Chapter 12 Amino acid oxidation and the production of urea
(아미노산의 산화와 요소 생산)

* Metabolic fates of amino groups(아미노기의 대사운명)
  - Transamination : aminotransferase, transaminase
* Nitrogen excretion and the urea cycle
* Pathways of amino acid degradation(아미노산의 분해경로)
  - Glucose alanine cycle
* **아미노산 산화가 일어나는 환경**

i) The amino acids released during protein breakdown will undergo oxidative degradation if they are not need for new protein synthesis.

ii) The amino acids ingested in excess of the body's need s for protein synthesis, the surplus may be catabolized (amino acid can not be stored)

iii) During starvation and in diabetes mellitus, body proteins are call upon as fuel

◎ 육식동물은 식후 필요에너지의 90%까지 아미노산의 산화를 통하여 얻는 반면 초식동물의 경우는 극히 일부를 아미노산의 산화로부터 얻는다.

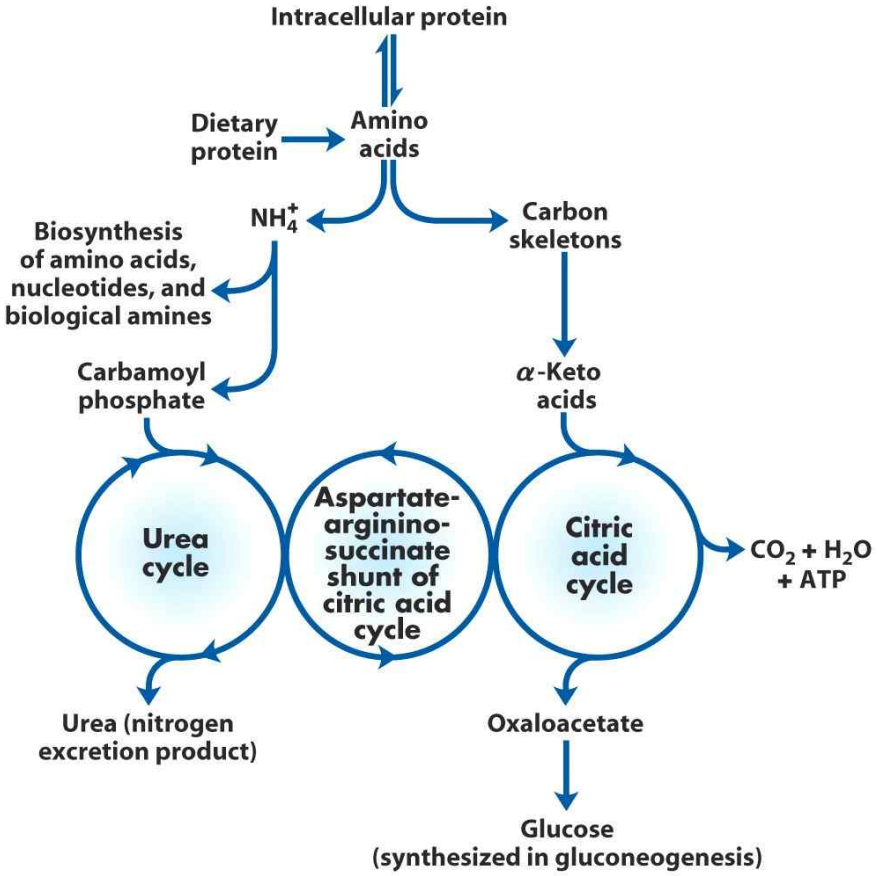


Fig. Overview of amino acid catabolism in mammals

1. Metabolic fates of amino groups

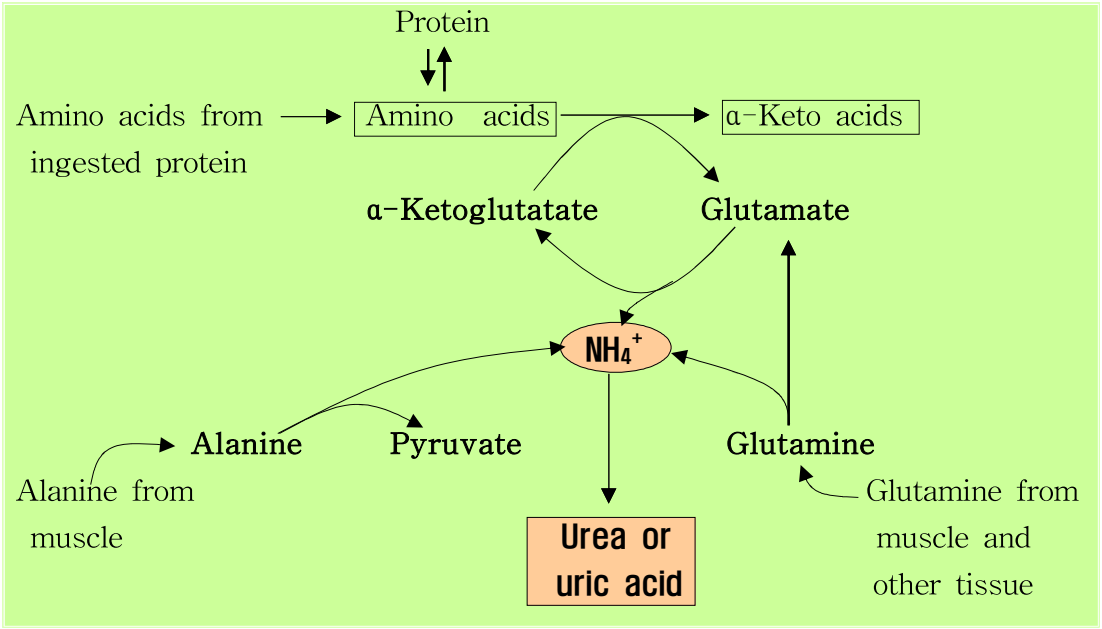


Fig. Overview of amino group catabolism in the verteberate liver.
Excess NH_4^+ is excreted as urea or uric acid

2. Protein degradation(단백질 분해)

* Dietary protein is enzymatically degraded to amino acids

1) In Stomach

- Dietary protein → gastrin release → HCl
  pepsinogen → pepsin
  [removed 42 amino acid residues]

- Pepsin hydrolyzes ingested proteins at peptide bonds on the amino-terminal side of the aromatic amino acid residues Tyr, Phe, Trp.

2) In small intestine

Acidic stomach contents
↓
Small intestine (십이지장) ☜ Secretin release
↓
Bicarbonate (pH increase) → Cholecystokinin release (십이지장)
↓
Pancreatic enzymes release
(Trypsin, Chymotrypsin, Carboxypeptidase)

◎ Secretin : [중탄산염분비촉진], Cholecystokinine : [소화효소분비촉진]

◎ Trypsinogen, Chymotrypsinogen, Procarboxypeptidase (zymogen)

↓ ← Free trypsin

Trypsin, Chymotrypsin, Carboxypeptidase (active form)

◎ Trypsinogen —(enteropeptidase)→ trypsin

◎ **Trypsin inhibitor** effectively prevents premature production of free proteolytic enzymes within the pancreatic cells.

◎ **Celiac disease (만성소화 장애증, 복부질병)**

Intestinal enzymes are unable to digest certain water-soluble proteins of wheat, particularity gliadin.

3. Amino acid oxidation (아미노산 산화)

1) **Pyridoxal phosphate participates in the transfer of α-amino groups to α-ketoglutarate**

① Transamination (아미노기 전달반응)

- 어떤 아미노산의 아미노기를 keto acid에 전달하여 새로운 아미노산을 생성하고 본래의 아미노산은 keto acid가 되는 반응
- **이 반응은 cytosol에서 일어난다.**
- **비필수 아미노산을 생체내에서 만들어 주는 중요한 기능을 한다.**

◎ Enzyme : Aminotransferase or transaminase

Amino acid ① + Keto acid ② ⇄ Keto acid ① + Amino acid ②

(donor) (acceptor) *Aminotransferase or transaminase*

◎ α-Ketoglutarate + L-amino acid ⇄ L-glutamate + α-Keto acid

glutamate aminotransferase

◎ α-Ketoglutarate + L-Alanine ⇄ L-glutamate + pyruvate

alanine aminotransferase

◎ **Pyridoxal phosphate : Pyridoxal-5-phosphate (PLP)**

- the coenzyme form of pyridoxine or vit B6
- function as an intermediate carrier of amino group at the active site of aminotransferases.

i) 아미노산의 α-amino 기와 함께 안정화된 쉬프염기(알디민)부가물을 형성

ii) 반응 중간물질을 안정화시키기 위하여 효과적인 전자 흡수체로 작용

◎ Pyridoxal phosphate + L-amino acid ⇄ Schiff's base (intermediate)

Schiff's base ⇄ pyridoxamine-Ⓟ + α-Keto acid [transamination]

Schiff's base ⇄ pyridoxal-Ⓟ + D-amino acid [racemization]

Schiff's base ⇄ pyridoxal-Ⓟ + Amine [decarboxylation]

↘ CO_2

- 중간산물(Intermediate) : Quinonoid

2) Glutamate releases its amino group as ammonia in the liver
(간에서 Glutamate 는 암모니아로서 아미노기를 방출한다)

① **Oxidative deamination** : catalyzed by **L-glutamate-dehydrogenase**
(present only in mitochondrial matrix)

◎ Glutamate + H_2O ⇄ α-ketoglutarate + NH_4^+

$NAD(P)^+$ $NADPH + H^+$

- GTP : negative modulator
- ADP : positive modulator

② **Transdeamination** : (aminotransferase + glutamate dehydrogenase)

Amino acid → α-ketoglutarate (**aminotransferase**) → α-Keto acid

α-ketoglutarate → glutamate (**glutamate dehydrogenase**) → $NADH + H^+ + NH_4^+$

NAD^+

◎ A few amino acids bypass the transamination pathway and undergo direct oxidative deamination

3) Glutamine은 혈류에서 암모니아를 운반한다.

* Ammonia is quite toxic to the animal tissues
* Glutamine is a major transport form of ammonia
* Glutamine은 **암모니아의 무독성 수송 형태로 많은 생합성반응의 아미노기의 공여체**로 작용한다.

Glutamate —(ATP, ADP, NH_4^+, Pi)→ Glutamine

Glutamine synthetase

Glutamine —(H_2O, NH_4^+)→ Glutamate → urea

Glutaminase

◎ **Glutamine** is a nontoxic, neutral compound that can readily pass through cell membrane, whereas glutamate, which bears a negative charge, cannot.

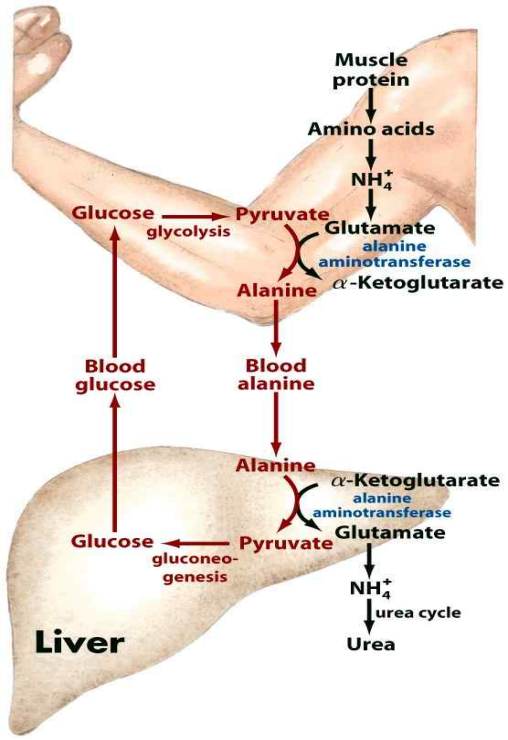
4) Alanine은 근육에서 간(liver)으로 암모니아를 운반한다.

* **Alanine 은 glucose-alanine cycle** 기전으로 무독성의 암모니아를 간으로 운반하는 특별한 역할을 한다.
* In muscle and certain other tissues that degrade amino acids for fuel, amino groups are collected in glutamate by transamination.
* Glutamate는 간으로 운반되기 위하여 glutamine으로 전환될 수 있다

*** Glucose-Alanine cycle**

- 알라닌은 근육에서 간으로 **암모니아 및 pyruvate의 운반체**로 작용한다.
- 간에 운반된 알라닌은 아미노기전이효소(alanine aminotransferase.)에 의해 pyruvate와 ammonia로 재 전환된다.
- Pyruvate는 새로운 glucose를 합성하는데 이용되고 NH_4^+은 간에 방출 되면 urea cycle에 의해서 요소로 전환되어 뇨 중으로 배출된다.

[Glucose-alanine cycle]



* 근육은 아미노질소로부터 요소를 합성할 수 없기 때문에 **glucose-alanine 회로**가 아미노질소를 간으로 전달하는데 이용된다.

5) Ammonia is toxic to animals (암모니아는 동물에 독성이 있다)

* The major toxic effects of ammonia in brain probably involve changes in **cellular pH and depletion of certain citric acid cycle intermediates**.
* Most of the ammonia generated in catabolism is present as **NH_4^+ at neural pH**

3. Nitrogen excretion and the urea cycle

1) Urea is formed in the liver

2) **The production of urea from ammonia involves five enzymatic steps**

- **Urea cycle begins** inside the mitochondria of hepatocytes, but the three steps occur in the **cytosol.**

HCO_3^- 2ATP 2ADP + Pi

NH_4^+ → Carbamoyl phosphate

Carbamoyl phosphate synthetase I

3) 요소회로는 글루코스 신생합성과 연결된다.

- 푸마르산은 glucose 합성의 전구물질 : fumarate → malate → oxaloacetate

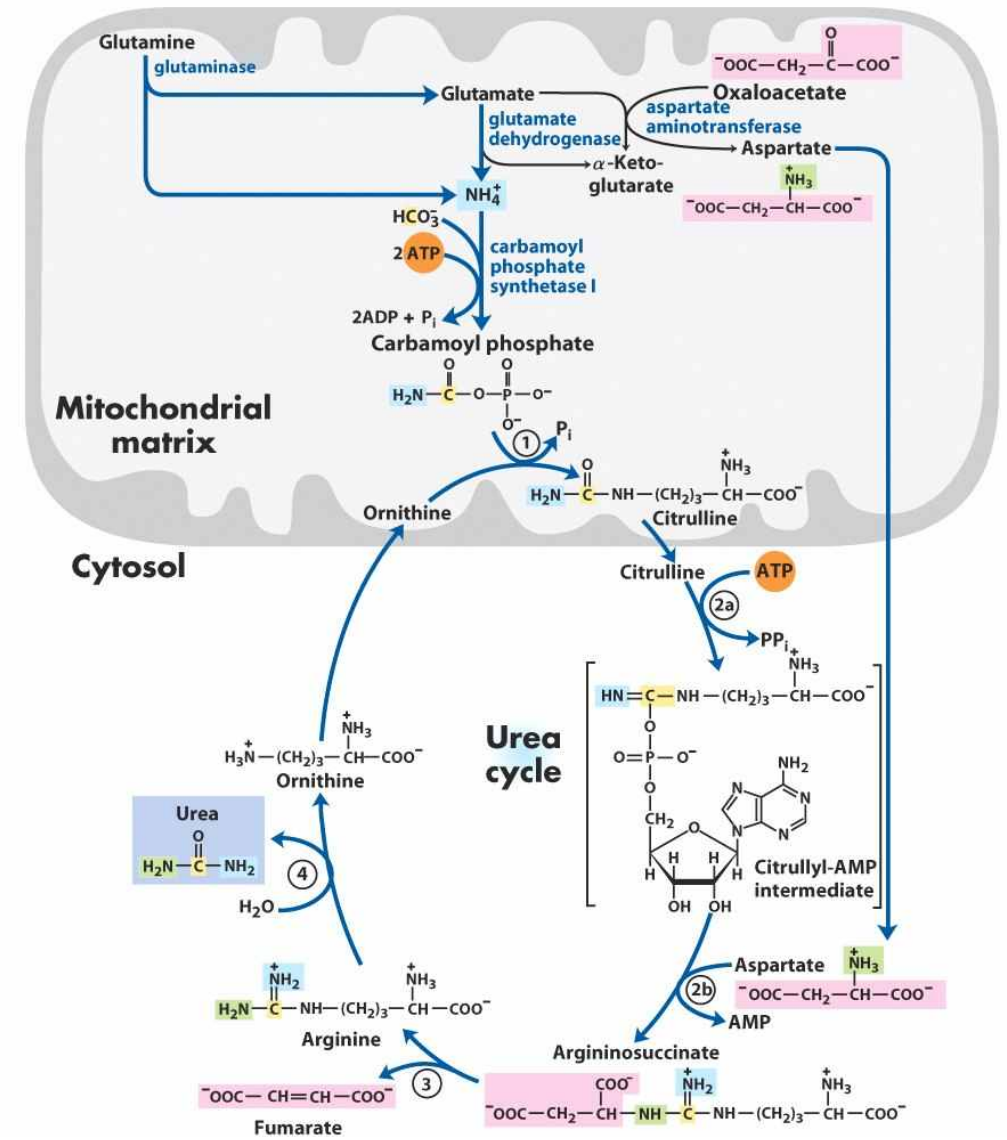


Fig. Urea cycle and reactions that feed amino groups into the cycle

3) The citric acid and urea cycles are linked

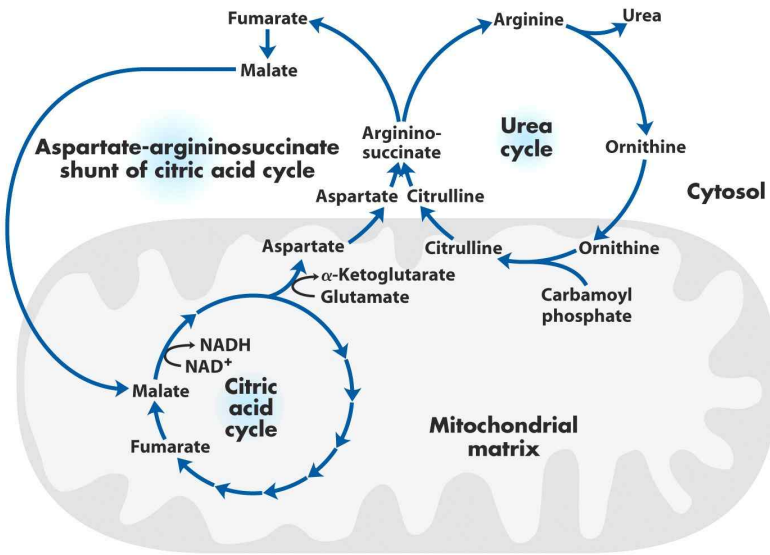


Fig. Links between the urea cycle and citric acid cycle

4) The activity of the urea cycle is regulated at two levels

① Starvation and high protein diet

- produce high level of the urea cycle enzymes.

② **Carbamoyl phosphate synthetase I**

- is allosterically activated by **N-acetylgluamate**

5) The urea cycle is energetically expensive (4ATP 소모)

$2NH_4^+ + HCO_3^- + 3ATP^{4-} + H_2O \longrightarrow$

$\text{Urea} + 2ADP^{3-} + 4Pi^{2-} + AMP^{2-} + 2H^+$

4. Pathways of amino acid degradation (아미노산의 분해경로)

* 일부아미노산은 **glucose로 전환**되고 일부아미노산은 **케톤체**로 전환된다.

1) Several enzymes cofactors play important roles in amino acid catabolism

① **Biotin** : 다양한 **카르복실화 반응**에서 **이동성카르복실기 운반체**로 작용

② **Tetrahydrofolate(THF)** : **활성화된 1-탄소단위를 운반**

- 모든 탄소에 대해서 1-탄소단위체의 공여체 와 수용체 역할

③ **S-Adenosylmethionine (SAM)** : 메틸기의 공여체 작용

- Methionine + ATP $\longrightarrow$ S-Adenosylmethionine + PPi + Pi

Methionine adenosyltransferase

◎ These cofactors are used to transfer one-carbon group in different oxidation state

◎ Tetrahydrobiopterin (reduced form) : 산화환원 Cofactor

2) Ten amino acids are degraded to acetyl-CoA

① Alanine, glycine, serine, cysteine, tryptophan → PVA

② Tryptophan, lysine, phenylalanine, tyrosine, leucine. isoleucine

↓

Acetyl-CoA

③ **Tryptophan**은 다른 중요한 분자의 생합성을 위한 전구체로서 작용한다.
(niacin, indole acetate, serotonin)

- Nicotinate(niacin) : precursor of NAD and NADP
- Indole acetate : plant growth hormone
- Serotonin : neurotransmitter(신경전달물질)

④ **Phenylalanine** catabolism

O_2, NADH NAD^+ H_2O

- Phenylalanine → Tyrosine

phenylalanine hydroxylase

◎ **Phenylketonuria (PKU) :**

- 페닐알라닌 수산산효소가 결핍되어 phenylalanine 분해되지 않고 축적되어 phenylpyruvate로 뇨 중으로 배설된다.
- 심각한 정신지체 증상을 나타낸다.

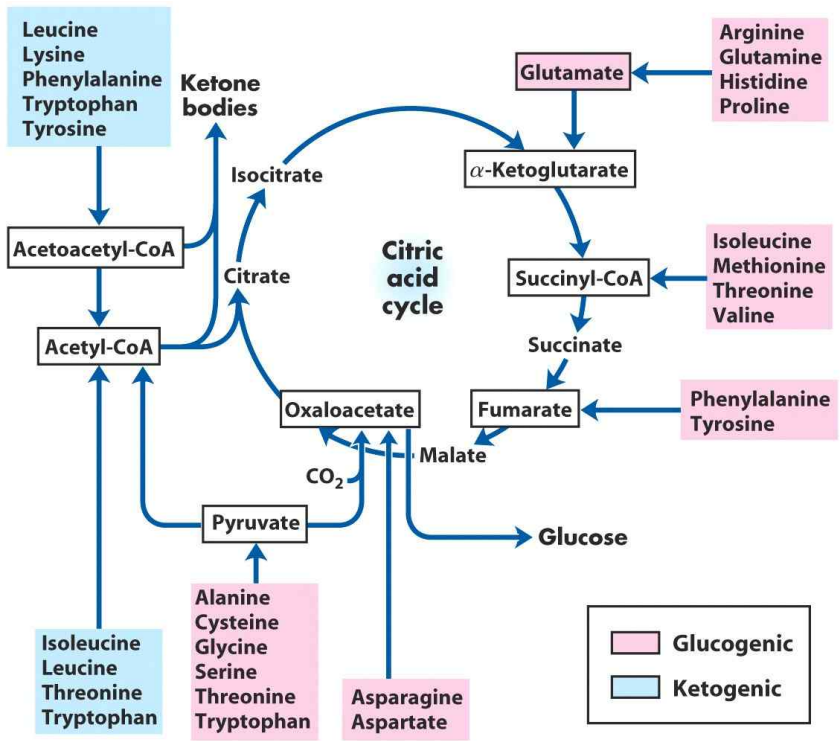


Fig. Summary of amino acid metabolism

3) Some amino acids can be converted to glucose, others to ketones

① **Ketogenic amino acids :**

- **Trp, Phe, Tyr, Ile, Thr, Leu, Lys,** can yield ketones in the liver by conversion of acetoacetyl-CoA into acetone and **β-hydroxybutyrate**.
- **Leu, Lys : 오직 케톤체만을 생성하는 케톤생성아미노산이다**

② **Glucogenic amino acids :**

- Amino acids can be converted into glucose and glycogen

4) Branched-chain amino acids are not degraded in the liver

- **Leucine, isoleucine, valine** are oxidized as fuels primarily in muscle, adipose, kidney, and brain tissue.(주로근육, 지방조직, 신장 그리고 뇌 등에서 산화되어 에너지를 생산한다)

5) Asparagine and aspartate are degraded to oxaloacetate

- Asparginase는 아스파라진을 가수분해하여 아스파르트산 생성을 촉진

5. 아미노산 유도체

1) Biosynthesis of the catecholamine

* Tyrosine → L-DOPA → Dopamine → Norepinephrine → epinephrine
[noraderenaline] [aderenaline]

- 뇌와 신경조직에서 생산되는 **카테콜아민은 신경전달물질**로 작용
- 부신에서 분비되는 **에피네피린과 노르에피네피린은 호르몬**으로 작용

* Dopamine : a tyrosine product (부신수질에서 생성)

- **dopamine 생성의 감소는 Parkinson's 질환의 원인**
- **뇌에서 도파민의 과잉생산은 정신분열증과 같은 정신 질환과 관련 있음**

2) Neurotransmitters (신경전달물질)

* amino acid와 그들의 유도체는 가끔 세포간의 communication에서 chemical messenger로서 작용한다.

① **γ-Aminobutyric acid (GABA) :** Glutamate decarboxylation product

- act as an **inhibitory neurotransmitter** in the central nerve system
- **혈압강하, 뇌기능 증진, 면역력 증강, 정신안정**

② Serotonin (a derivative of tryptophan) : 신경전달물질

③ Histamine (the decarboxylation product of histidine)

- 위에서 산의 분비를 촉진, allergic 반응의 potent local mediator

ex) Histamine 수용체 길항제 : **시메티딘, 타가메트**
위산의 분비를 억제 → 십이지장궤양치료제

④ Thyroxine : a tyrosine product

- 척추동물의 대사를 촉진하는 iodine을 함유한 thyroid (갑상선)호르몬

요약 및 중요용어

Summary

○ 아미노산 분해의 첫 단계는 질소의 제거이다.

○ 육지에 사는 대부분의 척추동물에서 암모늄이온은 요소로 전환된다.

○ 분해된 아미노산의 탄소원자들은 대사경로의 주요 중간산물들로 나타난다.

중요용어

1. 아미노기전이효소(aminotransferase or transaminase)
2. 글루탐산 탈수소효소(glutamate dehydrogenase)
3. 글루코스-알라닌 사이클(glucose-alanine cycle)
4. 요소회로 (Urea cycle)
5. 카르바모일 인산 합성효소(carbamoyl phosphate synthetase)
6. N-acetyl 글루탐산(N-acetyl glutamate)
7. 케톤체 생성아미노산(ketogenic amino acid)
8. 글루코스 생성아미노산(glucogenic amino acid)
9. 페닐케톤증(phenylketonuria)