METABOLISME UREA & ASAM AMINO

BIOKIMIA- MODUL ENTEROHEPATIK

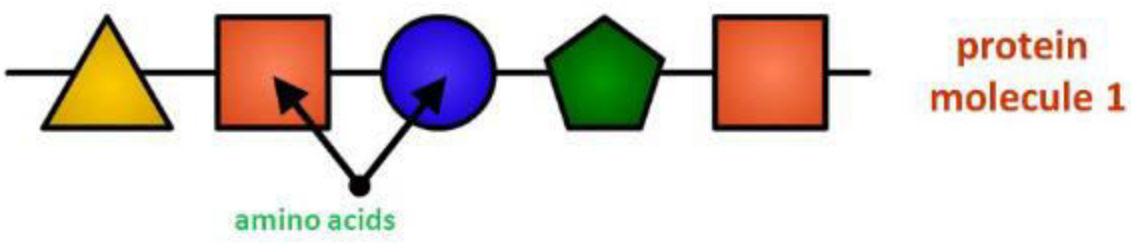
LEARNING OBJECTIVES

1. Protein turnover
2. Biosynthesis of Urea:
    a. Transaminasi
    b. Deaminasi Oksidatif
    c. Urea Cycle

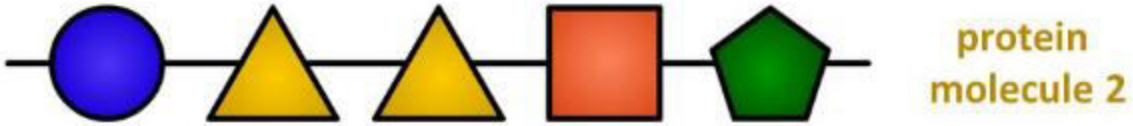
INTRODUCTION

- Amino acid catabolism is part of the whole body catabolism
- Nitrogen enters the body in a variety of compound present in food. Amino acid present in the dietary protein
- Nitrogen leaves the body as urea, ammonia, and other products derived from amino acid metabolism

PROTEIN

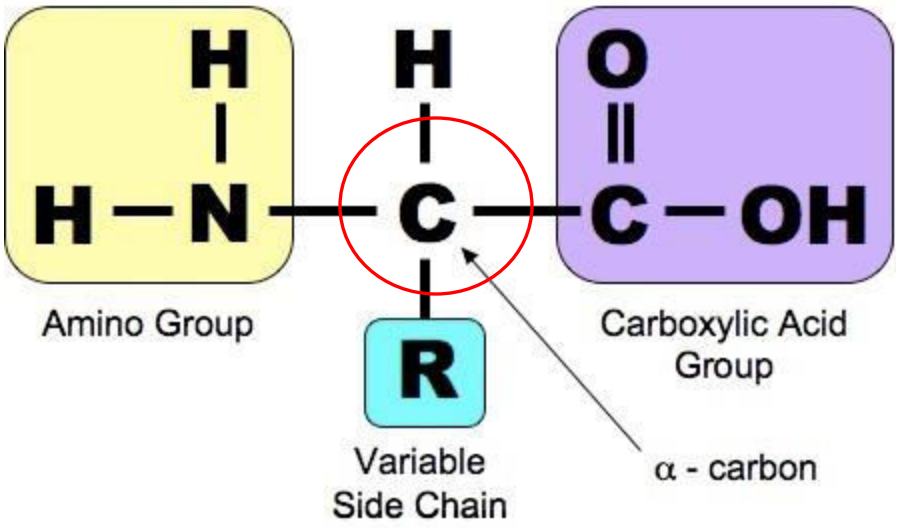


PROTEIN merupakan sekuens 20 jenis asam amino yang berderet



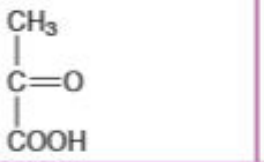
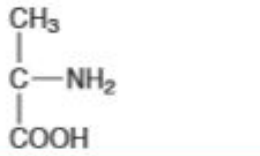
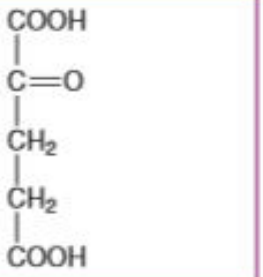
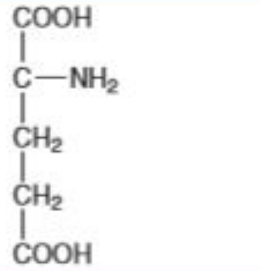
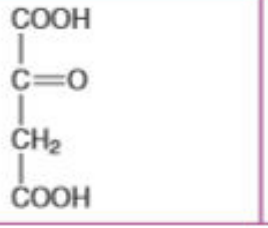
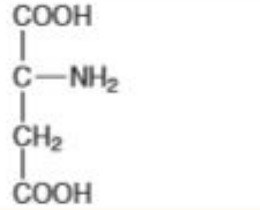
Urutan asam amino yang berbeda akan menghasilkan protein yang berbeda pula

STRUKTUR ASAM AMINO



Tiap asam amino punya karbon inti → a carbon, dilekati oleh 4 grup:

- Basic amino group
- An acidic carboxyl group
- A hydrogen atom
- A distinctive side chain

Pyruvate	Alanine
	
α-Ketoglutarate	**Glutamate**
	
Oxaloacetate	**Aspartate**
	

Comparison of common carbohydrate–amino acid pairs

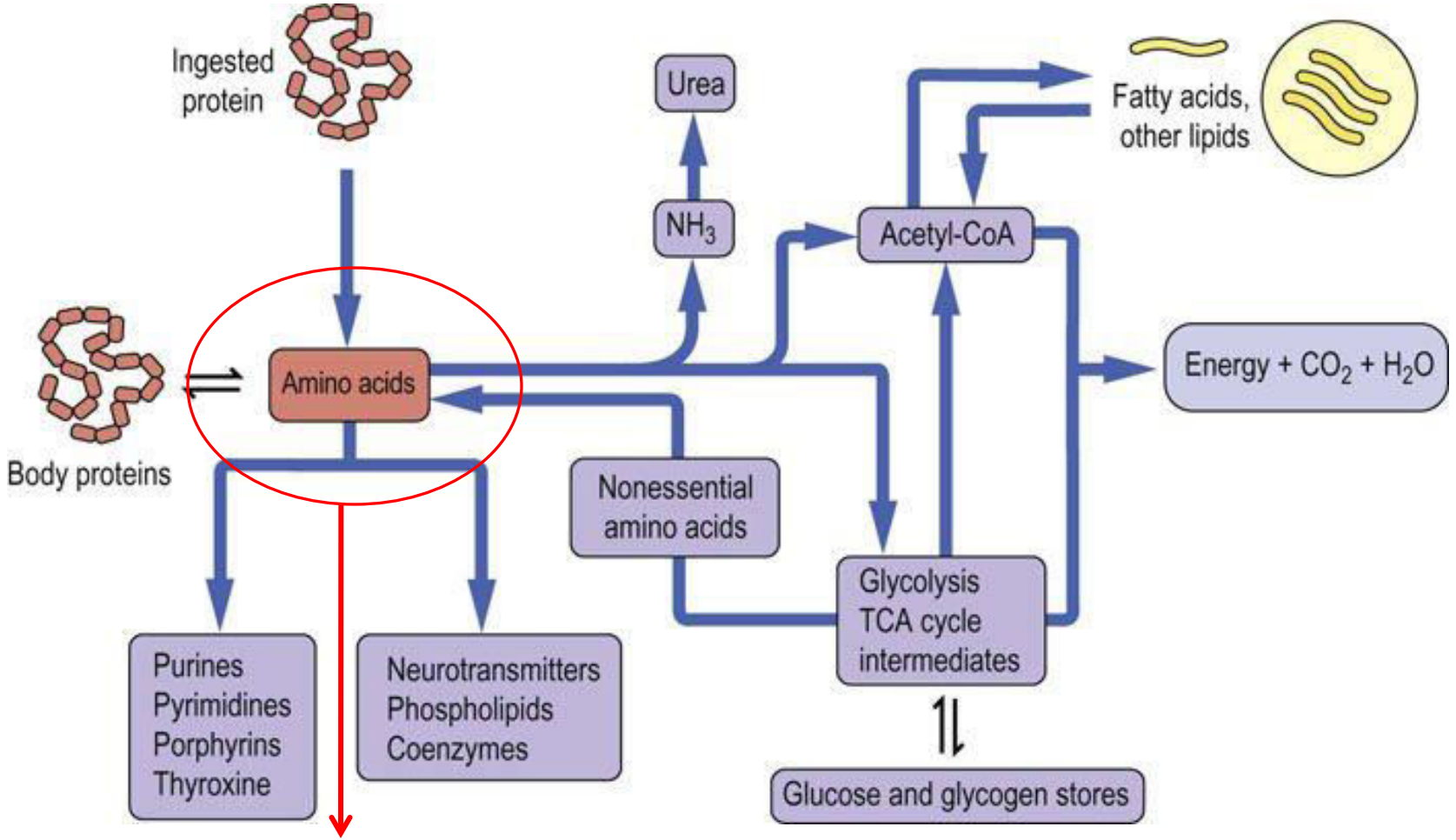
- ✓**Struktur asam amino ternyata = karbohidrat dg tambahan NITROGEN yang melekat**
- ✓**AA tidak diperlukan utk sintesis molekul lain → dikonversi → KARBOHIDRAT**
- ✓**NITROGEN yang dihilangkan dari AA → residual KH → dikonversi → PIRUVAT atau → into a citric acid cycle intermediate→energy production/ gluconeogenesis**

Relationship to central metabolism

- Protein tubuh mencerminkan cadangan energi potensial → tidak digunakan utk produksi energi
- Hanya digunakan dlm kondisi tertentu:

Puasa yg lama → protein otot dibongkar → menjadi asam amino (sintesis protein esensial) & asam keton (glukoneogenesis) → mempertahankan kadar gula darah & menyediakan karbon utk produksi energi

METABOLIC RELATIONSHIPS AMONG AMINO ACID



Diperoleh dari degradasi & turnover protein tubuh, & diet

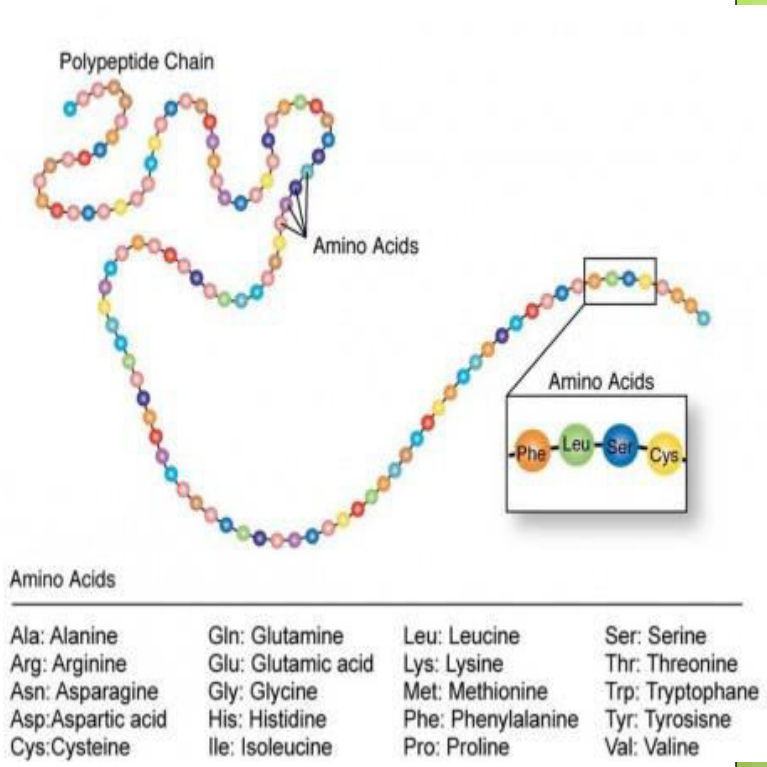
Protein tubuh punya waktu paruh & didegradasi secara rutin → diganti protein baru →Turnover protein

Carbon skeleton beberapa AA → produksi glukosa melalui glukoneogenesis (Glukogenic AA) → metabolic fuel for tissues that require glucose

Carbon skeleton beberapa AA → produksi acetyl Co-A atau acetoacetate (ketogenic AA) → can be metabolized to give immediate precursor of lipid or keton bodies

Konsumsi protein dalam jumlah yg adekuat → a significant quantity of AA may also be converted → carbohydrate (glycogen) or fat (tiaglycerides) → storage

AA do not have a STORAGE, unlike carbohydrate & fat



PROTEIN TURNOVER

Proses turnover: degradasi & sintesis protein seluler yang terjadi kontinyu di semua bentuk makhluk hidup

MANUSIA:
Sekitar 1-2% protein tubuh, terutama protein otot, mengalami turn over setiap hari

Laju degradasi protein TINGGI → jaringan yang mengalami structural rearrangement, misal: jaringan uterus selama kehamilan, otot skelet selama starvasi/kelaparan

75% AA yang dihasilkan dari degradasi protein → reutilisasi /digunakan kembali
AA sisanya → TIDAK dapat DISIMPAN → rapidly degraded

Major portion of Carbon skeleton AA → dikonversi jd senyawa AMFIBOLIK → Pada MANUSIA : AMINO NITROGEN → dikonversi menjadi UREA → diekskresi melalui URINE

INTERORGAN AMINO ACID EXCHANGE

Maintenance kadar AA plasma yg beredar dalam tubuh di periode antara waktu makan tergantung dari net balance:

- Cadangan protein endogen yang digunakan
- Utilisasi/penggunaan protein oleh jaringan

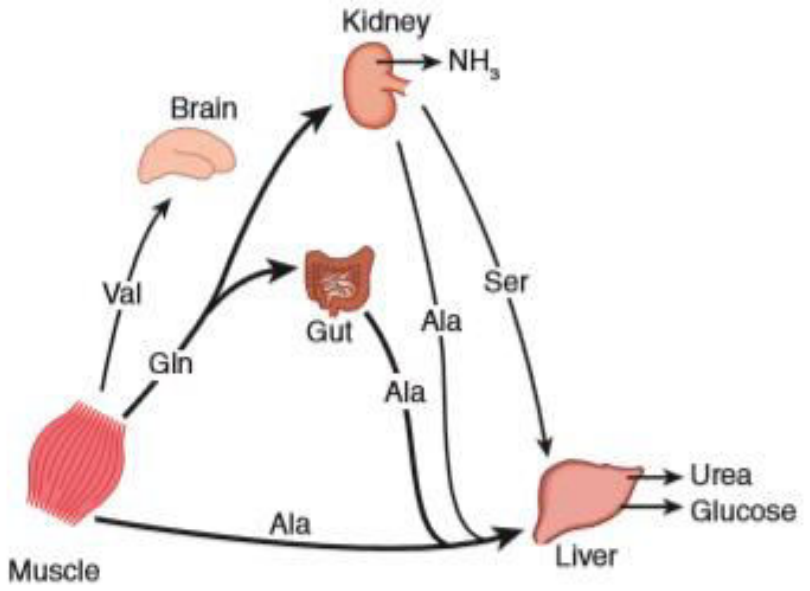
Muscle and liver thus play major roles in maintaining circulating amino acid levels

OTOT

Generates over half of the total body pool of free amino acids

LIVER

the site of the urea cycle enzymes necessary for disposal of excess nitrogen



Ala → key glucogenic amino acid

- The major site of AA degradation is the liver
- The amino group must be removed, as there are no nitrogenous compounds in energy-transduction pathways
- The α-ketoacid that result from deamination of AA metabolized → carbon skeletons can enter the metabolic mainstream as precursors to glucose or citric acid cycle intermediates

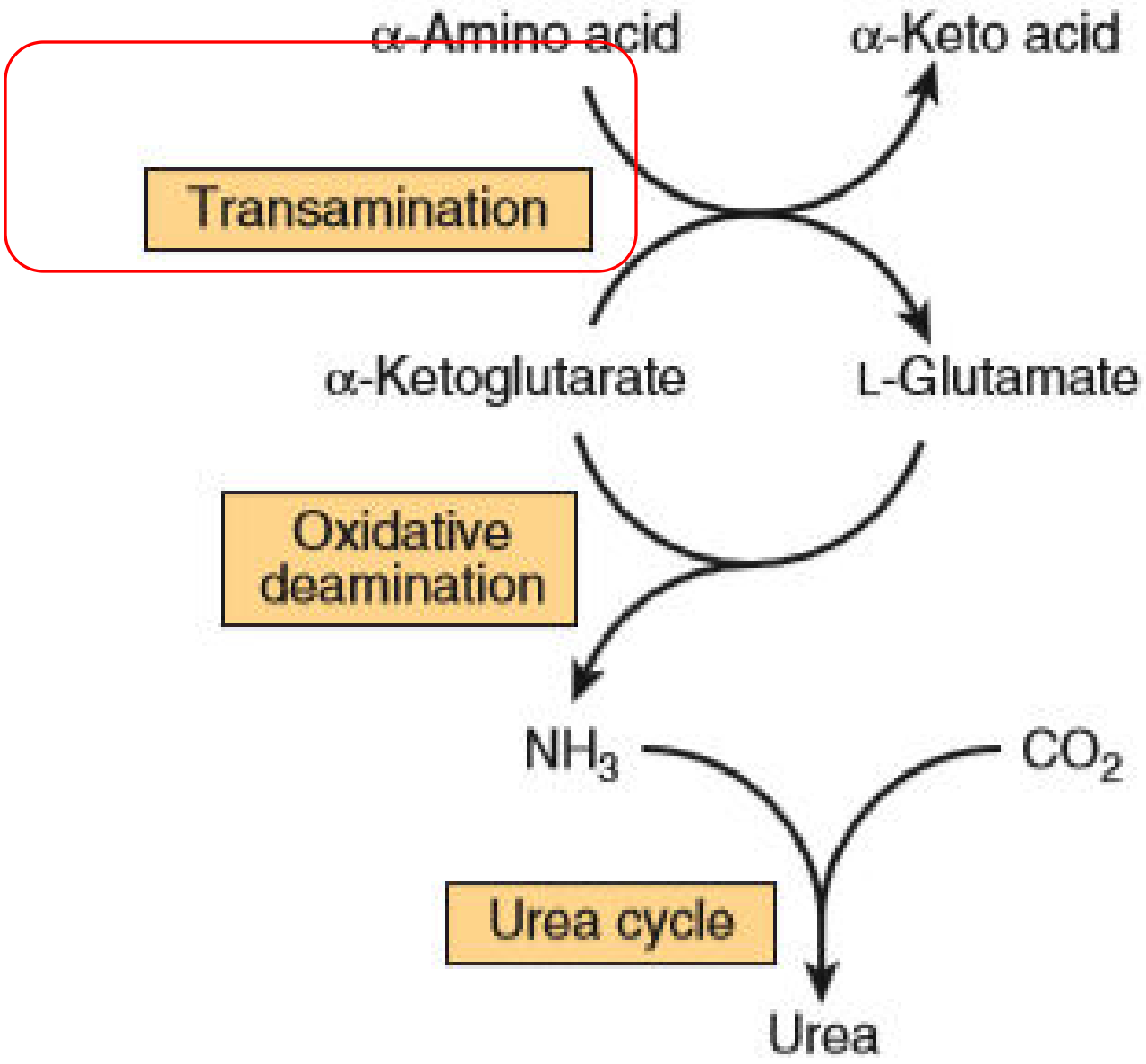
BIOSYNTHESIS OF UREA

The results from amino acid metabolism : NITROGEN → primary form: AMMONIA → quite toxic → must be converted → UREA, which is neutral, less toxic, very soluble, & excreted in urine

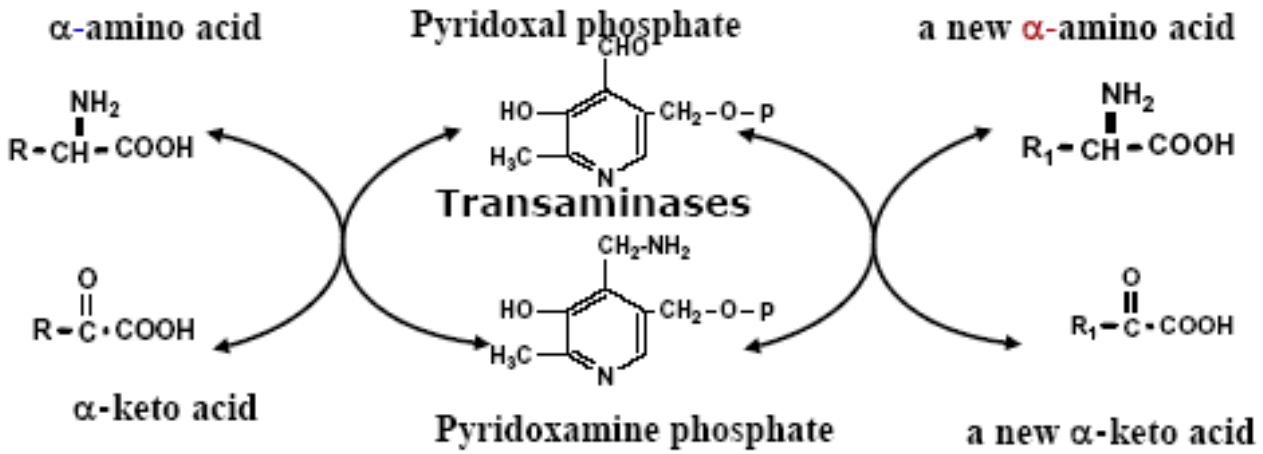
80% of the excreted nitrogen is in the form of urea → UREA CYCLE in the liver
Smaller amount of nitrogen → excreted in the form of uric acid, creatinine & ammonium ion

Amino acid nitrogen is transferred to the urea cycle in three steps:

1. Transamination
2. Formation of ammonia
3. Formation of urea


α-Amino acid
α-Keto acid
Transamination
α-Ketoglutarate
L-Glutamate
Oxidative deamination
NH_3
CO_2
Urea cycle
Urea

TRANSAMINASI



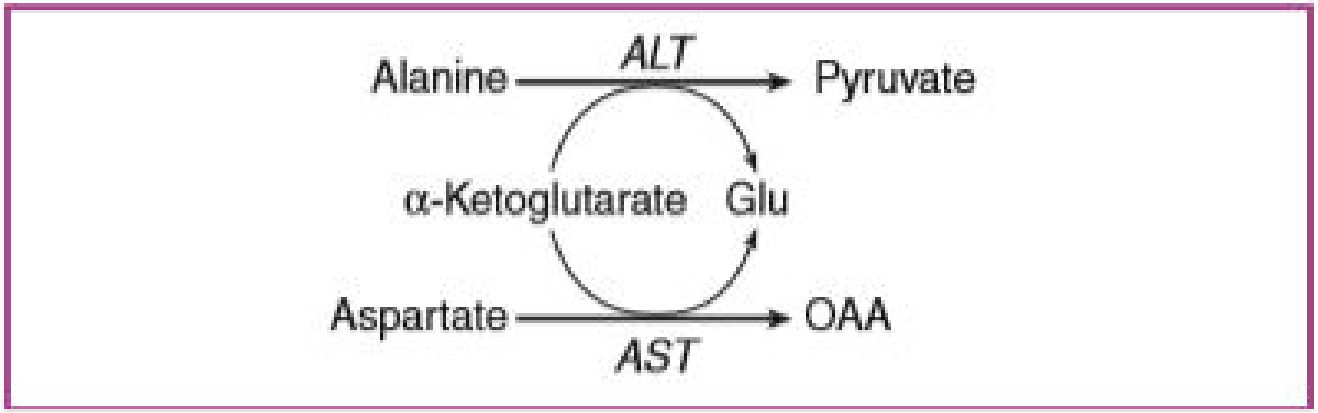
TRANSAMINASI:
Transfer (pindah) gugus amino → suitable keto acid receptor

Asam amino mengalami transaminasi (katalisator: transaminase) dg substrat α- keto glutarat → glutamat

Pyridoxal phosphate, the active form of vitamin B6 (pyridoxine), is required by transaminases as a coenzyme.

Central Role of Glutamate

- Acts as a collector of amino group of the amino acids
- All the amino nitrogen from AA undergo transamination can be concentrated in glutamate
- L-glutamate is the only amino acid that undergoes oxidative deamination



2 TRANSAMINASE berperan sebagai marker LIVER DAMAGE :

- **Aspartate aminotransferase (AST/SGOT): Catalyzes reversible transamination of nitrogen between aspartate and glutamate**

- **Alanine aminotransferas (ALT/SGPT): Catalyzes reversible transamination of nitrogen between alanine and pyruvate.**

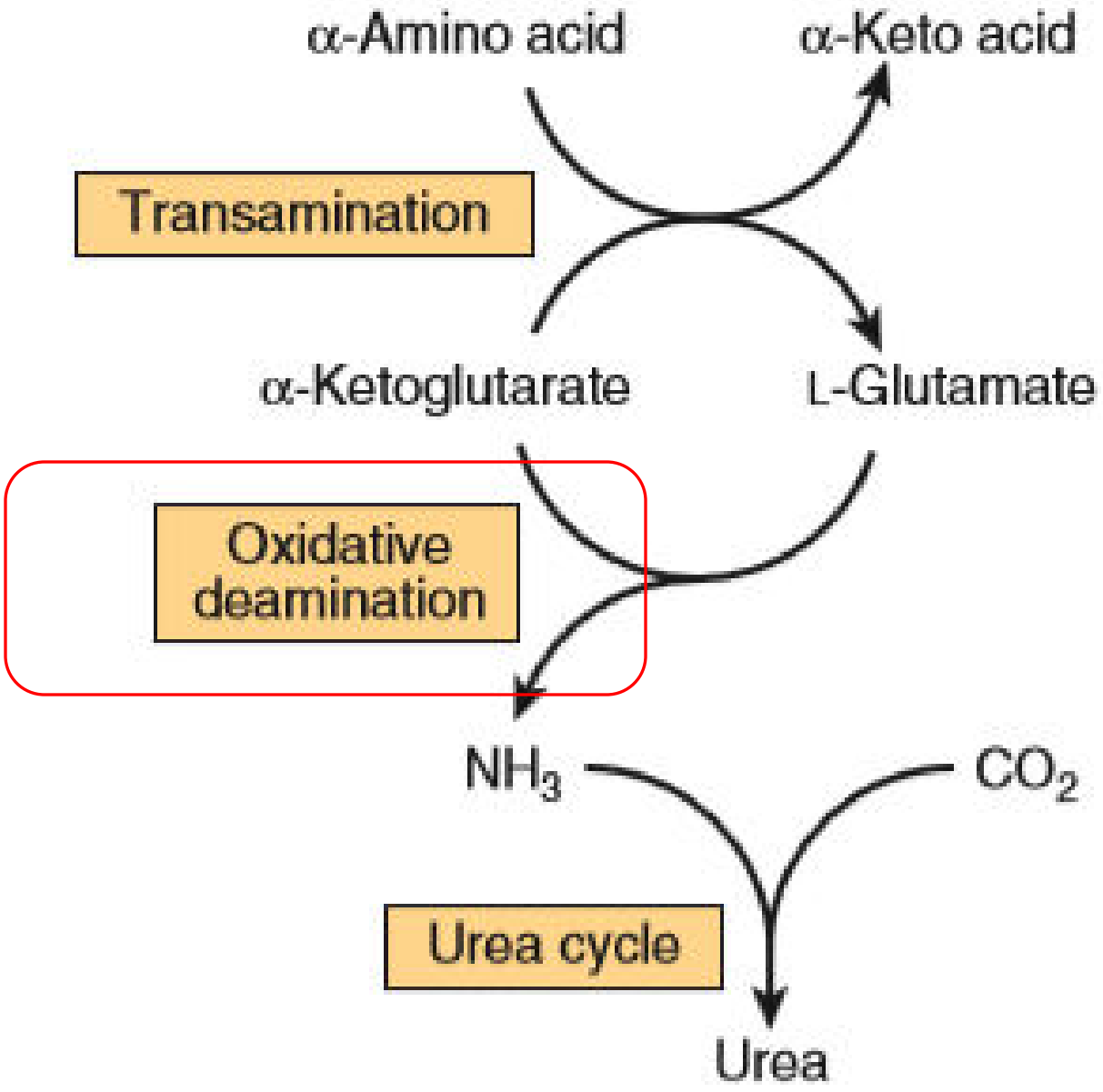
The transaminases

AST

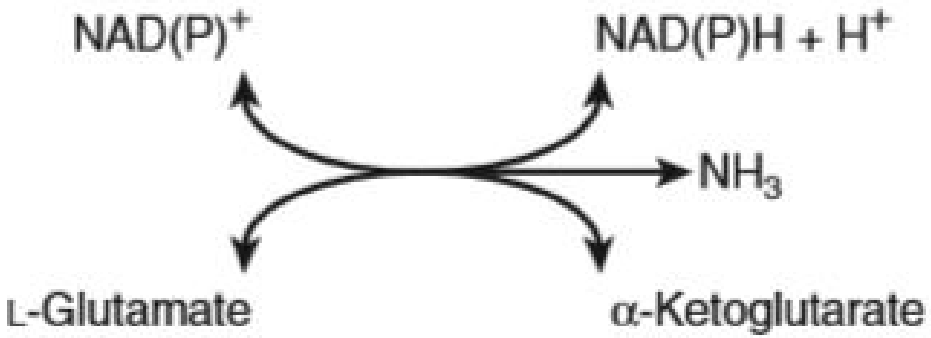
- Serum Glutamate Oxaloacetate Aminotransferase (SGOT)
- Found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, & erythrocytes
- Normal serum activity is 0-41 IU/L. the concentration is very high in myocardium

ALT

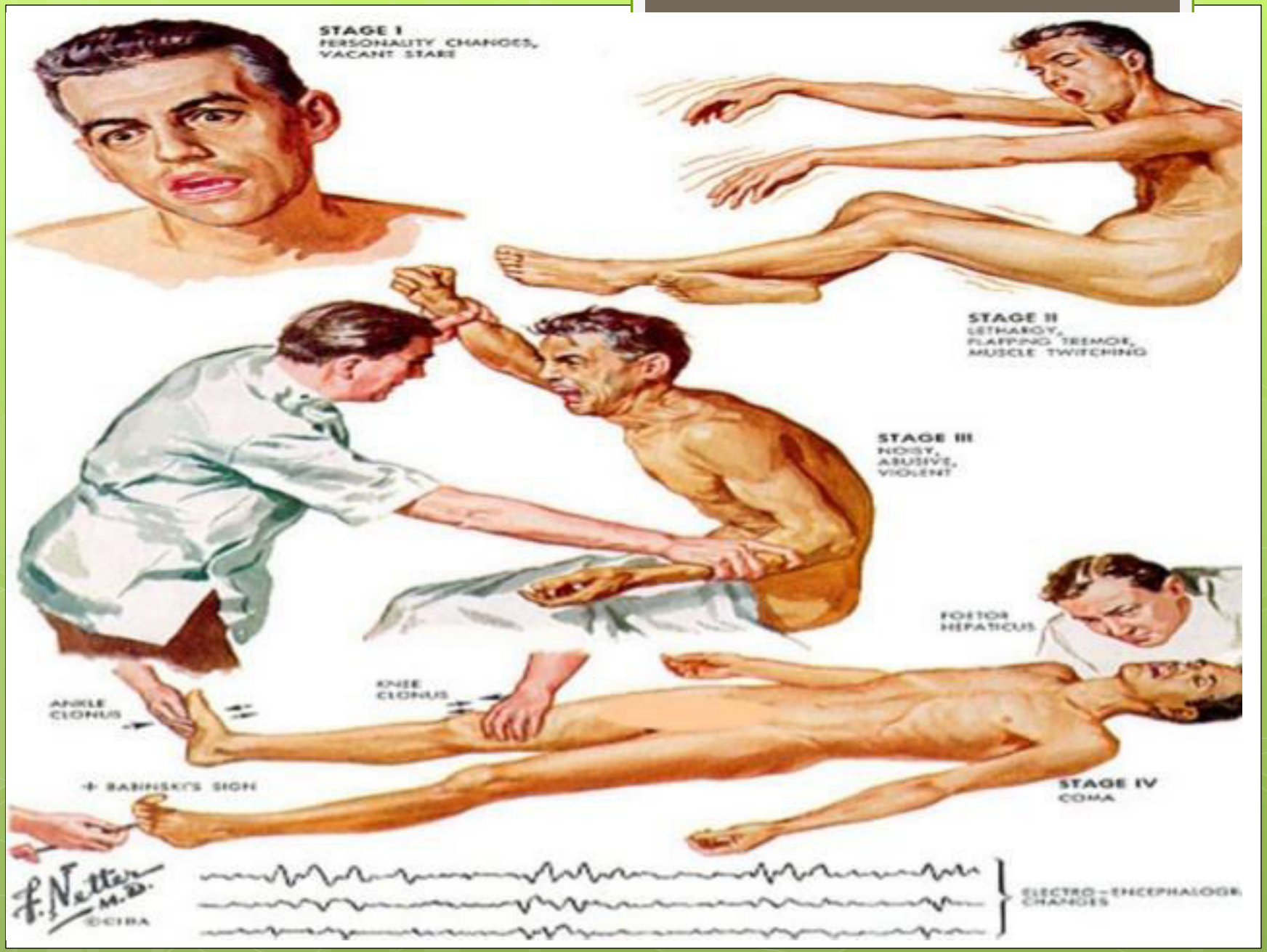
- Serum Glutamate Pyruvate Transferase (SGPT)
- Found primarily in liver
- Normal serum activity ranges between 0-45 IU/L


α-Amino acid
α-Keto acid
Transamination
α-Ketoglutarate
L-Glutamate
Oxidative deamination
NH_3
CO_2
Urea cycle
Urea

DEAMINASI OKSIDATIF



- **Menghilangkan gugus amin dari glutamat**
- **Memerlukan enzim Hepatic l-glutamate dehydrogenase (GDH)**
- **GDH menggunakan NAD+/NADP+ sebagai oksidoreduktan**
- **Hasil : AMMONIA**
- **Aktivitas Liver GDH dihambat : ATP, GTP, & NADH**
- **Aktivitas Liver GDH diaktifkan : ADP**


STAGE I
PERSONALITY CHANGES,
VACANT STARE
STAGE II
LETHARGY,
FLAPPING TREMOR,
MUSCLE TWITCHING
STAGE III
NOISY,
ABUSIVE,
VIOLENT
FOETOR
HEPATICUS
ANKLE
CLONUS
KNEE
CLONUS
+ BABINSKI'S SIGN
STAGE IV
COMA
F. Netter M.D.
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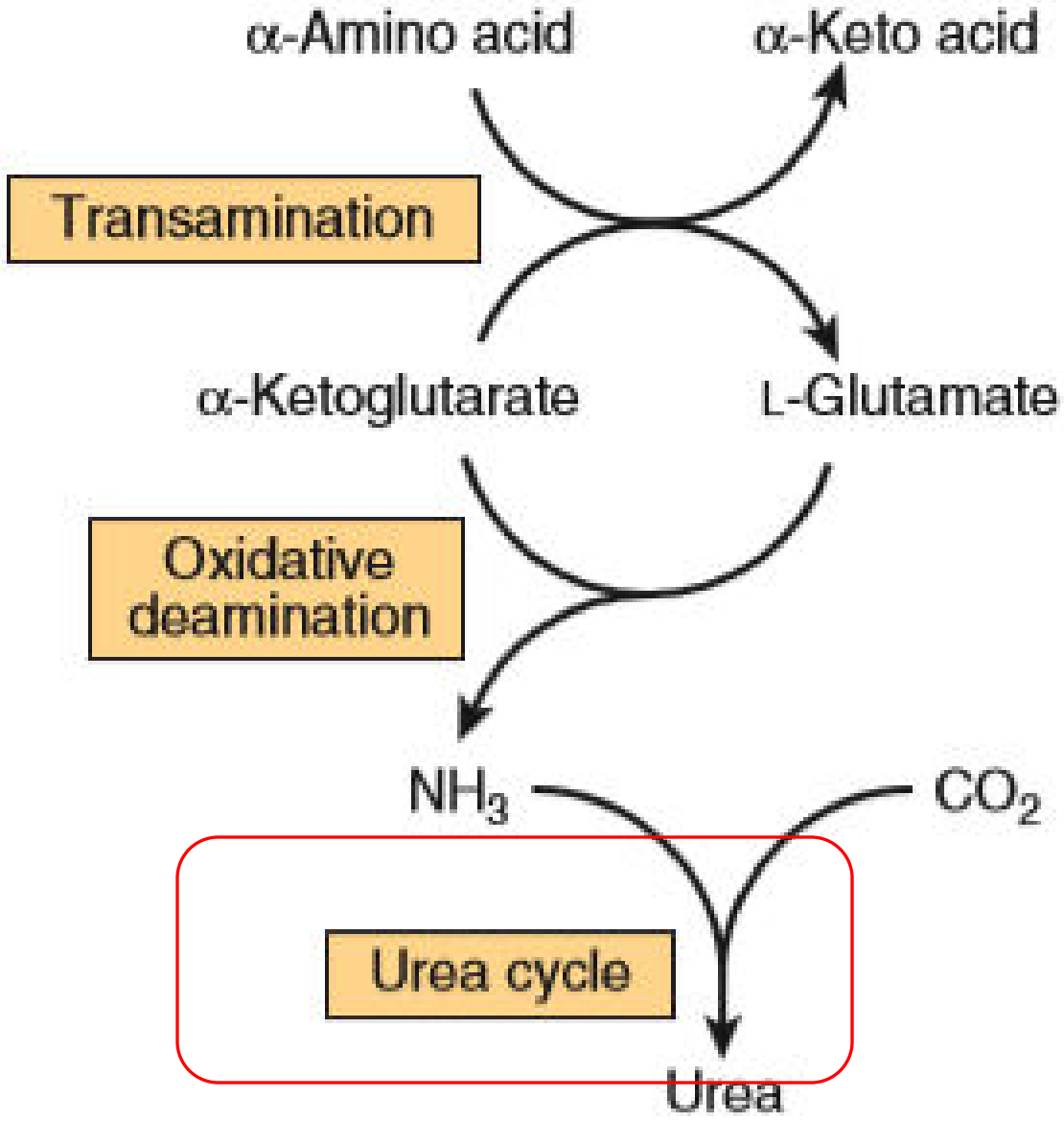
ELECTRO-ENCEPHALOGR
CHANGES


α-Amino acid
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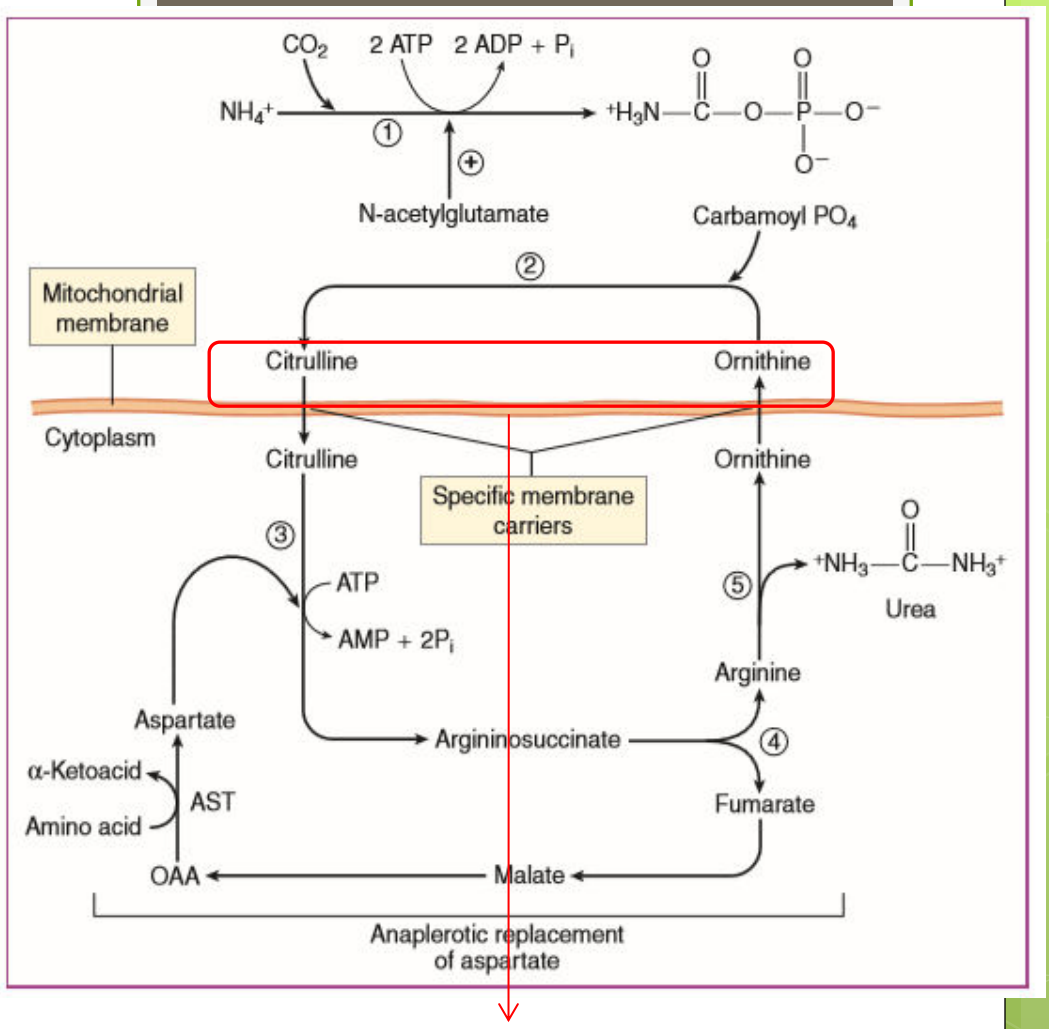
Transamination
α-Ketoglutarate
L-Glutamate
Oxidative deamination
NH_3
CO_2
Urea cycle
Urea

UREA CYCLE

Dimulai di matriks mitokondria → pembentukan urea di SITOPLASMA

1. CarbamoylphosphatesynthetaseI(CPSI): Ion Ammonium +CO2 +ATP → carbamoyl phosphate
2. Ornithine transcarbamoylase: Carbamoyl phosphate + ornithine → dipadatkan → citrulline.
3. Argininosuccinic acid synthetase: Di sitoplasma, citrulline & aspartic acid → memadat → argininosuccinate.
4. Argininosuccinase: Argininosuccinate dipecah →fumarate & arginine.
5. Arginase: Arginine is cleaved to release urea and regenerate ornithine.



Ornithine & citrulline punya specific membrane transport carriers di membran mitokondria

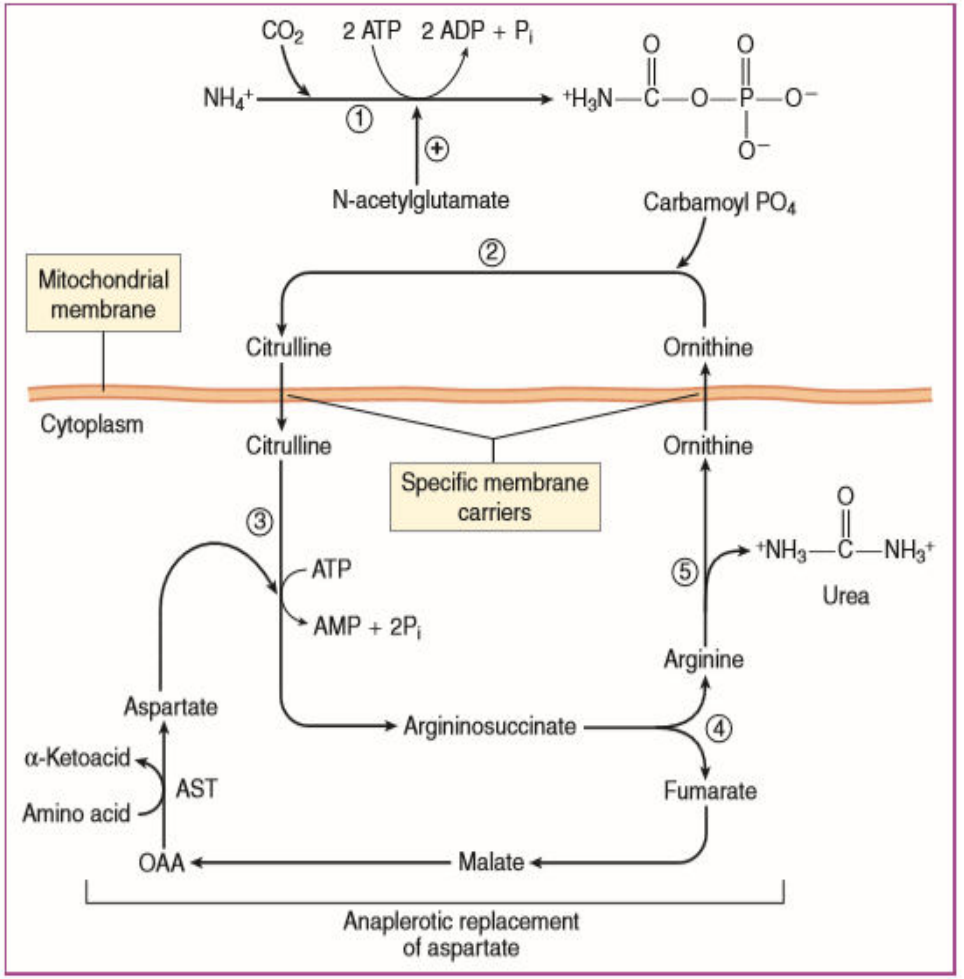
METABOLIC DISORDERS

Gangguan pada masing2 enzim yang berperan di siklus urea → gangguan metabolik

Ciri2:

- Hiperamonemia
- Ensefalopati
- Alkalosis respiratori

Defisiensi enzim carbamoyl phosphate synthase I, ornithine carbamoyl transferase, argininosuccinate synthase, and argininosuccinate lyase → akumulasi prekursor urea, t.u ammonia & glutamine



Kadar amonia darah yang tinggi → **HEMODIALISIS** + sodium benzoat & phenyllactate i.v (akan berkonjugasi dg glisin & glutamin → trapping amonia dalam bntuk non toksik → ekskresi via urin

Bakteri usus produksi amonia→ diserap mll v. porta
Dan Amonia yg diproduksi jaringan → rapidly removed dari sirkulasi oleh HEPAR → diubah jadi UREA → Sehingga kadar amonia dalam darah sangat sedikit (10-20 µg/dL)

Jika fungsi hepar sangat terganggu → atau terjadi kolateralisasi porta sistem dg vena sistemik (spt pd sirosis) → kadar amonia meningkat → toksik bagi SSP

INTOKSIKASI AMONIA

Gejala INTOKSIKASI AMONIA:
tremor, slurred speech, blurred vision, coma, and ultimately death.

Ammonia bersifat TOKSIK untuk OTAK krn amonia bereaksi dg α-ketoglutarate → glutamate.
The resulting depletion of levels of α-ketoglutarate then impairs function of the tricarboxylic acid (TCA) cycle in neurons.

AMMONIA TOXICITY TO THE BRAIN

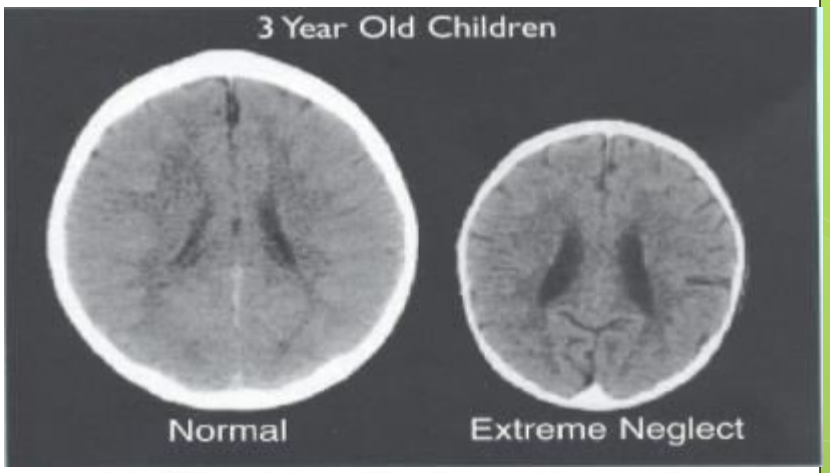
Otak anak2 lebih rentan mengalami efek yg tidak menguntungkan terhadap Hiperamonemia

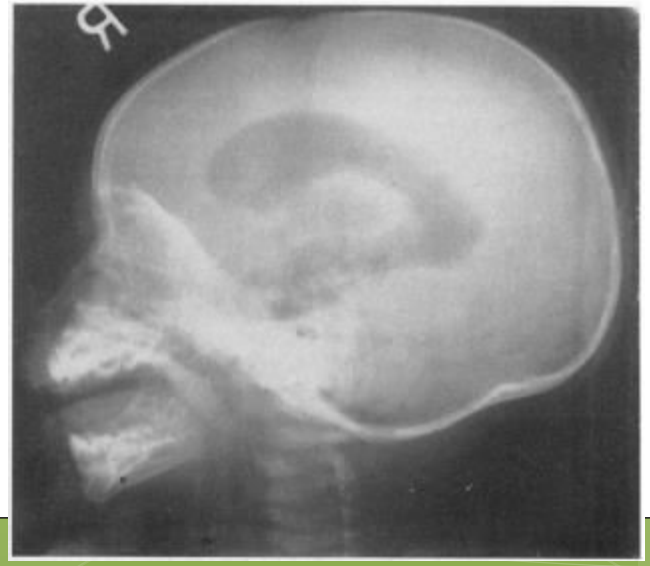
Hiperamonemia → kerusakan ireversibel thd SSP yg sedang berkembang →

- ❑ Cortical atrophy
- ❑ Ventricular enlargement
- ❑ Demielinasi

Hiperamonemia →

- ❖ Gangguan kognitif
- ❖ Kejang
- ❖ Cerebral palsy





AMMONIA TOXICITY TO THE BRAIN

Mekanisme pasti belum diketahui, beberapa hipotesis:

Amonium ganggu:

- ❑ Jalur asam amino
- ❑ Sistem neurotransmitter
- ❑ Metabolisme energi serebral
- ❑ Sintesis nitric oxide
- ❑ Stres oksidatif
- ❑ Jalur transduksi sinyal

→ Perubahan diferensiasi neuronal & perubahan pola cell death

Hiperamonemia pada Hepatic Encephalopathy (HE)

Astrosit: sel yang memetabolisme amonia, melalui reaksi sintesis glutamin dari glutamat → Primary victim of hyperammonemia

Acute Hyperammonemia →
Aliran darah serebral ↑ → edema otak
Amonia ↑ transpor asam amino aromatik (prekursor serotonin & dopamin→ melewati Blood Brain Barrier → efek sedatif & motoric impairment

ASAM AMINO

- Amino acid that can be synthesized & not required in diet → (NUTRITIONALLY NON ESSENTIAL AMINO ACID)
- Amino acid that cannot be derived from normal human metabolism, must be supplied in diet → (NUTRITIONALLY ESSENTIAL AMINO ACID)

AMINO ACID REQUIREMENT IN HUMANS

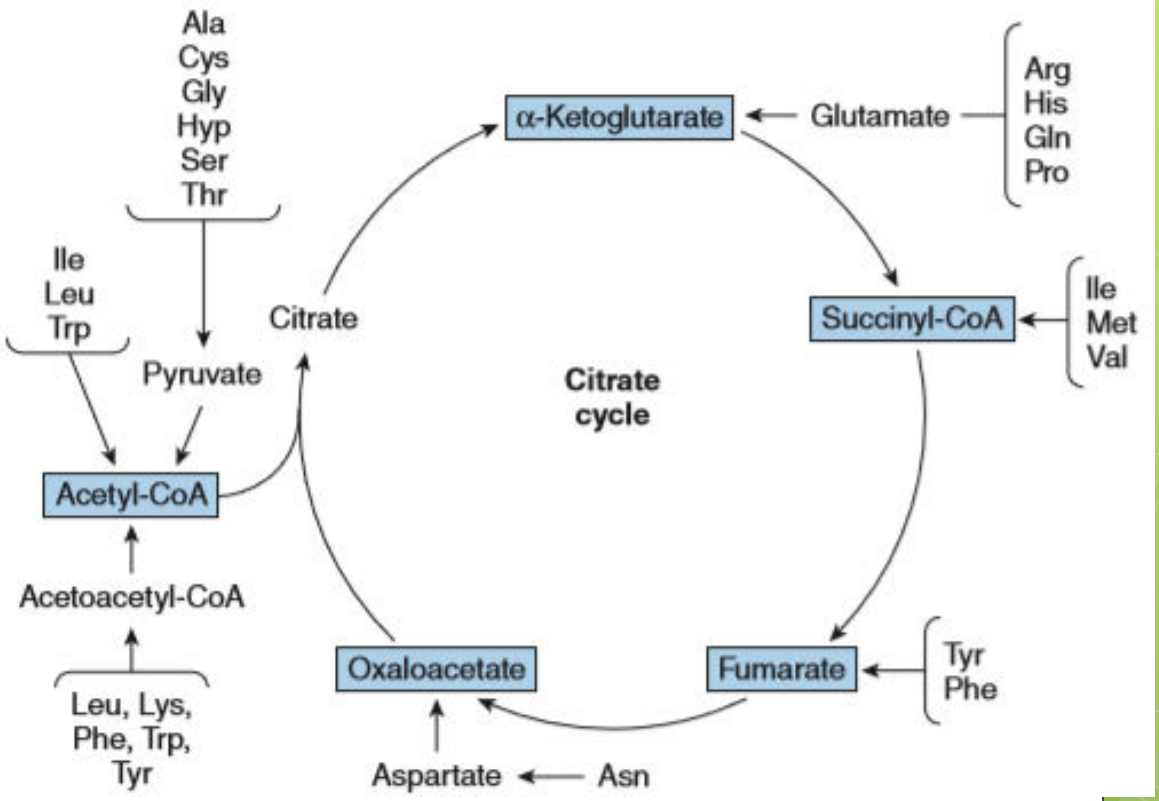
Nutritionally Essential	Nutritionally Nonessential
Arginine[a]	Alanine
Histidine	Asparagine
Isoleucine	Aspartate
Leucine	Cysteine
Lysine	Glutamate
Methionine	Glutamine
Phenylalanine	Glycine
Threonine	Hydroxyproline[b]
Tryptophan	Hydroxylysine[b]
Valine	Proline
	Serine
	Tyrosine

DEGRADASI ASAM AMINO

Transaminasi nitrogen AA→ sediakan carbon skeletons (sebagai a-keto acids) → masuk ke jalur intermediary metabolism sesuai dg konversi AA (menjadi pyruvate, acetyl-CoA, acetoacetyl-CoA, or citric acid cycle intermediates) → substrat gluconeogenesis ATAU produksi badan keton

AA Ketogenic → dikonversi → acetyl-CoA or acetoacetyl-CoA

AA glukogenic → dikonversi →pyruvate atau citric acid cycle intermediates



Karbon skeleton tiap asam amino → convertible →
Karbohidrat (13 AA)
Lemak (1 AA)
Both karbohidrat & lemak (5 AA)

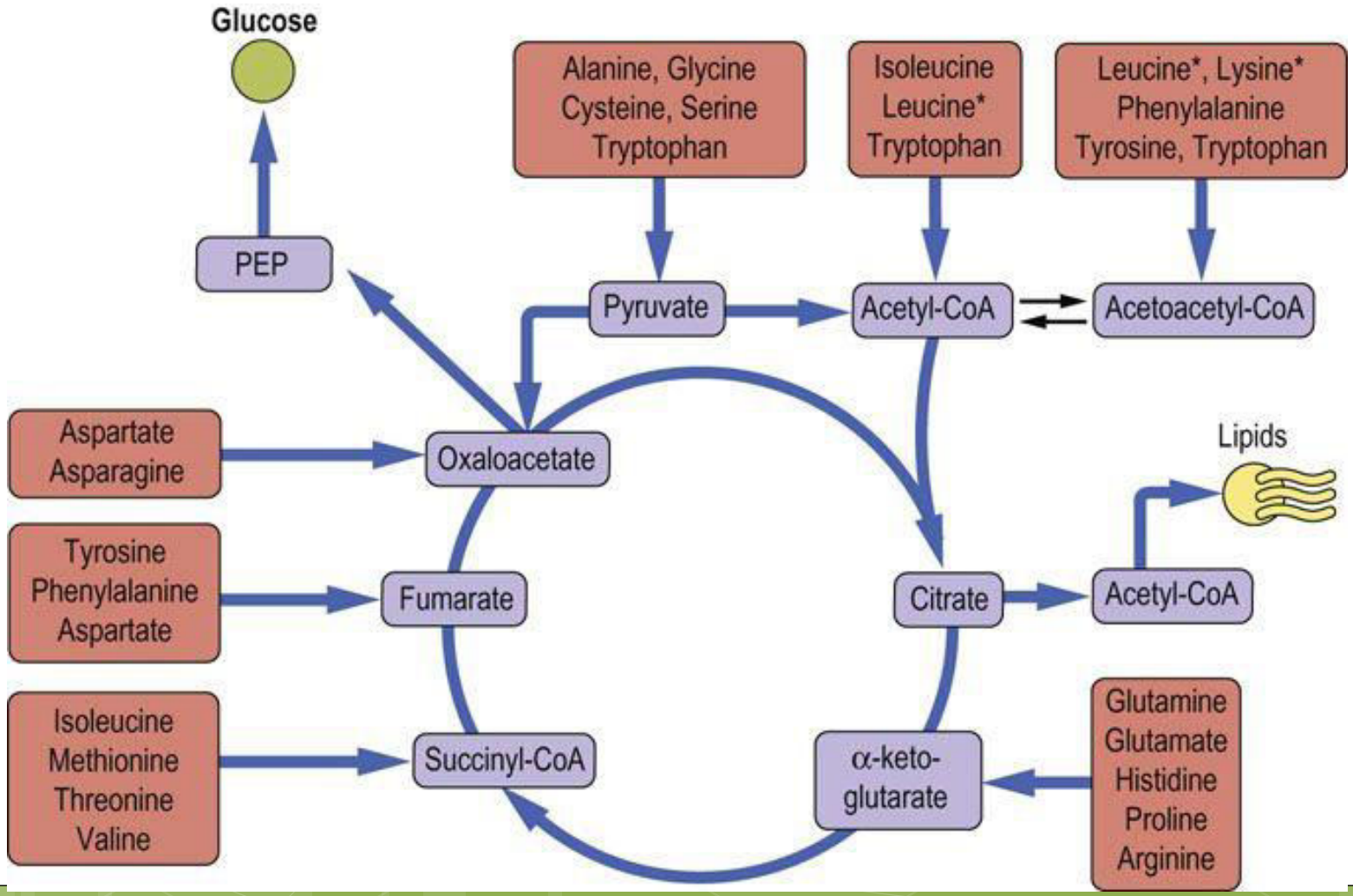
AA GLUKOGENIK
Karbon skeleton AA →produksi glukosa (melalui Glukoneogenesis) → sediakan energi utk jaringan yg memerlukan glukosa sbg sumber energi

AA KETOGENIK
Karbon skeleton AA → produksi asetil Ko-A atau asetoasetat → sediakan prekursor lipid atau badan keton sesegera mungkin

AA dg gugus aromatik → dapat membawa fragmen KETOGENIK & GLUKOGENIK sekaligus

GLUKOGENIK	KETOGENIK	BOTH
Alanin	Leucine	Isoleucine
Arginin		Fenilalanin
Aspartat		Lysine
Sistein		Triptofan
Glutamat		Tirosin
Glisin		
Histidin		
Hidroksiprolin		
Metionin		
Prolin		
Serin		
Treonin		
Valin		

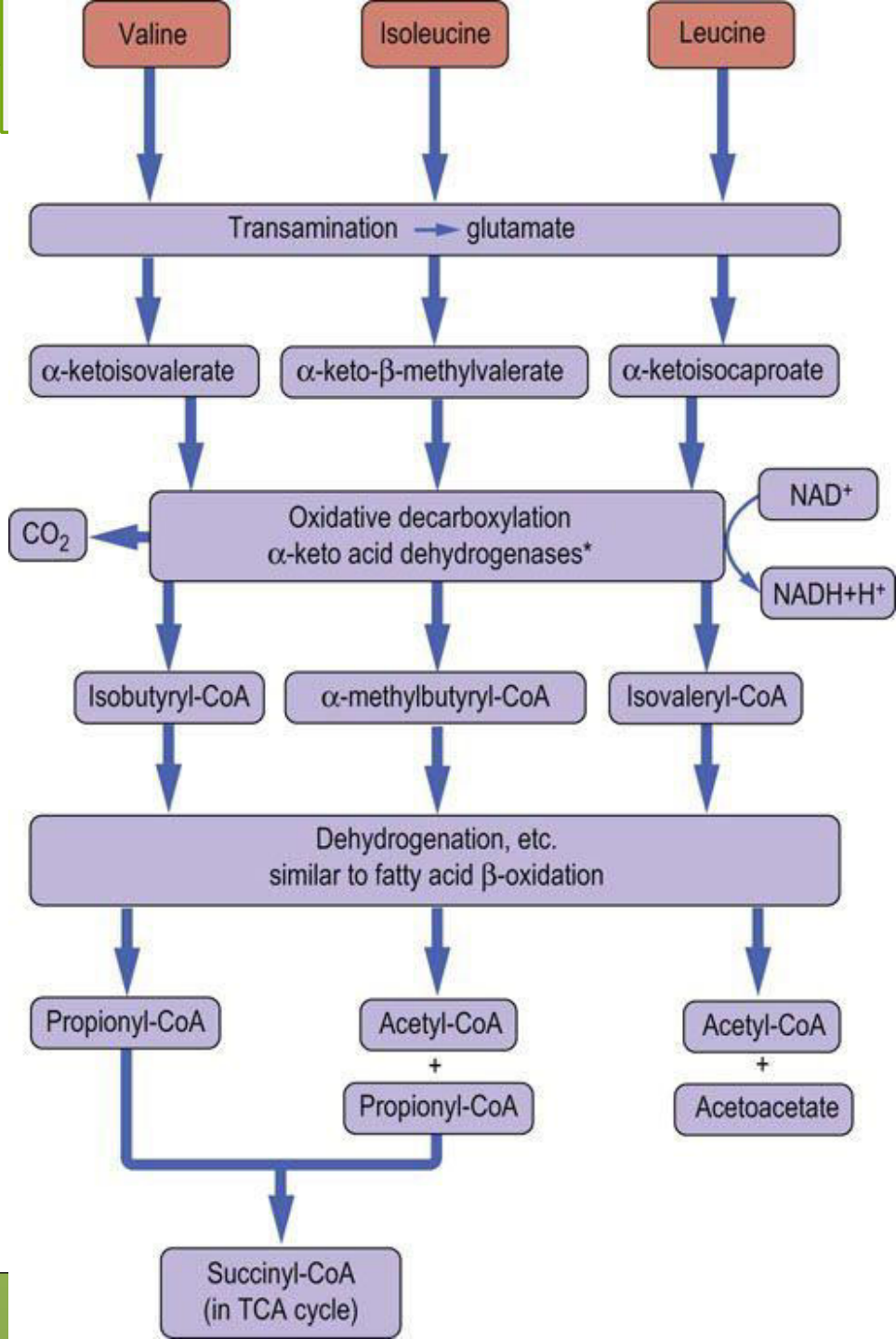
AMINO ACID METABOLISM & CENTRAL METABOLISM PATHWAYS



METABOLISME KARBON SKELETON ASAM AMINO

GLUKOGENIK AA (Ala, Asp, Glu):
Melalui TRANSAMINASI atau DEAMINASI OKSIDATIF → α keto acid → prekursor oxaloasetat → fosfoenolpiruvat → GLUKOSA (via GLUKONEOGENESIS)

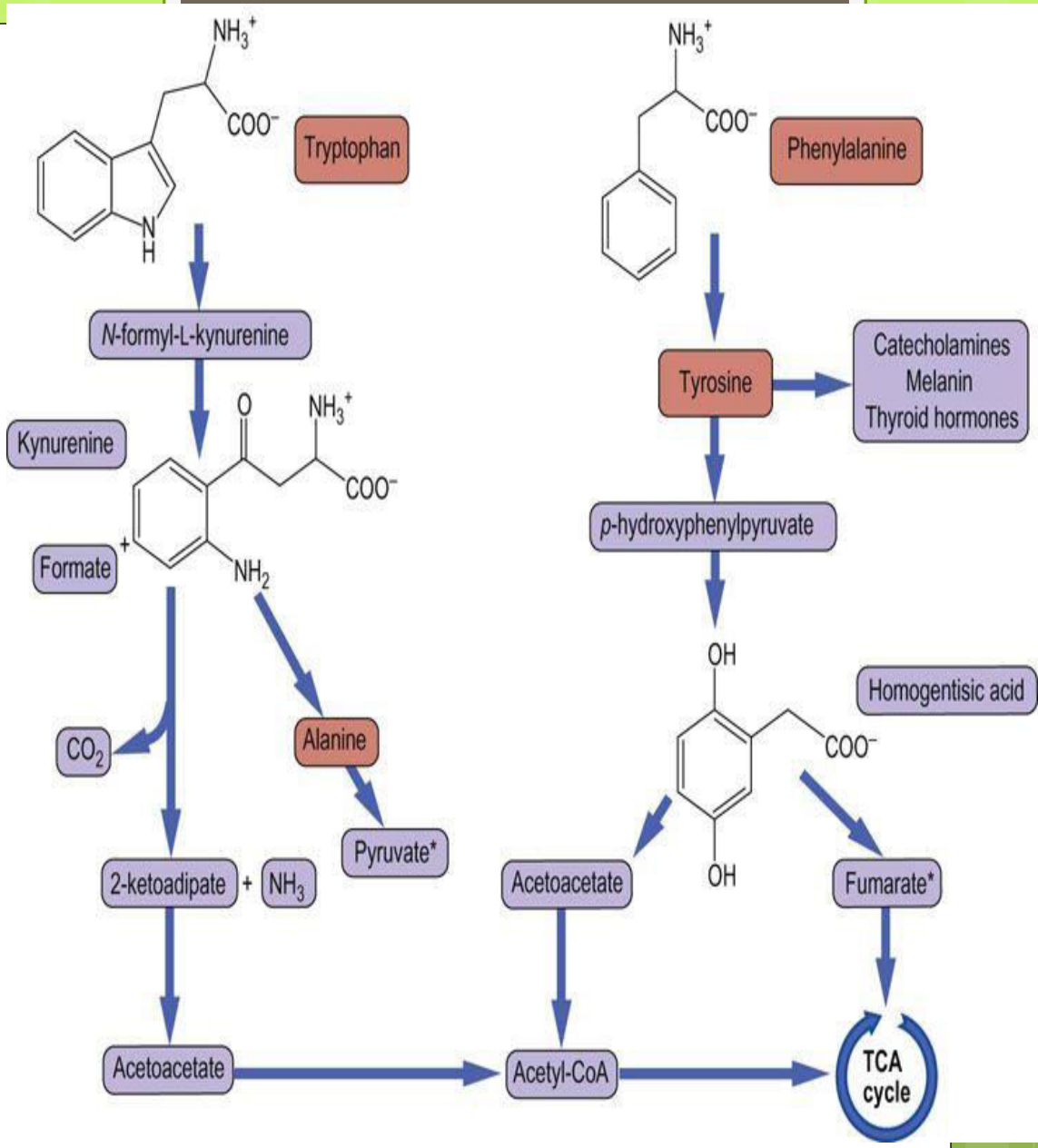
KETOGENIK AA (Leu):
Melalui TRANSAMINASI → 2-ketoisocaproate → OKSIDATIF DEKARBOKSILASI → 3-hidroksi 3-metil glutaril Co-A → prekursor asetil Co-A & badan Keton

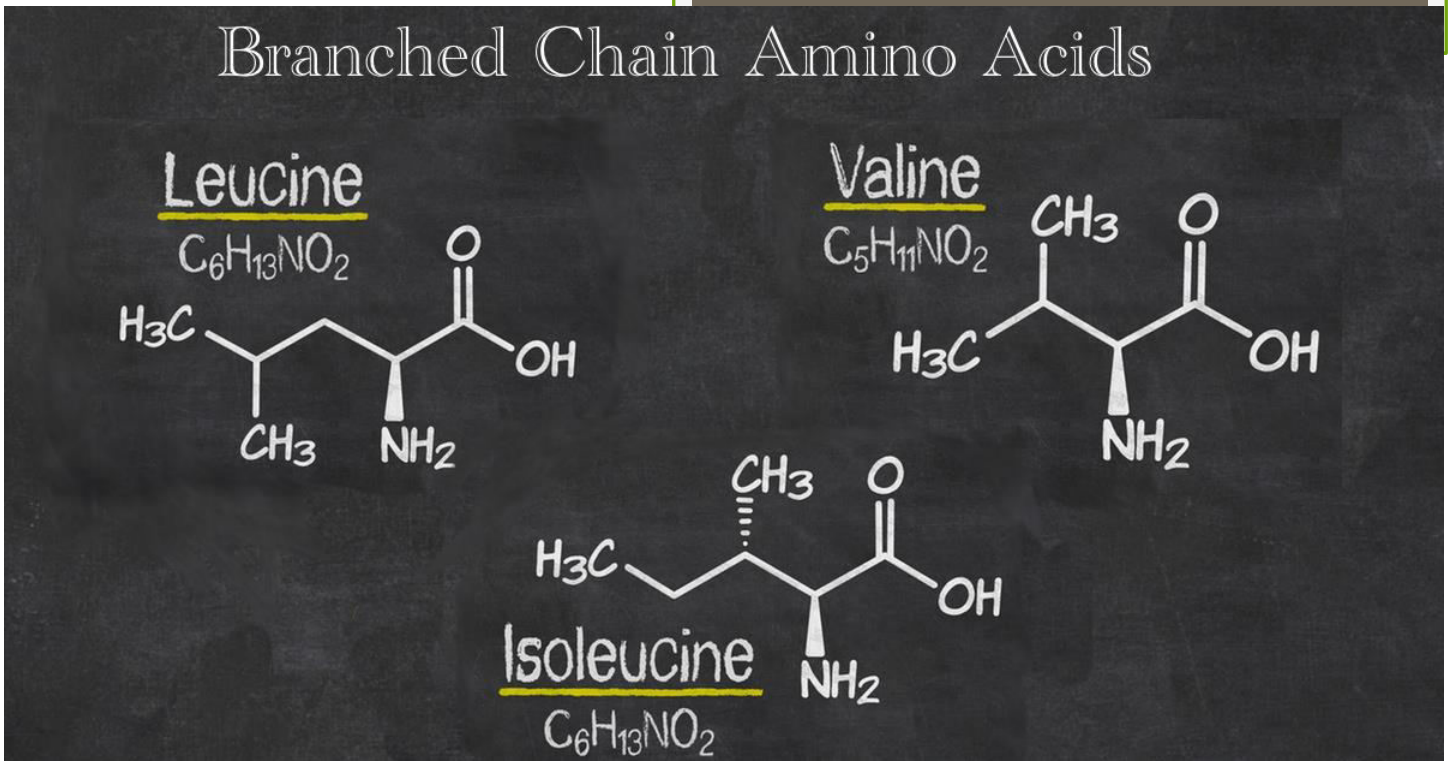


GLUKOGENIK & KETOGENIK AA (Trp):

Penguraian rantai heterosiklik → struktur inti AA dilepaskan → Ala (Glukogenik)

Sedangkan karbon skeleton → diubah menjadi glutaril Co-A (prekursor ketogenik)





METABOLIC ROLES :

✓ Promote protein synthesis & turnover
✓ Signalling pathways
✓ Glucose Metabolism
✓ Oksidasi BCAA → may increase fatty acid oxidation & play a role in obesity

PHYSIOLOGICAL ROLES:

✓ Immune system → lymphocyte growth & proliferation; Tc activity
✓ Brain function → neurotransmitter synthesis, & energy production

BIOSINTESIS ASAM AMINO

Biosintesis AA melibatkan sintesis karbon skeleton dari α-keto acid + adisi gugus amino melalui TRANSAMINASI

AA yang TIDAK bisa disintesis, dan diperoleh dari asupan makanan → (nutritionally) ESSENTIAL AA

Origin of nonessential amino acids

Alanine	from pyruvate
Aspartic acid	from citric acid cycle intermediates
Asparagine	
Arginine	
Glutamic acid	
Glutamine	
Proline	
Serine	from 3-phosphoglycerate
Glycine	from serine
Cysteine	from serine (Sulfur from methionine)
Tyrosine	from phenylalanine

Baynes and Dominiczak, Medical Biochemistry, Mosby 1999

Asam Amino Esensial	Keterangan
Fenilalanin	Prekursor tirosin
Valin	Branched chain amino acid
Threonine	Dimetabolisme spt BCAA
Tryptophan	Rantai heterosiklik indol nya tdk bisa disintesis manusia
Isoleucine	BCAA
Methionine	Sulfur nya → sistein
Histidine	Rantai heterosiklik imidazol nya tdk bisa disintesis manusia
Arginine	Berasal dari ornitin (siklus urea)
Leucine	AA ketogenik
Lysine	Tdk bisa mengalami transaminasi secara langsung

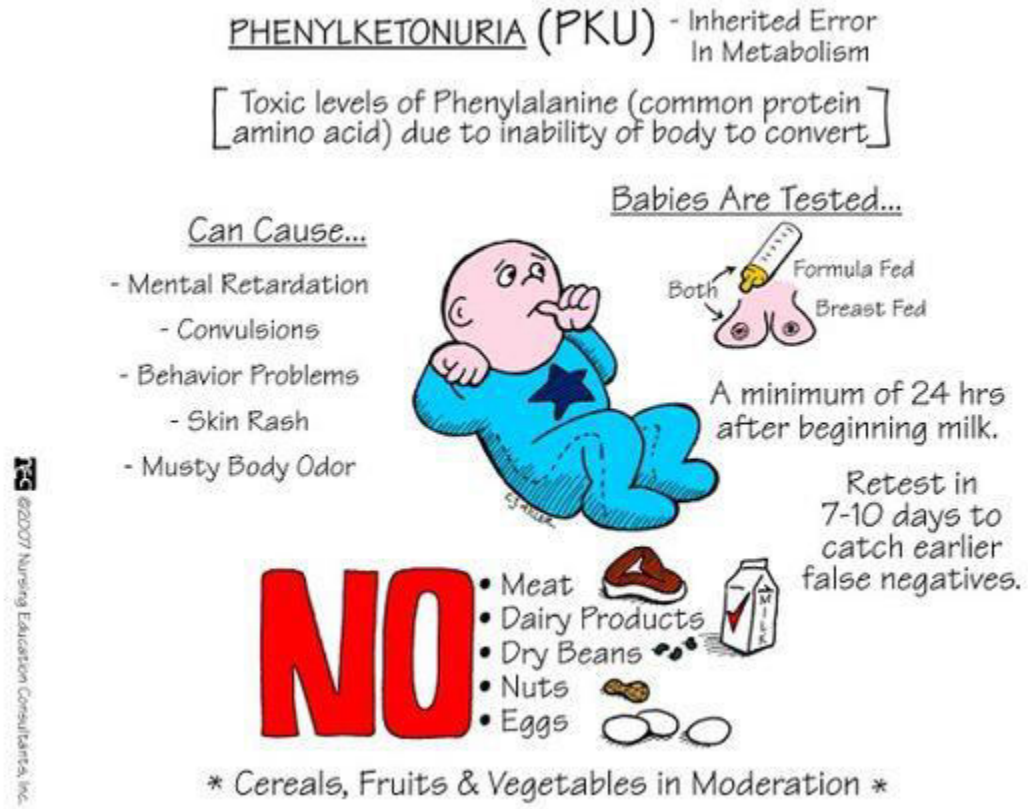
ASAM AMINO	EFFECTOR MOLECULE OR PROSTETHIC GROUP
Arginine	Immediate precursor of urea, precursor of nitric oxide
Aspartate	Excitatory neurotransmitter
Glycine	Inhibitory neurotransmitter; precursor of heme
Glutamate	Excitatory neurotransmitter; precursor of γ-amino butyric acid (GABA) → inhibitory neurotransmitter
Histidine	Prekursor histamin → mediator inflamasi, neurotransmitter
Tryptophan	Prekursor serotonin → stimulator kontraksi otot polos yang poten; prekursor melatonin → regulator ritme sirkadian
Tyrosine	Prekursor hormon & neurotransmitter : katekolamin, dopamin, epinefrin, norepinefrin, tiroksin

Protein and Amino Acid

DISODERS

TABLE 18-2 Some Human Genetic Disorders Affecting Amino Acid Catabolism

Medical condition	*Approximate incidence (per 100,000 births)*	*Defective process*	*Defective enzyme*	*Symptoms and effects*
Albinism	<3	Melanin synthesis from tyrosine	Tyrosine 3-monooxygenase (tyrosinase)	Lack of pigmentation: white hair, pink skin
Alkaptonuria	<0.4	Tyrosine degradation	Homogentisate 1,2-dioxygenase	Dark pigment in urine; late-developing arthritis
Argininemia	<0.5	Urea synthesis	Arginase	Mental retardation
Argininosuccinic acidemia	<1.5	Urea synthesis	Argininosuccinase	Vomiting; convulsions
Carbamoyl phosphate synthetase I deficiency	<0.5	Urea synthesis	Carbamoyl phosphate synthetase I	Lethargy; convulsions; early death
Homocystinuria	<0.5	Methionine degradation	Cystathionine β-synthase	Faulty bone development; mental retardation
Maple syrup urine disease (branched-chain ketoaciduria)	<0.4	Isoleucine, leucine, and valine degradation	Branched-chain α-keto acid dehydrogenase complex	Vomiting; convulsions; mental retardation; early death
Methylmalonic acidemia	<0.5	Conversion of propionyl-CoA to succinyl-CoA	Methylmalonyl-CoA mutase	Vomiting; convulsions; mental retardation; early death
Phenylketonuria	<8	Conversion of phenylalanine to tyrosine	Phenylalanine hydroxylase	Neonatal vomiting; mental retardation


PHENYLKETONURIA (PKU) - Inherited Error In Metabolism
[Toxic levels of Phenylalanine (common protein amino acid) due to inability of body to convert]
Can Cause...
- Mental Retardation
- Convulsions
- Behavior Problems
- Skin Rash
- Musty Body Odor
Babies Are Tested...
Both
Formula Fed
Breast Fed
A minimum of 24 hrs after beginning milk.
Retest in 7-10 days to catch earlier false negatives.
NO
• Meat
• Dairy Products
• Dry Beans
• Nuts
• Eggs
* Cereals, Fruits & Vegetables in Moderation *
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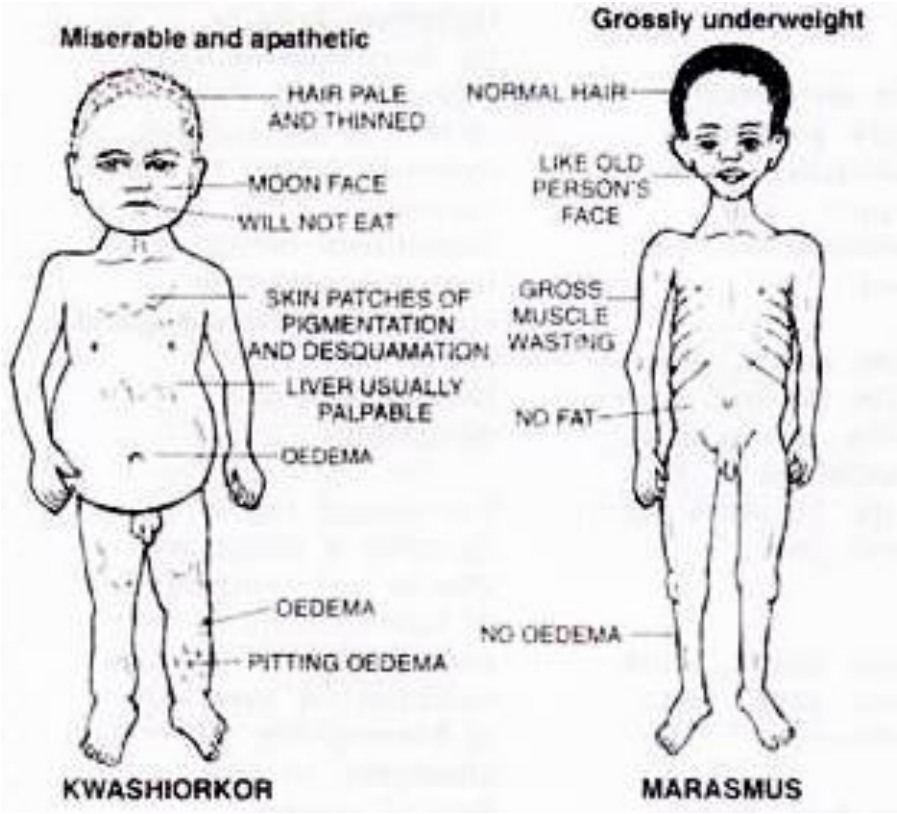
Albinism


Maple Syrup Urine Disease (MSUD)
For Information, Visit: www.epainassist.com
ePainAssist.com
ePainAssist.com
Normal Urine
Maple Syrup Disease Urine


Alkaptonuria

DEFISIENSI ASAM AMINO

DISEASES	DEFICIENCY
KWASHIORKOR	STARCHY DIET BUT POOR PROTEIN
MARASMUS	DEFICIENT CALORIC INTAKE & SPECIFIC AA
SCURVY	DEFICIENT VIT C & CONNECTIVE TISSUE : HYDROXYPROLINE, HYDROXYLYSINE
MENKES SYNDROME	DEFICIENT COPPER, ESSENTIAL COFACTOR ENZYME LYSYL OXIDASE → FORMATION COLLAGEN FIBERS


Miserable and apathetic
HAIR PALE AND THINNED
MOON FACE
WILL NOT EAT
SKIN PATCHES OF PIGMENTATION AND DESQUAMATION
LIVER USUALLY PALPABLE
OEDEMA
OEDEMA
PITTING OEDEMA
KWASHIORKOR
Grossly underweight
NORMAL HAIR
LIKE OLD PERSON'S FACE
GROSS MUSCLE WASTING
NO FAT
NO OEDEMA
MARASMUS

Vitamin C Deficiency

Deficiency disease: **Scurvy**

Deficiency symptoms:

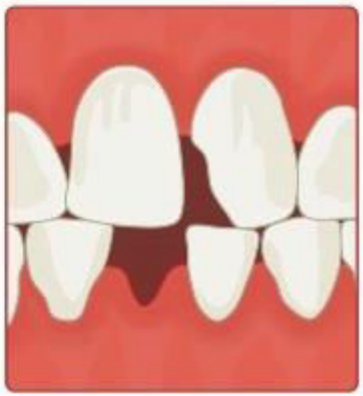
- **S**kin discoloration & bruising
- **H**emorrhaging
- **A**naemia
- **D**ental issues
- **E**xhaustion / fatigue
- **S**welling of joints (edema)

Mnemonic: **SHADES**

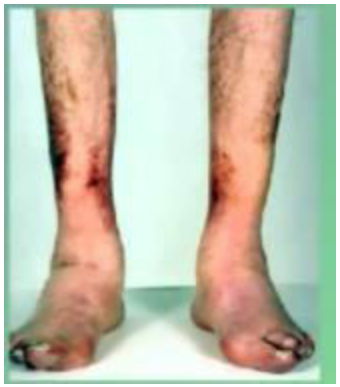
Normal Person

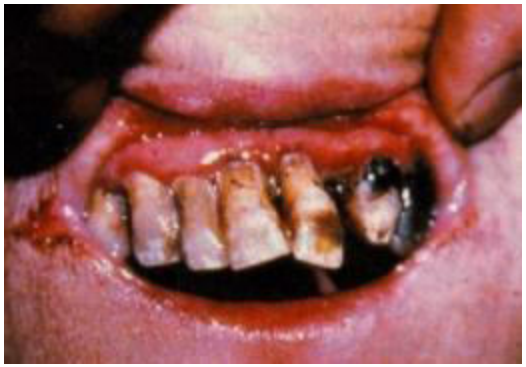
Healthy teeth and gums

Scurvy



Loosened teeth and bleeding / ulcerated gums





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