Biosynthesis of Food Constituents: Amino Acids: 3. Modified Proteinogenic Amino Acids – a Review

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Abstract

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This review article gives a survey of principal pathways that lead to the biosynthesis of the modified principal proteinogenic amino acids, i.e. cystine, 4-hydroxyproline, 5-hydroxylysine, 3-methylhistidine, and *O*-phosphoserine. Except the proteinogenic amino acids, peptides and proteins often contain several unusual amino acids arising by specific modifications (e.g. oxidation or esterification) of amino acid residues present in the already synthesised polypeptide chain. The post-translational products include, e.g., the oxidation of the thiol groups of two cysteine residues to form a disulfide bridge (cystine), thus allowing cross-linking of polypeptide chains; the hydroxylation of proline to 4-hydroxyproline and of lysine to 5-hydroxylysine; *N*-methylation of histidine to 3-methylhistidine; and the phosphorylation of serine to *O*-phosphoserine. There also exist several other modified proteinogenic amino acids that are of minor significance to foods.

Keywords: biosynthesis; amino acids; cystine; hydroxyproline; hydroxylysine; methylhistidine; phosphoserine

1 Cystine

Post-translational oxidation of the thiol groups of two L-cysteine (L-2-amino-3-mercaptopropionic acid) residues catalysed by the enzyme cystine reductase (EC 1.8.1.6, Figure 1) yields L-cystine, bis(L-2-amino-2-carboxyethyl)disulfide (Cy-S-S-Cy).

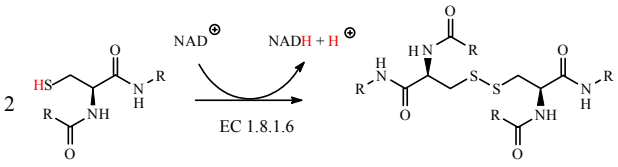

Figure 1

The cystine disulfide bridge has a significant role in the structure of many proteins as it joins either two different peptide chains or two cysteins in the same peptide chain. For example, the main globular protein in whey β-lactoglobulin contains 2 disulfide bonds and the glycoprotein ovomucoid in eggs is arranged in three tandem domains, each cross-linked by three intradomain disulfide bonds (Sengbusch; Velíšek 2002).

2 Hydroxyproline

Collagens are a family of proteins found essentially in all animal connective tissues. They form a diverse range of highly organised supramolecu-

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lar assemblies in the extracellular matrix. The biosynthesis of collagens involves several post-ribosomal modifications of procollagens, which include hydroxylation of prolyl and lysyl residues that are part of a polypetide chain. The structures formed are unique to collagens and essential for their functional activity. Hydroxyproline residues are crucial for the formation of the collagen triple helices and hydroxylysine has an important function in collagen intra- and inter-molecular cross-links formation *in vivo*, especially in weight-bearing and mineralised tissues such as bone and cartilage. The modification of hydroxylysine also provides the attachment sites for glycosylated hydroxylysine residues that may play a role in interactions between collagen molecules and with other extracellular matrix components.

The product of proline hydroxylation in -X-Pro-Gly- sequences in procollagens is (*E*)-4-hydroxy-L-proline (Hyp, L-4-hydroxypyrrolidine carboxylic acid, Figure 2) confined almost exclusively to the connective tissue collagens. The hydroxylation of prolines, and several other proteins that have collagen-like domains, is catalysed by prolyl 4-hydroxylase (EC 1.14.11.2). Hydroxyproline is also common in the metabolically active plant cell wall glycopeptide extensin. Analogously, the hydroxylation of prolines by prolyl 3-hydroxylase (EC 1.14.11.2) yields (*E*)-3-hydroxy-L-proline, which is the minor component of animal connective tissues (KEGG). Except 2-oxoglutaric acid, oxygen and collagenous polypeptide (procollagen) as the substrate, both prolyl hydroxylases require Fe^{2+} and L-ascorbic acid, which is essential for the regeneration of Fe^{2+} ions according to the equation: L-ascorbic acid + 2 Fe^{3+} → L-dehydroascorbic acid + 2 Fe^{2+} + 2 H^+.

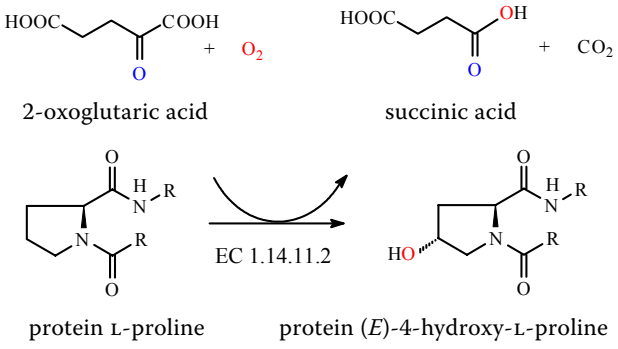

Figure 2

3 Hydroxylysine

Hydroxylation of helical L-lysine residues during the post-translational modifications of collagenous proteins in the -X-Lys-Gly- sequences within parts of the chains yields 5-hydroxy-L-lysine (Figure 3). The reaction is catalysed by the enzyme lysyl hydroxylase (EC 1.14.11.4) (KEGG). Analogously to prolyl hydroxylases, lysyl hydroxylase requires Fe^{2+} and L-ascorbic acid.

4 Methylhistidine

The amino acid 3-methyl-L-histidine is associated with skeletal muscle metabolism. The histidine residue at position 73 is post-translationally modified to 3-methylhistidine by protein-histidine *N*-methyltransferase (EC 2.1.1.85) in all actins known. *S*-adenosyl-L-methionine (SAM, AdoMet) acts as the methylation reagent yielding *S*-adenosyl-L-homocysteine (SAH, AdoHcy). The functional significance of this actin modification is unknown. It has been suggested that the methylhistidine side chain, by interaction with phosphate ion released

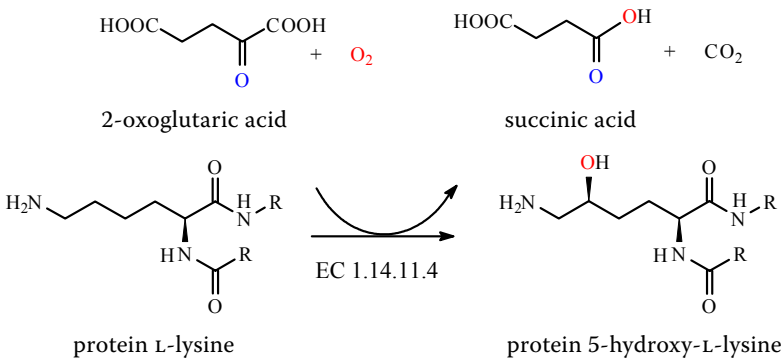

Figure 3

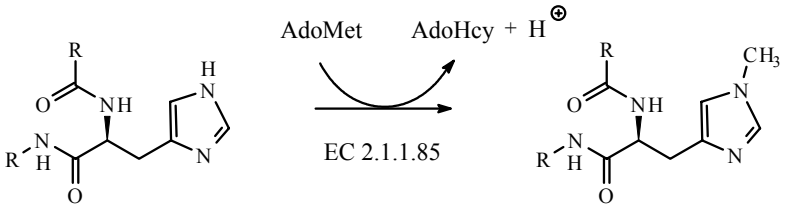

Figure 4

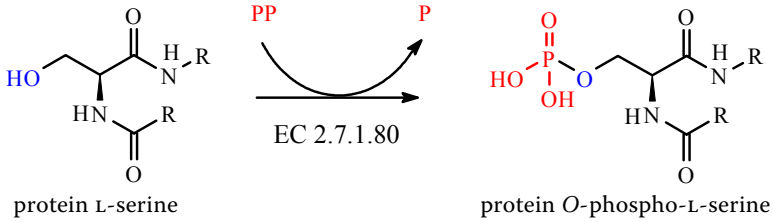

Figure 5

following hydrolysis of the actin-bound ATP, may play an important role in preventing the facile exit of the phosphate. This unusual modification of histidin is also found in some striated myosin isoforms (KEGG).

5 Phosphoserine

O-phospho-L-serine (Figure 5) arises by post-translational phosphorylation of L-serine catalysed by diphosphate-serine phosphotransferase (EC 2.7.1.80). It occurs in many proteins such as the main phosphoprotein in milk α_{S1}-casein (8 phosphoserine residues), β-casein (5 phosphoserine residues), and the glycophosphoprotein phosvitin in eggs (almost 50% of its amino acids are serine residues out of which 90% are phosphorylated) (KEGG).

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 the mechanistic confusion.

SAH	*S*-adenosyl-L-homocysteine (AdoHcy)
SAM	*S*-adenosyl-L-methionine (AdoMet)
NADH	nicotinamide adenine dinucleotide
P	phosphoric acid
PP	diphosphoric acid

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