AMINO ACID METABOLISM

Sri Widia A Jusman
Dept. of Biochemistry & Molecular Biology
FMUI

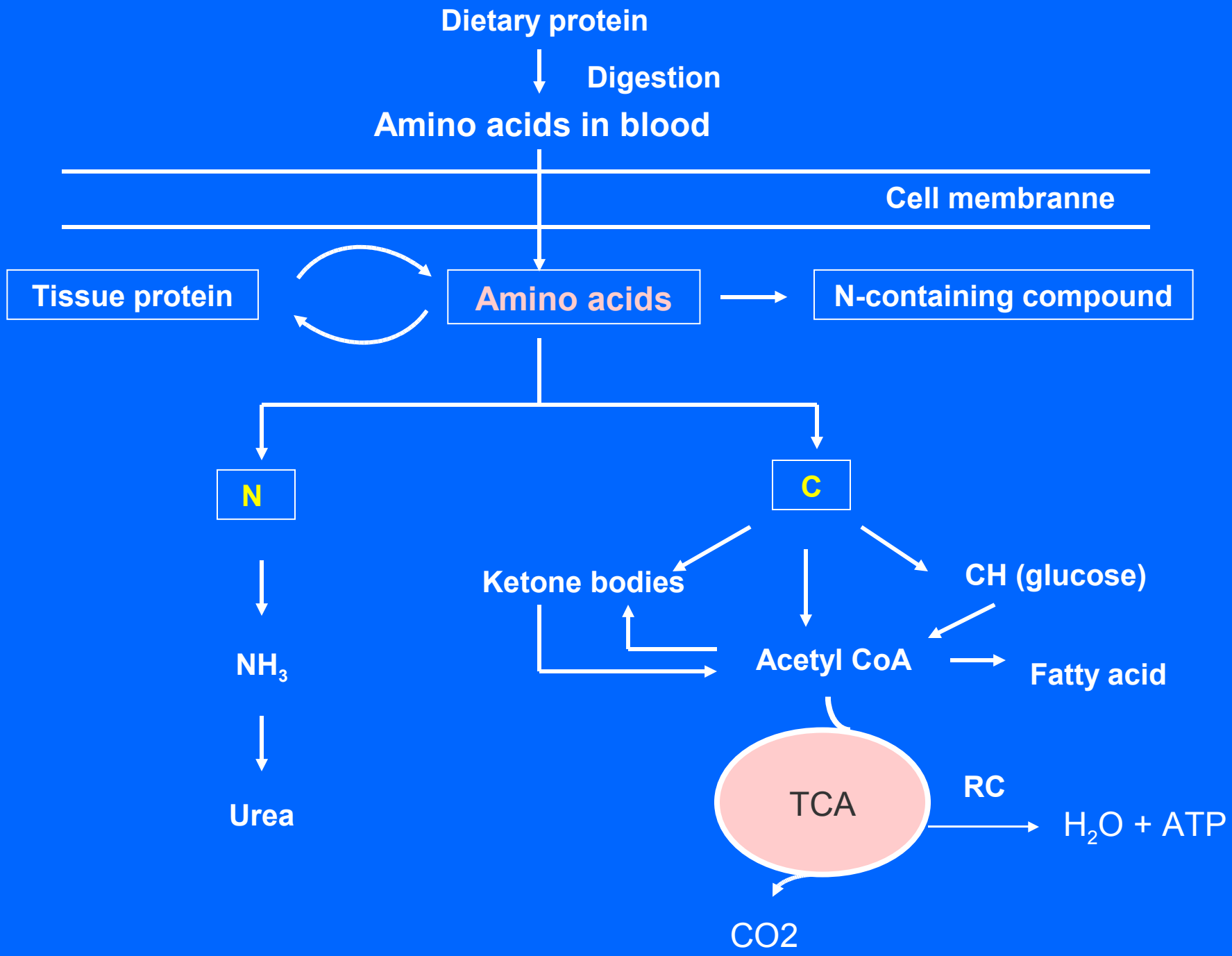
Amino acids – derived from dietary protein – absorbed from intestine through blood – taken up by tissues – used for

- biosynthesis of body protein
- oxidized to yield energy

Body protein always undergo turnover – constantly being synthesized and degraded

The AA released by body protein breakdown – enter the same pool of AA as the AA from the diet

AA also used for synthesis of N-containing compound


Dietary protein
Digestion
Amino acids in blood
Cell membranne
Tissue protein
Amino acids
N-containing compound
N
C
Ketone bodies
CH (glucose)
NH3
Acetyl CoA
Fatty acid
Urea
TCA
RC
H2O + ATP
CO2

- Metabolism of amino acid - more complex compared to carbohydrate and lipid metabolism
- In normal diet, 60-100 g proteins- most are used for synthesis of proteins in liver and other tissues
- Excessive amino acids in the diet – converted to glucose (energy) → fatty acid → t a g (energy depot)

Amino acid required for

- Biosynthesis of proteins
- precursor for N compounds
- oxidized - N atom → urea
  - C atom → - CH (glucose)
    - acetyl CoA – ketone bodies, fatty acid
    - non essential amino acid

Amino acids – 20 AA forming protein in nature

- Essential AA – must be present in the diet – can not be synthesized
- Non essential AA – can be formed by transamination of metabolic intermediates

11 from 20 AA-forming protein – can be synthesized in our body (non essential AA)

- 10 AA → can be synthesized from glucose
  - ser - asn
  - gly - glu
  - cys - gln
  - ala - pro
  - asp - arg

- 1 AA → synthesized from essential AA

  phe → tyr

- 9 AA → essential → must be present in our diet → its C atom – can not be synthesized
  - lys - trp
  - ile - phe
  - leu - met
  - thr - his
  - val - *arg

  (L I L T V T O P M H A)

  - **Arg** → semi essential
    children → essential
    adult → synthesis from urea cycle

DEGRADATION of AMINO ACIDS

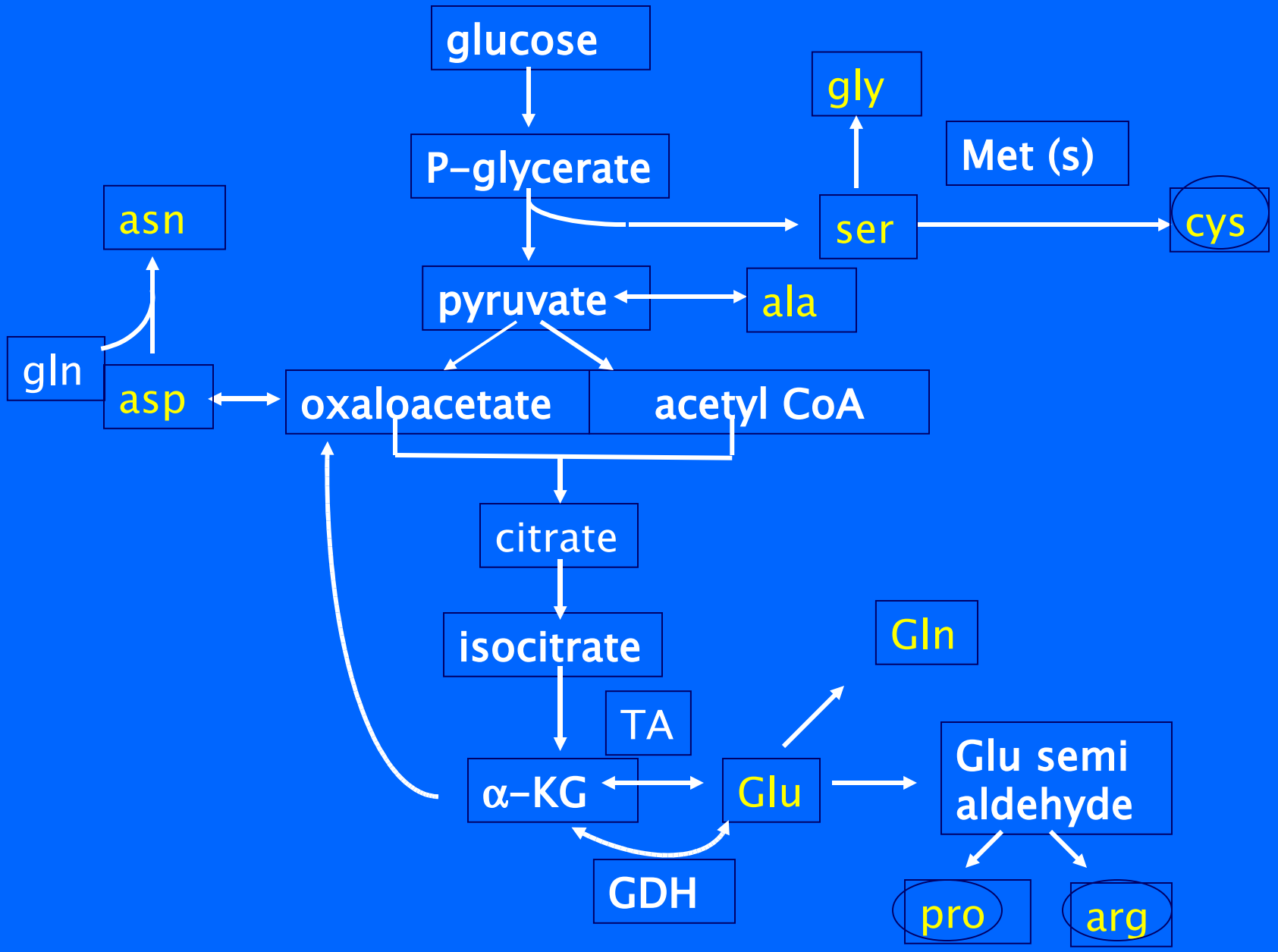
- their carbons converted to
  - CO_2
  - compounds that produce glucose in the liver (pyruvate, α-KG, succ CoA, fumarate, oxaloacetate)
  - ketone bodies

- glucogenic a a - if their C converted to glc
- ketogenic a a - if their C converted to acetyl CoA or acetoacetate

METABOLISM OF CARBON ATOM AA

11 non essential AA

- 10 AA – can be formed from glucose – through intermediate of glycolysis and TCA
  - **4 AA** – from **glycolysis intermediate**
    - ser
    - gly
    - cys
    - ala
  - **6 AA** – from **TCA cycle intermediate**
    - glu, gln, pro, arg – from α-KG
    - asp, asn – from oxaloacetate


glucose
P-glycerate
gly
Met (s)
ser
cys
asn
pyruvate
ala
gln
asp
oxaloacetate
acetyl CoA
citrate
isocitrate
Gln
TA
α-KG
Glu
Glu semi aldehyde
GDH
pro
arg

In fasting

- most of AA → pyruvate, intermediate of TCA cycle, acetyl CoA → formed glucose or ketone bodies → blood → energy for the tissues → CO_2 + H_2O + ATP

- AA synthesized from intermediate of glycolysis (non essential A) - produced` pyruvate on degradation

- A A synthesized from intermediate of Krebs cycle - produced this internediate during degradation

Glucogenic amino acids

- tryptophane → produced alanine → converted to pyruvate → glucose
- methionine, threonine, valine, isoleucine → succynil CoA → glucose
- Phenyl alanine→ converted to tyrosine → fumarate → glucose

Glucogenic and ketogenic amino acids :

- tryptophane, isoleucine, threonine → acetyl CoA
- phenyl alanine → acetoacetate

Ketogenic amino acids :

- lysine, leucine

- **During fasting** – muscle proteins were degraded to amino acids – some were oxidized to produce energy and converted to ala and ser

- In gut cells – glu converted to ala

- Ala & other amino acids – enter the liver

  - nitrogen converted to urea, excreted in the urine

  - carbons converted to glucose and ketone bodies – oxidized by various tissues for energy

- before the carbon skeleton of amino acids are oxidized, the nitrogen atom must be **removed**

- nitrogen atom from AA - formed ammonia (NH_3) – toxic to the body

- in liver NH_3 and $-NH_2$ group from AA - converted to urea

ROLE of GLUTAMATE in METABOLISM of AMINO ACID NITROGEN

- glu play role in synthesis and degradation of amino acids

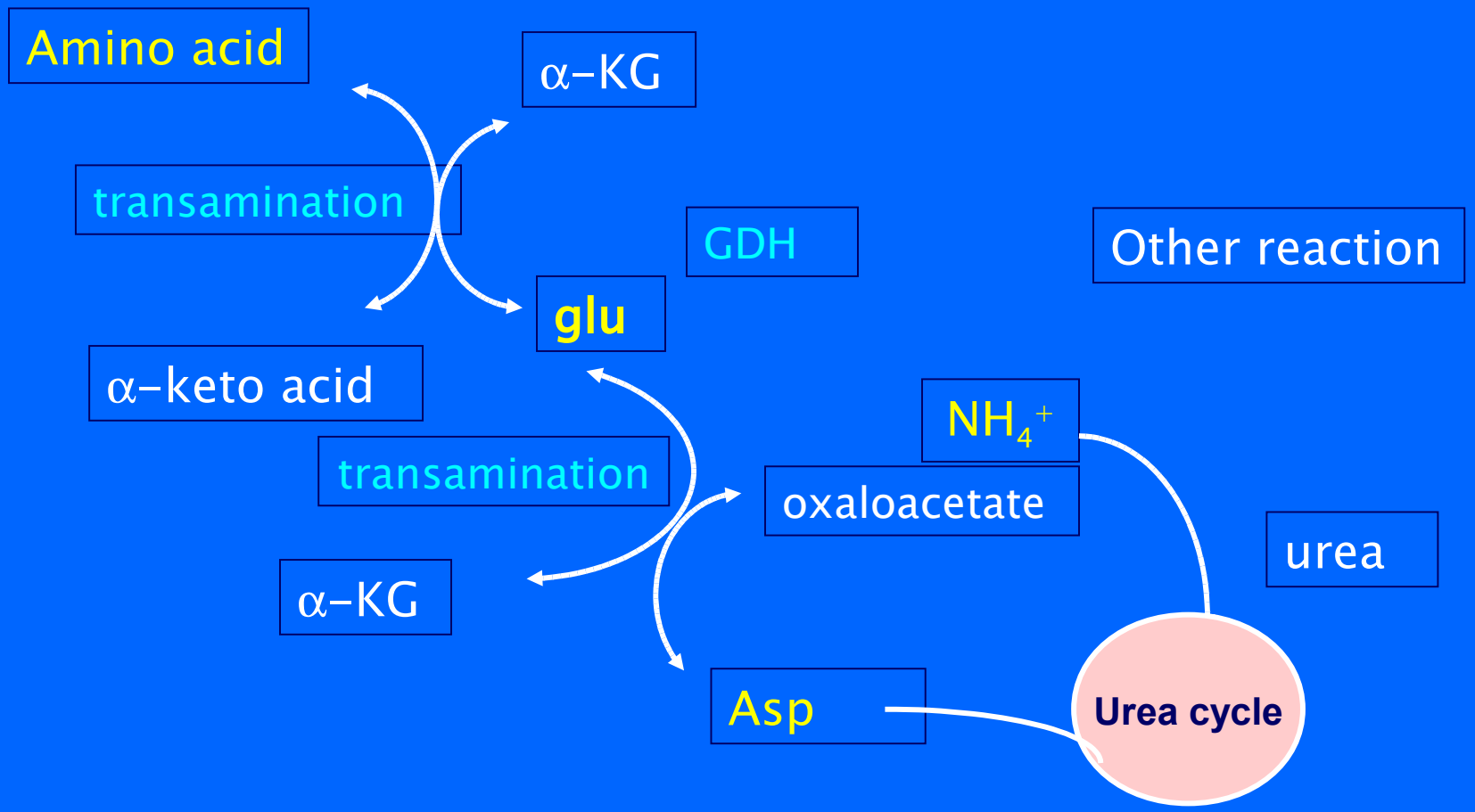
Role of glutamate in AA synthesis

- glu obtains N from other amino acid by
  - transamination reaction
  - from NH_4^+ by glu dehydrogenase reaction

- transfer NH_2 group from glu to α-ketoacid → produce corresponding amino acid

Role glutamate on AA degradation

- glu collect N from other amino acids by transamination reaction
- some of this N - released as NH_3 by glu dehydrogenase reaction



Role of glutamate in metabolism of AA nitrogen

- Glutamate can collect nitrogen from other amino acids (from transamination reactions) – then release NH_3 via glutamate DH reaction
- His - directly deaminated to form NH_4^+
- Ser and thr - dehydrated, need PLP - form NH_4^+
- Gln and asn - deamidated - form NH_4^+, glu and asp, catalyzed by glutaminase / asparaginase

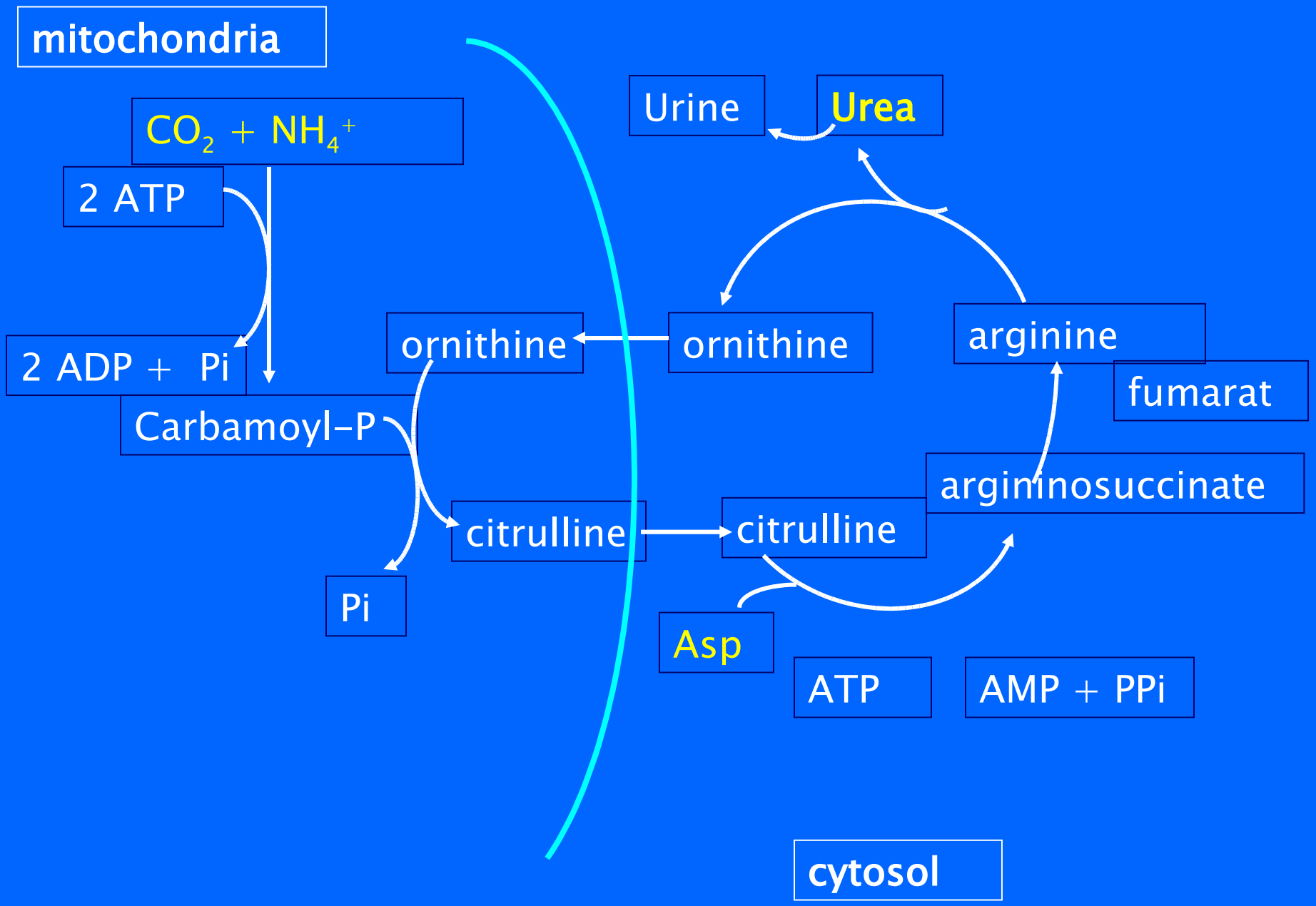
UREA CYCLE

STEPS

- synthesis of carbamoyl phosphate (in mitochondria) from NH_4^+, CO_2 and ATP

- production of arginine
  - carbamoyl P + ornitihine → citrulline
  - citrulline transported across mitoch. membrane -enter cytosol
  - in cytosol, citrulline + aspartate → arginino-succinate, cleave by argininosuccinase → fumarate + arginine

- Arginine cleave by arginase → urea + ornitihine
  ornithine transported into mitoch,for another round of the cycle


mitochondria
$CO_2 + NH_4^+$
2 ATP
2 ADP + Pi
Carbamoyl-P
ornithine
citrulline
Pi
Urine
Urea
ornithine
arginine
fumarat
argininosuccinate
citrulline
Asp
ATP
AMP + PPi
cytosol

Urea excretion in fasting

- **Fasting** – important role of liver to maintain blood glucose

  AA from muscle protein → substrate for gluconeogenesis

  AA → **C atom → glucose**

  AA → **N atom → urea**

  → **urea excretion ↑** in fasting state

- **Prolonged fasting**

  Brain →did not depend on glucose, use ketone bodies as energy

  → sparing blood glucose – less muscle protein is cleaved to provide AA for gluconeogenesis → **urea excretion ↓**

Transfer of -NH_2 group between AA

- Non essential AA – can be synthesized from its keto acid (if needed), via transfer of -NH_2 group from AA to keto acid, catalyzed by **transaminase** or aminotransferase

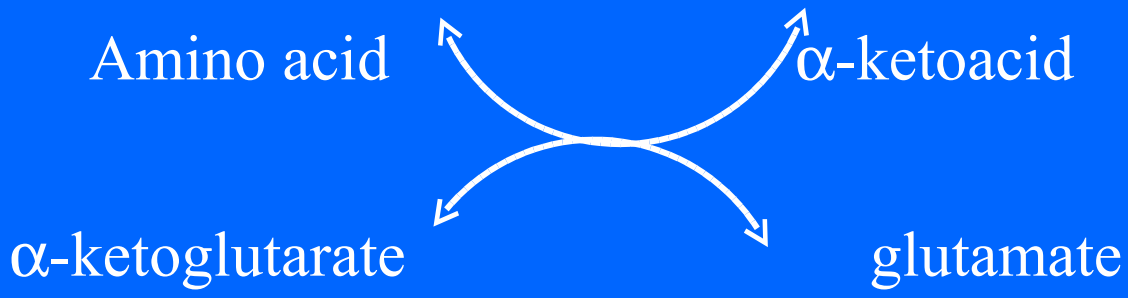
- Transfer of -NH_2 also occur in degradation of AA

- Reaction is reversible – in hyperamononemia – disturbance in N excretion - supplementation of keto acid in the diet

- Example of transaminase – SGOT (=AST), SGPT (=ALT)

Transamination reaction .

- the major process for removing nitrogen from amino acids
- nitrogen transferred from original amino acids to α-ketoglutarate → glutamate + α-ketoacid, catalyzed by transaminase, pyridoxalphosphate (PLP) as cofactor



- all amino acids (excepts lys & thr) – can undergo transamination

Oxidative deamination.

- nitrogen of certain amino acids released as ammonia (NH_3) or ammonium (NH_4^+)

- Glutamate (glu) oxidatively deaminated by glutamate dehydrogenase (Glu DH), produces NH_4^+ + α-ketoglutarate
  - NAD^+ or $NADP^+$ as cofactor
  - occur in mitochondria

- Enzymes important in the process of inter conversion of amino acids and removing nitrogen
  - transaminase
  - glutamate dehydrogenase
  - deaminase

- Conversion of amino acid nitrogen to urea – occur mainly in the liver – through urea cycle – from precursor
  - NH_4^+
  - CO_2
  - ATP
  - nitrogen of aspartate

NITROGEN BALANCE

- Healthy adult - **N balance N (N intake = N excreted as urea))**
- In well fed state – N excreted – come from
  - Intake of protein >> or
  - Normal "turnover" protein
- **Positive N balance → N intake > N excreted**
  - Growth & development
  - Pregnancy
  - Convalescence
- **Negative N balance → N excreted > N intake**
  - Starvation
  - Disease
  - Deficiency of essential AA

N- containing product from AA

- Cellular protein
- Hormone (tyroxine, epinephrine, insulin)
- Neurotransmitter
- Creatine-P
- Heme of Hb, Mb, cytochrome
- Melanine pigment
- Purine and pirimidine base

N-CONTAINING COMPOUND FROM AMINO ACIDS

1. Creatine

- synthesized from gly, arg and S-adenosylmethio-nine (SAM)
- + ATP → creatine P (stores and transport high energy phosphate within cells)
- creatine P spontaneously → creatinine (excreted in urine)
- serum creatinine - indicator of GFR of the kidney
- urinary creatinine - assessing the quantity of other compounds excreted in the urine

2. Glycine

used for conjugation reaction with other compounds (in phase II xenobiotic metabolism) - increased water solubility - easier to excrete in the urine (bile salts, metabolites, drugs)

3. Heme

produced by condensation of gly and succ CoA $\rightarrow$ δ-aminolevulinic acid, precursor of heme

4. Purine base ring

entire gly molecule incorporated into ring + other N provided by gln and asp + CO_2 + tetrahydrofolate

5. Pyrymidine base ring - formed from asp + carbamoyl P

6. Neurotransmitter, hormone, pigment

γ-aminobutyric acid (GABA), histamine, serotonin, dopamine, norepinephrine,epinephrine, insulin, thyroid hormone, NO_2, melanine

INTEGRATION OF METABOLISM

In well fed state

- After meal – fuels are oxidized – to meet our energy needs

- Any excess of fuel is stored
  - mainly as triacylglycerol in adipose tissue
  - as glycogen in muscle and liver

- Amino acids – converted to body proteins, particularly in muscle

During fasting

- ± 1 hour after meal – blood glucose ↓ - insulin ↓, glucagon ↑
- Liver glycogenolysis ↑ - supplying glucose to the blood
- Adipose tissue lipolysis ↑ - glycerol ↑ and FFA ↑ in blood
- FFA – major fuel that oxidized by muscle and liver
- Liver use FA to produce ketone bodies – to the blood – taken up by extrahepatic tissues for energy
- Brain & erythrocyte – use glucose as energy

As fasting progress

- liver produce glucose from gluconeogenesis – from substrate glycerol, lactate, glucogenic amino acid
- If C atom of AA converted to glucose – the N atom converted tu urea → urea excretion ↑

Prolonged fasting

- Muscle decreases its use of ketone bodies – ketone bodies ↑ in blood
- Brain oxidizes ketone bodies as energy – brain need less glucose – liver decreases its rate of gluconeogenesis – muscle protein is spared – because degradation of protein to AA ↓ → urea excretion ↓


Thank you