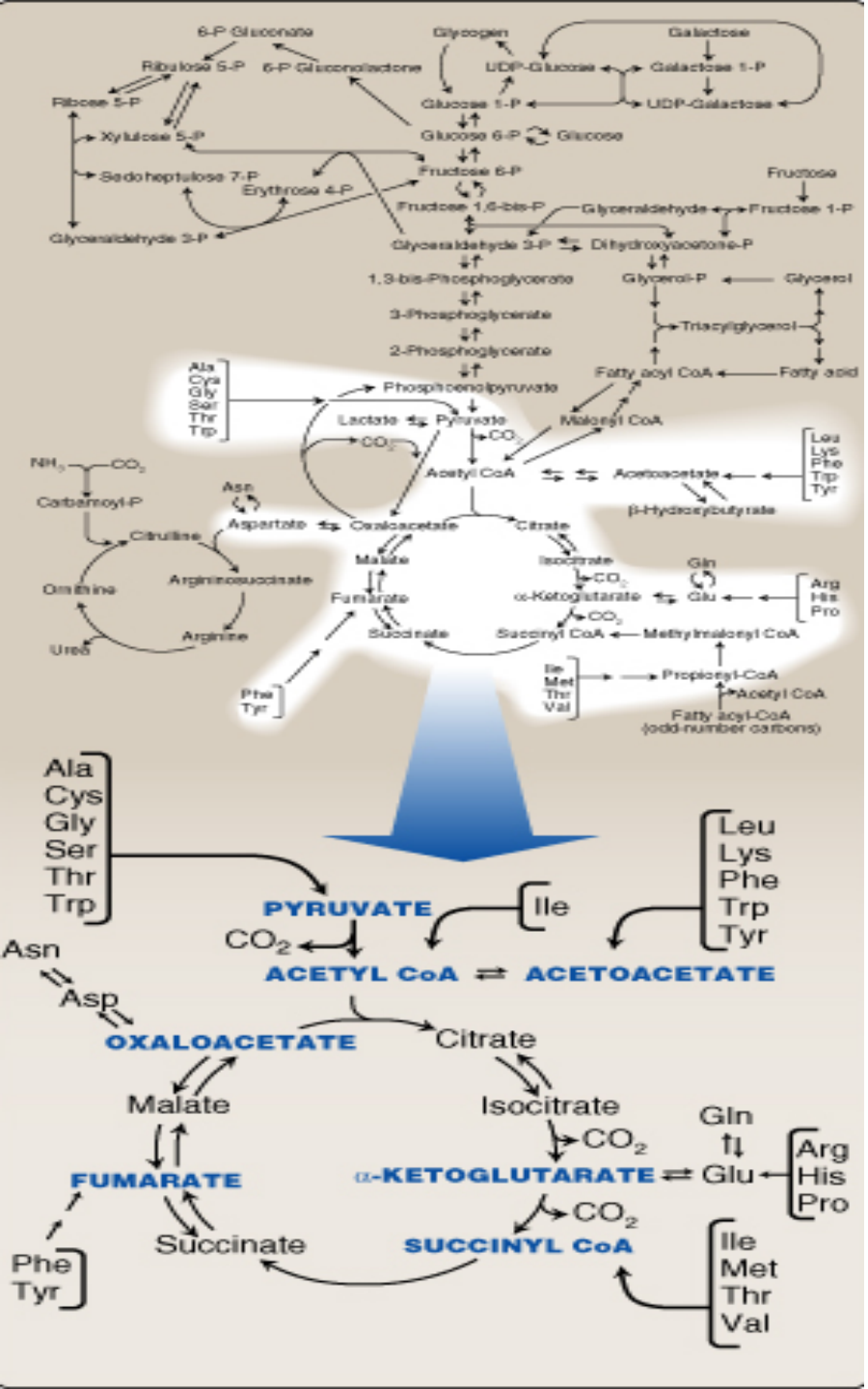
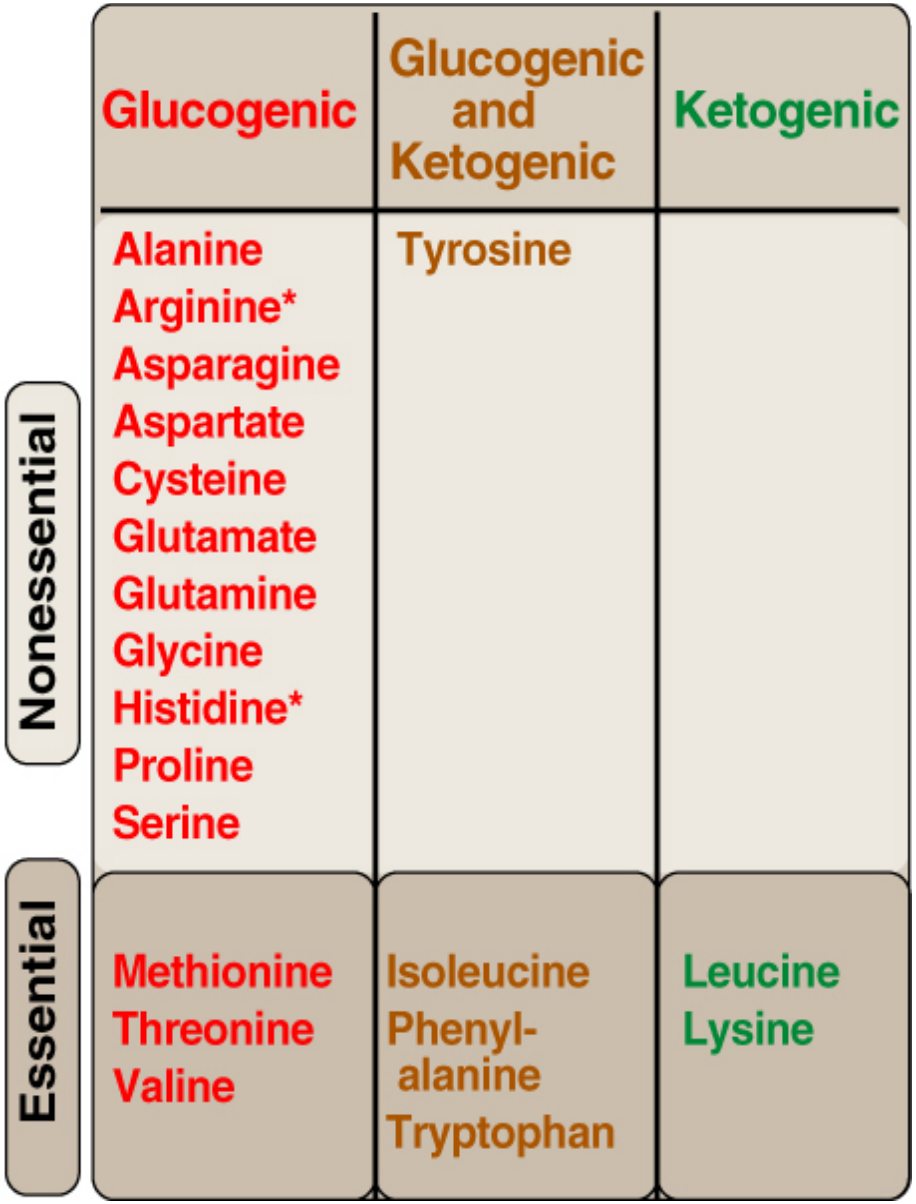


- The catabolism of the amino acids found in proteins involves the removal of α-amino groups, followed by the breakdown of the resulting carbon skeletons. These pathways converge to form seven intermediate products: oxaloacetate, α-ketoglutarate, pyruvate, fumarate, succinyl CoA, acetyl Coa, and acetoacetyl CoA. These products directly enter the pathways of intermediary metabolism, resulting either in the synthesis of glucose or lipid, or in the production of energy through their oxidation to CO_2 and water by the citric acid cycle. The figure provides an overview of these pathways, with a more detailed summary presented later.

GLUCOGENIC AND KETOGENIC



AMINO ACIDS

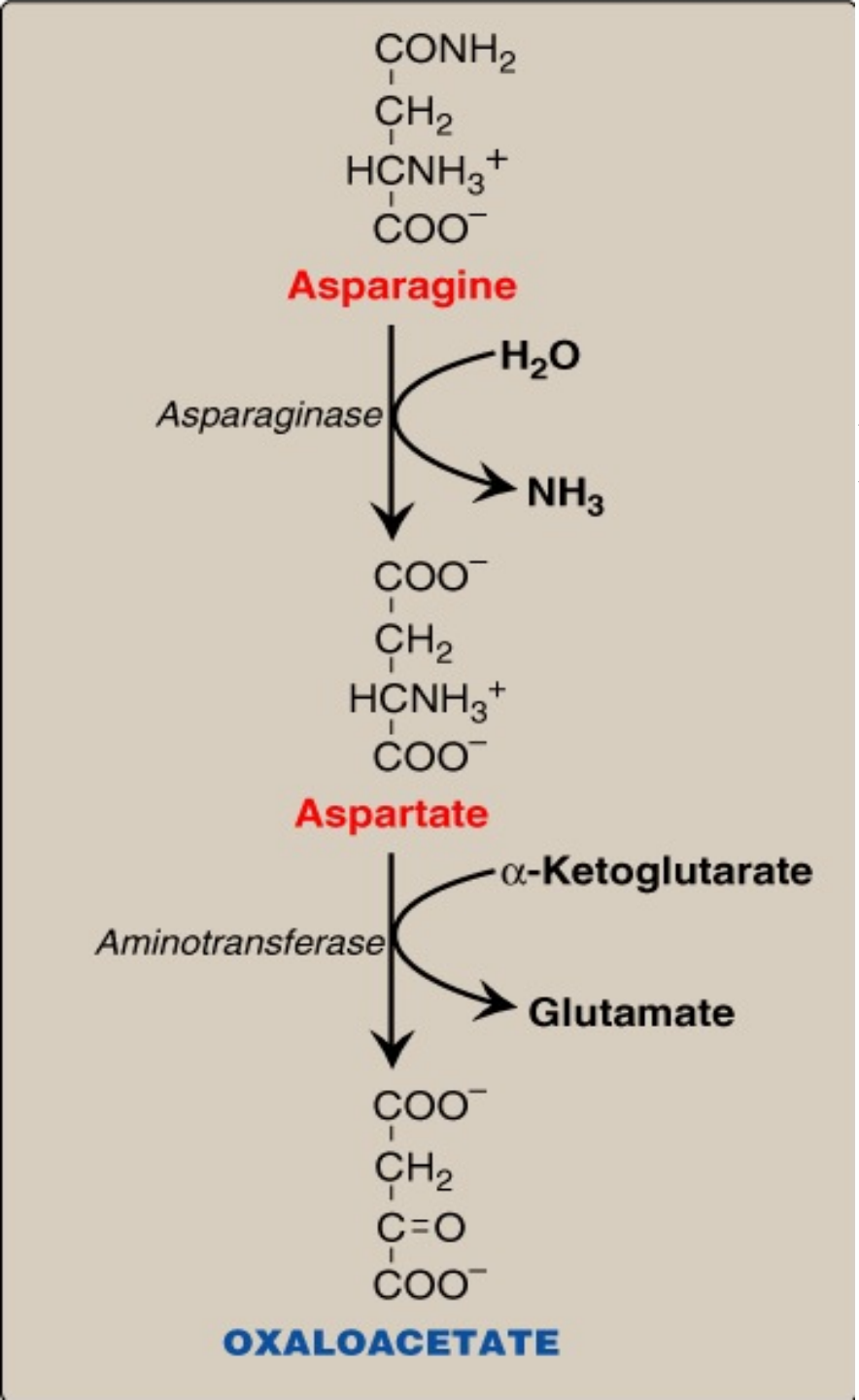
Amino Acids can be classified as glucogenic or ketogenic based on which of the seven intermediates are produced during their catabolism.

Glucogenic amino acids

Amino acids whose catabolism yield pyruvate or one of the intermediates of the citric acid cycle are termed glucogenic or glycogenic. These intermediates are substrates for gluconeogenesis and, therefore, can give rise to the net formation of glucose or glycogen in the liver and glycogen in the muscle.

Ketogenic amino acids

Amino acids whose catabolism yield either acetoacetate or one of its precursor are termed ketogenic. Acetoacetate is one of the "ketone bodies", which also include 3-hydroxybutyrate and acetone. Leucine and lysine are the only exclusively ketogenic amino acids found in proteins. Their carbon skeletons are not substrates for gluconeogenesis and, therefore, cannot give rise to the net formation of glucose or glycogen in the liver, or glycogen in the muscle.



CATABOLISM OF THE CARBON SKELETONS OF AMINO ACIDS

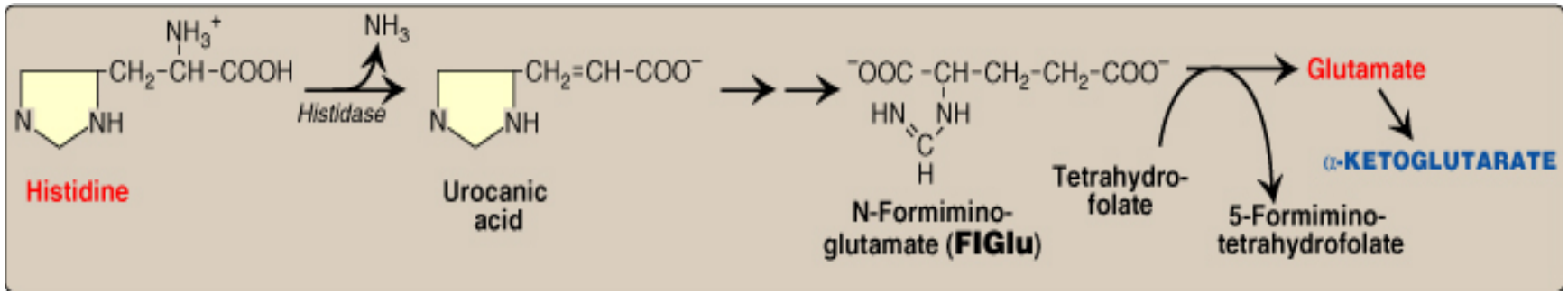
The pathways by which amino acids are catabolized, are conveniently organized according to which (or more) of the seven intermediates listed above is produced from a particular amino acid.

Amino acids that form oxaloacetate

Asparagine is hydrolyzed by asparaginase, liberating ammonia and aspartate. Some rapidly dividing leukemic cells are unable to synthesize sufficient asparagine to support their growth. This makes asparagine an essential amino acid for these cells, which therefore require asparagine from the blood. Asparaginase, which hydrolyzes asparagine to aspartate, can be administered systematically to treat leukemic patients. Asparaginase lowers the level of asparagine in the plasma and, therefore, deprives cancer cells of a required nutrient. Aspartate loses its amino group by transamination to form oxaloacetate. **Takes 2 AS for an Ox**

Amino acids that form α-ketoglutarate

- Histidine is oxidatively deaminated by histidase to urocanic acid, which subsequently forms N-formiminoglutamate (FIGlu). FIGlu donates its formimino group to tetrahydrofolate, leaving glutamate, which is degraded as described in the figure. (Go Get A Hamburger Peter) GGAHP



Glutamate, Glutamine, Arg, Histidine, Proline GGAHP

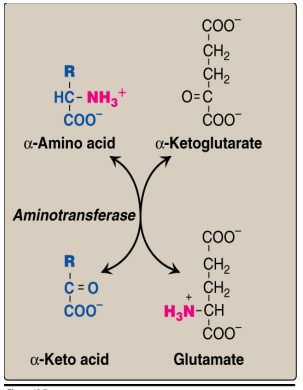
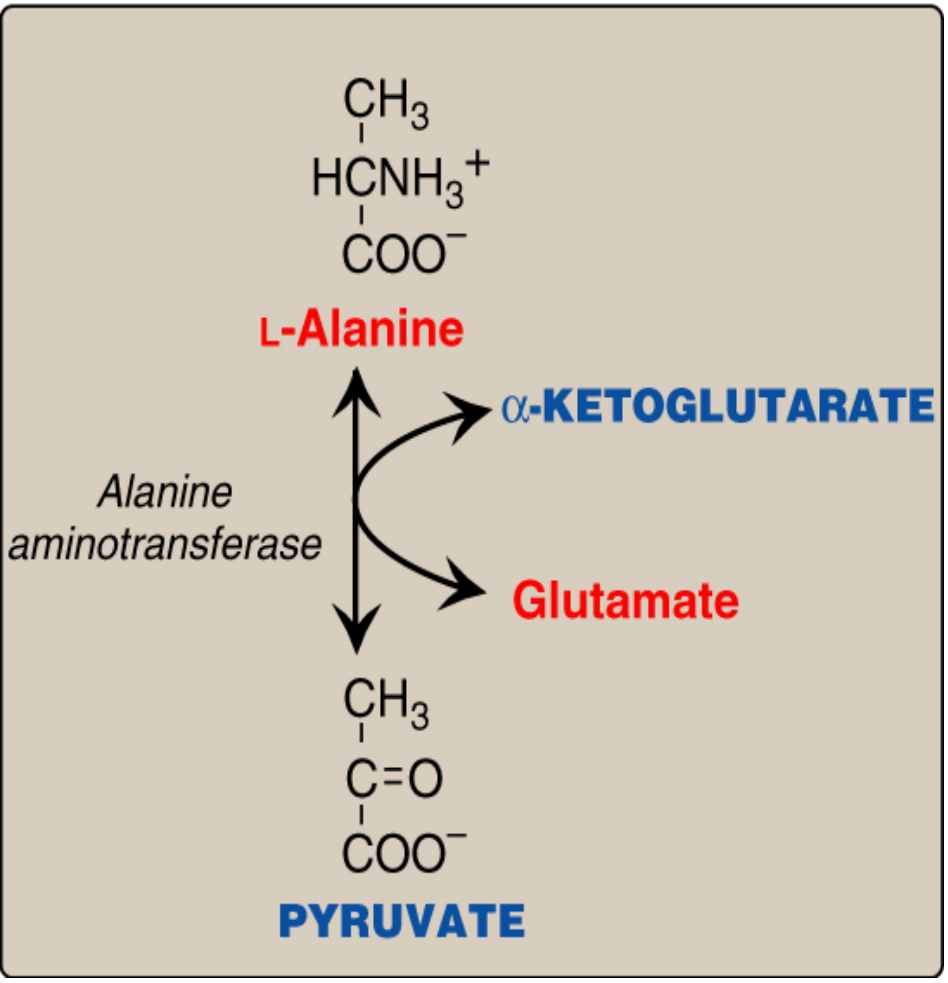
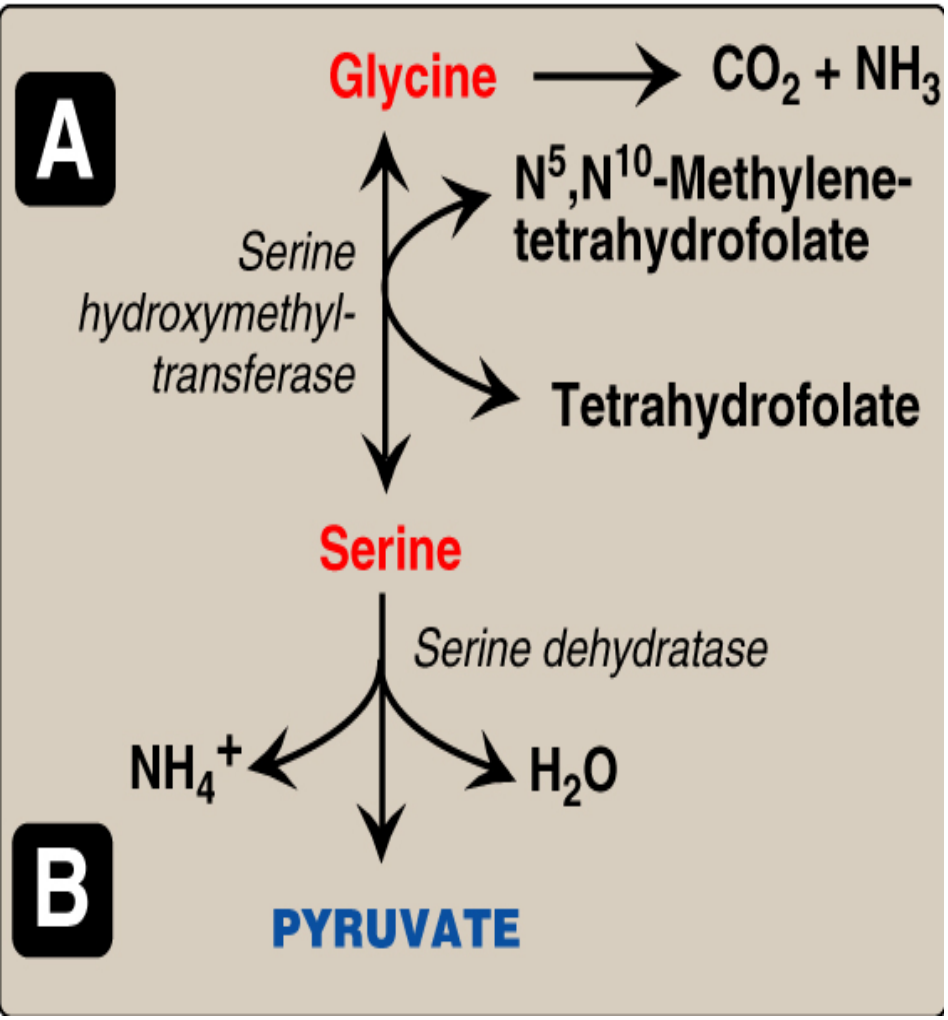


Figure 19.7
Aminotransferase reaction using α-ketoglutarate as the amino-group acceptor.

Amino acids that form pyruvate

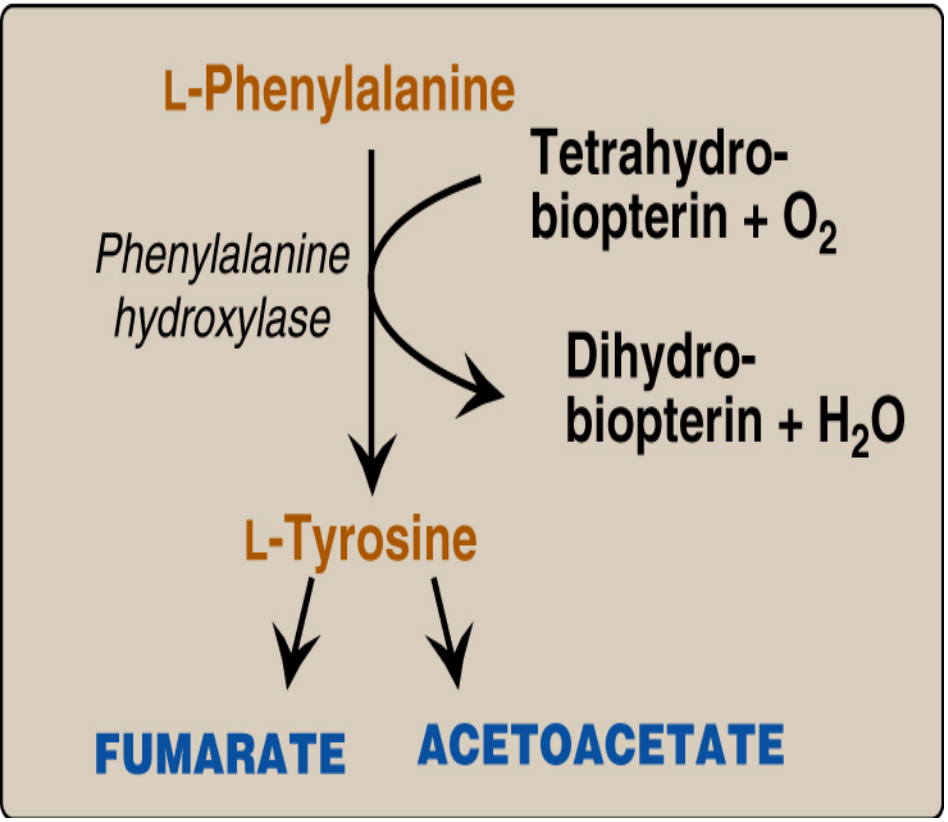


- Alanine loses its amino group by transamination to form pyruvate. (ASCG2T)



- Serine can be converted to glycine and N^5, N^{10}-methylenetetrahydrofolate. Serine can also be converted to pyruvate by serine dehydratase.
- Glycine can either be converted to serine by addition of a methylene group from N^5,N^{10}-methylenetetrahydrofolic acid, or oxidized to CO_2 and NH_4^+

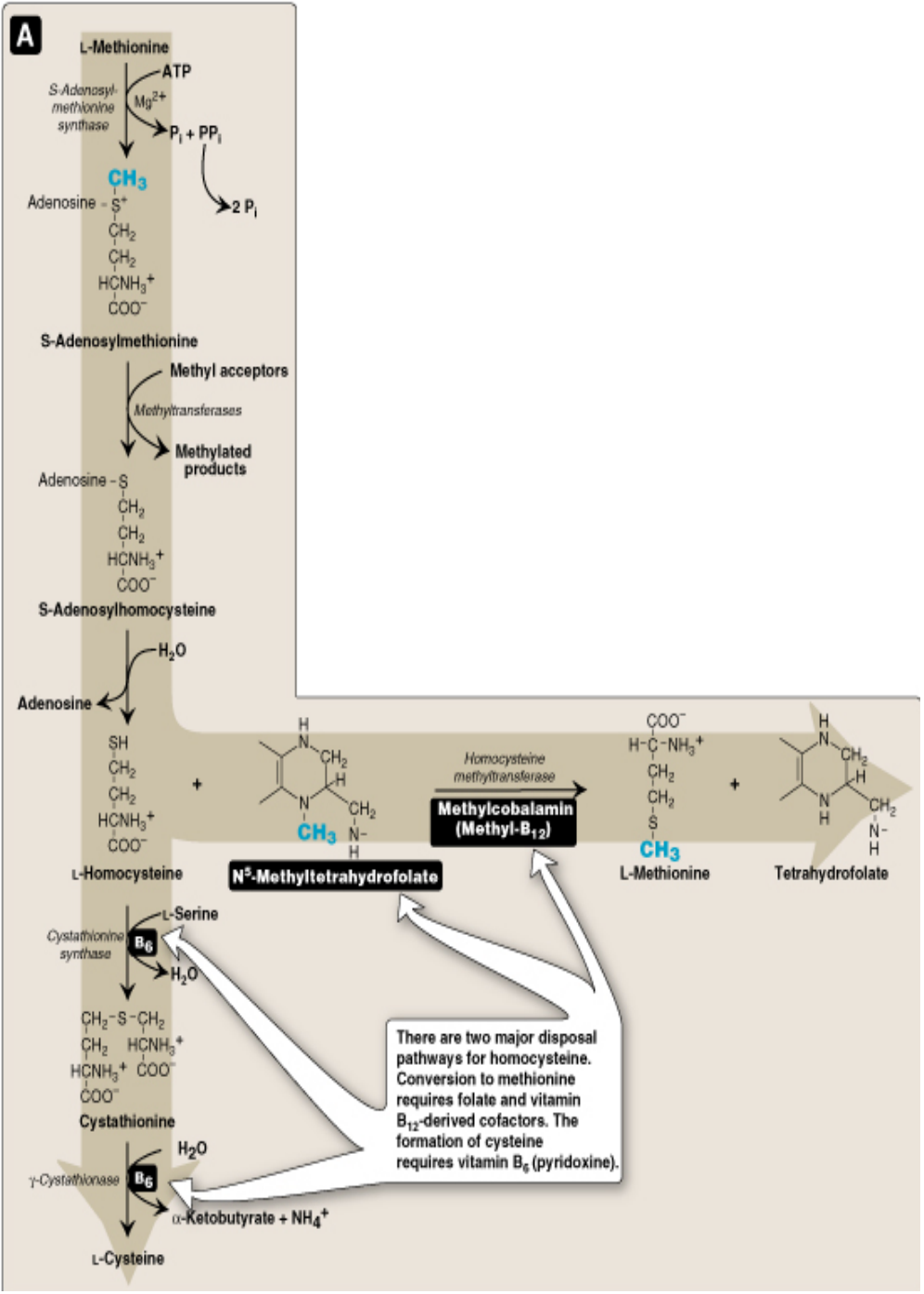
Amino acids that form fumarate



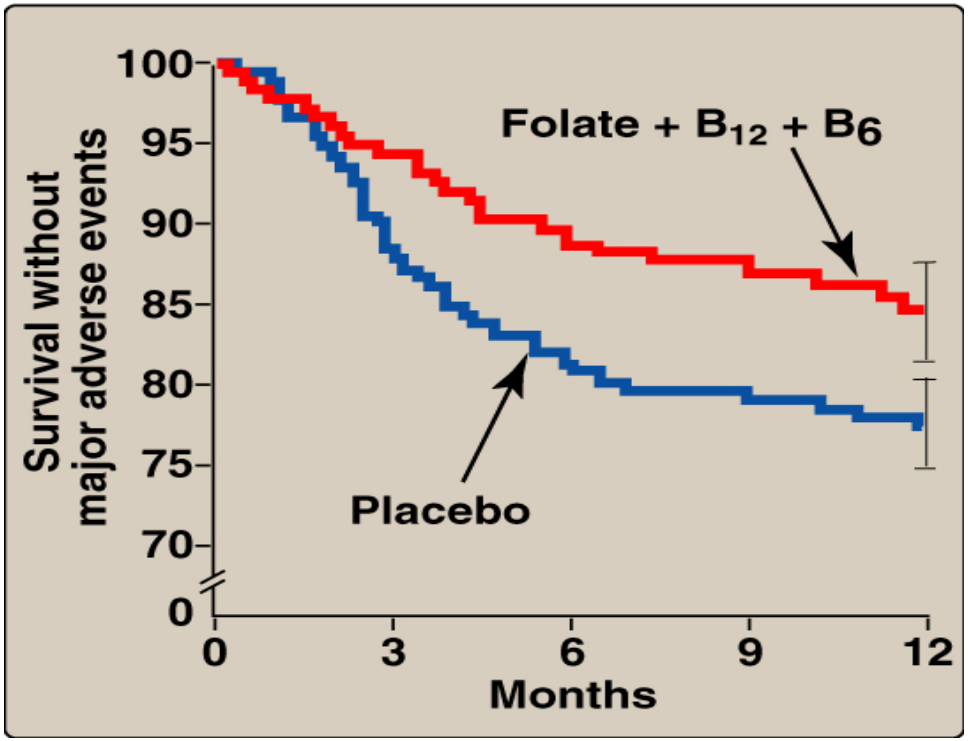
- Phenylalanine and tyrosine: hydroxylation of phenylalanine leads to the formation of tyrosine. This reaction, catalyzed by phenylalanine hydroxylase, is the first reaction in the catabolism of phenylalanine. Thus, the metabolism of phenylalanine and tyrosine merge, leading ultimately to the formation of fumarate and acetoacetate. Phenylalanine and tyrosine are, therefore, both glucogenic and ketogenic.

Perfect Total Feeling

Degradation and resynthesis of methionine

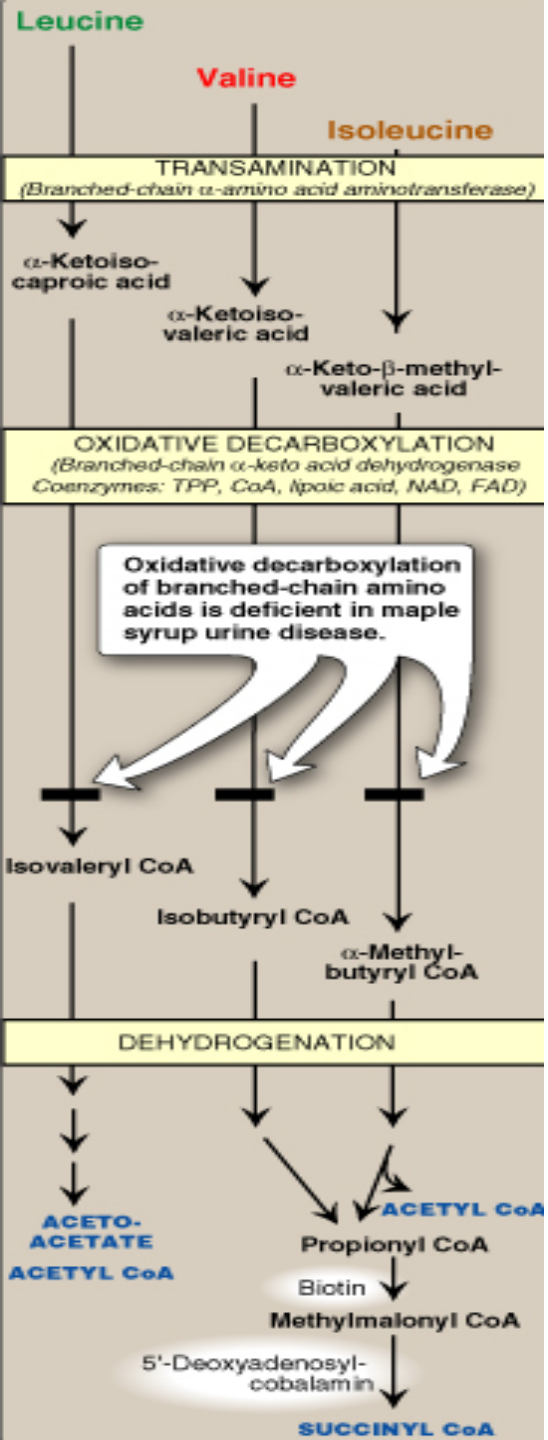


- Synthesis of SAM: Methionine condenses with Adenosine using ATP, forming SAM- a high energy compound that is unusual in that it contains no phosphate. The formation of SAM is driven, in effect, by hydrolysis of all three phosphate bonds in ATP.
- Activated methyl group: the methyl group attached to the tertiary sulfur in Sam is "activated", and can be transferred to a variety of acceptor molecules, such as ethanolamine in the synthesis of choline. The methyl group is usually transferred to oxygen or nitrogen atoms, but sometimes to carbon atoms. The reaction product, S-adenosylhomocysteine, is a simple thioether, analogous to methionine. The resulting loss of free energy accompanying the reaction makes methyl transfer essentially irreversible.
- Hydrolysis of SAM: after donation of the methyl group, S-adenosylhomocysteine is hydrolyzed to homocysteine and adenosine. Homocysteine has two fates. If there is a deficiency of methionine, homocysteine may be remethylated to methionine. If methionine stores are adequate, homocysteine may enter the transulfuration pathway, where it is converted to cysteine.



- Vascular disease: High levels of homocysteine in blood, cardiovascular risk factor (coronary artery disease) B6 and B12 (previous slide) Homocystinuria (cystathionine synthase deficiency)
- Effect of homocysteine-lowering therapy with folic acid, vitamin B_{12}, and vitamin B_6 on clinical outcome after coronary angioplasty.

Note: Balloon angioplasty is a noninvasive procedure in which a balloon-tipped catheter is introduced into a diseased blood vessel. As the balloon is inflated, the vessel opens further, allowing for placement of a stent and improved flow of blood.



Catabolism of the branched-chain amino acids

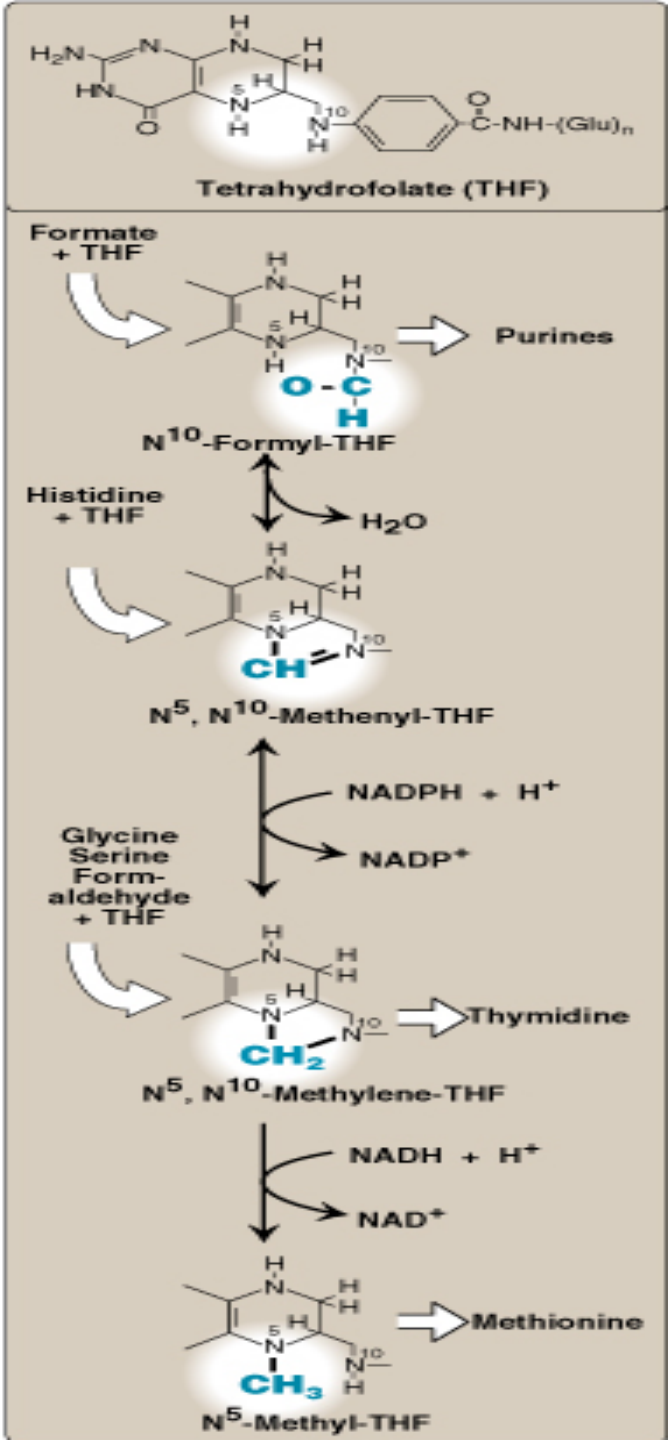
- The branched-chain amino acids, isoleucine, leucine, and valine, are essential amino acids. In contrast to other amino acids, they are metabolized primarily by the peripheral tissues, rather than by the liver. Because these three amino acids have similar route of catabolism, it is convenient to describe them as a group.

1. Transamination
2. Oxidative decarboxylation

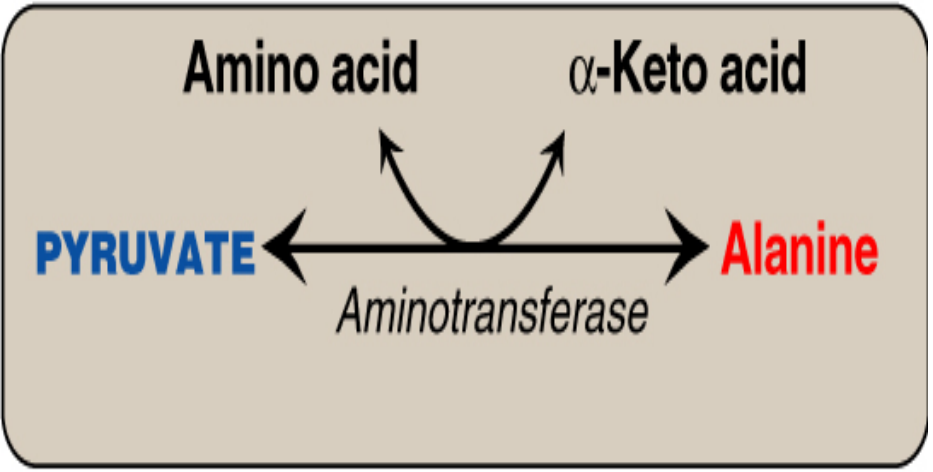
(Branched Chain α-keto acid dehydrogenase)

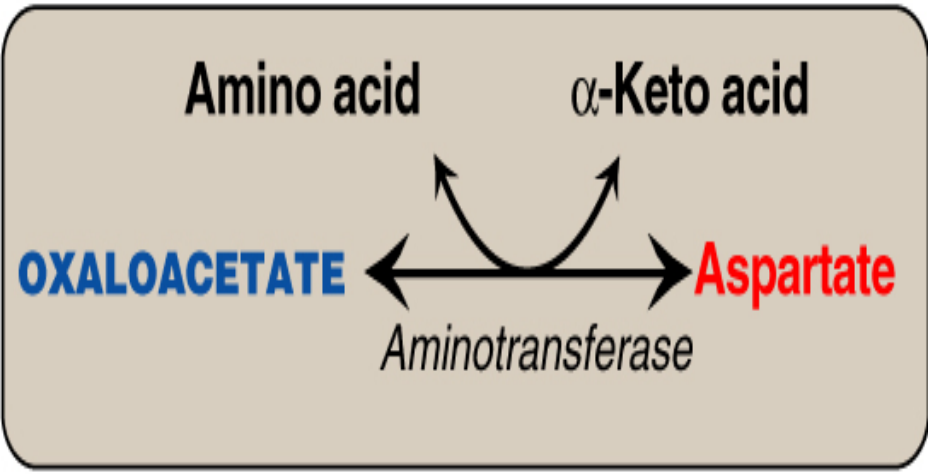
3. Dehydrogenation
4. End products

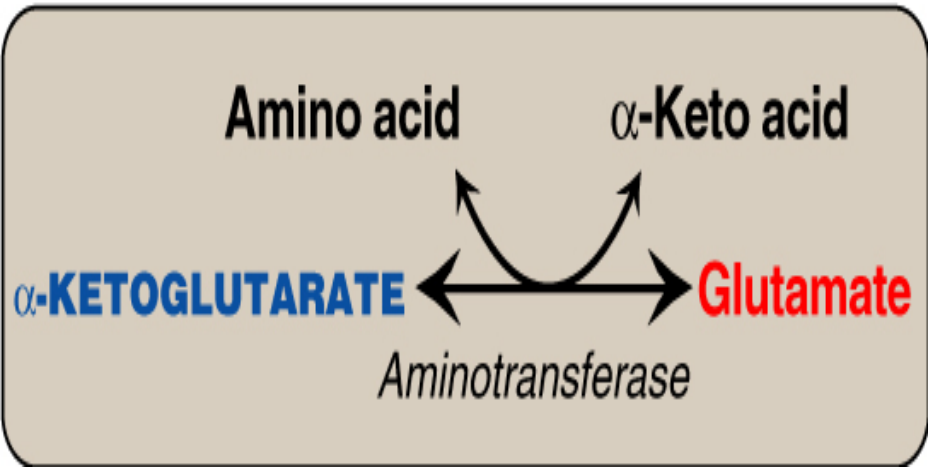
Role of folic acid in amino acid metabolism



- The active form of folic acid, tetrahydrofolic acid (THF), is produced from folate by dihydrofolate reductase in a two-step reaction requiring two moles of NADPH. The carbon unit carried by THF is bound to nitrogen N^5 or N^{10}, or to both N^5 and N^{10}. THF allows one-carbon compounds to be recognized and manipulated by biosynthetic enzymes. The figure shows the structures of the various members of the THF family, and indicates the sources of the one-carbon units and the synthetic reactions in which the specific members participate.

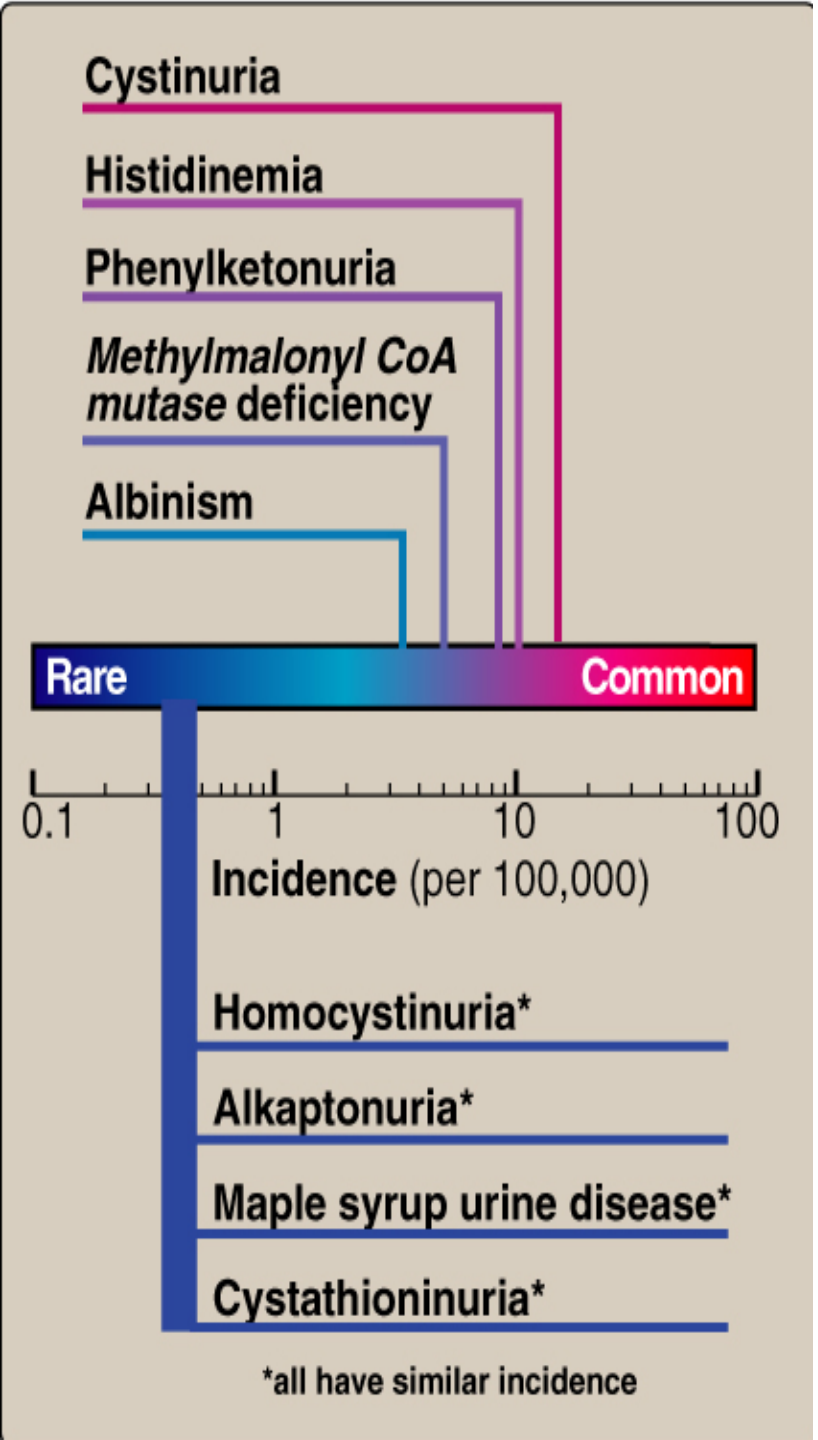






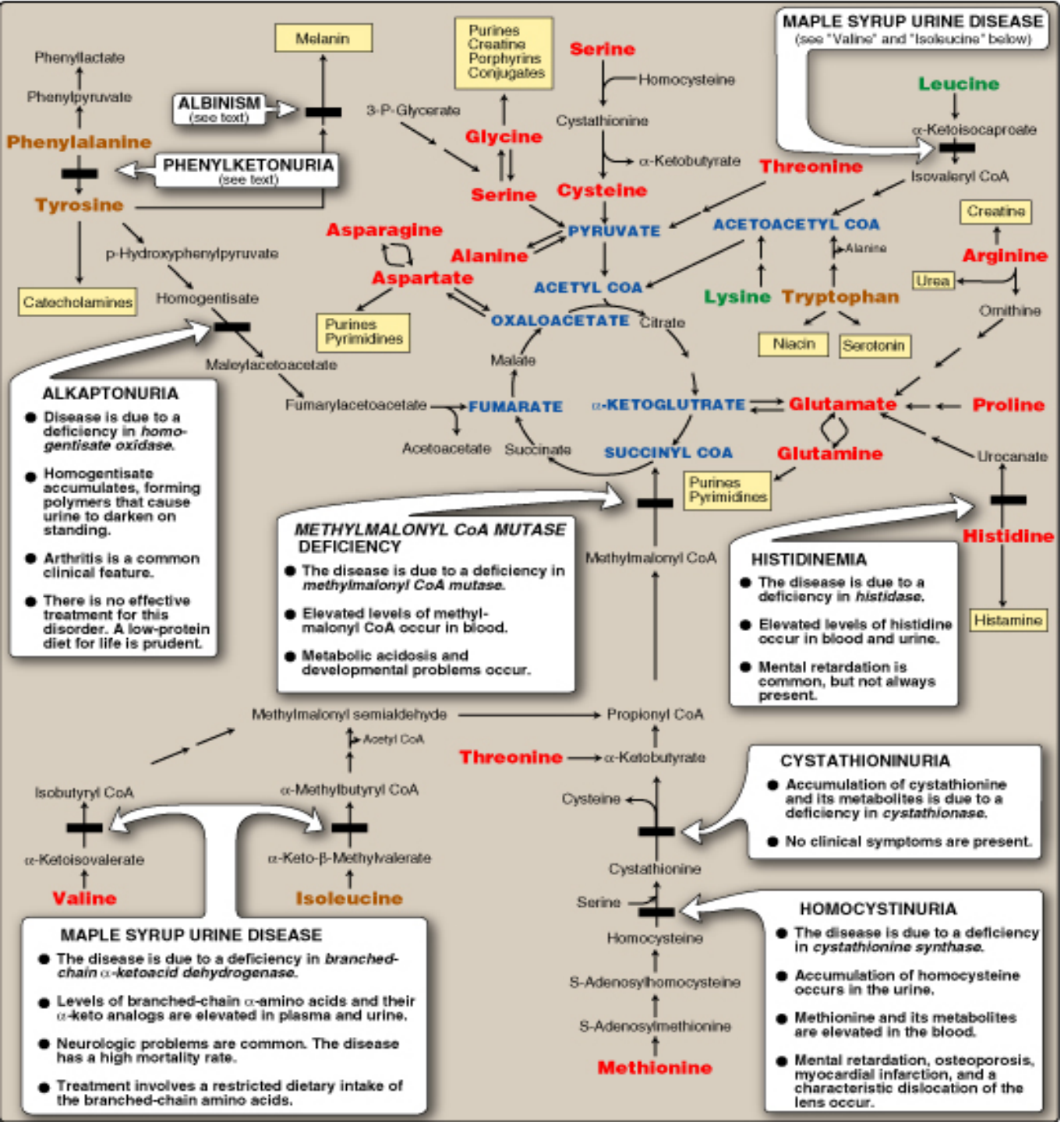
Biosynthesis on non-essential amino acids

- They are synthesized from intermediates of metabolism or from essential amino acids like the case of tyrosine and cysteine. Histidine and arginine are generally classified as non-essential depending on conc.
- From α-keto acids
- From amidation (glutamine) formed from glutamate important in synthesis and degradation providing detoxification of ammonia in liver and brain as previously discussed in Urea cycle. Asparagine formed from aspartate
- Proline formed from glutamate
- Serine (from 3 phosphoglycerate-3 phosphopyruvate-3 phosphoserine-serine and glycine), glycine(serine) and cysteine (homocysteine- cystathionine-cysteine depends on methionine (essential)
- Tyrosine (20.7) phenylalanine (essential) requires BH4 tetrahydrobiopterin



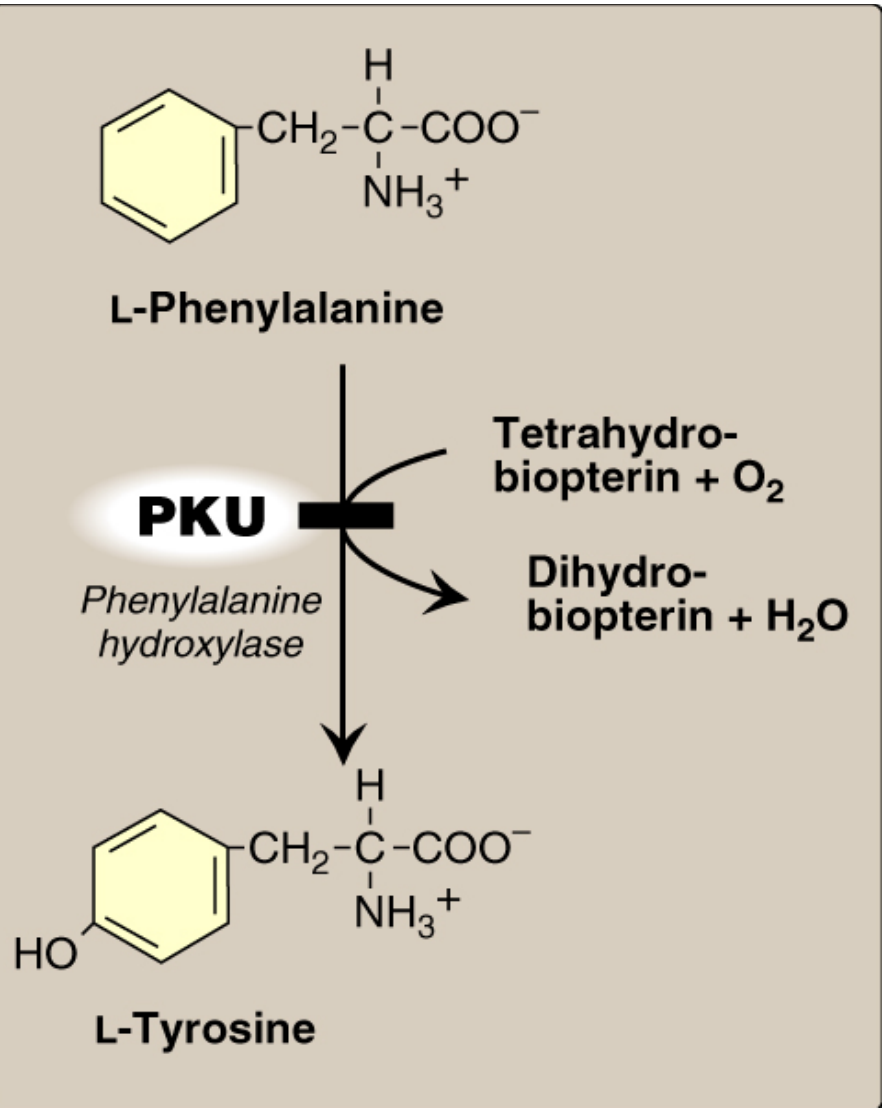
Metabolic defects in amino acid metabolism

- Caused by mutant genes resulting in abnormal proteins, total lost or partial deficiency (more often). Can result in mental retardation or developmental abnormalities. As much as fifty disorders have been described but are rare (why?) 1:250,000 however, we expect this number to increase (why?). These are some of the most commonly encountered diseases with the incidences in most populations. Phenylketonuria, maple syrup urine disease, albinism, homocystinuria and alkaptonuria.



Good review slide for metabolism of amino acids and diseases caused by enzyme deficiency. Notice glucogenic and ketogenic amino acids and metabolites of each amino acid

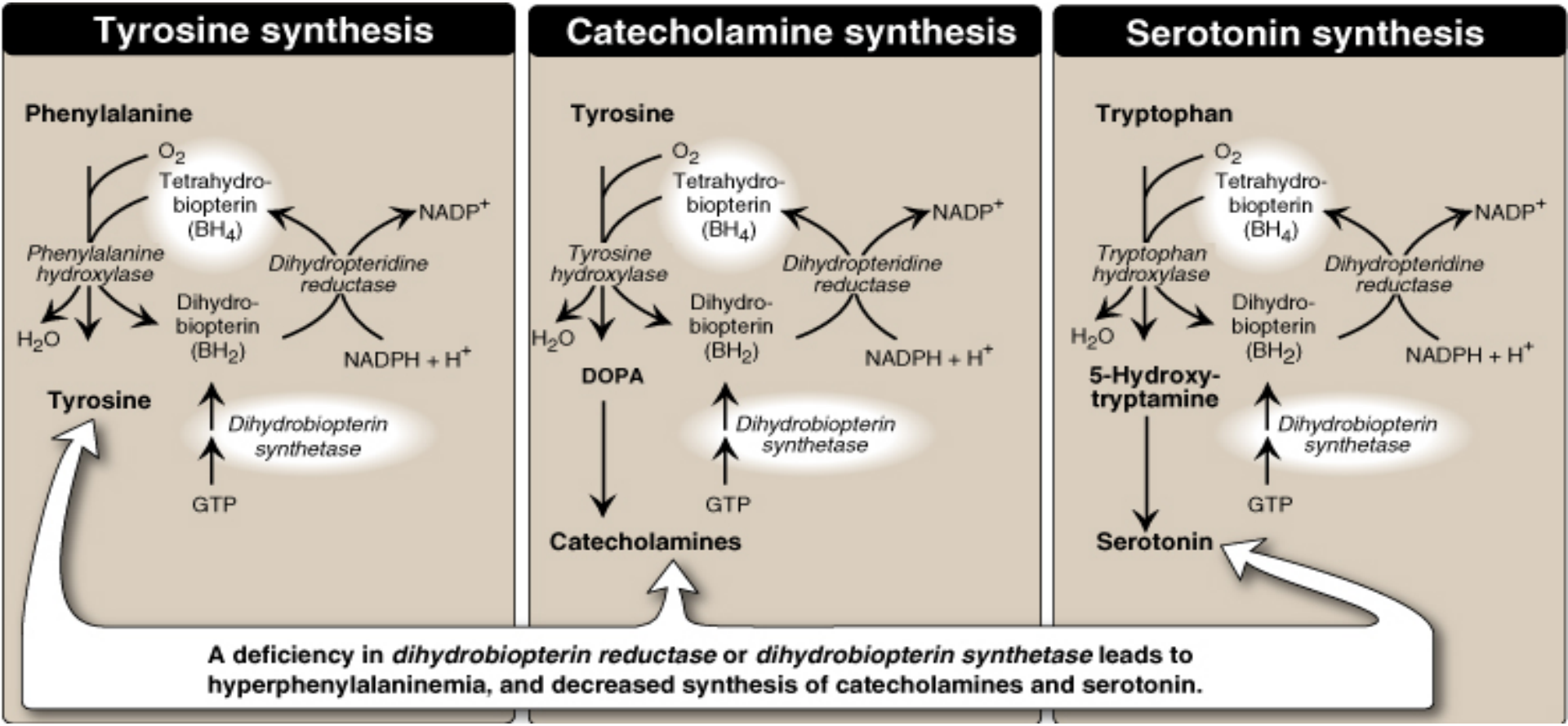
Phenylketonuria (PKU)

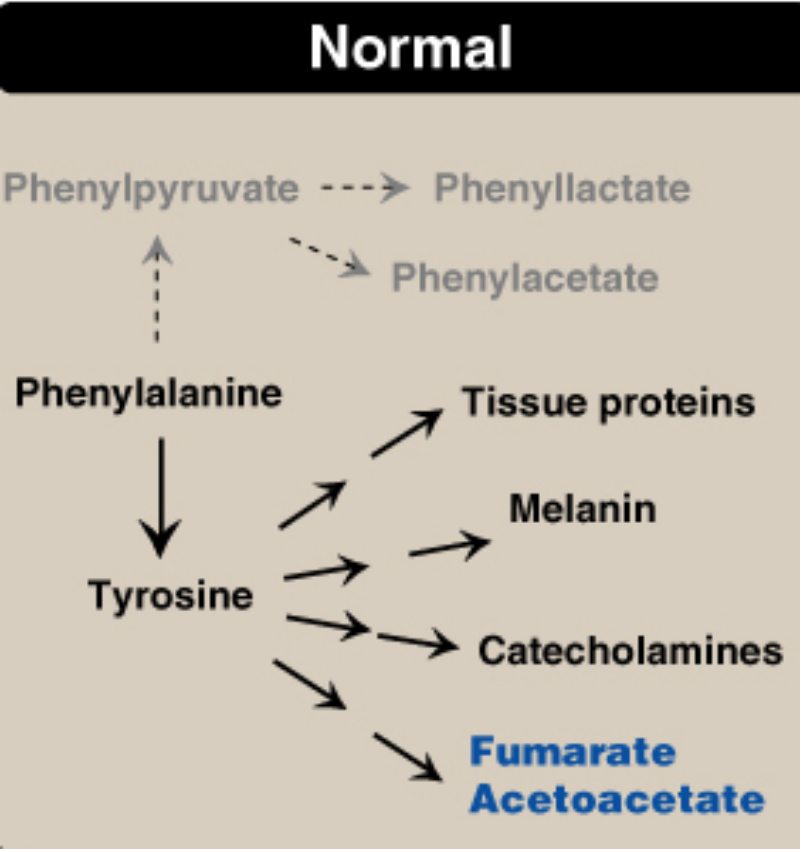


- Caused by a deficiency in phenylalanine hydroxylase 1:11,000. Hyperphenylalaninemia deficiency in enzymes involved in synthesis of the coenzyme tetrahydrobiopterin BH_4

Hyperphenylalaninemia

- Dihydrobiopterin (BH_2) synthetase
- Dihydropteridine (BH_4) reductase
- They are very important in synthesis of neurotransmitters, serotonin and catecholamines, dietary restriction of phenylalanine does not reverse CNS effects replacement therapy with BH_4 and 5-hydroxytryptophan and DOPA (sueño?)



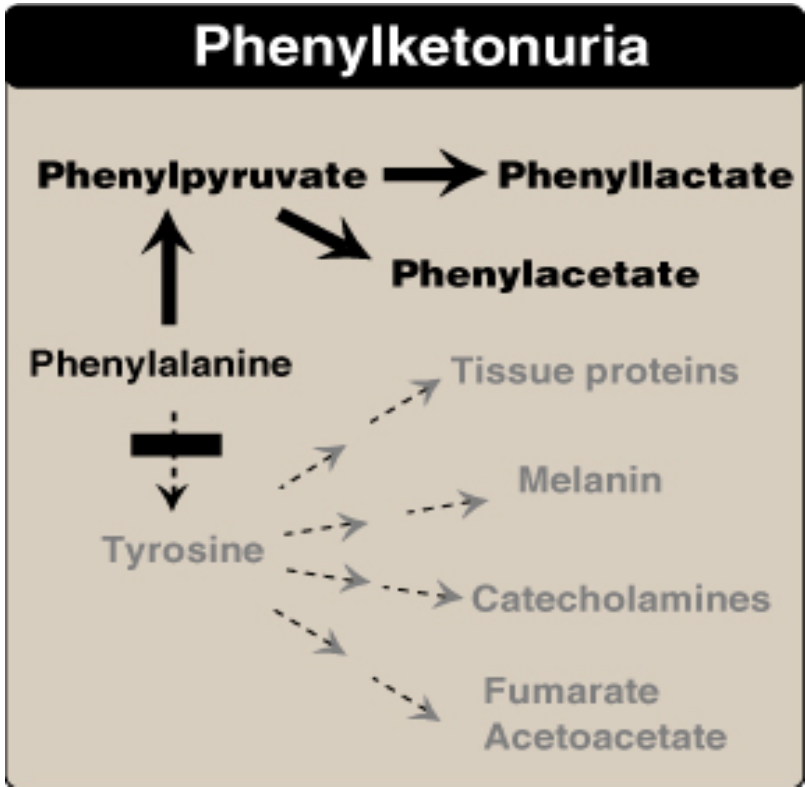


Characteristics of PKU

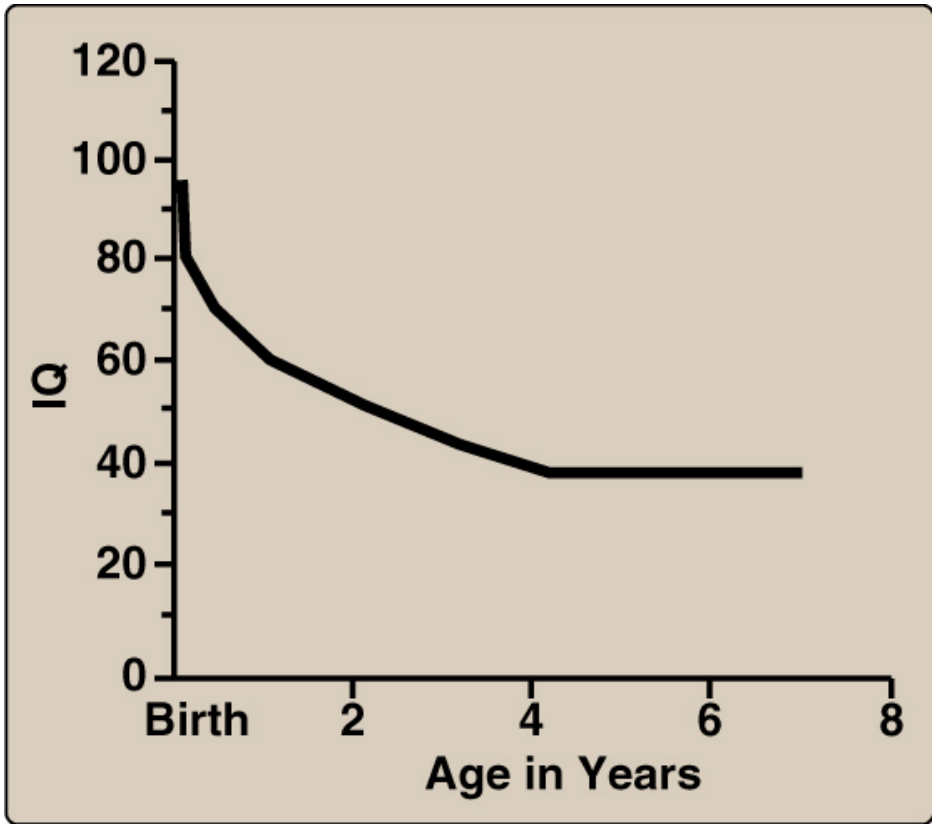
• Elevated phenylalanine (tissue, plasma, and urine. Phenylpyruvate, Phenyllactate and Phenylacetate also elevated when normally not . Musty (hongo) odor urine.

•Mental retardation failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, failure to grow. IQ below 50.

•Hypopigmentation deficiency in pigmentation (fair hair, light skin and blue eyes) due to hydroxyation of Tyrosine to melanin which is inhibited by high levels of phenylalanine



Intellectual ability in untreated PKU patients of different ages.

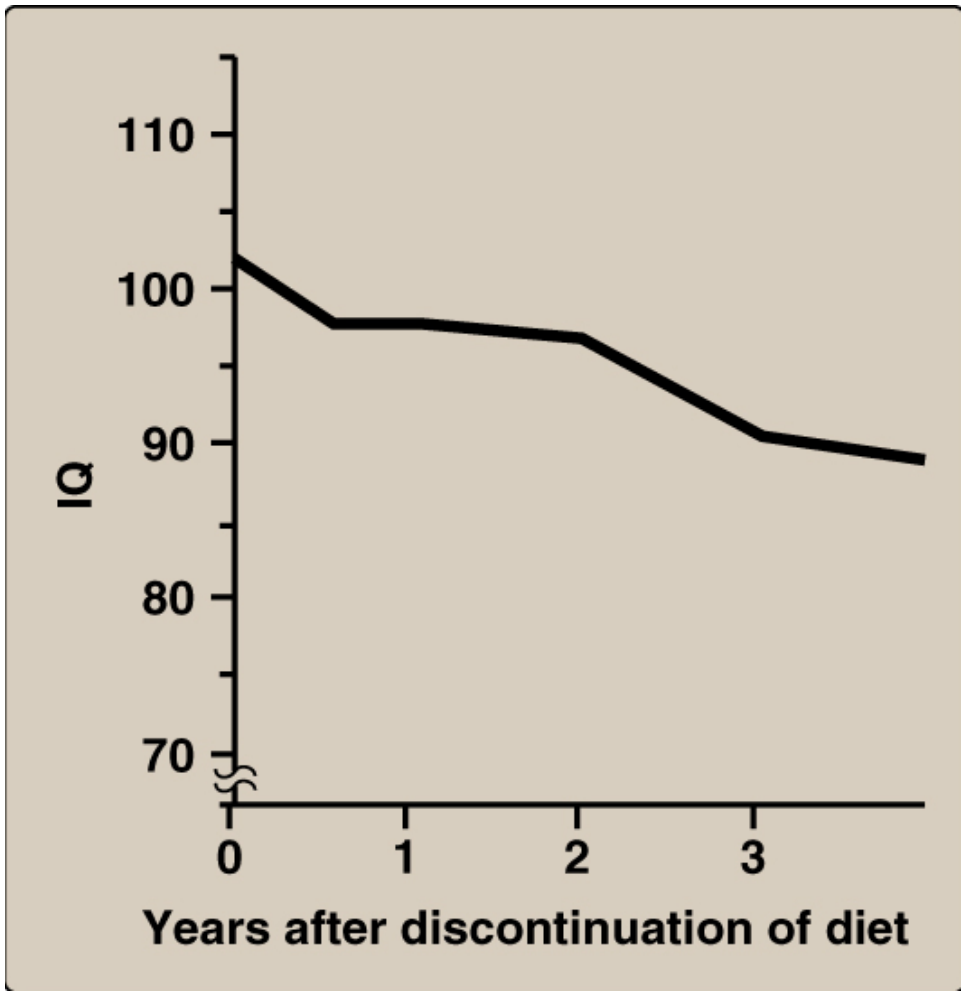


- Maternal PKU syndrome causes microcephaly, mental retardation and congenital heart abnormalities.
- 40 different mutations of the gene phenylalanine hydrohylase 6-10 are cause PKU.
- Feeding synthetic amino acid preparations low in phenylalanine, with natural foods fruits,vegetables & certain cereals.

Treatment must start within7-10 days of life to prevent retardation

Changes in IQ scores after discontinuaton of low-phenylalanine diet in patients with PKU

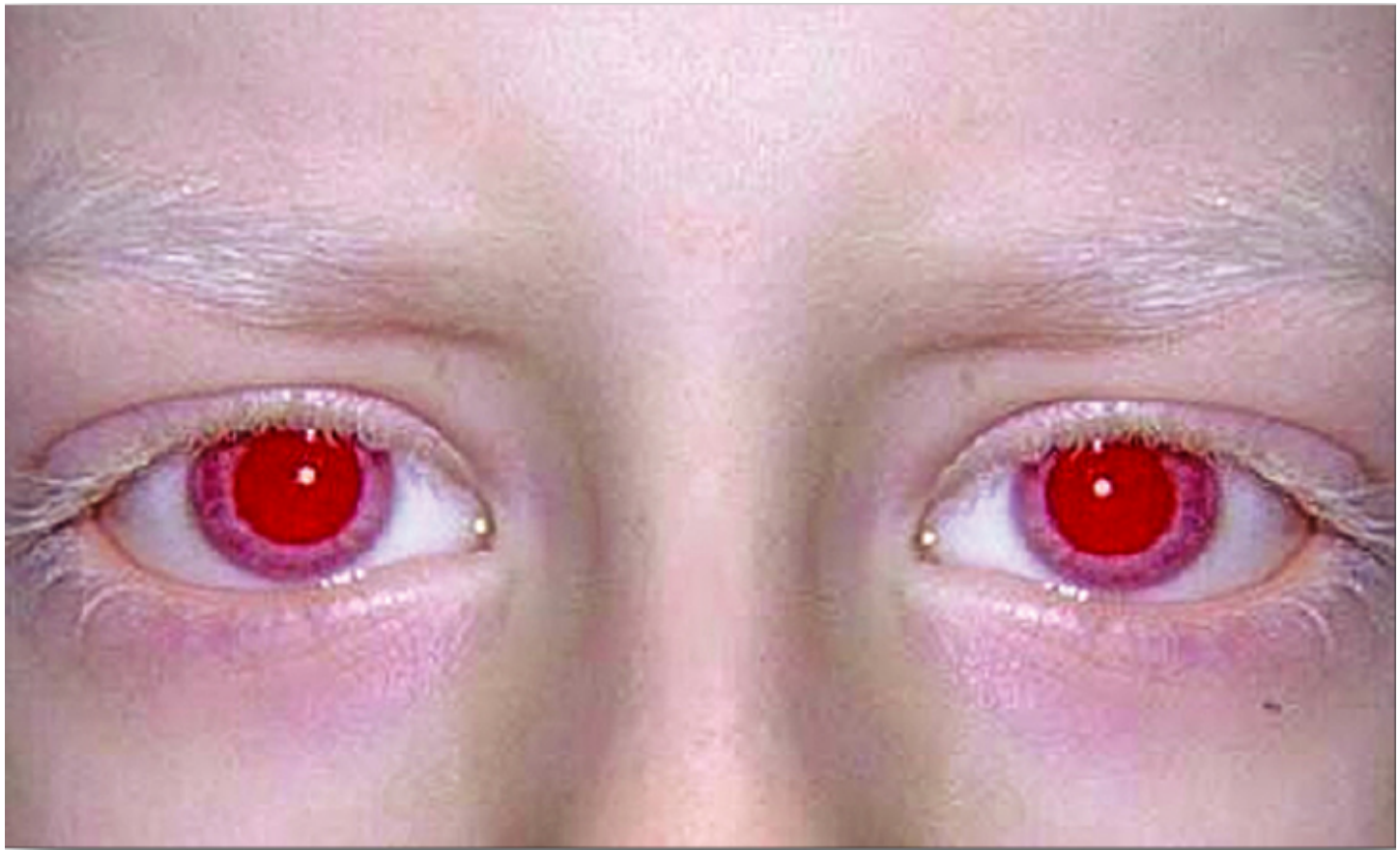
Synthetic formula with limited ammounts of leucine,isoleucine and valine.



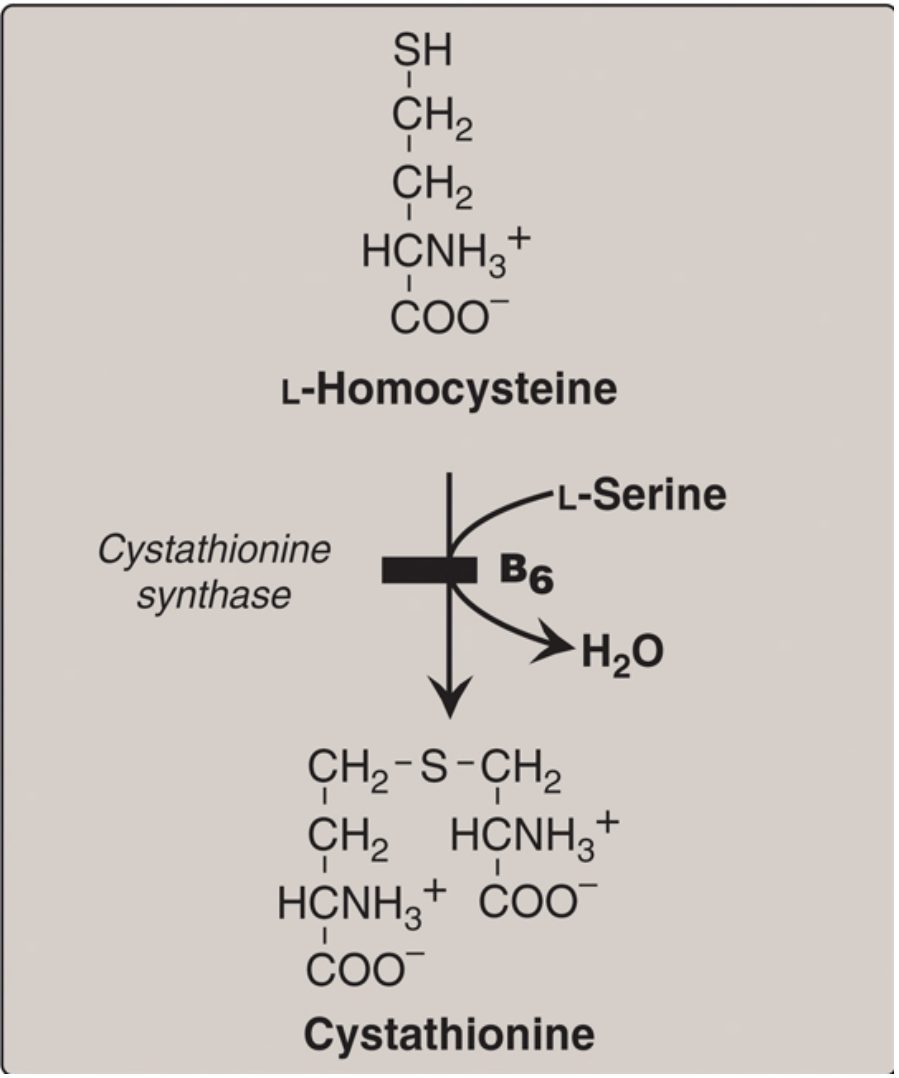
- Life long restriction of dietary phenylalanine is recommended
- Maple syrup urine disease (MSUD) recessive disorder deficiency in the branched-chain α-ketoacid dehydrogenase enzyme that decarboxylates leucine, isoleucine and valine these amino acids and their α-ketoacids accumulate in blood with toxic effects that interferes with brain function. Feeding problems, vomiting, dehydration, severe metabolic acidosis and maple syrup odor. Mental retardation, phsical disability and death.

Albinism

A group of conditions with a defect of in tyrosine metabolism in a deficiency in the production of melanin. This suggest that melanin production depends on this pathway and other pathways are not available. Autosomal recessive, autosomal dominant and X-linked. Photophobia, they sunburn easilyand do not tan.



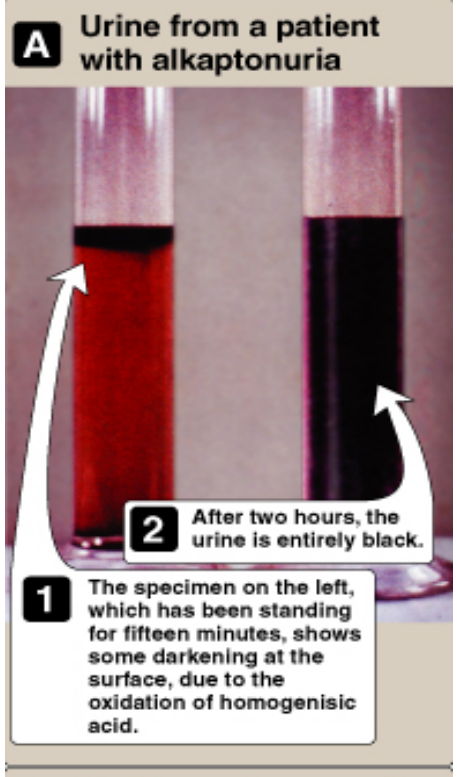
Homocystinuria

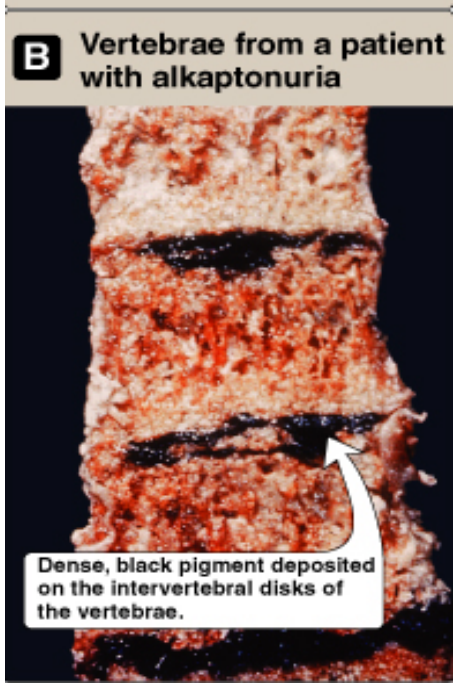


- Disorder involving defects in the metabolism of homocysteine (autosomal recessive) High plasma and urinary levels of this amino acid and methionine and low levels of cysteine. Common cause is the defect of cystathionine synthase which converts homocysteine to cystathionine. Homozygous show ectopia lentis (displacement of the lens) skeletal abnormaliities, premature arterial disease, osteoporosis and mental retardation. Patients could or not be responsive to vitamin B_6 (cofactor).

TREATMENT: restriction of methionine intake and supplement with vitamins B_6 and B_{12} and folate.

Alkaptonuria





- Rare metabolic disease involving the deficiency in homogentisic acid oxidase, resulting in accumulation of homogentisic acid (degradative pathway of tyrosine) Symptoms
- Homogentisic aciduria (high levels of this acid in urine gives it a dark color upon standing (Fig. A)
- Large joint arthritis
- Pigmentation of cartilage (Fig. B)asymptomatic until age of forty
- Diets low in protein recommended although no treatment as such

Metabolism of amino acids

Catabolism of amino acids

involves

- Removal of α-amino group
- Metabolism of carbon skeletons

converges to produce

Seven products

consisting of

ACETYL CoA	PYRUVATE
ACETOACETYL CoA	OXALOACETATE
	FUMARATE
	α-KETOGLUTARATE
	SUCCINYL CoA

Classified as	Classified as
Ketogenic	Glucogenic
provide	*provide*
Lipids	Lipids
Energy	Energy
	Glucose

Synthesis of amino acids

involves

- Transamination of α-keto acids, for example, pyruvate → alanine
- Amidation, for example, asparate → asparagine
- Synthesis from other amino acids, for example, phenylalanine → tyrosine

Some clinically important amino acids

Methionine

- Source of methyl groups in metabolism
- Precursor of homogentisic acid

Arginine

- Member of urea cycle
- Precursor of nitric oxide

Glutamine

- Storage and transport form of ammonia
- Precursor of purines and pyrimidines

Phenylalanine

- Precursor of tyrosine
- Elevated in phenylketonuria

Histidine

- Precursor of histamine
- Elevated in histidinemia

Tryptophan

- Precursor of serotonin

Alanine

- Transport form of ammonia from muscle

Metabolic defects in amino metabolism

characterized by

Family of defects in enzymes of amino acid metabolism

caused by

Point mutations, deletions, splicing errors — *usually* → **Inherited as recessive; heterozygotes usually do not show symptoms**

which can lead to

Partially or completely inactive enzyme

which leads to

Accumulation of substrate and a deficiency in product of defective enzyme

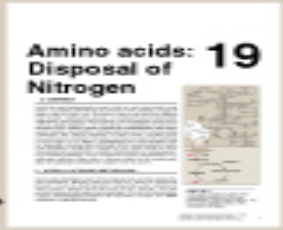
which leads to

Disturbances in metabolism, particularly the CNS

which leads to

Seizures, mental retardation, other CNS effects

Concept connect



Summary

Amino acids that yield Pyruvate or intermediates in the TCA cycle are called glycogenic. They can give rise to glycogen or glucose in the liver and glycogen in muscle. Amino acids that whose catabolism yield acetyl CoA, acetoacetyl Co A are termed ketogenic (Tyrosine, phenylalanine, tryptophaisoleucine are both ketogenic and glucogenic Leucine and lysine are ketogenic. Non-essential AA can be synthesized from metabolic intermediates or carbon skeletons of essential AA. Alanine, aspartate, glutamate, glutamine, asparagine, proline, cysteine,serine, glycine, and tyrosine.

Essential AA in diet methionine, phenylalanine.

Metabolic diseases

PKU (-) phenylalanine hydroxylase,

Hyperphenylalanine (-) BH_4 Synthetase or reductase coenzyme of PH tetrahydrobiopterin. Untreated patients of PKU suffer mental retardation failure to walk or talk, seizure, hyperactivity, tremor etc. Tyrosine becomes essential under this condition.

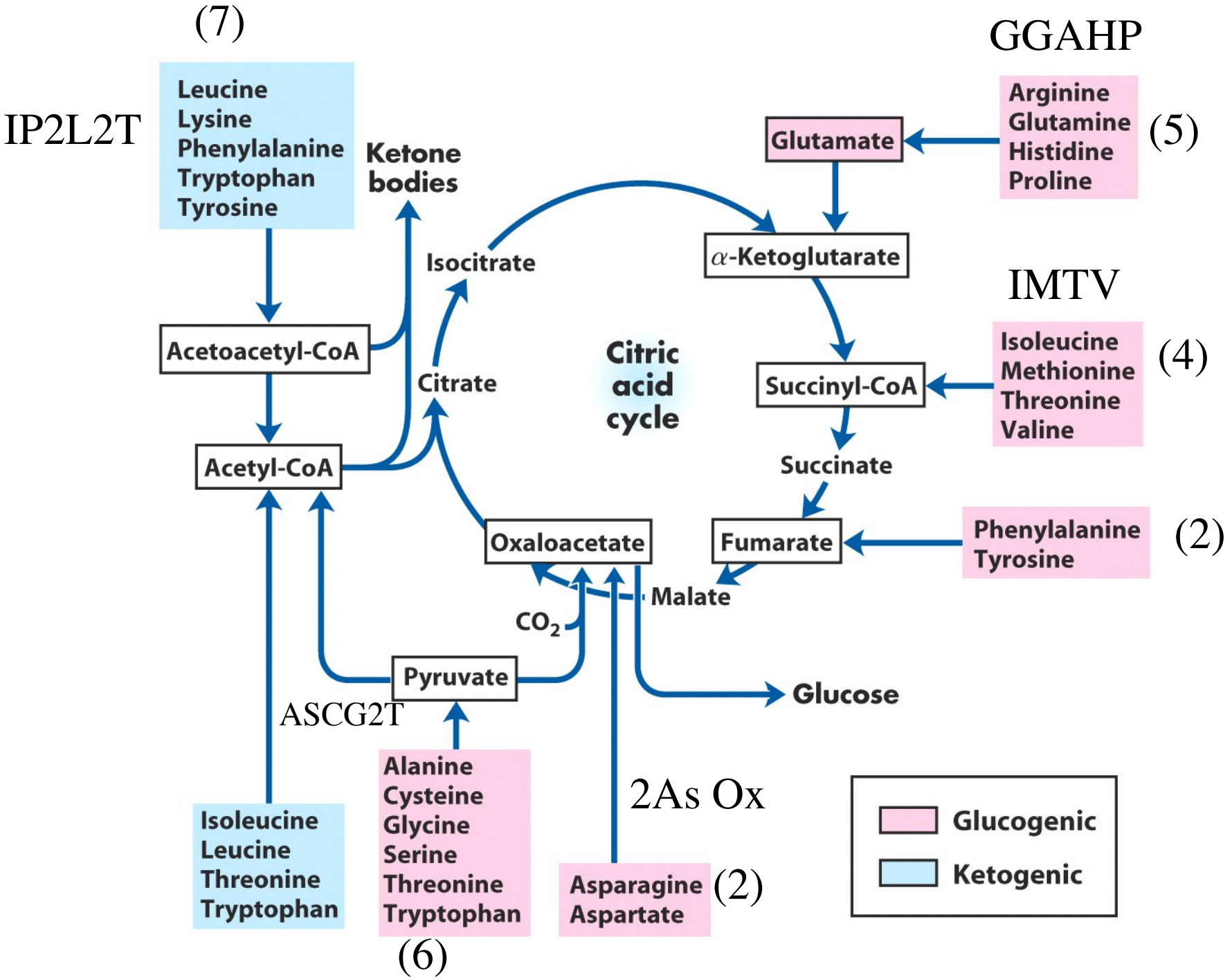
(MSUD) (-) branched chain α-ketoacid dehydrogenase

Albinism (-) tyrosinase

Alkaptonuria (-) homogentisic acid oxidase

homogentisic aciduria, large joint arthritis, pigmentation of cartilage

Homocystinuria (-) cystahionine β-synthase (vitamin B_6)


(7)
GGAHP
IP2L2T
Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine
Ketone bodies
Arginine
Glutamine
Histidine
Proline
(5)
Glutamate
Isocitrate
α-Ketoglutarate
IMTV
Acetoacetyl-CoA
Citric acid cycle
Isoleucine
Methionine
Threonine
Valine
(4)
Citrate
Succinyl-CoA
Acetyl-CoA
Succinate
Oxaloacetate
Fumarate
Phenylalanine
Tyrosine
(2)
Malate
CO2
Pyruvate
Glucose
ASCG2T
Alanine
Cysteine
Glycine
Serine
Threonine
Tryptophan
2As Ox
Isoleucine
Leucine
Threonine
Tryptophan
Asparagine
Aspartate
(2)
(6)
Glucogenic
Ketogenic