

Biosynthesis of Food Constituents: Amino Acids: 4. Non-protein Amino Acids – a Review

JAN VELÍŠEK, ROMAN KUBEC and KAREL CEJPEK

*Department of Food Chemistry and Analysis, Faculty of Food and Biochemical
Technology, Institute of Chemical Technology Prague, Prague, Czech Republic*

Abstract

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This review article gives a brief survey of the principal pathways that lead to the biosynthesis of the most important non-protein amino acids occurring in foods and feeds. These amino acids have been divided into the following groups: 3-amino acids and 4-amino acids, *N*-substituted amino acids, alicyclic amino acids, hydroxyamino acids, sulfur-containing amino acids, basic amino acids, and taurine.

Keywords: biosynthesis; 3-amino acids; 4-amino acids; *N*-substituted amino acids; alicyclic amino acids; hydroxyamino acids; sulfur-containing amino acids; basic amino acids; taurine

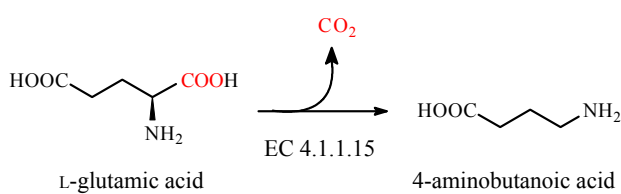
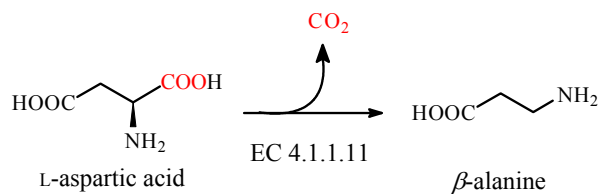
Plants and microorganisms are able to generate all 20 amino acids necessary for the protein synthesis and they can even synthesise many more amino acids. For example, more than 700 of non-protein amino acids have been isolated from plants as secondary metabolites. Some of these amino acids appear to play an important role as intermediates in the biosynthesis of the plant signalling molecules, vitamins, and other constituents (e.g. alkaloids, bile salts, and pigments). They represent storage forms of nitrogen or sulfur, some of them play a role in the enhancement of tolerance against abiotic stress, some act in the plant chemical defence system against a variety of organisms as they manifest antimetabolic effects in viruses, bacteria, fungi, as well as in lower and higher plants and animals. Many of these amino acids are, however, considered to be only biochemical oddities. Some of these amino acids also show

beneficial properties as they exhibit significant antioxidative and anticarcinogenic activities in animals. In animals, some non-protein amino acids act in intracellular metabolic processes (e.g. in the metabolism of lipids), as macroergic substrates, and neurotransmitters, and intermediates in the synthesis of some biologically active compounds (e.g. hormones) and stimulants.

1 3-AMINO ACIDS AND 4-AMINO ACIDS

β -Alanine (3-aminopropanoic acid) is involved in the biosynthesis of pantothenic acid, coenzyme A (HS-CoA), and some histidine dipeptides (VELÍŠEK *et al.* 2006). The principal pathway of β -alanine formation (KEGG) is the decarboxylation of *L*-aspartic acid catalysed by the pyridoxal 5'-phosphate protein aspartate-1-decarboxylase (EC 4.1.1.11) (Figure 1).

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γ -Aminobutanoic acid (GABA, 4-aminobutanoic acid) acts as a chemical messenger in the cell communication. It predominantly occurs in the brain tissue (but also in plant and microbial cells) where it acts as a neurotransmitter inhibitor. It is also a constituent of some peptides, e.g. nisine. γ -Aminobutanoic acid is predominantly formed by decarboxylation of L-glutamic acid catalysed by the pyridoxal 5'-phosphate protein, i.e. glutamate decarboxylase (EC 4.1.1.15) (Figure 2) (KEGG).

2 N-SUBSTITUTED AMINO ACIDS

2.1 Sarcosine and glycine betaine

Glycine *N*-methyltransferase (EC 2.1.1.20)¹ catalyses the transfer of the methyl group of *S*-adenosyl-methionine (SAM or AdoMet) to glycine to form *S*-adenosylhomocysteine (AdoHcy) and *N*-methylglycine (sarcosine, Figure 3). The enzyme is unique among methyltransferases since the methylated product has no physiological activity. It has been suggested that the major role of glycine *N*-methyltransferase is to regulate the *S*-adenosyl-

methionine/*S*-adenosylhomocysteine ratio rather than to synthesise sarcosine² (KEGG).

Glycine betaine (*N,N,N*-trimethylglycine, trimethylammoniumacetobetaine) is produced by certain higher plants and bacteria. It is synthesised at elevated rates in response to various types of environmental stress via two distinct pathways: oxidation of choline, or *N*-methylation of glycine (CHEN & MURATA 2002). For almost all biological systems, including most animals, plants (e.g. plants of the family *Chenopodiaceae*, such as spinach), and microorganisms, glycine betaine biosynthesis is accomplished in chloroplasts by the first pathway, conversion of choline via the unstable intermediate betaine aldehyde (JAIN & SELVARAJ 2000). The first step of choline oxidation is catalysed by ferredoxin-dependent choline monooxygenase (EC 1.14.15.7), and the second one by NAD(P)-dependent betaine aldehyde dehydrogenase (EC 1.2.1.8)³ (Figure 4).

2.2 Carnitine

L-Carnitine [3-hydroxy-4-(*N,N,N*-trimethyl)-aminobutyric acid] is required for the transfer of ac-

¹In addition to its enzymatic role, glycine *N*-methyltransferase has been shown to be a major folate binding protein in the rat liver cytosol, to be a polycyclic aromatic hydrocarbon-binding protein and a mediator of cytochrome *P4501A1* gene expression.

²Sarcosine is also formed as a product of choline and creatine catabolism. Both compounds have several metabolic fates. Choline may be converted into acetylcholine, to phosphatidylcholine or to *N,N*-dimethylglycine, which is then converted to sarcosine and ultimately to glycine. Dimethylglycine dehydrogenase (EC 1.5.99.2) is an enzyme catalysing the oxidative demethylation of *N,N*-dimethylglycine to form sarcosine. Subsequently, sarcosine dehydrogenase (EC 1.5.99.1) converts sarcosine into glycine. Hydrolysis of creatine by creatinase (EC 3.5.3.3) yields sarcosine and urea. The product of creatinine hydrolysis by creatinine deamidase (EC 3.5.4.21), *N*-methylhydantoin, yields *N*-carbamoylsarcosine by the catalysis of *N*-methylhydantoinase (ATP-hydrolysing) (EC 3.5.2.14).

³Bacteria *Escherichia coli* also form glycine betaine from choline but do not use choline monooxygenase (EC 1.14.15.7) as they have choline dehydrogenase (EC 1.1.99.1) instead that generates hydrogen peroxide. Glycine betaine biosynthesis in the microorganisms *Arthrobacter globiformis* requires only one enzyme choline oxidase (EC 1.1.3.17). Recently, a novel pathway of glycine betaine biosynthesis from glycine via sarcosine (glycine *N*-methyltransferase, EC 2.1.1.20) and *N,N*-dimethylglycine was found in two extremely halophilic microorganisms *Ascino-polyspora halophila* and *Ectothiorhodospira halochloris*.

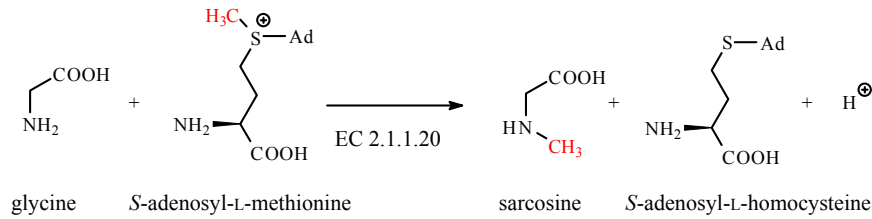


Figure 3

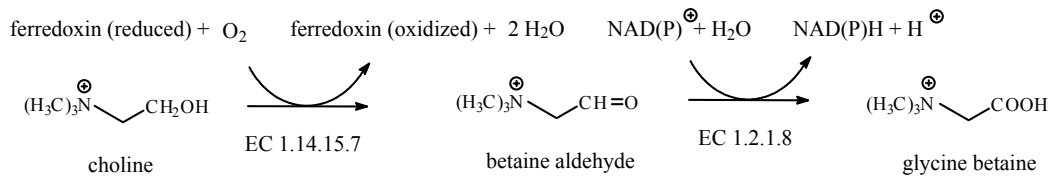


Figure 4

tivated acyl groups across intracellular membranes. Many organisms, ranging from bacteria to mammals, are able to synthesise carnitine from lysine and methionine. Lysine becomes available in the form of ϵ -(*N,N,N*-trimethyl)lysine after lysosomal hydrolysis of proteins that contain this amino acid as a result of the post-translational methylation of lysine residues by lysine *N*-methyltransferase (EC 2.1.1.43), using SAM as the methyl donor.

In the first step of the carnitine biosynthesis, ϵ -(*N,N,N*-trimethyl)lysine is hydroxylated to β -hydroxy- ϵ -(*N,N,N*-trimethyl)lysine [3-hydroxy- ϵ -(*N,N,N*-trimethyl)lysine] by trimethyllysine dioxygenase (EC 1.14.11.8). Subsequently, β -hydroxy- ϵ -(*N,N,N*-trimethyl)lysine is cleaved by retroaldolisation into glycine and 4-(*N,N,N*-trimethyl)aminobutanal [γ -(*N,N,N*-trimethyl)amin-

obutyraldehyde] by the pyridoxal 5'-phosphoric acid protein β -hydroxy- ϵ -(*N*-trimethyl)lysine aldolase (EC 2.1.2.1). 4-(*N,N,N*-trimethyl)aminobutanal is subsequently oxidised by NAD(P)-dependent 4-trimethylaminobutyraldehyde dehydrogenase (EC 1.2.1.47) or aldehyde dehydrogenase (NAD⁺) (EC 1.2.1.3) to form 4-(*N,N,N*-trimethyl)aminobutanoic acid (γ -butyrobetaine). Finally, 4-(*N,N,N*-trimethyl)aminobutanoic acid is hydroxylated at the C-3 position by γ -butyrobetaine hydroxylase (EC 1.14.11.1) to form carnitine (Figure 5). Like lysyl hydroxylase (EC 1.14.11.4, VELÍŠEK & CEJPEK 2006), trimethyllysine dioxygenase and 4-trimethylaminobutyraldehyde dehydrogenase are non-heme ferrous-iron dioxygenases that require 2-oxoglutaric acid and molecular oxygen as substrates, and Fe²⁺ and L-ascorbic acid (for regeneration of Fe²⁺

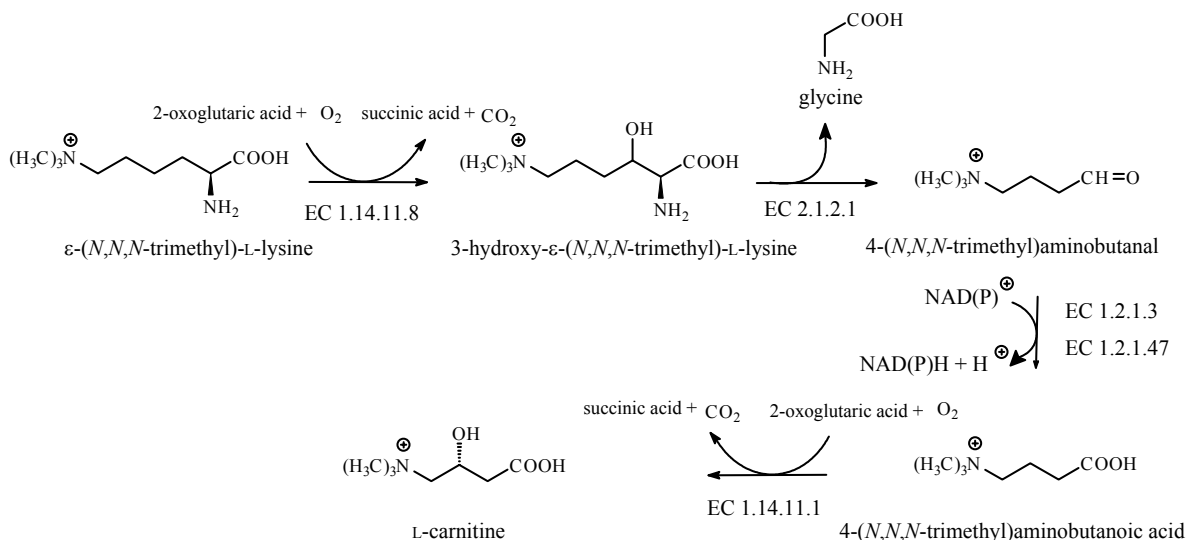


Figure 5

ions) as cofactors (VAZ *et al.* 1998; SWIEGERS *et al.* 2002).

3 ALICYCLIC AMINO ACIDS

3.1 1-Aminocyclopropane-1-carboxylic acid

Ethylene is a gaseous, plant signalling molecule (hormone) that regulates many processes of seed germination, plant growth and development, flowering, fruit ripening, abscission, and senescence. Plant cells can also synthesise ethylene when they encounter various stress factors, such as physical wounding, pathogen attack, flooding, chilling injury, or the presence of heavy metals. The induction of ethylene synthesis also plays a crucial role in a certain herbicide mode of action.

The biosynthesis of ethylene in higher plants proceeds in several steps. The immediate ethylene precursor is 1-aminocyclopropane-1-carboxylic acid that is synthesised from methionine via SAM (VELÍŠEK & CEJPEK 2006). The formation of 1-aminocyclopropane-1-carboxylic acid is catalysed by the pyridoxal 5'-phosphate protein, 1-aminocyclopropane-1-carboxylate synthase (EC 4.4.1.14). The enzymatic conversion of this acid into ethylene

proceeds via unstable *N*-hydroxy-1-aminocyclopropane-1-carboxylic acid, which breaks down into ethylene (derived from the C-2 and C-3 carbons of 1-aminocyclopropane-1-carboxylic acid) and cyanoformic acid. The latter compound is further decomposed into hydrogen cyanide and CO₂ as shown in Figure 6. The enzyme involved in this process is 1-aminocyclopropane-1-carboxylic acid oxidase (EC 1.14.17.4), a member of the ferrous-dependent family of non-heme oxygenases. Like other members of the family, it requires ferrous ions and utilises molecular oxygen and ascorbic acid. It also requires bicarbonate ions or CO₂ as activators (BARLOW *et al.* 1997; CHARNG *et al.* 2001).

3.2 Hypoglycin and related amino acids

The unripe fruits of the Jamaican ackee tree (*Blighia sapida*, *Sapindaceae*) contain an unusual free amino acid called hypoglycin, i.e. (2*S*,4*S*)-3-(methylenecyclopropyl)alanine, also known as *L*-β-(methylenecyclopropyl)alanine, *L*-3-(methylenecyclopropyl)alanine or 2-amino-4,5-methanohex-5-enoic acid. The free amino acid (hypoglycin A) is found in the arils and seeds of the fruit

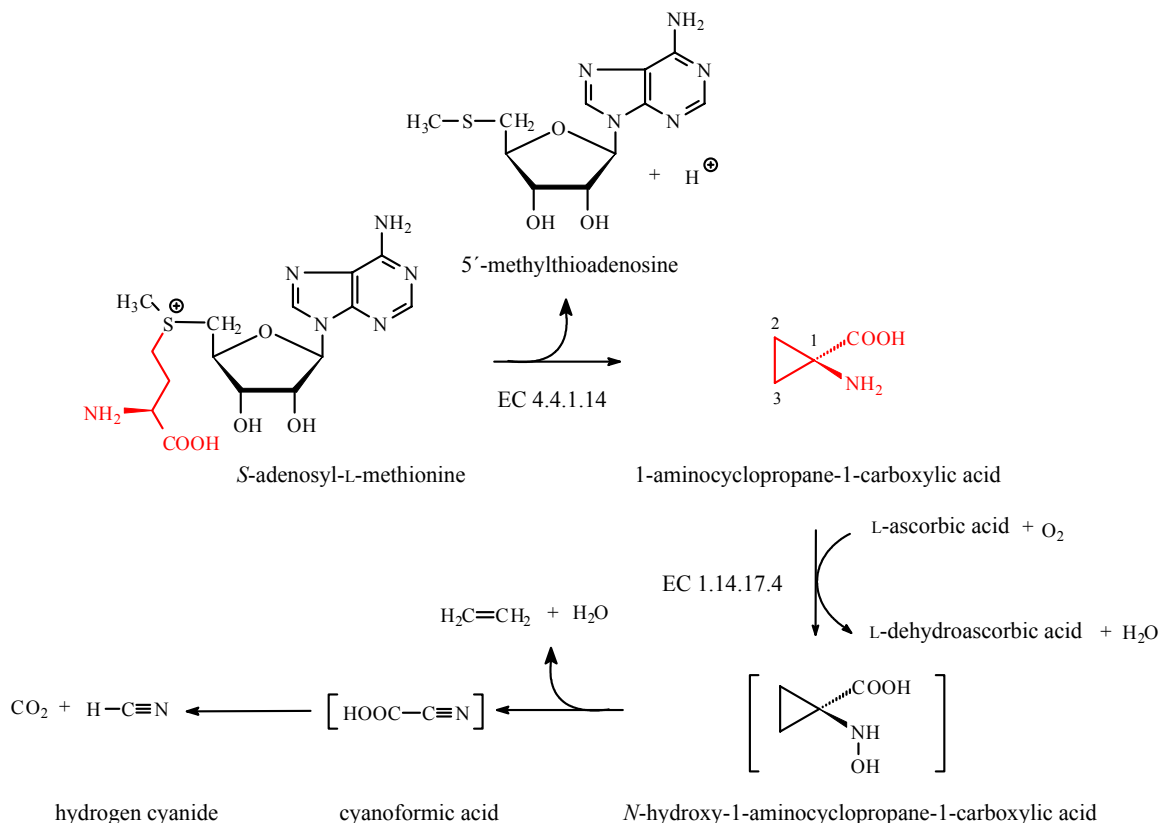


Figure 6

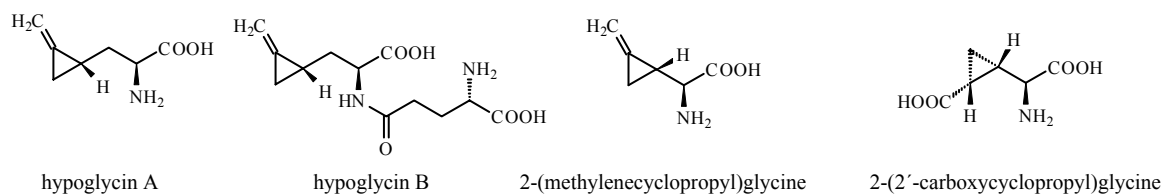


Figure 7

and its content significantly decreases in the arils with ripeness (from 1000–1110 mg/kg to less than 100 mg/kg)⁴. γ -Glutamyl hypoglycin (hypoglycin B) is found only in the ackee seeds. Traces of the lower homologue of hypoglycin A with hypoglycaemic activity, i.e. 2-(methylenecyclopropyl)glycine, its γ -glutamyl dipeptide, and (2*S*,1'*S*,2'*S*)-2-(2'-carboxycyclopropyl)glycine (Figure 7) are present in the immature seeds (SHERRATT 1986; KEAN 1989; NATALINI *et al.* 2000).

Significant amounts of hypoglycin A and hypoglycin B occur also in the seeds of *Billia hip-*

pocastanum (*Hippocastanaceae*) from Costa Rica and *Acer pseudoplatanus* (*Aceraceae*), a common sycamore of temperate zones. The lower homologue of hypoglycin, L- α -(methylenecyclopropyl)glycine, was found in the seeds of *Litchi sinensis* (*Sapindaceae*) (KEAN 1989).

Symptoms of ackee poisoning (commonly known as Jamaican vomiting sickness or more accurately the toxic hypoglycaemic syndrome) occur 6–48 h after the ingestion of unripe arils and include nausea, vomiting, drowsiness, muscular and mental exhaustion, and hypoglycaemia. The

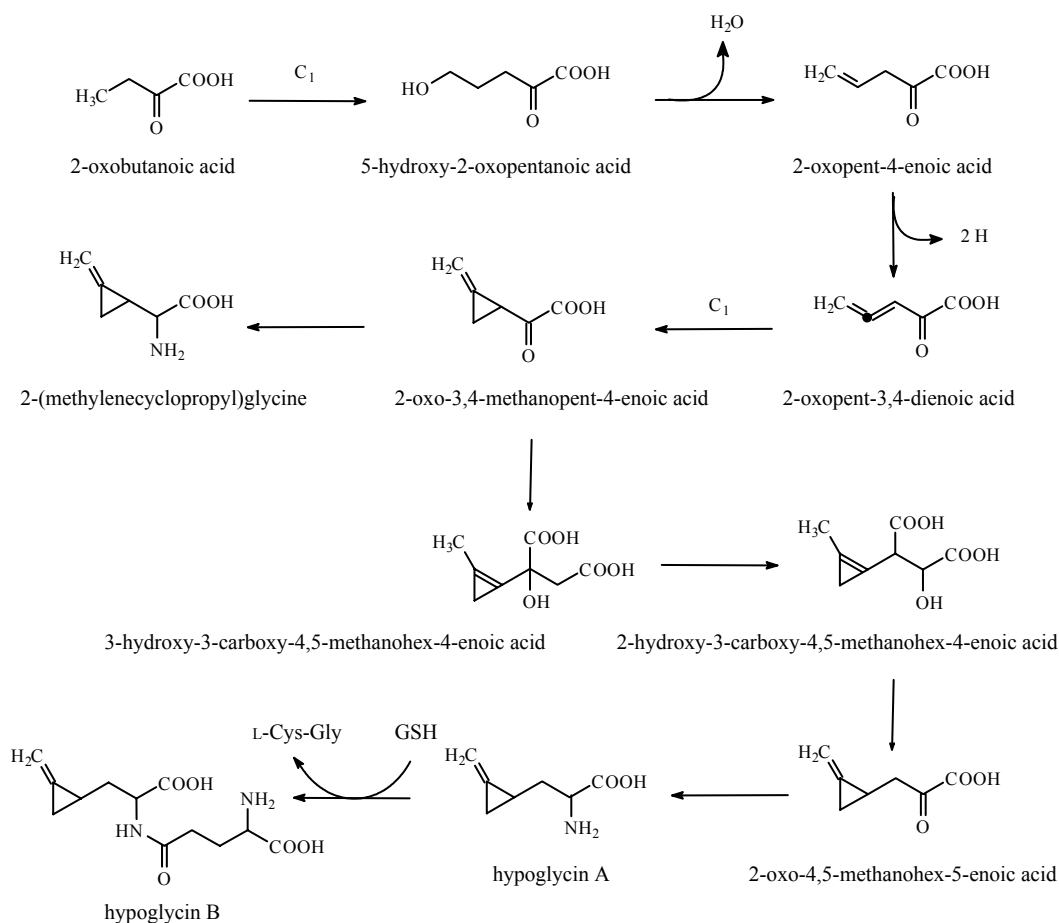


Figure 8

⁴The Food and Drug Administration and Health Canada set the limit of 100 mg/kg (BLAKE *et al.* 2004).

mechanism of action is in that the toxin follows a similar metabolic pathway as branched chained amino acids, thus producing the active metabolite methylenecyclopropylacetyl-CoA. It is known that this metabolite then irreversibly binds to FAD and thereby inactivates medium chain acyldehydrogenases that are essential for the complete β -oxidation of fatty acids (HENRY *et al.* 1998; BLAKE *et al.* 2004).

Only a few reports exist on the biosynthesis of hypoglycin, which links to the lower homologue, L- α -(methylenecyclopropyl)glycine. It is inferred that the first step is analogous to isoleucine biosynthesis as it starts with the dehydration and deamination of threonine to yield 2-oxobutyric (2-oxobutanoic) acid. The addition of the C₁ unit from methionine (probably from SAM) to 2-oxobutanoic acid is supposed to give 5-hydroxy-2-oxopentanoic acid which eliminates water to yield 2-oxopent-4-enoic acid. 2-Oxopent-4-enoic acid is oxidised to allenic acid (2-oxopent-3,4-dienoic acid) to which methionine adds the second C₁ unit giving rise to 2-oxo-3,4-methanopent-4-enoic acid. The formation of α -(methylenecyclopropyl)glycine is then accomplished by transamination (Figure 8) (KEAN & LEWIS 1981; KEAN 1989).

Acetyl-CoA is subsequently added to 2-oxo-3,4-methanopent-4-enoic acid by the same mechanism by which (S)-2-isopropylmalic acid is formed in the leucine biosynthetic pathway (the relevant enzymes of the leucine pathway appear not to be absolutely specific). The product, 2-hydroxy-2-(2-methylcycloprop-1-en-1-yl)butane-1,4-dioic acid (3-hydroxy-3-carboxy-4,5-methanohex-4-enoic acid), then exactly follows the remaining steps of that pathway, the sequence of which

being isomerisation to 2-hydroxy-3-(2-methylcycloprop-1-en-1-yl)butane-1,4-dioic acid (2-hydroxy-3-carboxy-4,5-methanohex-4-enoic acid) and dehydrogenation with decarboxylation yielding 2-oxo-4,5-methanohex-5-enoic acid. Finally, transamination of the latter compound, β -(methylenecyclopropyl)pyruvic acid, leads to hypoglycin A. The enzyme γ -glutamyl transpeptidase (EC 2.3.2.2) catalyses the reaction in which glutathione (GSH), acting as donor, forms γ -glutamyl peptide (i.e. hypoglycin B) with acceptor hypoglycin A (Figure 8).

4 HYDROXYAMINO ACIDS

4.1 Dihydroxyphenylalanine

A relatively small number of tyrosine molecules are directly hydroxylated to give 3,4-dihydroxy-L-phenylalanine (L-DOPA, levodopa)⁵. This reaction is catalysed by (6R)-5,6,7,8-tetrahydro-L-biopterin (L-erythro-5,6,7,8-tetrahydrobiopterin, BH₄)-dependent monooxygenase enzyme (tyrosine hydroxylase, EC 1.14.16.2) (Figure 9) (IUBMB 2003).

5 SULFUR-CONTAINING AMINO ACIDS

5.1 S-Alk(en)ylcysteines and their sulfoxides

S-Alk(en)ylcysteines and their sulfoxides belong to the most common non-protein amino acids. Although their occurrence was thought to be associated almost exclusively with *Allium* species, their distribution in the plant kingdom appears to be much broader. They commonly occur in many

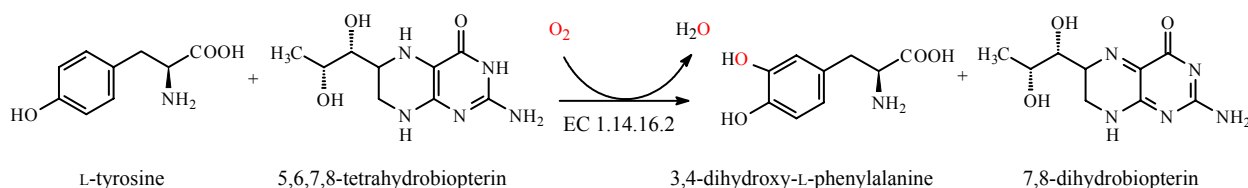
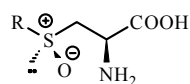


Figure 9

⁵DOPA can undergo various biochemical fates in all living organisms. In animals, it is involved in melanogenesis and neurotoxicity as oxidation reactions catalysed by tyrosinase (EC 1.14.18.1) convert DOPA into a heterogeneous polymer melanin, the main pigment in the mammalian skin, hair and eyes, other reactions can lead to formation of catecholamines, e.g. the neurotransmitter noradrenaline (norepinephrine) and the hormone adrenaline (epinephrine) (VELÍŠEK 2002). Its metabolism in plants is of particular importance as it leads to formation of some food constituents, such as alkaloids (e.g. salsalinol in bananas is a product from dopamine and acetaldehyde combining via the Pictet-Spengler reaction), certain pigments (betalains), and undesirable bitter substances (i.e. verbascoside and oleuropein in olives).



S-alk(en)yl-L-cysteine sulfoxides

Figure 10

other plants (e.g. genera *Brassica*, *Vigna*, *Petiveria*, *Tulbaghia*, *Scorodocarpus* and *Acacia*, among many others) as well as in several mushrooms (e.g. genera *Marasmius*, *Collybia*, *Lentinus*) and marine algae (e.g. genera *Chondria* and *Undaria*).

Garlic (*Allium sativum*), onion (*A. cepa*), and other members of the genus *Allium* (*Liliaceae*) typically contain 1–5% dry weight of S-alk(en)ylcysteines sulfoxides. The pool generally consists of varying relative proportions of four major derivatives – (R_C, S_S)-S-allyl-, (R_C, S_S)-S-methyl-, (R_C, S_S)-S-propyl- and (R_C, R_S)-(E)-S-(prop-1-en-1-yl)cysteine sulfoxides (alliin, methiin, propiin and isoalliin) (Figure 10). The presence of two other derivatives, namely (R_C, S_S)-S-ethyl- and (R_C, S_S)-S-butylcysteine sulfoxides, was also reported (KUBEC *et al.* 2000, 2002). However, due to their very low abundance, the contribution of the latter two compounds to the aroma formation is rather limited in the most common edible *Allium* species.

The typical flavour of *Allium* vegetables is formed by the enzymatic cleavage of odourless S-alk(en)ylcysteine sulfoxides when the cellular tissue is disrupted⁶. In the intact tissue, alliin and the other S-alk(en)ylcysteine sulfoxides are located in the cytoplasm and the C–S lyase enzyme (alliinase, EC 4.4.1.4) in the vacuole. Disruption of the plant tissue (by cutting, slicing, chopping etc.)

results in the release of alliinase and subsequent α, β -elimination of S-alk(en)ylcysteine sulfoxides, affording the corresponding alk(en)ylsulfenic acids and α -aminoacrylic acid. The latter compound spontaneously decomposes to yield ammonia and pyruvic acid (via α -iminoacrylic acid). Condensation of the arising alk(en)ylsulfenic acids leads to the formation of thiosulfates, the flavour principles of freshly disrupted *Allium* vegetables (Figure 11). The most typical amino acid of onion, S-(prop-1-en-1-yl)cysteine sulfoxide (isoalliin), enzymatically decomposes yielding prop-1-en-1-ylsulfenic acid (Figure 12). This sulfenic acid can be either spontaneously transformed into prop-1-en-1-yl-containing thiosulfates or, by the action of the lachrymatory factor synthase, it yields the irritating lachrymatory factor of onion, (Z)-propanethial S-oxide (IMAI *et al.* 2002). The arising S-alk(en)yl alkanethiosulfates can participate in an astonishing variety of subsequent reactions which strongly depend on the conditions (particularly on the polarity of medium and temperature), and which afford miscellaneous types of organosulfur compounds, such as sulfides, vinylidithiins, ajoenes, etc. (BLOCK 1992) (Figure 13). These compounds exhibit a broad spectrum of health-promoting activities, e.g. hypolipidemic, antithrombotic, antioxidant, hypocholesterolemic, cancer-preventive and anticancer effects.

S-Alk(en)ylcysteine sulfoxides are rather inert metabolites and probably are not active intermediates of the main metabolic chains. They are generally considered to serve as storage, waste/

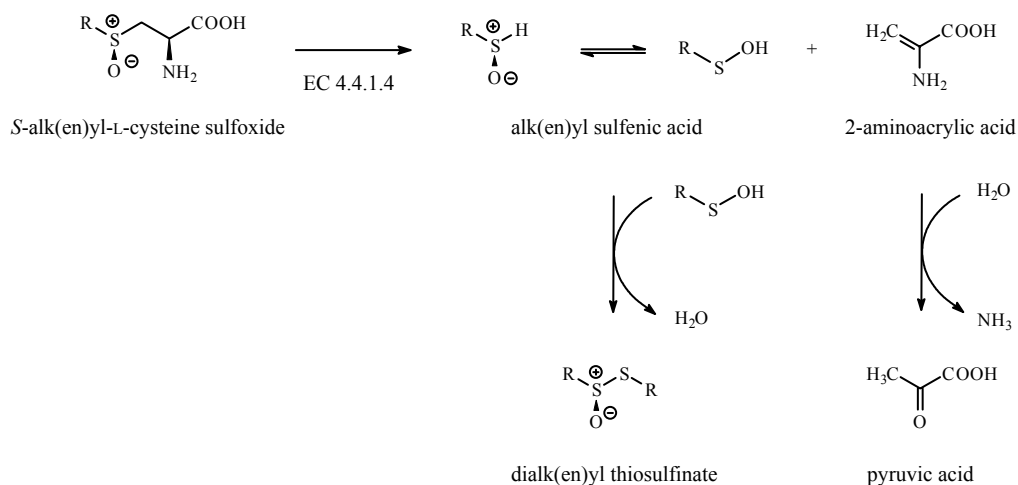


Figure 11

⁶S-Alk(en)ylcysteines and γ -glutamyl dipeptide forms are not cleaved by alliinase.

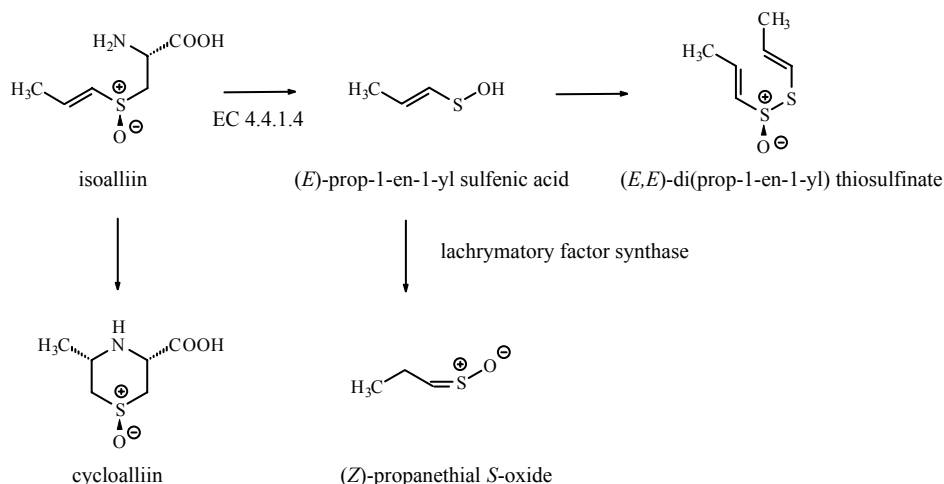


Figure 12

end products or chemical defence agents against predators. Several biosynthetic pathways for the formation of *S*-alk(en)ylcysteine sulfoxides have been proposed. The generally accepted mechanism involves sulfate assimilation into cysteine, which subsequently enters the glutathione cycle. Michael addition of γ -glutamylcysteine to methacrylic acid (originating from valine) affords γ -glutamyl-*S*-(2-carboxypropyl)cysteine, which undergoes sequential decarboxylation to γ -glutamyl-*S*-(1-propenyl)cysteine and oxidation to γ -glutamyl-*S*-(1-propenyl)cysteine sulfoxide (PARRY & SOOD 1985). The latter is cleaved by γ -glutamyltranspeptidase (EC 2.3.2.1) to isoalliin. Parallel processes probably consist of Michael addition of glutathione to methacrylic acid, giving *S*-(2-carboxypropyl)glutathione (VELÍŠEK *et*

al. 2006), which is subsequently converted into γ -glutamyl-*S*-(2-carboxypropyl)cysteine. Methylation of glutathione yields *S*-methylglutathione, conversion of the latter compound leads to the formation of γ -glutamyl-*S*-methylcysteine. The situation with alliin biogenesis is less clear. Perhaps, alliin is also formed by decarboxylation of γ -glutamyl-*S*-(2-carboxypropyl)cysteine, i.e. by a process of a different regioselectivity than the formation of isoalliin (LANCASTER & SHAW 1989; JONES *et al.* 2004).

5.2 *S*-Methylmethionine

Apart from its incorporation into proteins and other functions, methionine is the precursor of *S*-methylmethionine, a compound that serves

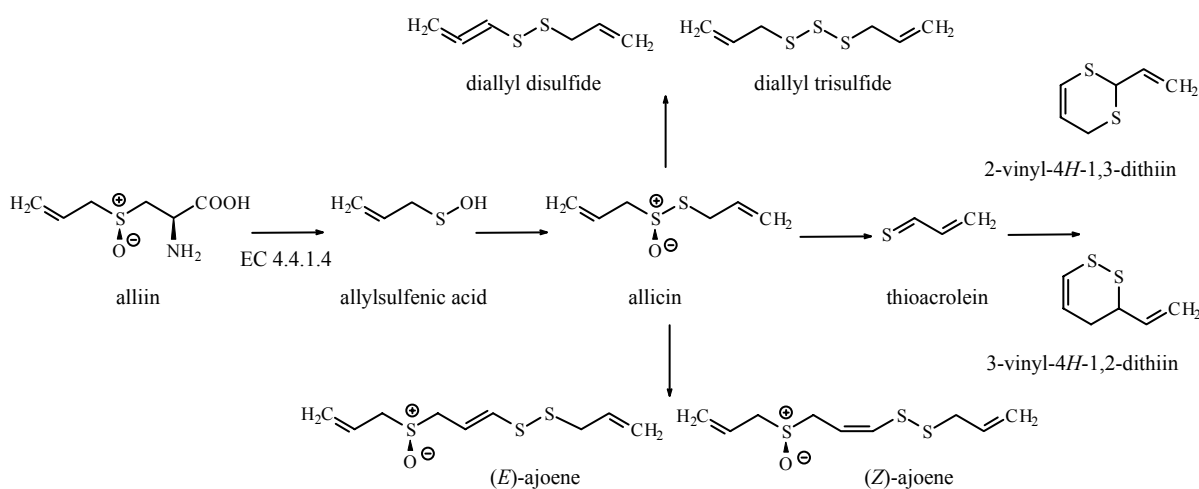


Figure 13

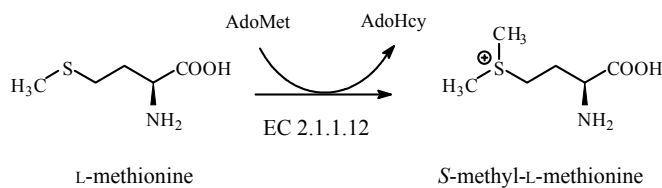


Figure 14

as the storage form of “labile” methyl groups in plants and/or plays a role in preventing SAM accumulation (GAKIERE *et al.* 2002). *S*-Methylmethionine (also called vitamin U or cabbigen) has been shown to prevent formation of duodenum and stomach ulcers and hyperlipidaemia. High levels of *S*-methylmethionine occur in vegetables belonging to the *Brassicaceae* family. It is found in higher levels in kohlrabi (90 mg/kg) and in cabbage (75 mg/kg). The levels in other vegetables are lower and those found in fruits are about 1 mg/kg (VELÍŠEK 2002).

S-Methylation is the only reaction step in the biochemical production of *S*-methylmethionine from methionine in plants (STEFELS 2000). This reaction, catalysed by methionine *S*-methyltransferase (EC 2.1.1.12), is dependent on SAM and requires Zn^{2+} or Mn^{2+} ions (KEGG) (Figure 14).

6 BASIC AMINO ACIDS AND RELATED AMINO COMPOUNDS

6.1 Creatine and phosphocreatine

The biosynthesis of creatine from glycine, which reacts with the guanidyl group of arginine to form

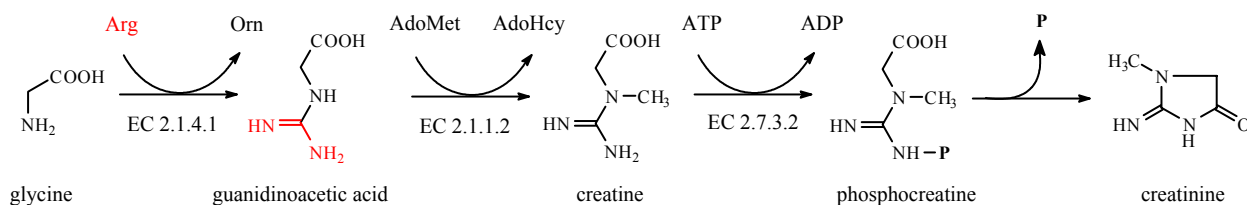


Figure 15

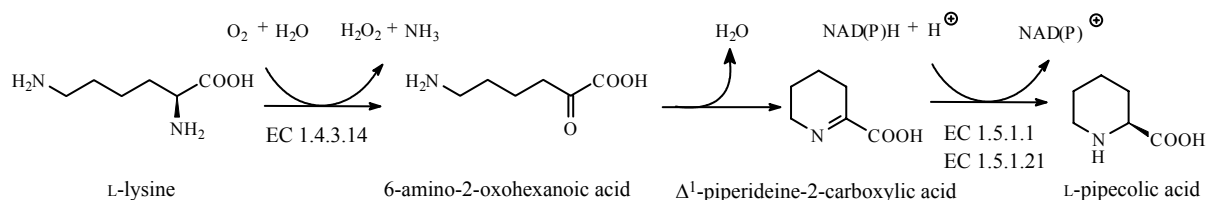


Figure 16

guanidinoacetic acid, is catalysed by glycine amidinotransferase (EC 2.1.4.1). Under the catalysis of guanidinoacetate *N*-methyltransferase (EC 2.1.1.2), SAM is the source of the *N*-methyl group to form creatine, which is phosphorylated by ATP by the action of creatine kinase (EC 2.7.3.2). Spontaneous slow cyclisation of phosphocreatine (creatine phosphate) yields creatinine (Figure 15), which is also formed by thermal cyclisation of creatine (IUBMB 2003).

6.2 Pipecolic acid

The higher homologue of proline, pipecolic acid (*L*-2-piperidine carboxylic acid), occurs frequently in higher plants. Pipecolic acid also occurs in animal tissues (e.g. in brain) where it acts as a stimulant of γ -aminobutanoic acid (GABA) receptors. It appears to be universally derived from lysine through oxidative deamination of the α -amino group catalysed by lysine oxidase (EC 1.4.3.14). The reaction product, 6-amino-2-oxohexanoic acid, spontaneously forms Δ^1 -piperideine-2-carboxylic acid, which is reduced by either NAD(P)-dependent Δ^1 -piperideine-2-carboxylate reductase (EC 1.5.1.21) or Δ^1 -pyrroline-2-carboxylate reductase (EC 1.5.1.1),

MEYER & GROBBELAAR 1986) (Figure 16). Monohydroxypipelic acids (occurring, e.g., in *Inga* species, *Mimosaceae*) are synthesised from pipelic acid, whereas dihydroxypipelic acids are derived from monohydroxypipelic acids with the same absolute stereospecificity (MORTON 1998).

6.3 Substituted alanines

About 2000 plant species are known to produce cyanide (mainly in the form of cyanogenic glycosides) as a part of their chemical defence systems. Furthermore, all vascular plants and numerous fungi and algae produce cyanide as a by-product in the synthesis of the plant hormone ethylene and during early germination of many seeds. Therefore, plants had to evolve effective detoxifying strategies (LARSEN *et al.* 2004). All vascular plants possess the enzyme β -cyanoalanine synthase (EC 4.4.1.9) which couples hydrogen cyanide with cysteine to produce β -cyanoalanine⁷. β -Cyanoalanine can be then converted into γ -glutamyl- β -cyanoalanine by γ -glutamyltransferase (EC 2.3.2.2). In the next metabolic step, the enzyme β -cyanoalanine hydratase (EC 4.2.1.65) produces asparagine (Figure 17), an amino acid important for nitrogen storage (VELÍŠEK & CEJPEK 2006), which can be further metabolised to aspartic acid and ammonia by the action of the enzyme asparaginase (EC 3.5.1.1).

β -Cyanoalanine synthase enzymes (EC 4.4.1.9) reported in plants and bacteria can also catalyse some other reactions. For example, they act as *O*-acetylserine(thiol)lyases (EC 2.5.1.47). *Vice versa*, *O*-acetylserine(thiol)lyase enzymes usually catalyse the insertion of hydrogen sulfide into *O*-acetylserine to yield cysteine and acetic acid (VELÍŠEK & CEJPEK 2006), and they are also capable of cyanide detoxification via cysteine consumption,

resulting in the formation of L-3-cyanoalanine (β -cyanoalanine) and hydrogen sulfide.

Moreover, *O*-acetylserine(thiol)lyases-like proteins function (they possess additional catalytic activity) in plant secondary metabolism through synthesis of various β -substituted heterocyclic alanines in the presence of suitable precursors. *O*-Acetylserine serves as the donor of the alanyl moiety. Some of these amino acids are toxic to, or physiologically active in, organisms in which they do not normally occur. β -Cyanoalanine itself is a neurotoxic amino acid occurring in higher quantities in *Vicia* and *Lathyrus* species (*Fabaceae*). β -(Isoxazolin-5-on-2-yl)alanine or 2-(2-amino-2-carboxyethyl)isoxazolin-5-one from *Lathyrus*, *Vicia*, *Pisum*, and *Lens* species (*Fabaceae*) shows antimycotic activity towards the yeast *Saccharomyces cerevisiae*. Being a structural analogue (antagonist) of L-glutamic acid, this amino acid exhibits neuroexcitatory activity and can act as a precursor of 3-aminopropionitrile, L-2,4-diaminobutanoic acid and the neurotoxic 3-(*N*-oxalyl)-L-2,3-diaminopropionic acid (β -*N*-oxalyl-L-alanine) in some *Vicia* and *Lathyrus* species. L-Quisqualic acid (Figure 18) present in *Quisqualis* species (*Combretaceae*) has neuroexcitatory (it is a stimulant of L-glutamic acid receptors) activity and is used as a vermicide in Chinese medicine (Figure 18) (KUO & LAMBEIN 1991; IKEGAMI *et al.* 1992; YIGZAW *et al.* 2001).

By contrast, some other β -substituted heterocyclic alanines are synthesised by specific synthases from *O*-acetylserine and suitable heterocyclic precursors (IKEGAMI & MURAKOSHI 1999). The formation of β -(pyrazol-1-yl)alanine from pyrazole (*Citrullus* species) is catalysed by pyrazolealanine synthase (EC 2.5.1.51), while L-mimosine synthase (EC 2.5.1.52) acts on 3,4-dihydroxypyridine and

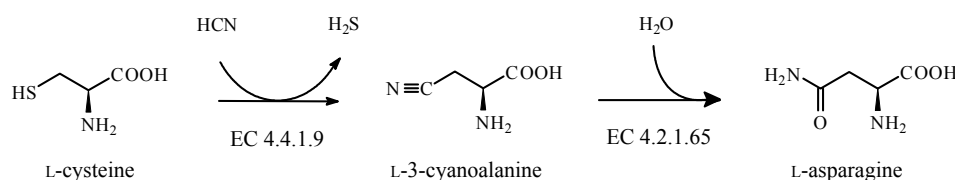


Figure 17

⁷Except β -cyanoalanine synthase (EC 4.4.1.9), the enzymes involved in cyanide catabolism are cyanide hydratase (EC 4.2.1.66) and rhodanese (EC 2.8.1.1). Cyanide hydratase has been reported to occur in a variety of fungal species. Rhodanese has been found in almost the whole spectrum of living forms, from bacteria to animals (such as centipedes, beetles and few species of butterflies).



2-(2-amino-2-carboxyethyl)isoxazolin-5-one L-quisqualic acid

Figure 18

yields L-mimosine present in *Mimosa* and *Leucaena* species (*Leguminosae*). L-Willardiine in *Pisum*, *Acacia*, and *Fagus* species and isomeric L-isowillardiine from *Pisum* and *Crotalaria* species are formed from uracil by the action of willardiine synthase (isowillardiine synthase, EC 2.5.1.53) (Figure 19). L-Lupinic acid is produced from (*E*)-zeatin under the catalysis of lupinic acid synthase (EC 2.5.1.50) in *Lupinum* species. Mimosine is a thyrotoxic amino acid which shows depilatory activity (causes the loss of hair in growing animals). Uracilylalanine L-willardiine in *Pisum*, *Acacia*, and *Fagus* species is a neuroactive amino acid. Lupinic acid is a metabolite of the cytokinin (*E*)-zeatin, which is also present in plants as a riboside⁸ (Figure 19).

6.4 Substituted aminobutanoic acids

The higher homologues of heterocyclic β -substituted alanines with one more carbon in the side chain can be considered either as a group of homoserine derivatives or as a group of γ -substi-

tuted 2-aminobutanoic acids (KLAIR *et al.* 1998). *N*-(3-Amino-3-carboxypropyl)azetidione-2-carboxylic acid from the beechnut seeds (*Fagus sylvatica*), nicotianamine from the beechnut seeds and tobacco (*Nicotiana tabacum*), mugineic acid from rice (*Oriza sativa*), the higher homologue of β -(isoxazolin-5-on-2-yl)alanine derived from 2-aminobutanoic acid (VELÍŠEK & CEJPEK 2006), e.g. α -amino- γ -(isoxazolin-5-on-1-yl)butanoic acid or 2-(3-amino-3-carboxypropyl)isoxazolin-5-on from the grass pea (*Lathyrus sativus*) seeds, L-canavanine and L-canaline occurring in the jack beans (*Canavalia ensiformis*) and sword beans (*C. gladiata*) are examples of some other non-protein amino acids bearing the 3-amino-3-carboxypropyl moiety (Figure 20).

N-(3-Amino-3-carboxypropyl)azetidione-2-carboxylic acid, nicotianamine, mugineic acid and its analogues act as phytosiderophores (iron-chelating amino acids) produced in higher plants that promote the uptake of iron from the soil (MORI 1994). All these amino acids (similarly to 1-aminocyclopropane-1-carboxylic acid) are derived from SAM as the donor of the 3-amino-3-carboxypropyl side chain. For example, the biosynthesis of nicotianamine catalysed by nicotianamine synthase (EC 2.5.1.43) requires three molecules of SAM (Figure 21).

2-(3-Amino-3-carboxypropyl)isoxazolin-5-on has been shown to cause neurotoxic symptoms similar to neurotoxicogenic L-2,4-diaminobuta-

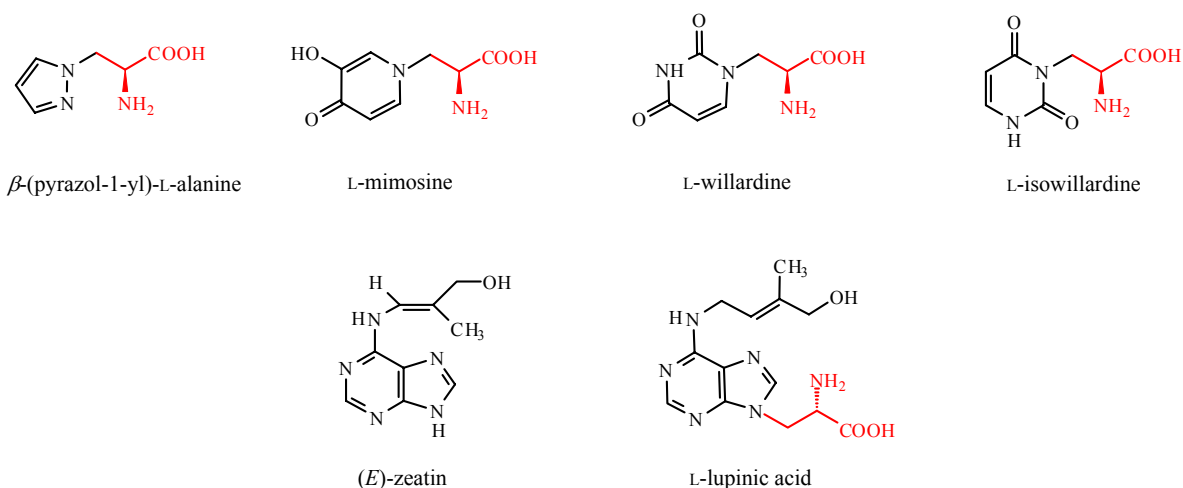


Figure 19

⁸The function of cytokinins is reflected by changes in the levels of the individual cytokinin forms. For example, *cis/trans* isomerization, *O*-glucosylation, formation of lupinic acid, and degradation by cytokinin oxidase (EC 1.4.3.6) can destroy their activity.

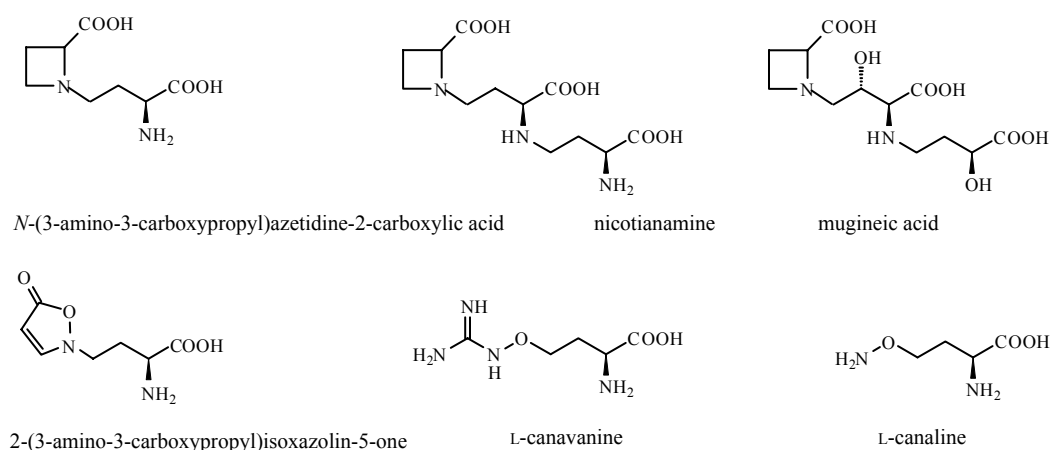


Figure 20

noic acid as it acts as its precursor. It has also been linked to the biosynthesis of 2-cyanoethylisoxazolin-5-one present in the shoots and seedlings of *L. sativus*, which can cause osteolathyrism in animals. The proposed biosynthetic pathways for the neurotoxic amino acids in *Lathyrus* species are given in Figure 22. The formation of 2-(2-amino-2-carboxyethyl)isoxazol-5-one from *O*-acetylserine is catalysed by cysteine synthase (EC 2.5.1.47). 3-Aminopropionitrile, L-2,4-diaminobutanoic acid and 3-(*N*-oxalyl)-L-2,3-diaminopropionic acid can also form from L-3-cyanoalanine.

Canavanine, L-2-amino-4-(guanidinoxy)butanoic acid, an analogue of arginine, is a potent

arginine antagonist being able to manifest antimetabolic effects in bacteria and fungi, as well as in higher plants and animals. This amino acid can replace arginine as a substrate in most metabolic reactions. Canavanine-containing plants employ this amino acid in their chemical defence systems (as a protective allelochemical), as its storage creates an effective protective barrier to herbivore predation and various diseases. Canavanine is known to possess cytotoxicity to tumour cells in culture and experimental tumours *in vivo* (ROSENTHAL 1991; JANG *et al.* 2002).

Canaline, L-2-amino-4-(aminoxy)butanoic acid, a structural analogue of ornithine, is a lysine an-

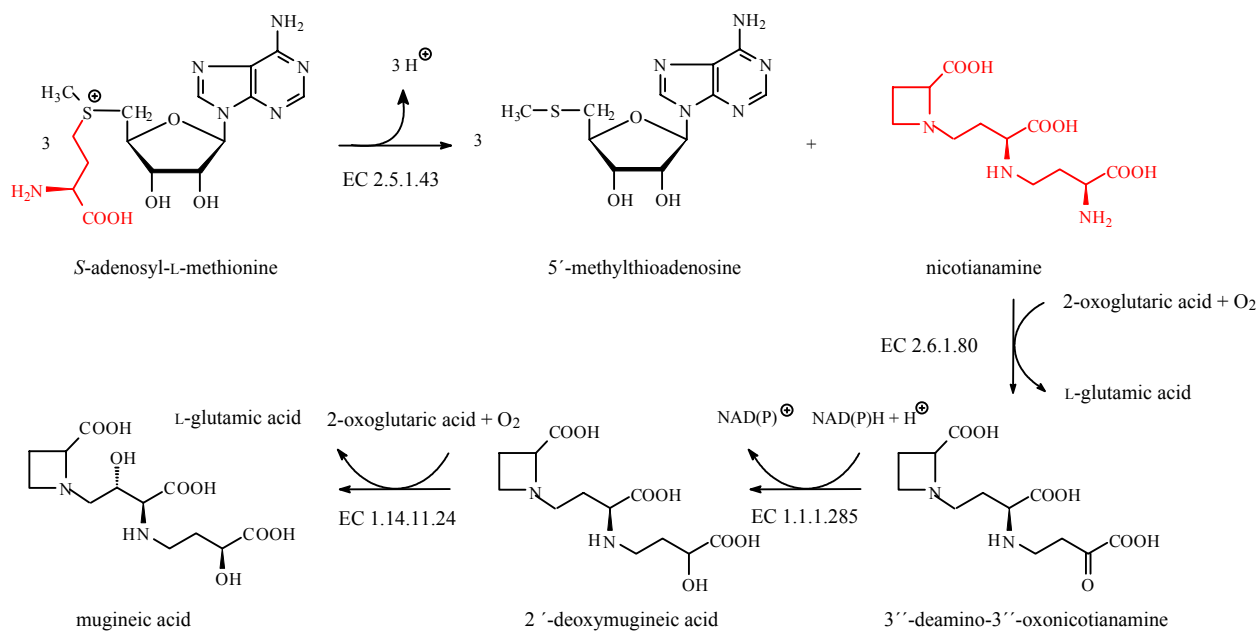


Figure 21

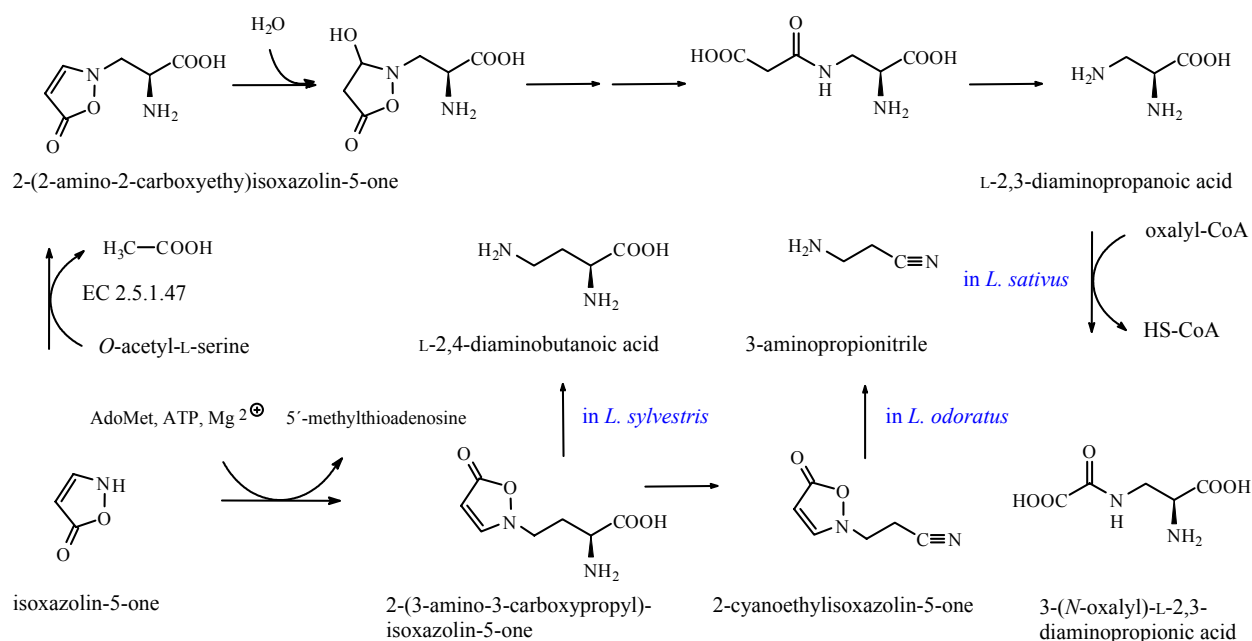


Figure 22

tagonist. It is unique by being the only naturally occurring amino acid possessing an aminoxy moiety. It is a highly toxic compound that represents a protective allelochemical against insects and predators. It reacts with the pyridoxal 5'-phosphate moiety of many aminotransferases and decarboxylases to form a covalently bound oxime that inactivates, often irreversibly, the enzyme (ROSENTHAL 1997; LEE & KWON 2000).

It was proposed that canaline originates from aspartic acid but the precise mechanism by which this amino acid is formed needs to be elucidated. Ca-

navanine is biosynthesised from canaline through the urea (ornithine) cycle via *O*-uredohomoserine (ornithine carbamoyltransferase, EC 2.1.3.3) and canavaninosuccinic acid (argininosuccinate synthase, EC 6.3.4.5), which splits off succinic acid (probably by the action of argininosuccinate lyase, EC 4.3.2.1) to yield canavanine (Figure 23) (NATELSON *et al.* 1977; LEE *et al.* 1997).

Canavanine is catabolised to canaline and urea by arginase (EC 3.5.3.1). The transamination reaction then possibly leads to the formation of 4-aminoxy-2-propanoic acid. Its decarboxyla-

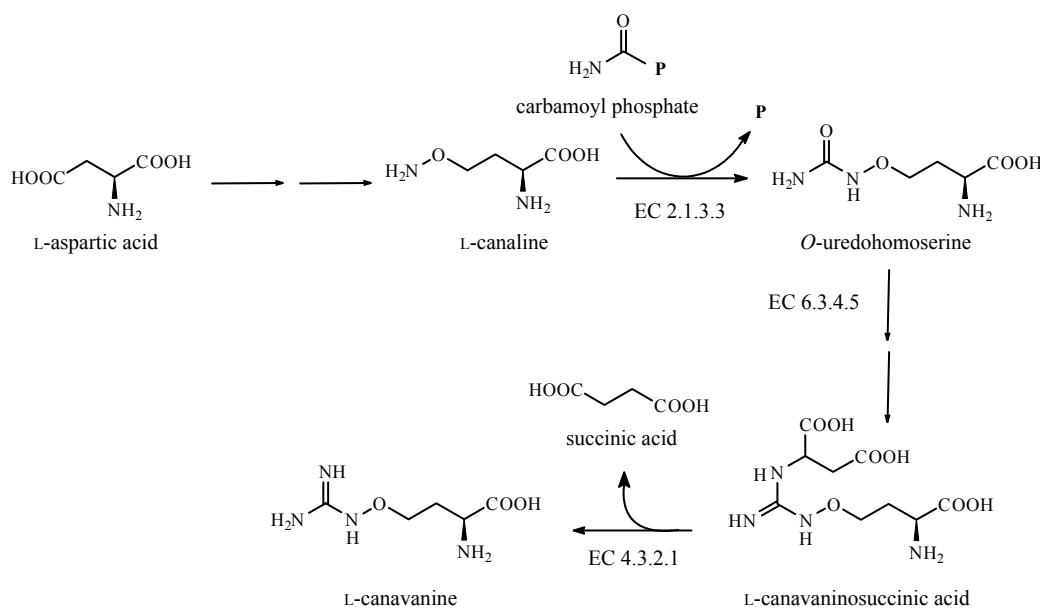


Figure 23

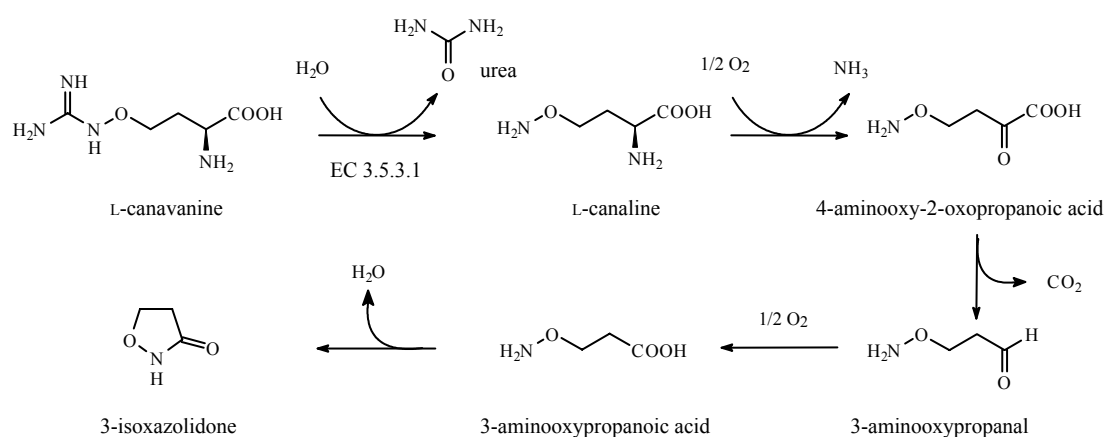


Figure 24

tion and oxidation of the aldehyde formed finally yield 3-isoxazolidone that occurs in relatively high levels in the Jack bean seedlings (Figure 24) (SUGII *et al.* 1981).

7 TAURINE

In mammalian tissues, taurine (1-aminoethane-2-sulfonic acid) is a ubiquitous semi-essential amino acid occurring as a free compound, although its concentrations in different tissues and fluids vary widely. Good sources of taurine include meat (0.02–0.1% fresh weight) and some types of seafood, the latter being particularly rich sources. In mammalian tissues, taurine is the most abundant amino acid in the skeletal muscle, heart, retina,

brain, and leukocytes. It also occurs in insect tissues and is particularly abundant in the flight muscle and eye. On the other hand, taurine is completely absent from plants.

Taurine is essential for many biological processes, such as bile salt synthesis (the major pathway of taurine metabolism), development of the brain and eyes, reproduction, osmoregulation as well as the anti-inflammatory activity of leukocytes (LOMBARDINI 1991; PARK *et al.* 2002). It also plays a significant role as an antioxidant preventing the oxidative damage that occurs during the aging process (EPPER & DAWSON 2001).

Recent studies provide an evidence that taurine is also a constituent of some biological macromolecules. For example, taurine-containing modified

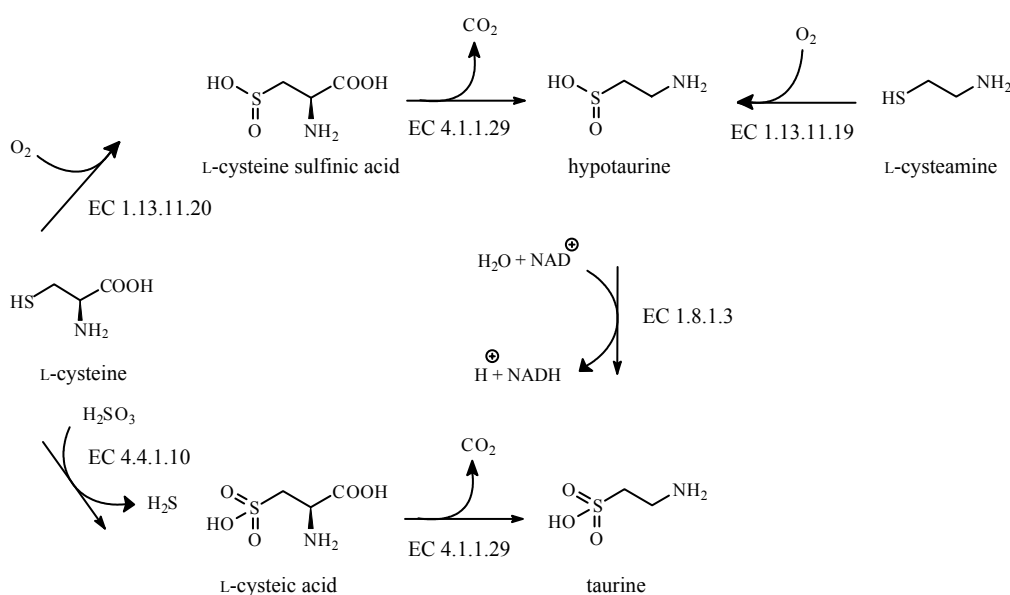


Figure 25

uridines have been found in the human mitochondria. Taurine combined with higher fatty acids, such as 2-(octadecanoylamino)ethanesulfonic acid, occurs in the lipotaurine fraction of some protozoa cells (e.g. *Tetrahymena thermophila*) (KAYA & SANO 1991).

The estimated mean daily intake of taurine is around 58 mg. Taurine-containing health drinks, usually containing 4 g/l of taurine, are marketed worldwide for the treatment of various physiological conditions, for the improvement of the athletic performance, and for the general well being (SCHULLER-LEVIS & PARK 2003). Taurine is biosynthesised from cysteine by two distinct pathways (Figure 25). The so-called cysteine sulfinic pathway is the major route for taurine biosynthesis in the liver and also in the brain. It includes oxidation of the thiol group of cysteine by cysteine dioxygenase (EC 1.13.11.20), which requires Fe²⁺ and NAD(P)H to form cysteine sulfinic acid (3-sulfinoalanine). This enzyme is important in the regulation of amino acid levels, such as the level of cysteine and methionine, and the peptide glutathione. The decarboxylation of cysteine sulfinic acid by cysteine sulfinic acid decarboxylase (EC 4.1.1.29) generates hypotaurine (1-aminoethane-2-sulfinic acid). Subsequent oxidation of the latter compound by hypotaurine dehydrogenase (EC 1.8.1.3) yields taurine. Hypotaurine can also be formed by oxidation of cysteamine by the action of cysteamine dioxygenase (EC 1.13.11.19).

Cysteine sulfinic acid decarboxylase is the rate-limiting enzyme in taurine biosynthesis. It is a pyridoxal 5'-phosphate-dependent enzyme and its activity can be repressed by several factors, such as thyroid and steroid (estrogen) hormones, and high-protein diets (KAISAKIA *et al.* 1995; EPPER & DAWSON 2001).

Cysteine sulfinic acid decarboxylase is also responsible for the direct transformation (decarboxylation) of cysteic acid (cysteine sulfonic acid) to taurine. Cysteic acid is formed from cysteine by the action of cysteine lyase (EC 4.4.1.10) (DO & TAPPAZ 1996).

EC (Enzyme Commission) numbers and some common abbreviations

EC (Enzyme Commission) numbers, assigned by IUPAC-IUBMB, were taken from KEGG: Kyoto Encyclopedia of Genes and Genomes, <http://www.biologie.uni-hamburg.de>. In many structures, the abbreviation

P is used to represent the phosphate group and **PP** the diphosphate group. At physiological pH, these and some other groups will be ionised, but in pictures the unionised forms are depicted to simplify the structures, to eliminate the need for counter-ions, and to avoid mechanistic confusion.

SAH	S-adenosyl-L-homocysteine (AdoHcy)
SAM	S-adenosyl-L-methionine (AdoMet)
ADP	adenosine 5'-diphosphate
ATP	adenosine 5'-triphosphate
CoA	coenzyme A as a part of a thioester
DOPA	3,4-dihydroxy-L-phenylalanine
FAD	flavine adenine dinucleotide
GSH	glutathione (reduced)
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
P	phosphoric acid

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Corresponding author:

Prof. Ing. JAN VELÍŠEK, DrSc., Vysoká škola chemicko-technologická v Praze, Fakulta potravinářské a biochemické technologie, Ústav chemie a analýzy potravin, Technická 5, 166 28 Praha 6, Česká republika
tel.: + 420 220 443 177, fax: + 420 233 339 990, e-mail: jan.velisek@vscht.cz
