaged and delivered to muscle and adipose tissues.

2) Hormones trigger mobilization of stored triacylglycerols

(호르몬이 저장된 중성지방의 이동을 유발한다)

* Human lipid storage : 피하조직, 근육과 장간막 조직에 **지질방울 (lipid droplet)형태로 저장**
* 대구, 어류의 lipid storage : 간에 lipid 저장

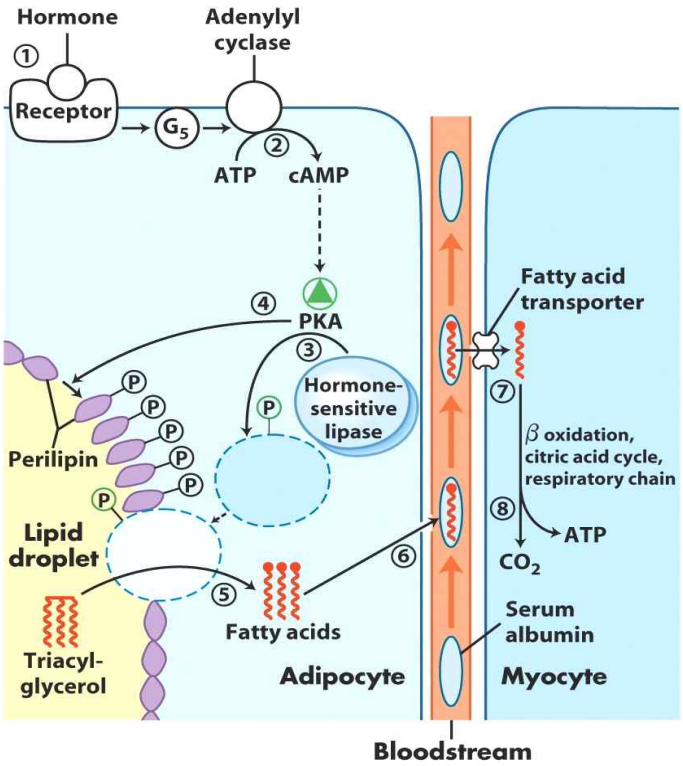


Fig. Mobilization of triacylglycerols stored in adipose tissue.

혈당치의 저하가 글루카곤의 분비를 촉진→ 호르몬이 지방세포막에 있는 수용체에 결합 → **G 단백질을 통하여 adenylate cyclase를 자극하여 cAMP 생산을 촉진하면** cAMP는 PKA를 활성화 → PKA는 Lipase 활성화하여 지질분해 촉진

◎ **페리리핀(perilipin) : 지질방울의 표면을 둘러싸고 있는 단백질**

[기능] 지질방울(lipid droplets)에 접근하는 것을 제한하는 기능
지질이 이동하는 것을 방해하는 기능

◎ **알부민(Albumin) : water soluble 단백질로 혈장단백질의 약 50%를 차지**

[기능] 혈액의 삼투압조절, 유리지방산 수송에 중요한 기능 (Albumin – FFA)

◎ **중성지방분해기작 : 지질이동(분해, 방출) → 지방산활성화 → 베타산화**

Starvation, 운동, 공포, stress

[호르몬 분비]

↓

Epinephrine (blood) + hormone receptor (adipocyte)

↓

Lipase (activation)

↓

Triacylglycerol → diacylglycerol → monoacylglycerol

glycerol + Free fatty acid

3) Fatty acids are activated and transported into mitochondria
(지방산은 활성화되어 사립체 안으로 운반된다)

① **Fatty acid activation (지방산의 활성화)**

Fatty acid + CoA + ATP ⟷ fatty acyl-CoA + AMP + PPi

acyl CoA synthetase

② **Transfer fatty acyl-CoA into mitochondria**

* **Carnitine acyltransferase I**
  - 지방산 아실-CoA에서 **지방산 아실-carnithine생성**하기 위하여 에스터 교환반응(transesterification)을 촉매한다
* **Carnitine acyltransferase II**
  - 카르니틴으로부터 미토콘드리아내의 CoA로 **지방산 아실기**가 운반되는 반응을 촉매한다.

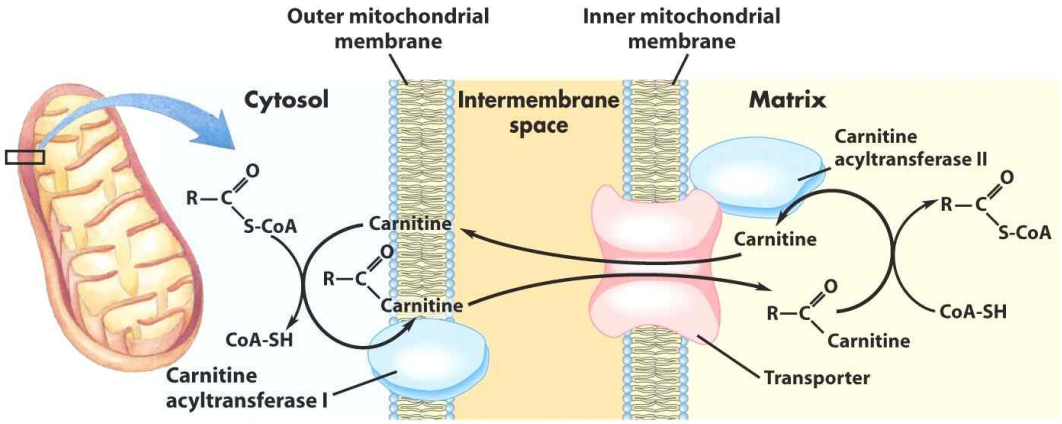


Fig. Fatty acid entry into mitochondria via the acyl-carnitine/carnitine transporter

2. β-산화(β-Oxidation)

1단계 (β-산화), 2단계 (Citrate cycle), 3단계 (전자전달과 산화적 인산화)

1) β-oxidation of saturated fatty acids has four basic steps
(포화지방산의 산화는 기본적인 4단계로 진행된다)

2) The four steps are repeated to yield acetyl-CoA and ATP

* Palmitoyl-CoA + CoA + FAD + NAD^+ + H_2O ⟶
  miristoyl-CoA + Acetyl-CoA + $FADH_2$ + NADH + H^+
* Palmitoyl-CoA + 7CoA + 7FAD + $7NAD^+$ + $7H_2O$ ⟶
  8 acetyl-CoA + $7FADH_2$ + 7NADH + $7H^+$

* **Palmitoyl-CoA + 7CoA + $7O_2$ + 28Pi + 28ADP**
  8 acetyl-CoA + 28 ATP + $7H_2O$

☞ **NADH → 2.5 분자의 ATP 생성, FADH → 1.5ATP**

3) Acetyl-CoA can be further oxidized via the citric acid cycle

* 8 acetyl-CoA + $16O_2$ + 80Pi + 80 ADP ⟶
  8 CoA + 80 ATP + 16 H_2O + 16 CO_2
* Palmitoyl-CoA + 23 O_2 + 108 Pi + 108 ADP ⟶
  CoA + 108 ATP + 16 CO_2 + 23 H_2O

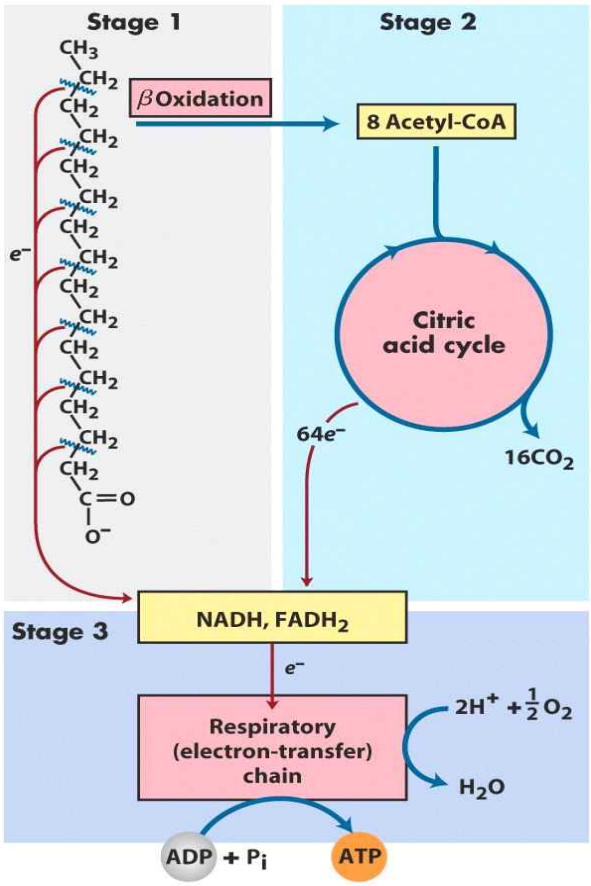


Fig. Stages of fatty acid oxidation.

Stage 1 : β-oxidation, Stage 2 : Citric acid cycle, Stage 3 : Electron transfer chain

TABLE 17-1 Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to CO_2 and H_2O

Enzyme catalyzing the oxidation step	*Number of NADH or $FADH_2$ formed*	*Number of ATP ultimately formed**
Acyl-CoA dehydrogenase	7 $FADH_2$	10.5
β-Hydroxyacyl-CoA dehydrogenase	7 NADH	17.5
Isocitrate dehydrogenase	8 NADH	20
α-Ketoglutarate dehydrogenase	8 NADH	20
Succinyl-CoA synthetase		8†
Succinate dehydrogenase	8 $FADH_2$	12
Malate dehydrogenase	8 NADH	20
Total		108

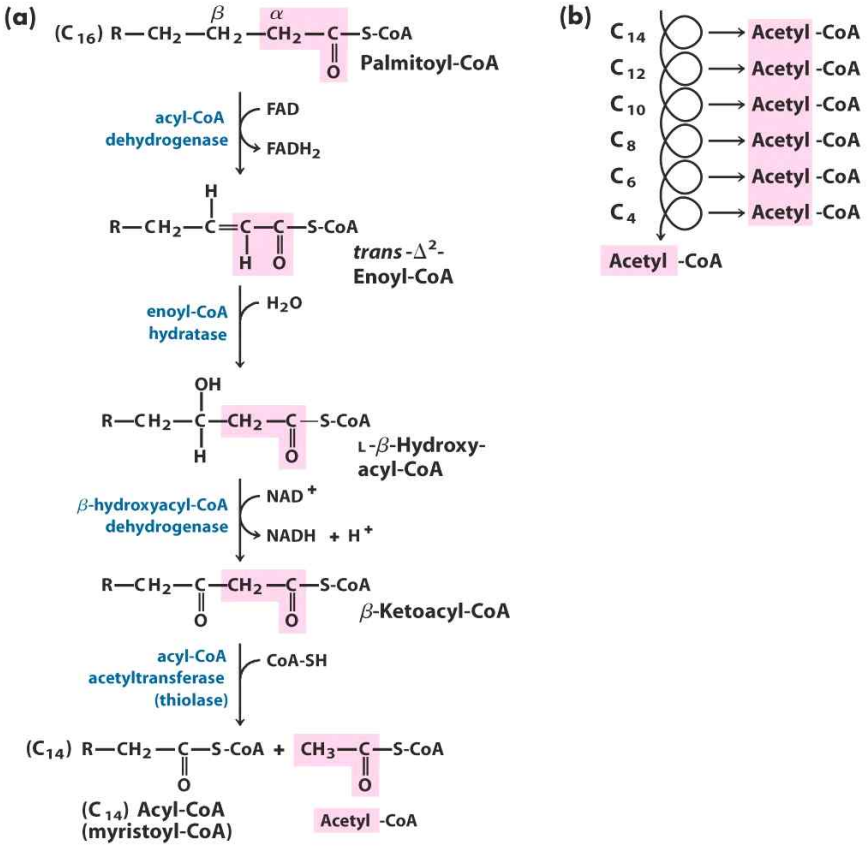


Fig. Fatty acid oxidation (β-oxidation) pathways

◎ **Medium-chain acyl-CoA dehydrogenase (MCAD) 결핍지환**

- 미국(북유럽인)의 지방산 분해에서 가장 흔한 유전적 결함으로 심각한 질환 유발

4) Oxidation of unsaturated fatty acids requires two additional reactions

* cis-form unsaturated fatty acid ⟶ trans-form unsaturated fatty acid

[enoyl-CoA isomerase]

*** Oxidation of polyunsaturated fatty acid**

[2,3-dienoyl-CoA reductase, enoyl-CoA isomerase]

5) Oxidation of odd chain fatty acids requires three extra reactions

* Odd number fatty acids ⟶ **propionyl CoA (최종생성물)**
(β-oxidation)

*** In Animal**

[carboxylase]

Propionyl-CoA ⟶ D-methylmalonyl-CoA

[CO_2, ATP, biotin]

[epimerase]

L-methylmalonyl-CoA

vitB12

[mutase]

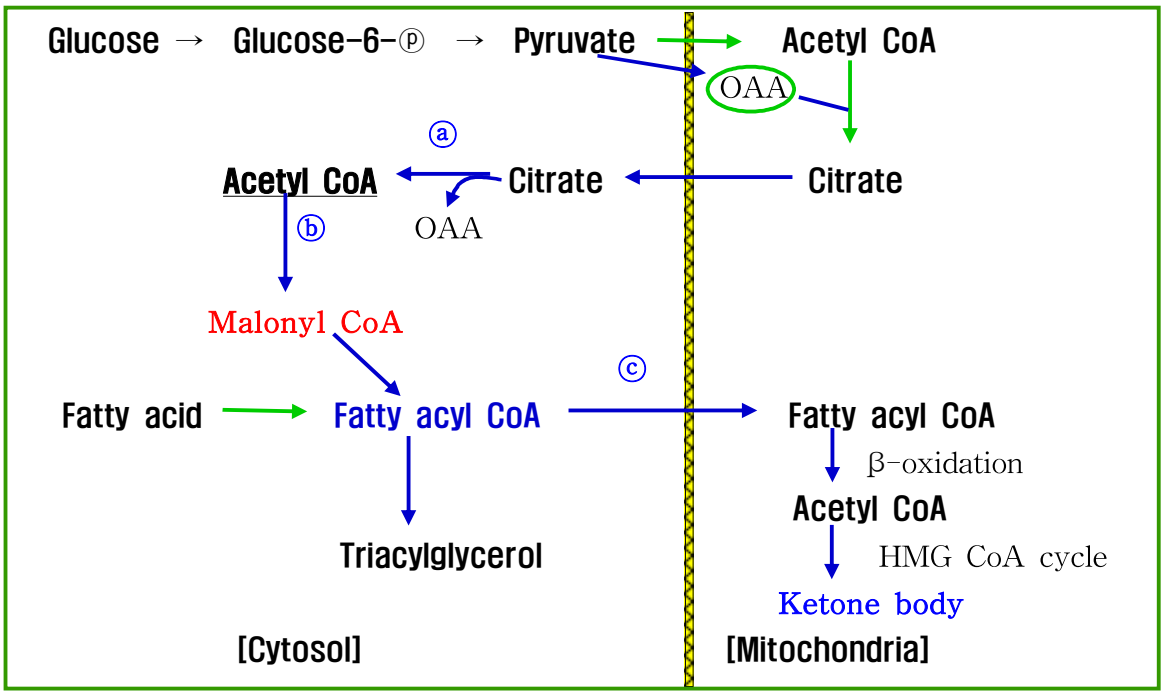
Succinyl-CoA (TCA 회로의 중간산물)

3. Regulation of fatty acid metabolism

◎ Fatty acyl-CoAs formed in the cytosol have two main pathways
- In mitichondria : β-oxidation
- In cytosol : conversion into triacylglycerols and phospholipids

1) Fatty acid oxidation is tightly regulated : malonyl-CoA

① 고당질식이 (Glucose → triacylglycerol)



ⓐ Citrate lyase : citrate에 의하여 활성화
ⓑ Acetyl CoA carboxylase : citrate에 의하여 활성화
ⓒ Carnitine acyltransferase I : malonyl CoA에 의하여 불활성화

◎ **세포내 탄수화물농도가 높다 : 인슐린분비 증가**
β 산화는 불필요하게 되고 → Malonyl-CoA가 카르니틴 아실 transferase I 의 활성을 억제하여 지방산이 미토콘드리아 내로 들어가는 것을 방해한다.

◎ **Fatty acyl-CoA dehydrogenase 의 유전적 결핍**
- 중성지방이 근육수축을 위한 주요에너지원
- 지방산을 산화시키는 기능의 저하는 심각한 건강문제를 초래
- **MCAD (medium-chain acyl-CoA dehydrogenase) : 북유럽에 가장 흔한 유전적 결함**

◎ **과산화소체(peroxisome) : β 산화수행**

◎ **ω 산화 : 오메가탄소에서 산화**

2) 호르몬은 지방산 대사를 조절한다.

- 지방산의 산화는 혈액에 있는 지방산의 농도에 의하여 주로 조절된다.
- 혈액내의 지방산 농도는 hormone-sensitive triacylglycerol lipase에 의하여 지방조직내의 triacylglycerols의 가수분해에 의하여 조절된다.

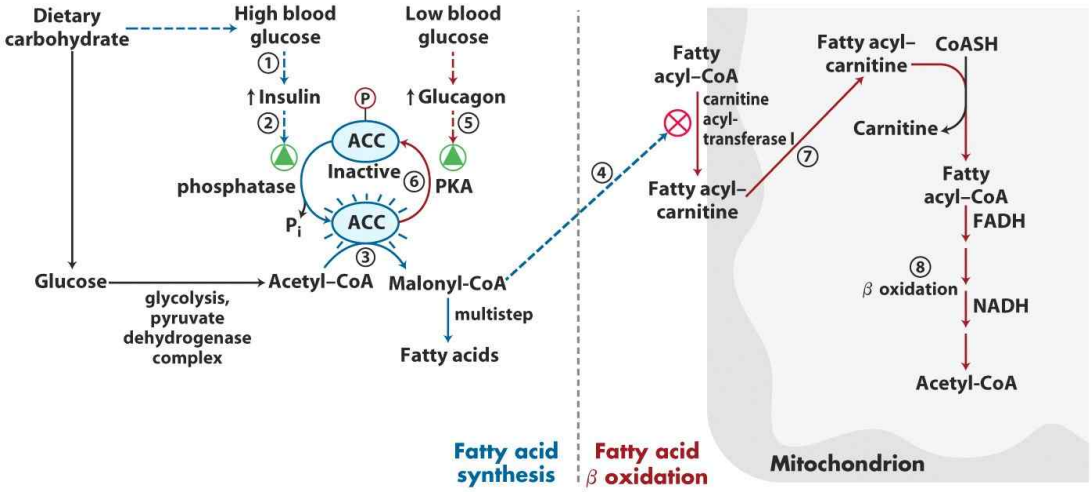


Fig. Coordinated regulation of fatty acid synthesis and breakdown

4. Ketone bodies (케톤체)

1) Ketone bodies formed in the liver are exported to other organ

* brain & red muscle등에서 분해

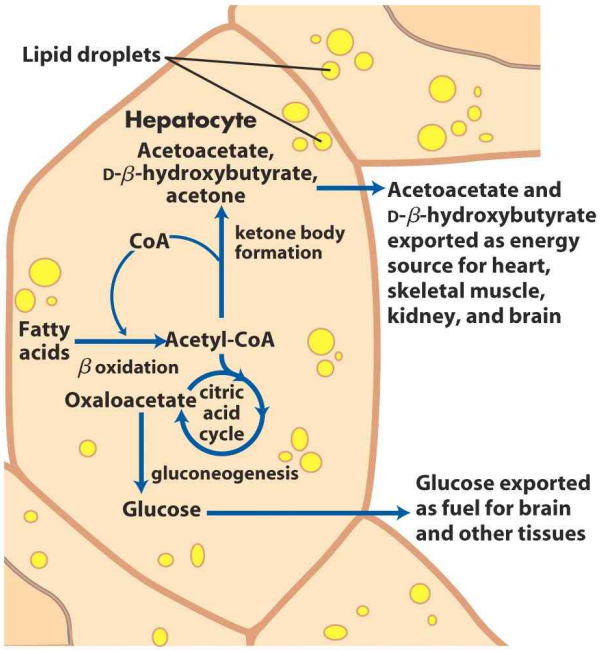


Fig. Ketone body formation and export from the liver.

2) Extrahepatic tissues use ketone bodies as fuels

3) Ketone bodies 의 특성

- very soluble in blood and urine
- tolerate at high concentration
- diffuse rapidly through membrane
- rapid metabolized to CO_2 and H_2O

4) Ketone bodies are overproduced in diabetes and during starvation

* In liver : ketone body를 이용하지 못함

*** kidney, muscle, brain에서 중요한 에너지원**

① 고지방식이 (Ketone body 생성)

- Acetyl-CoA ⟶ Ketone body로 전환
- **Kidey and liver에 있는 미토콘드리아에서 일어난다.**

Triacylglycerol (중성지방)

↓ **β-oxidation**

Acetyl CoA(high conc.) ⟶ **Acetyl CoA carboxylase** 활성저해

↓

Malonyl CoA 수준저하

↓

Carnitine acyltransferase I 활성화

↓

Triacyl CoA ⟶ **mitochondria 막을통과**

↓ ☜ β-oxidation

Acetyl CoA 축적

↓

Ketone body ⟵ **HMG-CoA cycle**

② 당뇨와 절식시 (Diabetes and fasting)

[세포내 탄수화물농도가 낮다 : 글루카곤 분비]

[당신합성반응이 증가된다.]

↓

TCA cycle이 느려진다 (why : oxaloactate 고갈)

↓

Acetyl-CoA 축적 → → acetoactate의 생성 증가

↓

Ketone bodies 생성 증가

5. 지질생합성(Biosynthesis of lipid)

1) 지방산 생합성(Biosynthesis of fatty acids)

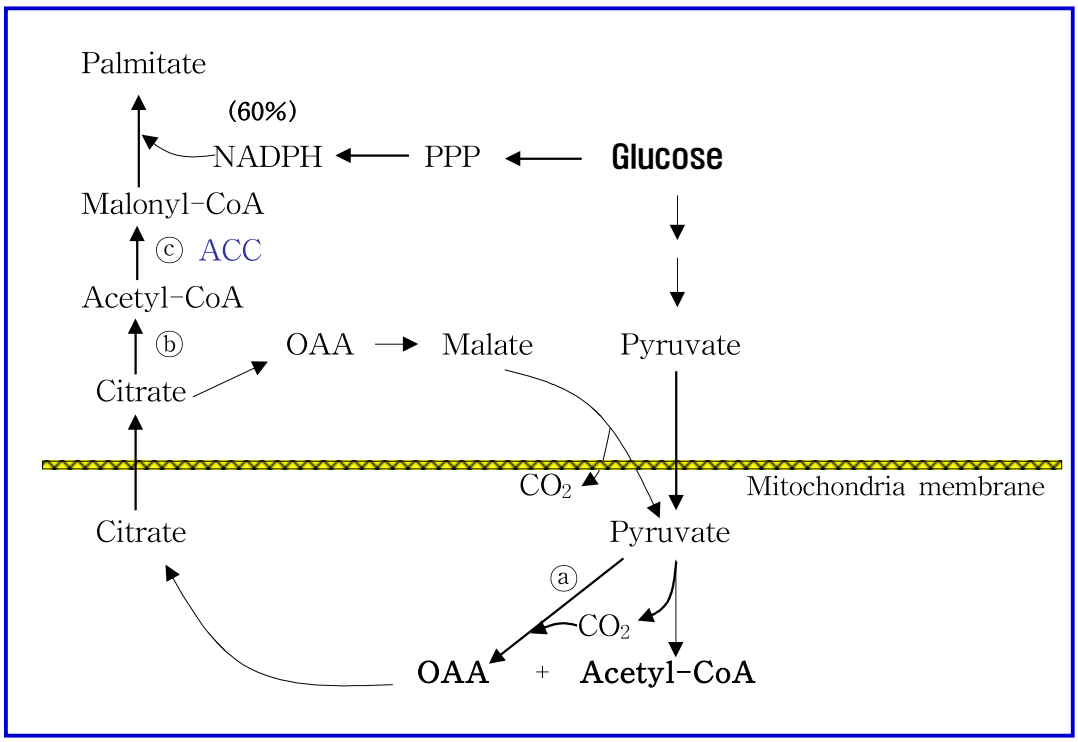
① **Malonyl CoA** is formed from acetyl CoA and bicarbonate

* Enzyme : **Acetyl-CoA carboxylase (ACC)**
* Activator : **citrate**
* Inhibitor : **glucagon, epinephrine, palmitoyl-CoA**

② **The fatty acid synthase complex has seven different active sites**
(지방산합성효소 복합체는 7개의 다른 활성화자리를 가지고 있다)

* Acyl carrier protein (ACP) : 아실기 운반 단백질
* Prosthetic group(보결원자단) : 4′phosphopantetheine
  - intermediate in the synthesis of coenzyme A

[Palmitate (C16:0) Biosynthesis]



③ The fatty acid synthesis reactions are repeated to form palmitate
(지방산 합성반응은 팔미트산을 형성하기 위해서 반복된다)

* 1st step : the formation of seven **malonyl-CoA** molecules
  - 7 Acetyl-CoA + $7CO_2$ + 7ATP ⟶ 7 malonyl-CoA + 7ADP + Pi
* 2nd step : the seven cycles of condensation and reduction
  - Acetyl-CoA + 7 malonyl-CoA + 14NADPH + $14H^+$ ⟶
    palmitate + $7CO_2$ + 8CoA + $14NADP^+$

* **The overall process (전체적인 과정) :**

- **8 Acetyl-CoA + 7ATP + 14NADPH + $14H^+$** ⟶

palmitate + 8CoA + $6H_2O$ + 7ADP + 7Pi + $14NADP^+$

* **ATP** is required to attach CO_2 to acetyl CoA to make malonyl-CoA
* **NADPH** is required to reduce the double bonds
* **Key enzyme** : acetyl-CoA carboxylase (ACC)
* **Malonyl CoA** : inhibits carnitine acyltransferase I

④ **Acetate is shuttled out of mitochondria as citrate**

⑤ Fatty acid biosynthesis is tightly regulated by acetyl-CoA carboxlase
Long chain fatty acids are synthesized from palmitate

⑥ Some fatty acids are desaturated by fatty acyl-CoA desaturase

⑦ Triacylglycerol biosynthesis in animals is regulated by hormone(insulin)
(동물에서 중성지방의 생합성은 인슐린에 의해서 조절된다)

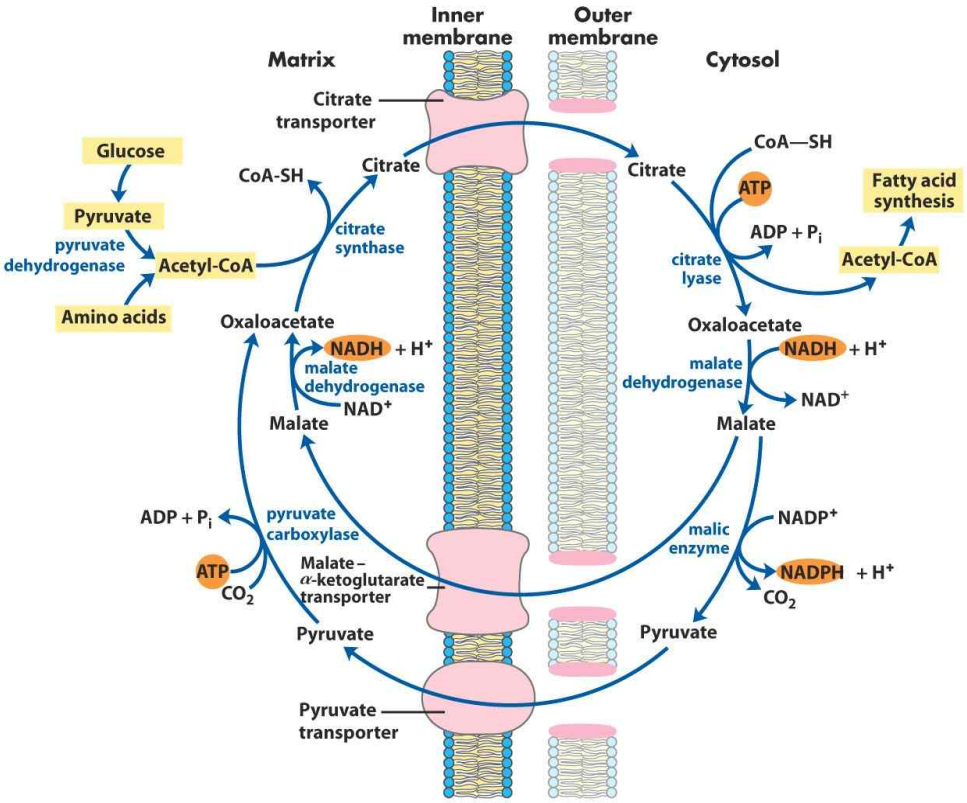


Fig. Shuttle for transfer of acetyl groups from mitichondria to the cytosol

2) 불포화 지방산의 생합성(Biosynthesis of unsaturated fatty acid)

① 최초의 이중결합 도입

* 호기적경로 : In animal

$$\text{Stearoyl-CoA} + O_2 + \text{NADPH} \xrightarrow[\text{desaturase}]{} \text{Oleoyl-CoA} + \text{NADP}^+ + 2H_2O$$

② 혐기적 경로 : eubacteria (진균류)

* Cis-이중결합이 C_{10} 수준에서 도입

③ **부가적 이중결합의 도입 (in plant)**

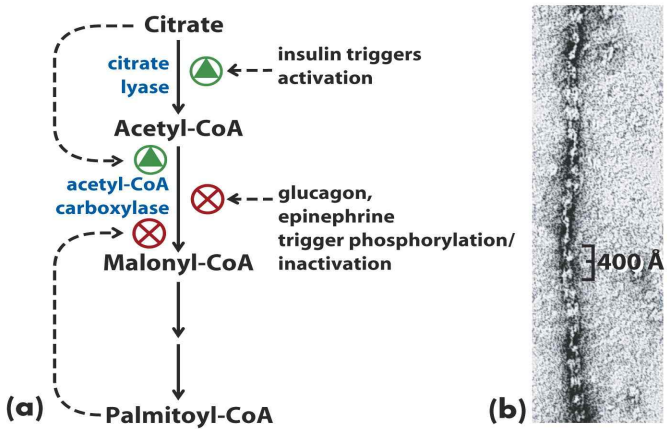
* C18 : 2(9,12) $\xrightarrow{-2H}$ C18 : 3(6,9,12) $\xrightarrow{+C_2}$ C20 : 3(8,11,14) $\xrightarrow{+2H}$ C20 : 4(5,8,11,14)
  linoleic　　ɣ-linolenic　　Homo-ɣ-linolenic　　arachidonic

④ Desaturase (불포화효소)

* 포유동물 : microsome에 존재
  기　　질 : acyl-CoA
  보조효소 : NADPH, NADH, O_2

*** 불포화단계는 카르복시기의 방향으로 일어난다.**

3) Regulation of fatty acid synthesis (지방산합성조절)



4) 세포막 대사 (Membrane metabolism)

① Phospholipid (인지질)

* 지질 생합성은 SER에서 일어난다.
* 인지질의 대사회전(turnover)은 빠르다.
* 지질생합성에는 **CTP가 중요**(**CDP-diacylglycerol**)
* Phosphatidylethanolamine $\xrightarrow[\text{SAM (methyl group donor)}]{}$ Phophatidylcholine
* **인지질의 종류** : Phosphatidylcholine(lecithin), Phosphatidyl ethanolamine, Phosphatidyl serine, Phosphatidyl glycerol, Cardiolipin

② Sphingolipid

* **Sphingosine (아미노알콜), ceramide(스핑고신유도체)**

* Palmitoyl-CoA + Serine ⟶ **Ceramide** → Galactocerebroside
  Sphingomyelin ← Ceramide → Glucosylceramide

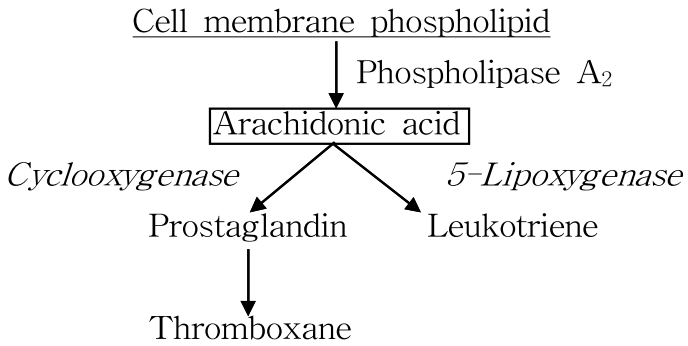
  - Glucosylceramide : ceramide + UDP-glucose
  - Sphingomyelin : ceramide + phosphatildylcholine
  - Galactosylceramide : ceramide + UDP-galactose

* Sulfatide : Galactocerebroside + PAPS

* 황산염 공여체 : PAPS(3′-Phosphoadenosine-5′-phosphosulfate)

* **Spingolipid(스핑고지질)은 lysosome 내에서 분해된다**

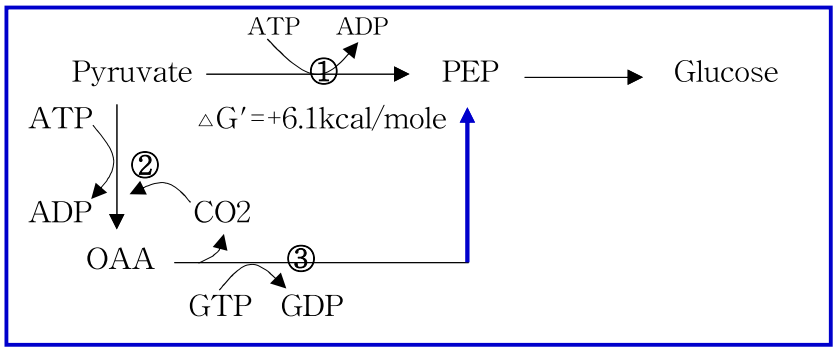
5) Eicosanoid Metabolism



[Pathway from arachidonic acid to leukotrienes]

6. The comparison of glucose and fatty acid synthesis

1) Glucose synthesis (Gluconeogenesis)



* The overall reaction :

  Pyruvate + 2ATP ⟶ PEP + 2ADP + Pi

  △G′=+0.2kcal/mole

① pyruvate kinase

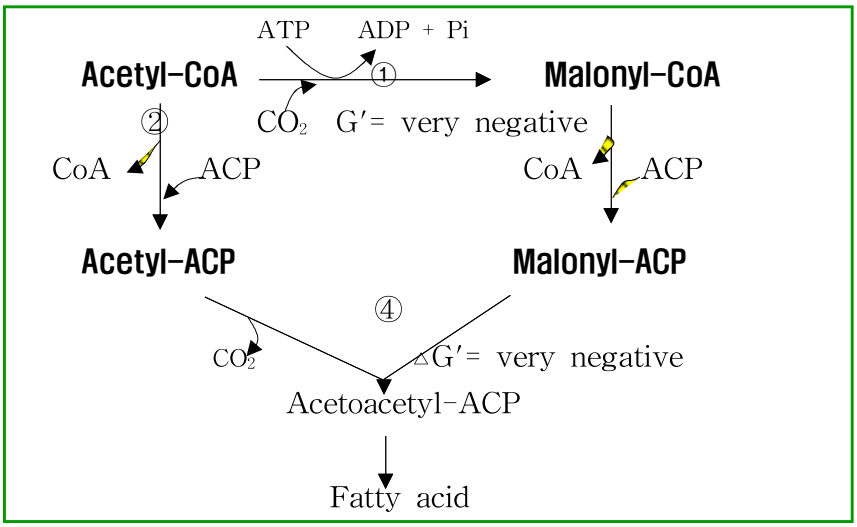
② pyruvate carboxylase

③ PEP carboxylase

2) Fatty acid synthesis

* 2Acetyl-CoA ⟶× Acetoactyl-CoA

△G′=+7kcal/mole



① Acetyl-CoA carboxylase ② Acetyl transferase

③ Malonyl transacylase ④ Keto acyl synthetase

7. Cholesterol Metabolism

1) Cholesterol synthesis

* synthesized in the liver
* Cholesterol is made from acetyl-CoA
* 혈액내의 cholesterol수준은 **LDL receptor 에 의해 조절**

① **Synthesis of mevalonate from acetate**

- 2**Acetyl-CoA** ⟶ **Acetoacetyl-CoA**

CoA

β-Hydroxyl-β-methylglutaryl-CoA

[HMG-CoA]

HMG-CoA reductase

2NADPH

Mevalonate

② **Mevalonate** ⟶ activated **isoprene unit**(isopentenyl pyrophosphate)

③ **Isopentenyl pyrophosphate** ⟶ **Squalene**

④ **Squalene** ⟶ **Lanosterol** ⟶ **Cholesterol**

* Cholesterol is exported in one of two forms : bile acids or cholesteryl esters

Fatty acyl-CoA CoA-SH

* **Cholesterol** ⟶ **Cholesteryl ester**

Acyl-CoA-cholesterol acyl transferase(ACAT)

* Cholesterol + lecithin ⟶ cholesteryl ester + lysolecithin

Lecithin-cholesterol acyl transferase(LCAT)

* Cholesteryl esters enter cells by **receptors-mediated endocytosis**

2) 콜레스테롤 생합성의 조절(Regulation of cholesterol biosynthesis)

* Cholesterol synthesis is a complex and energy expensive process
* Cholesterol production is regulated by intracellular cholesterol conc. and by the hormone glucagon and insulin

◎ **High intracellular Cholesterol**

- ACAT 활성을 증가
- HMG-CoA reductase 합성과 활성을 저해
- 간 외의 다른 조직에서 cholesterol 합성을 저해
- LDL 수용체 합성 억제
- Blood로부터 cholesterol의 흡수를 느리게 한다.

◎ **LDL 수용체의 결핍은 고콜레스테롤혈증과 동맥경화증을 일으킨다.**

◎ **Cholesterol degradation**

Cholesterol ⟶⟶⟶ Cholic acid ⟶⟶ Glycocholate(담즙산염)
Glycine

◎ Regulation of cholesterol biosynthesis]

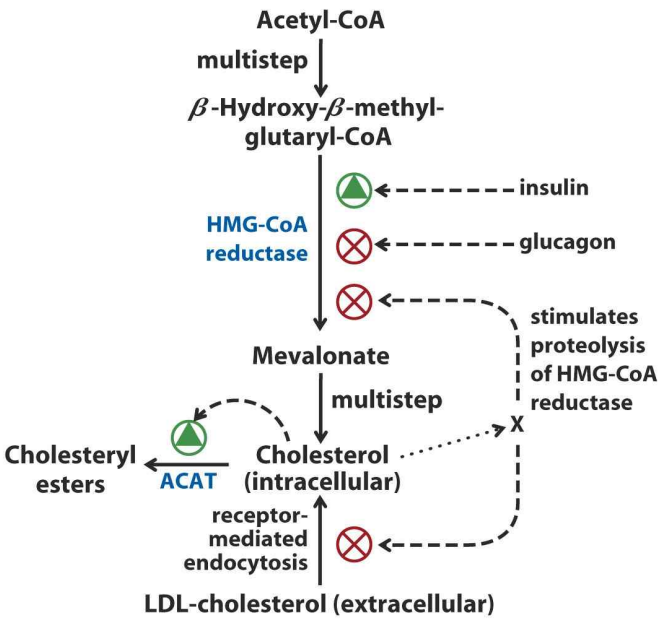
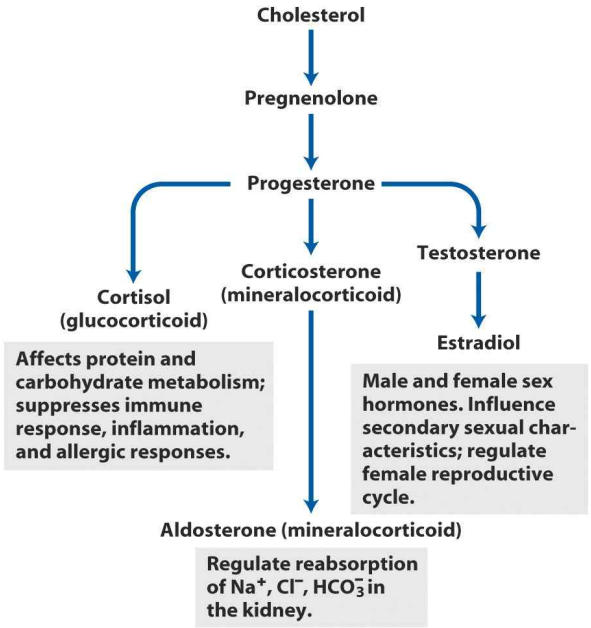


Fig. Regulation of cholesterol formation balances synthesis with dietary uptake

3) Steroid Hormone synthesis

- Some steroid hormones derived from cholesterol
- Cholesterol 생합성의 중간체는 여러 가지 합성경로로 간다.

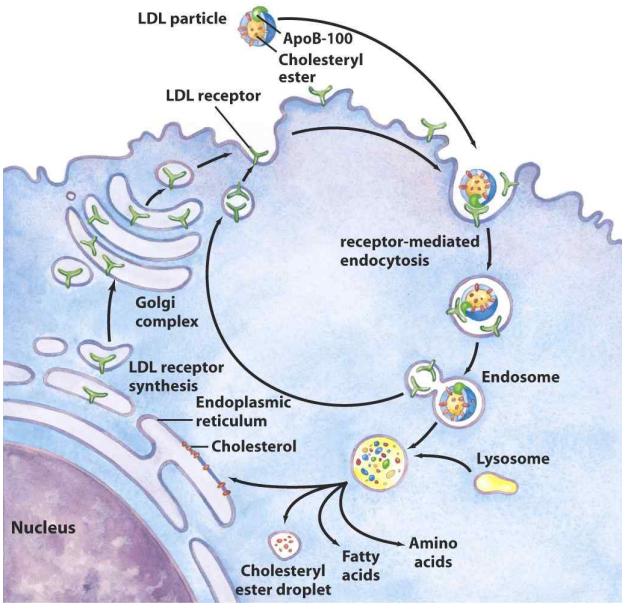


◎ 글루코코르티코이드 : 단백질과 탄수화물대사에 영향을 줌

- 면역반응, 염증반응, 알레르기 반응 등을 억제함

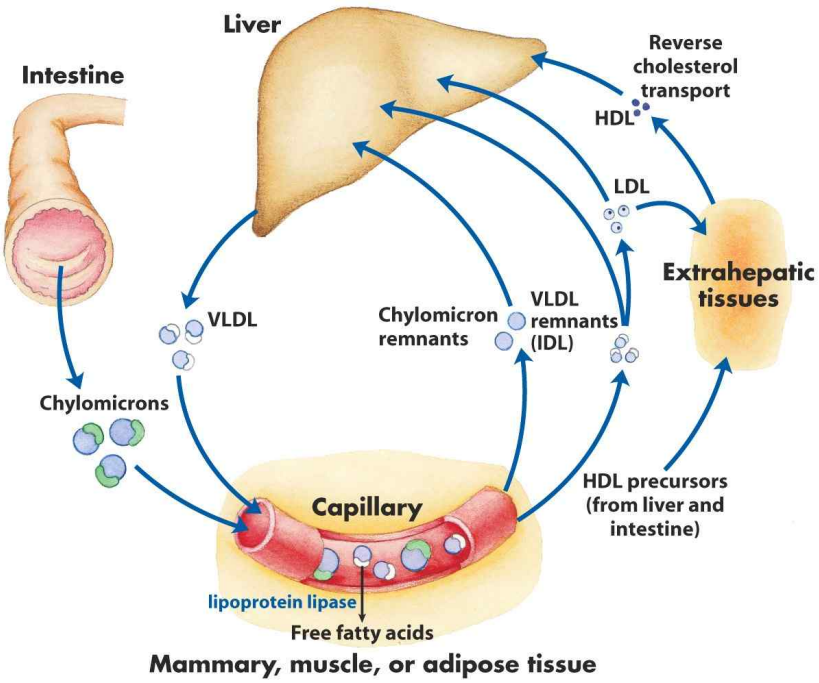
4) Cholesterol 흡수

- Uptake of cholesterol by receptor-mediated endocytosis

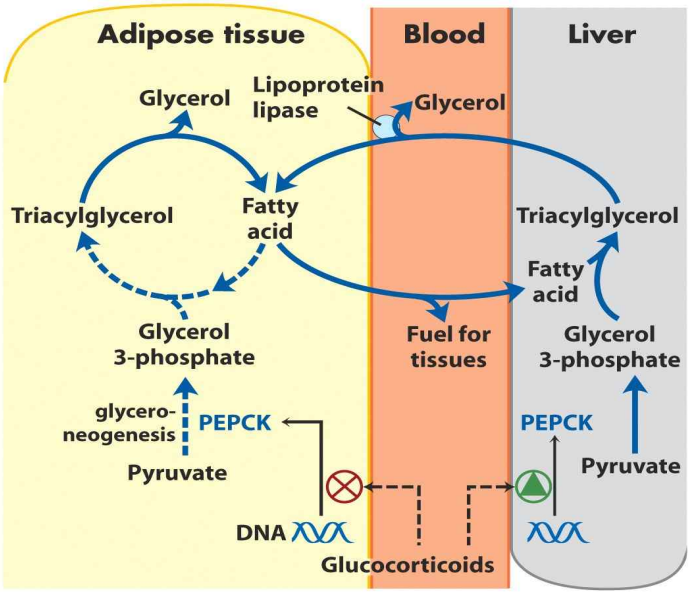


[지질단백질과 지질운반]

- 지질은 혈류내에서 기능이 다르며, 단백질과 지질의 조성에 따라 밀도가 다른 지질단백질 상태로 운반된다
- 간에서 일부 cholesterol은 담즙산염으로 전환된다.



[글리세롤 신합성의 조절]



- 글루코코르티코이드 호르몬은 간에서 글리세롤 신합성과 glucose신합성을 촉진시키고 지방조직에서는 글리세롤 신합성을 억제한다
- PEPCK : PEP carboxykinase