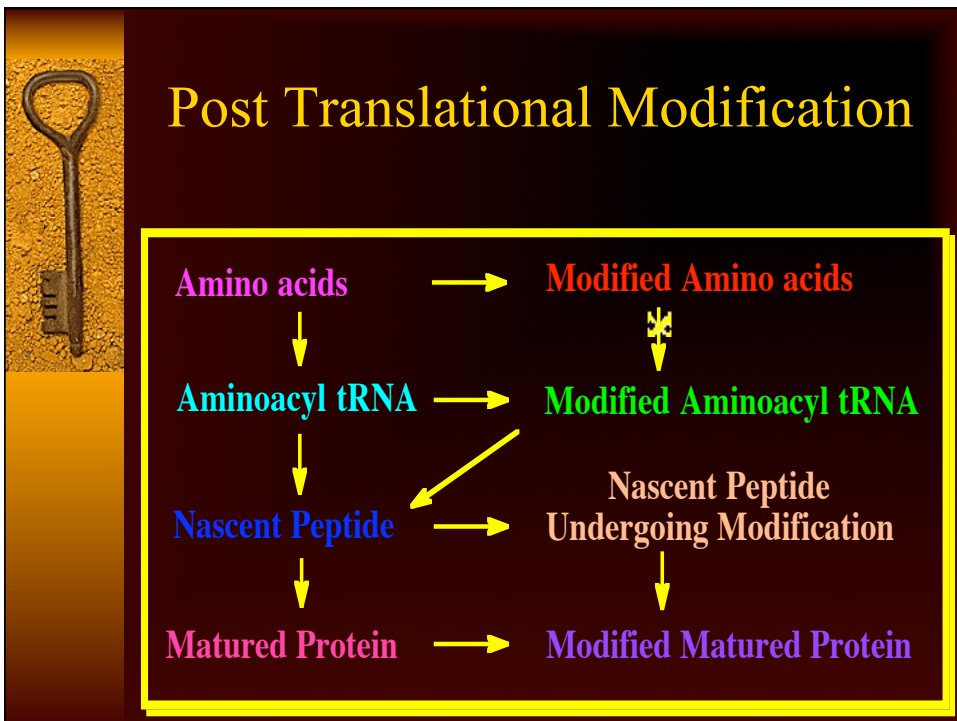


Post translational modification in proteins

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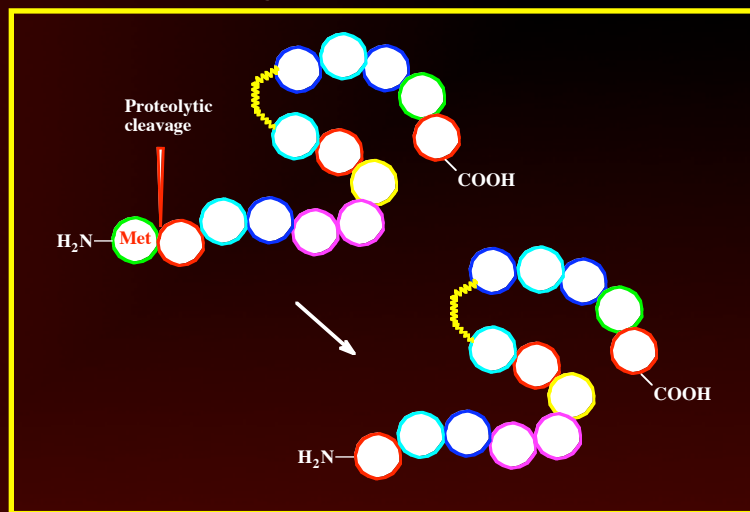


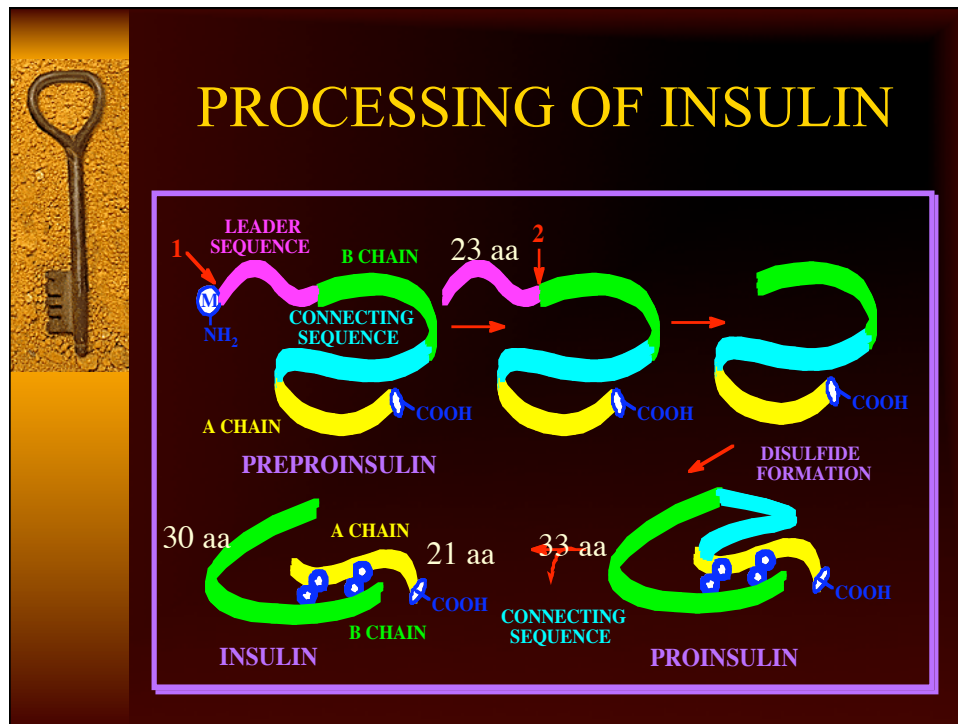
First modification - Modification of N-terminal met.

- ◆ AUG is the universal Starting codon.
- ◆ Hence, Met is the first amino acid in all proteins.
- ◆ But met has to be cleaved.
- ◆ It occurs as and when the protein is being synthesized.
- ◆ Eukaryotes:
Removal of Met to expose new amino terminal.
- ◆ Prokaryotes:
A) Removal of Formyl group.
B) Removal of formyl met group.

First Post translational modification


- ◆ N-terminal Met (or formylmet) of all proteins are trimmed first to generate a new N-terminus.






N-Terminal Acylation.

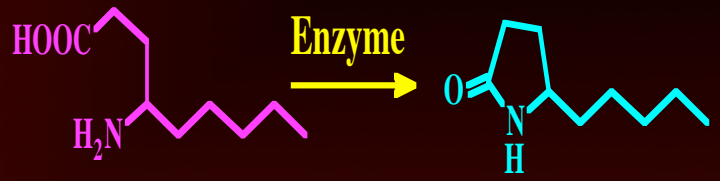
- ◆ Formylation.
- ◆ Acetylation.
- ◆ Pyruvoyl formation.
- ◆ α -ketobutyryl formation.
- ◆ Glucuronylation.
- ◆ α -amino acylation.
- ◆ Pyroglutamyl formation.
- ◆ Murein addition.




Pyruvoyl group formation at N-terminal of some enzymes.



N-Terminal glutamic acid is specifically converted to pyroglutamic acid in some proteins.

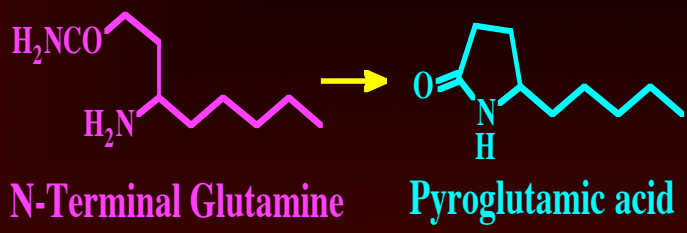


N-Terminal Glutamic acid Pyroglutamic acid




N-Terminal glutamine

N-terminal glutamine undergoes spontaneous cyclization with the elimination of ammonia to form pyroglutamic acid.

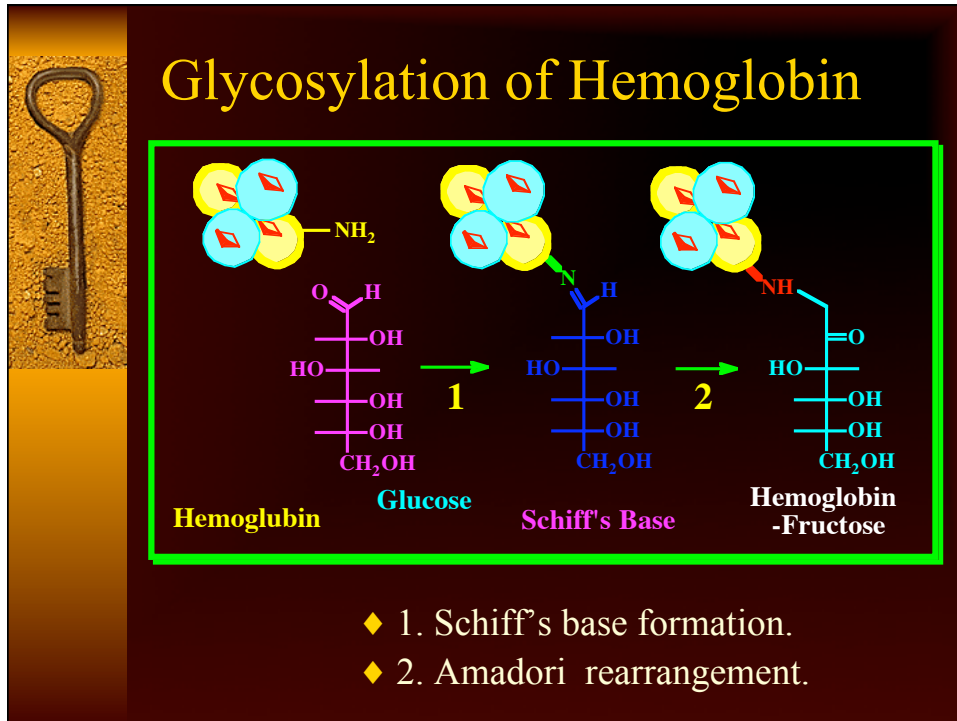


N-Terminal Glutamine Pyroglutamic acid



N-terminal alkylation


- ◆ Glycosylation:
High concentration of glucose in blood results in glycosylation of aminoterminal valine in hemoglobin to give 1-deoxy,1-(N- α -valine)-fructose.
- ◆ N-methylation of some ribosomal proteins at met, ala, and pro.



C-Terminal Processing


In some proteins, C-terminal peptide is cleaved
Much like the N-terminal signal processing.

- Three modifications of C-terminal.
 - .. 1. Conversion of COOH to CONH₂
 - .. 2. ADP-Ribosylation of C-terminus
Lysine in Histone H1.
 - .. 3. Substituted amide formation by
addition of tyrosine to C-terminal carboxyl
group.




Transformations of arginine

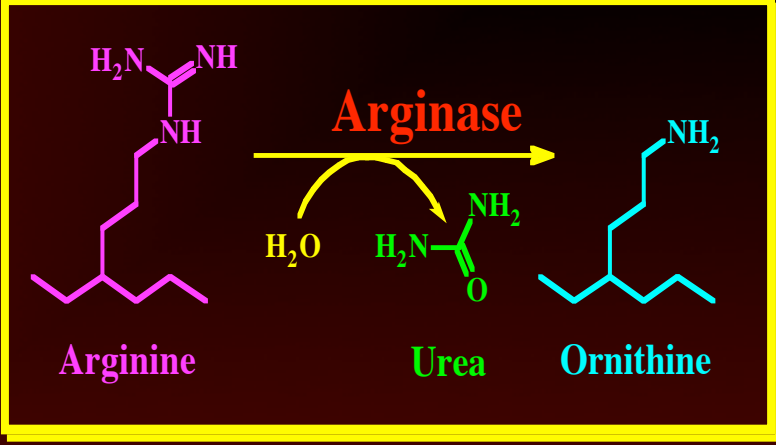
1. Methylation.
(Mono & dimethyl)
2. ADP-ribosylation
3. Phosphorylation
4. Citrulline formation
5. Ornithine formation



Arginine



Ornithine formation in some proteins is probably catalyzed by Arginase



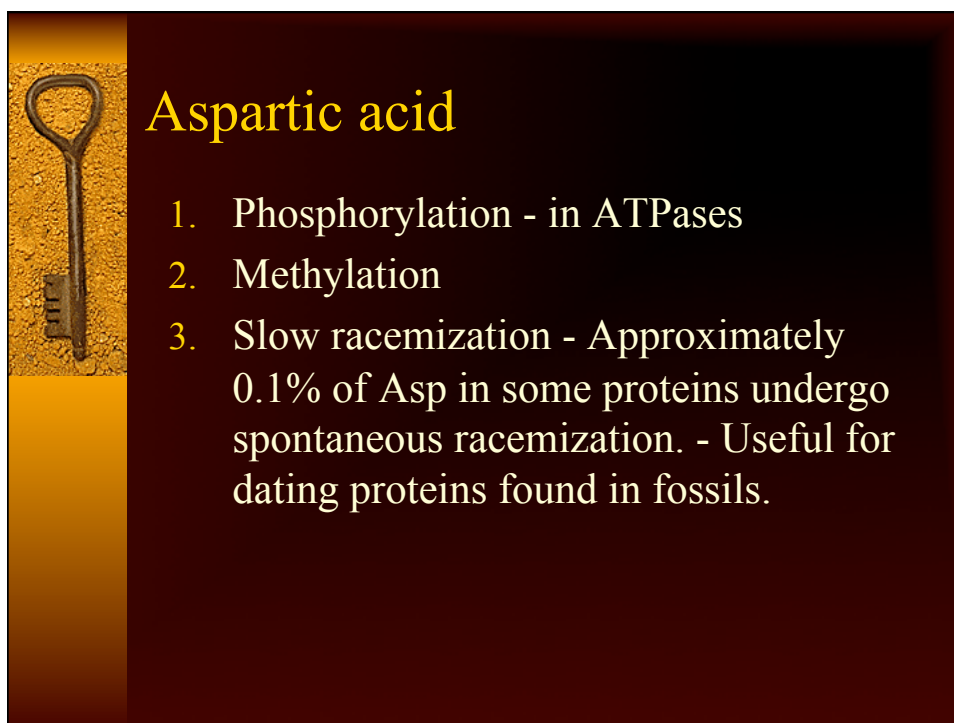
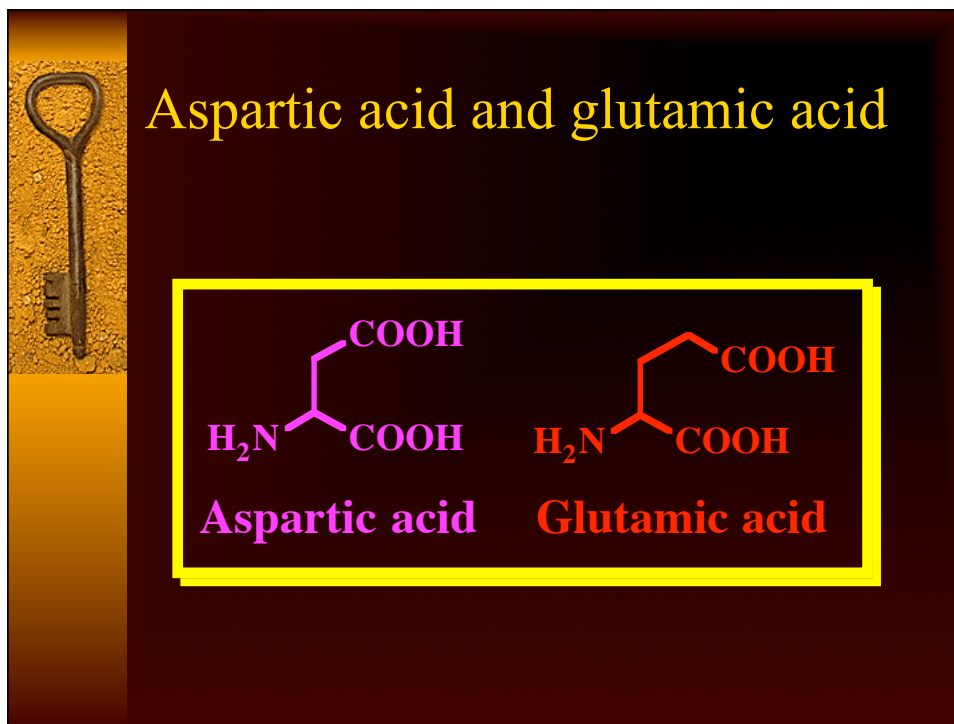
Arginine

Arginase

H₂O

Urea

Ornithine



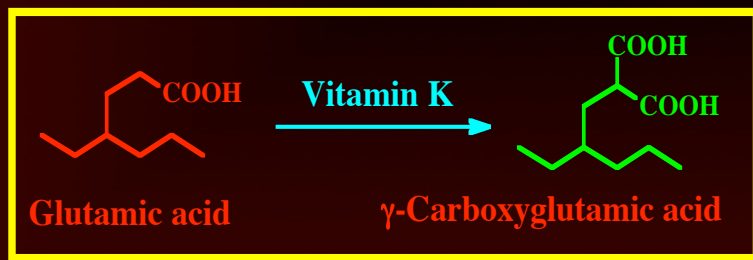


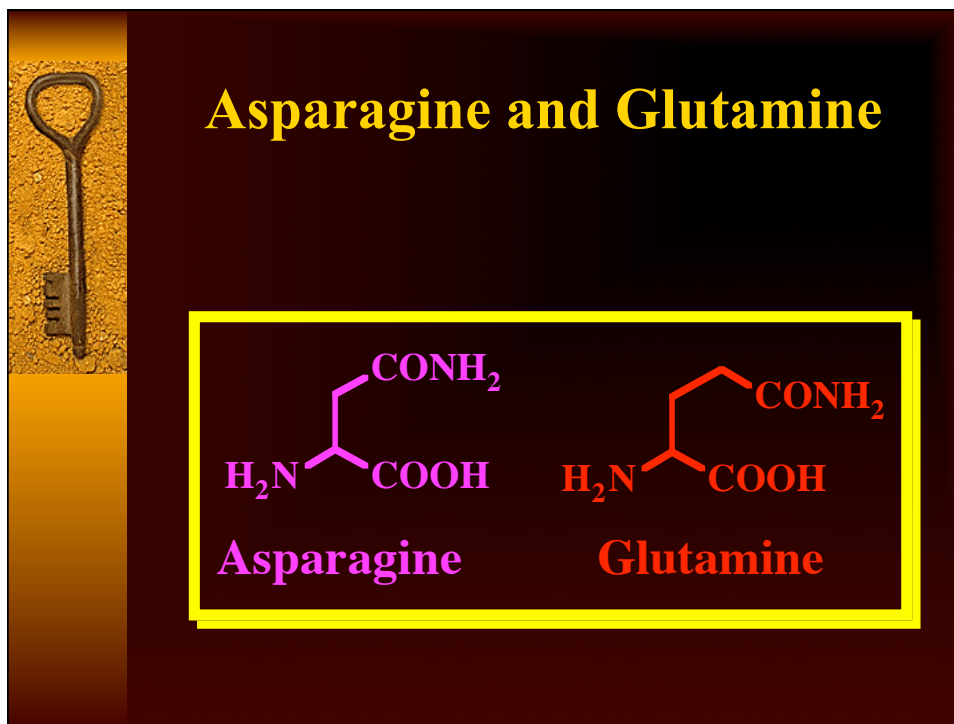
Modifications of Glutamic acid


- ◆ γ -carboxyglutamic acid formation - blood clotting, bone calcification.
- ◆ Methylation - bacterial chemotaxis.
- ◆ ADP-ribosylation in histones.
- ◆ γ -glutamyl cysteine formation - α 2-macroglobulin.
- ◆ γ -glutamyl serine - in proline reductase.
- ◆ Silent modification - Conversion to gln.
In some yeast, Glu-tRNA is modified to Gln-tRNA (There is no charging enzyme for Gln).




γ -Carboxyglutamic acid formation






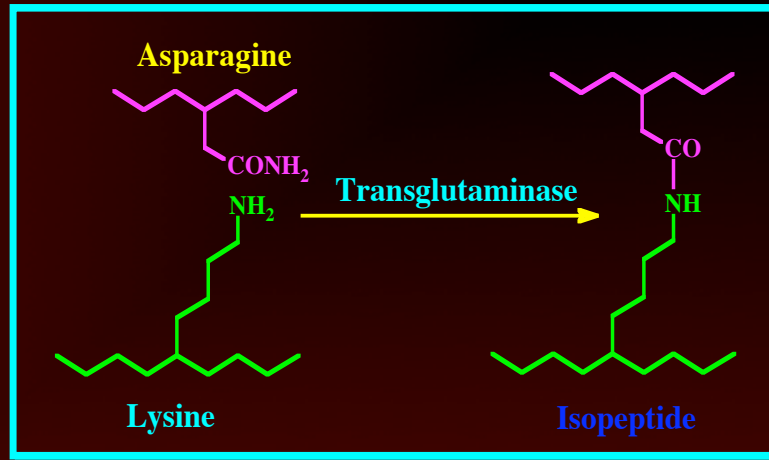
- 
- ## Modifications of Asparagine
1. Asparagine linked oligosaccharide formation is a major modification of this amino acid.
 2. Isopeptide bond formation with ϵ -amino group of lysine in peptides.
 3. Silent modification to aspartic acid. Neutral amino acid to acidic amino acid formation in proteins.

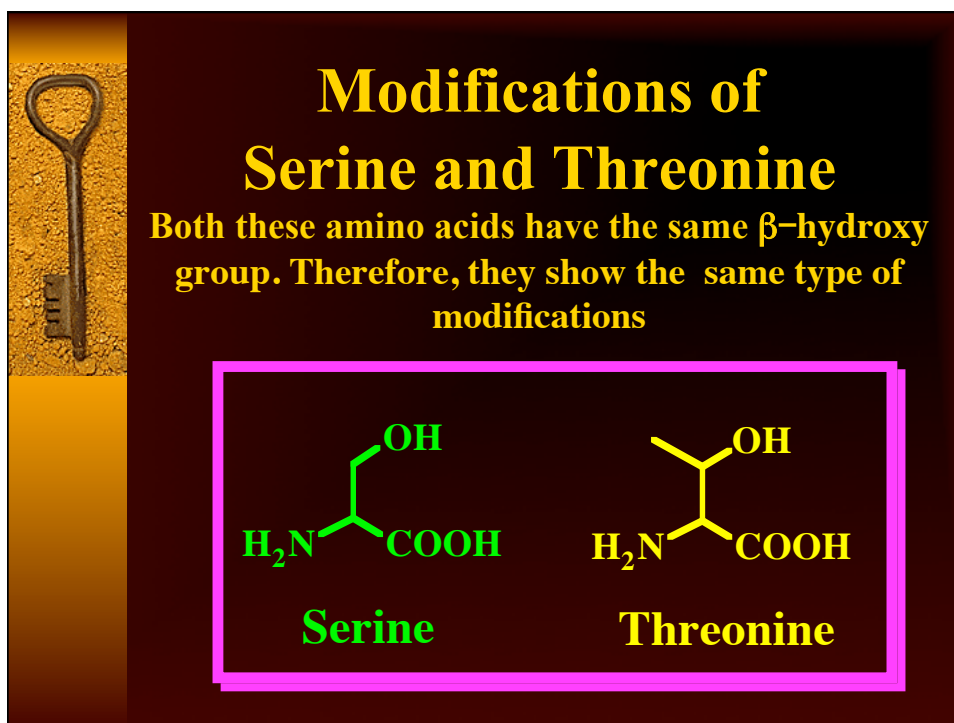
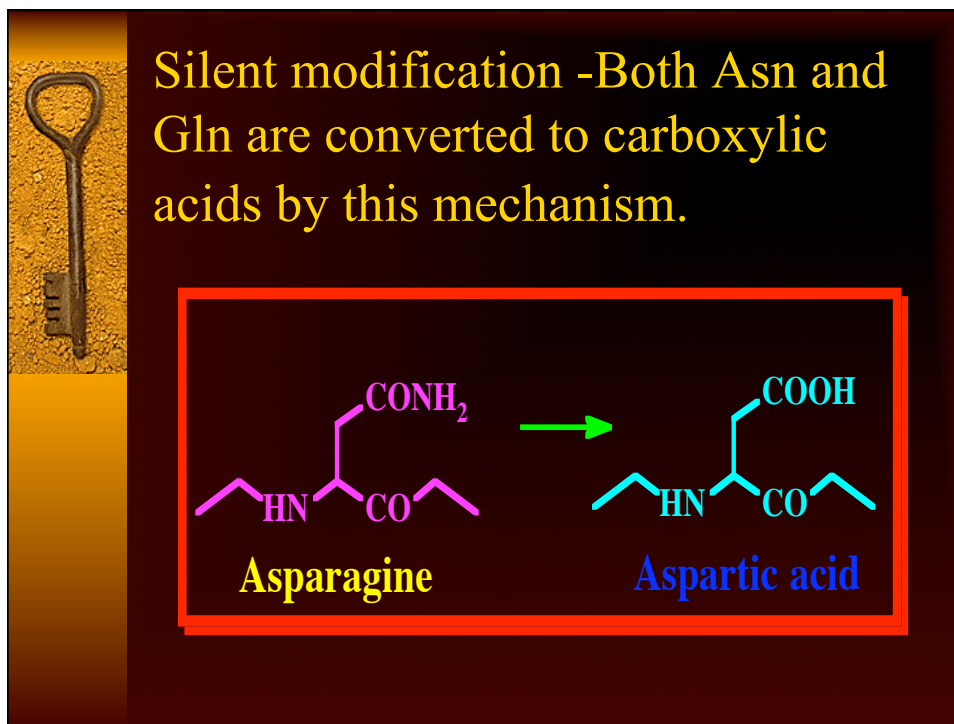



Asparagine - Oligosaccharide addition.



Isopeptide bond formation -Both Asn and Gln undergo this reaction.









Serine and Threonine

- A. O- linked oligosaccharide formation.
- B. Phosphorylation -
 - Regulation of enzyme activity.
- C. Phosphodiester formation
 - ser-P-ser and ser-P-pantetheinine.
 - ADP- Ribosylation.
 - carbohydrate-P- ser
- D. Other possible modifications
 - (methylation and esterification)



Modifications of histidine

1. Phosphorylation (N)
2. Methylation (N)
3. Iodination (4C)
4. Flavin addition (N)
5. ADP-ribosylation (N)



Histidine

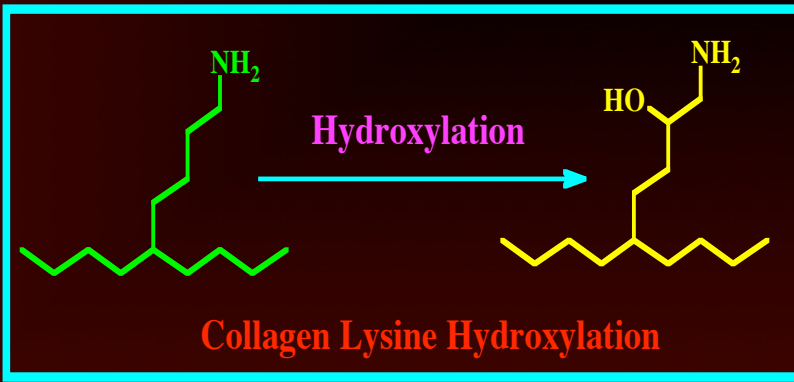


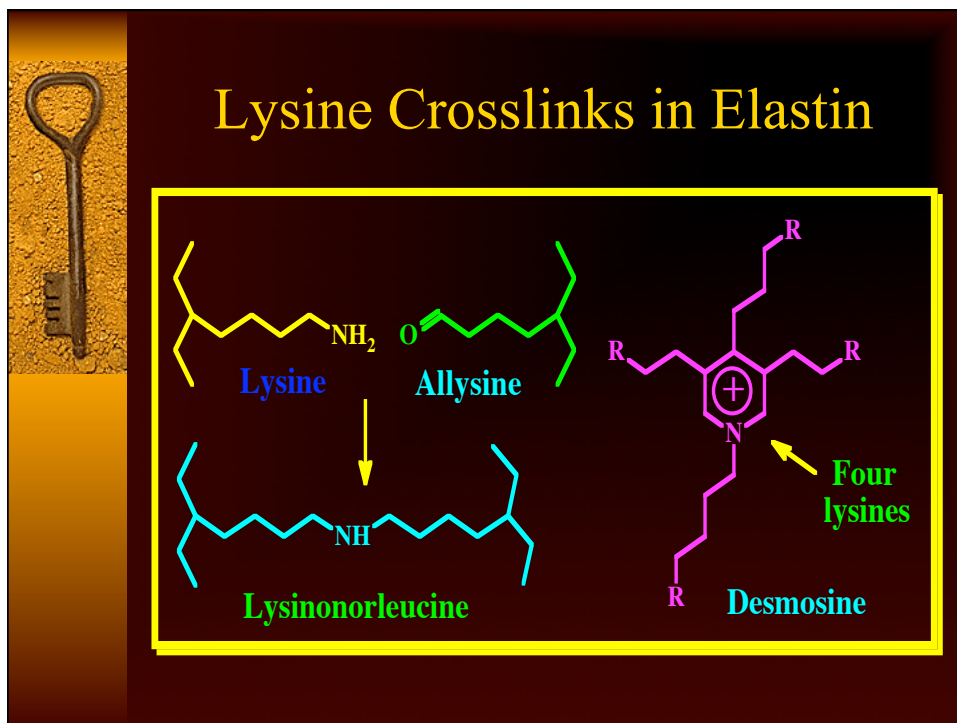
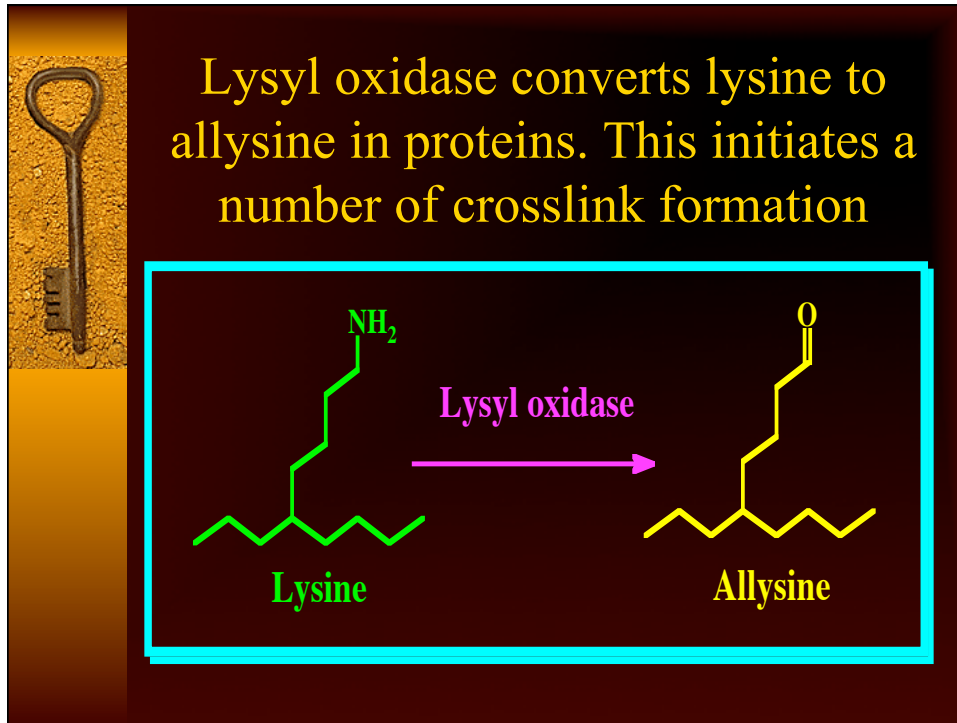
Lysine modifications

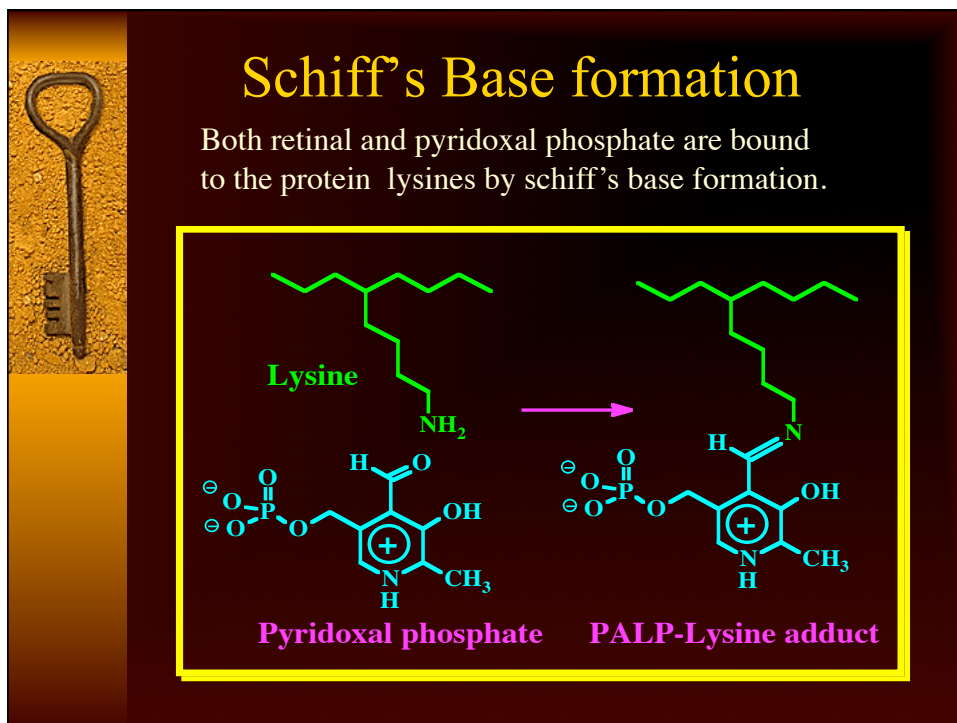
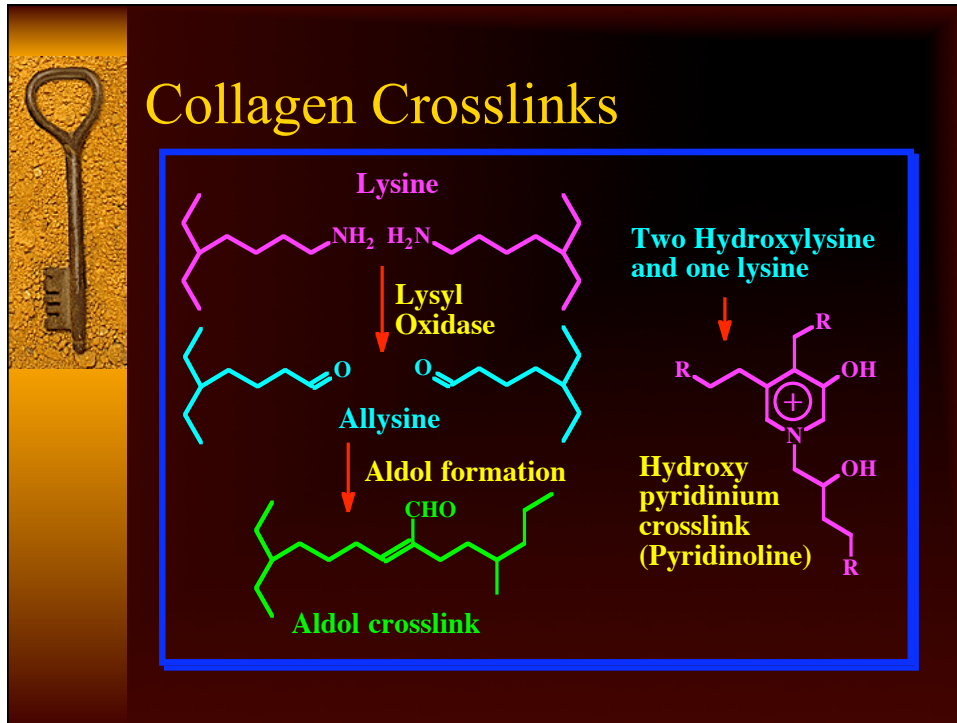
- ◆ Lysyl hydroxylation - Hydroxylysine production.
- ◆ Lysyl oxidation (conversion to allysine).
- ◆ Glycosylation (hemoglobin) (Seen already).
- ◆ Schiff's base formation - retinal, pyridoxal phosphate addition in proteins.
- ◆ Acylation - phosphate, acetyl, N-methylalanyl, dimethyl pimelyl, biotinyl, lipoyl, glutamyl and aspartyl groups (the last two in isopeptide bond).
- ◆ Methylation - mono, di and tri methyl lysines.

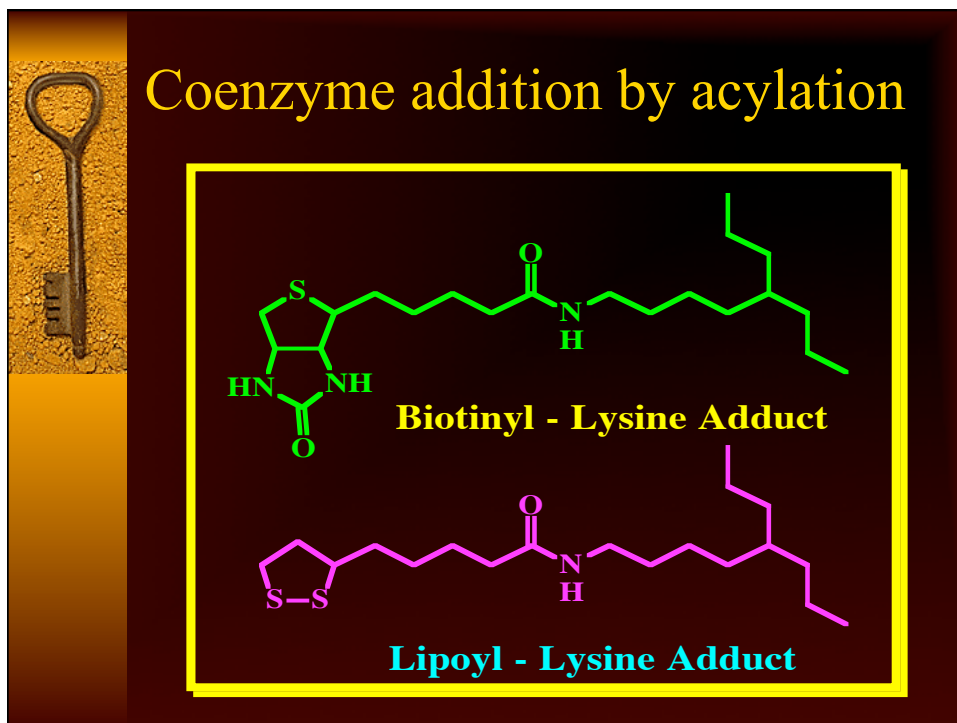
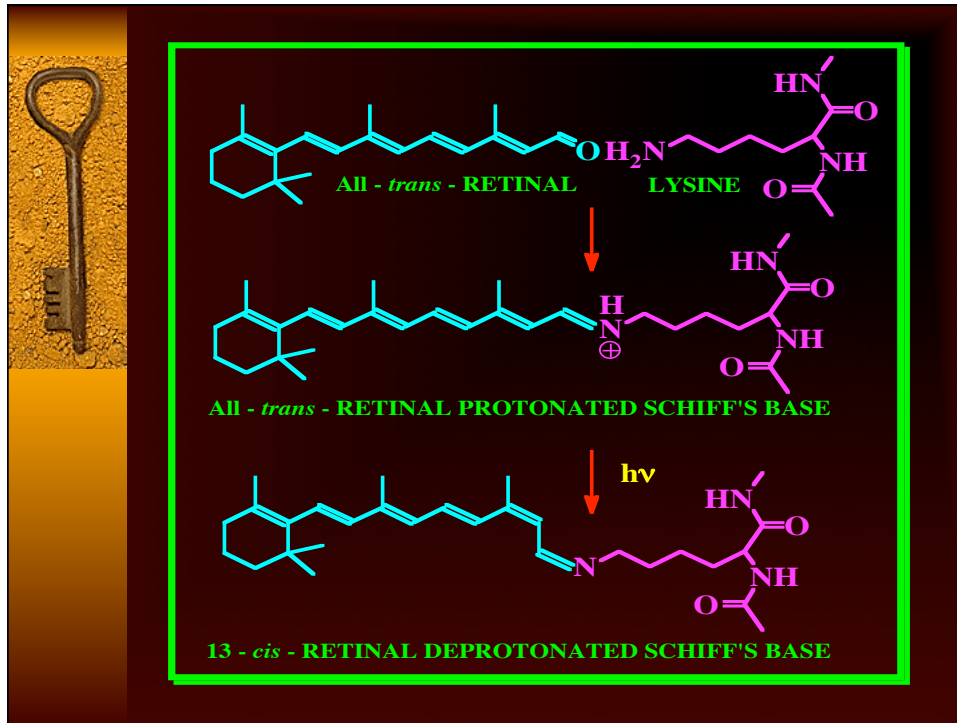



Lysine undergoes hydroxylation in protein to form δ -hydroxylysine











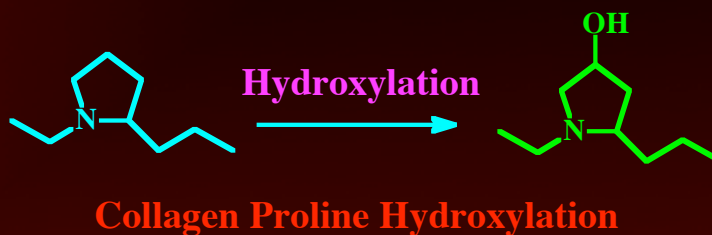
Hydroxylysine undergoes the same modifications as lysine

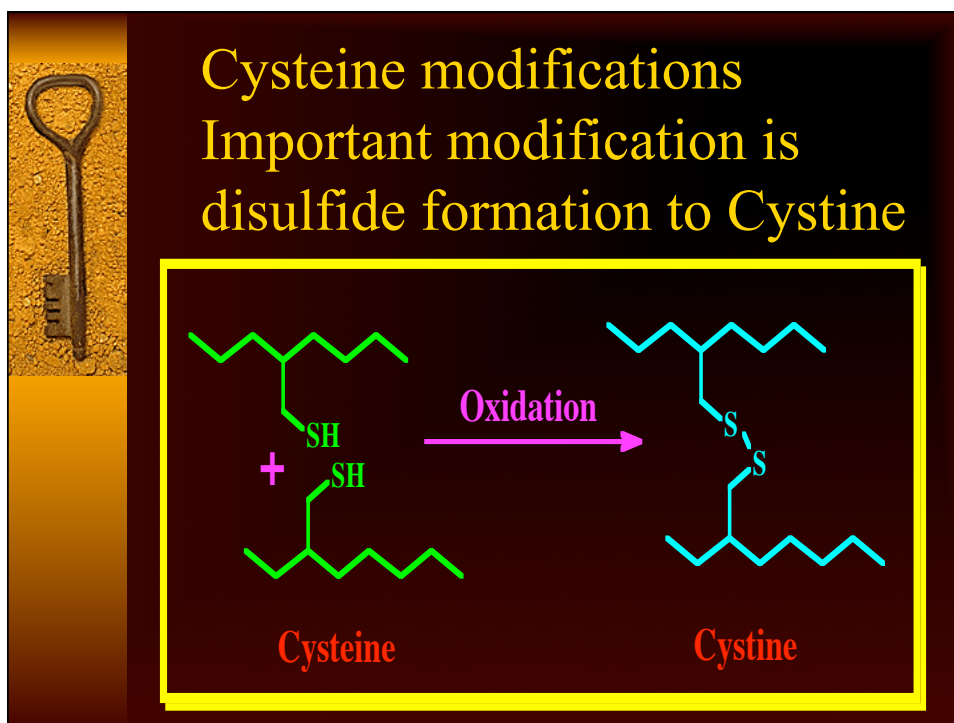
In addition, it also undergoes carbohydrate addition on the newly formed hydroxyl group.




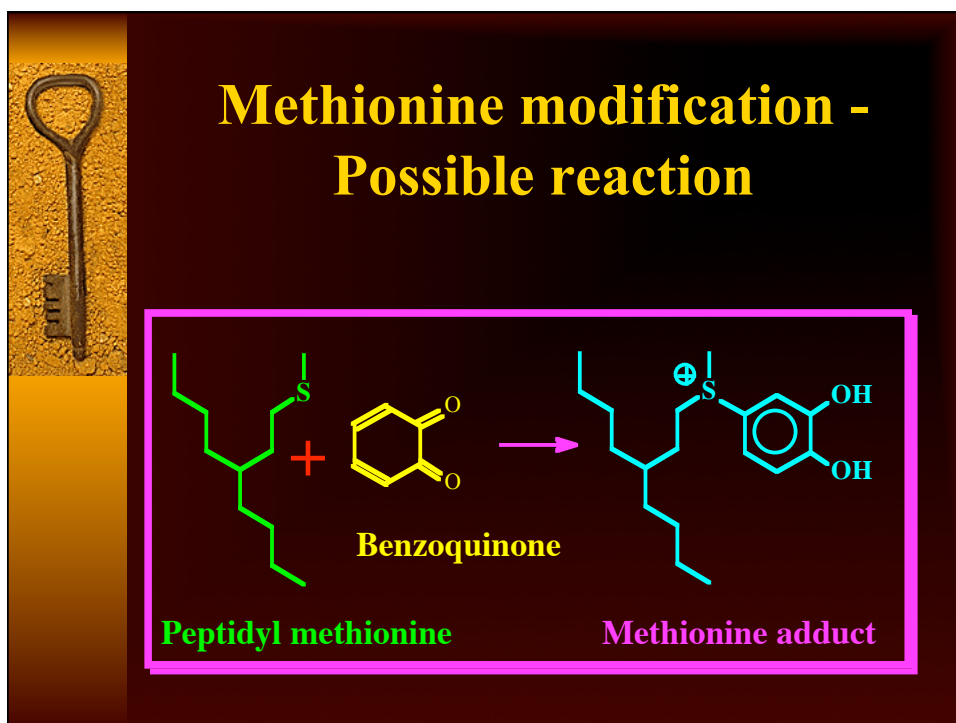
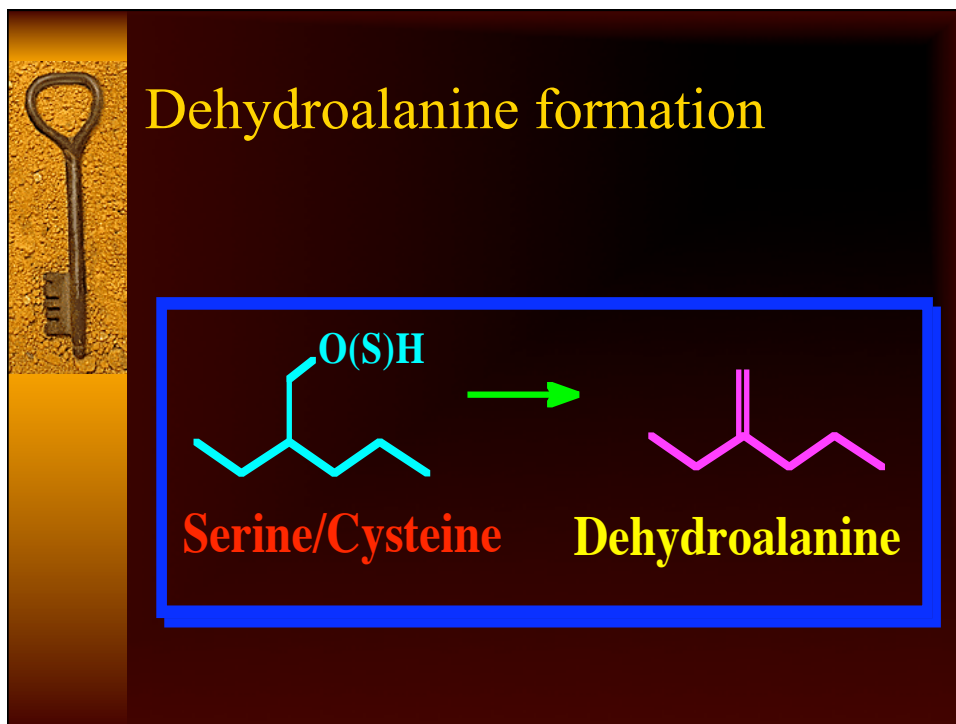
Proline Modifications

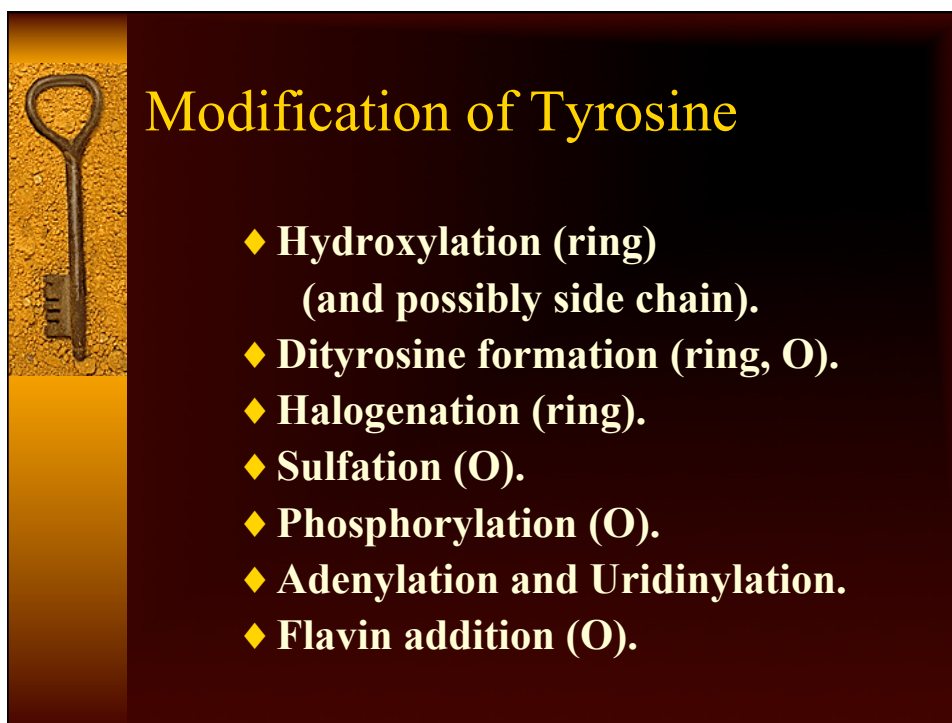
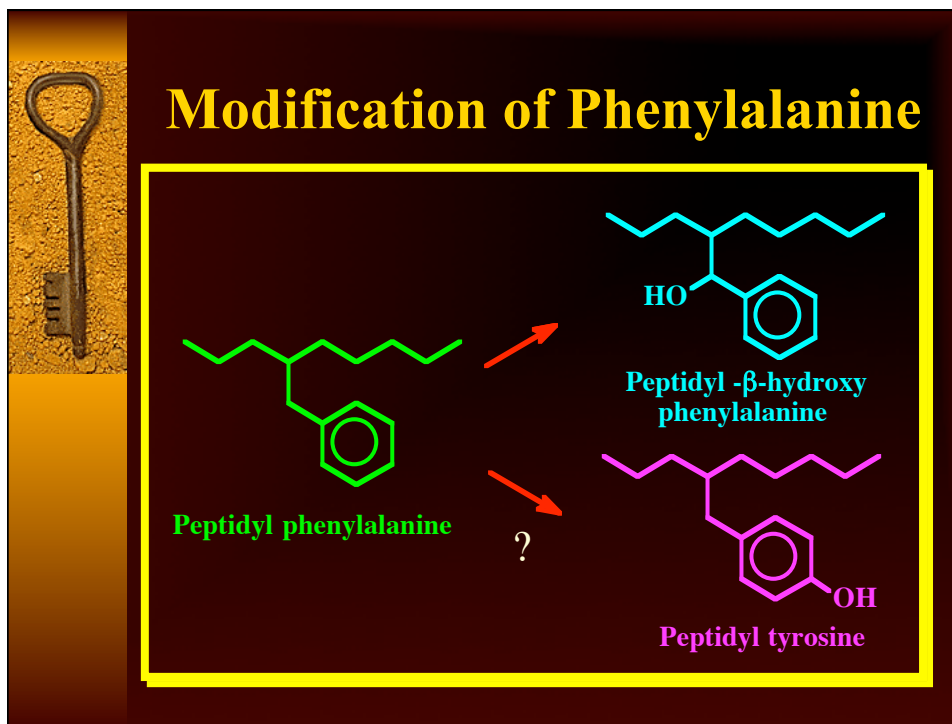
4-Hydroxyproline and 3-hydroxyproline (to some extent 3,4-dehydroproline) formation by protein proline hydroxylases is the major modification. The resultant hydroxyl group is the site of attachment of carbohydrates in some proteins.





- 
- ## Cysteine - Other modifications
- ◆ Glycosylation
 - ◆ Heme addition
 - ◆ Flavin addition
 - ◆ Phycocyanobilin addition
 - ◆ Thiohemiacetal formation
 - ◆ Dehydroalanine formation







Halogenation of Tyrosine

Simple Halogenation:

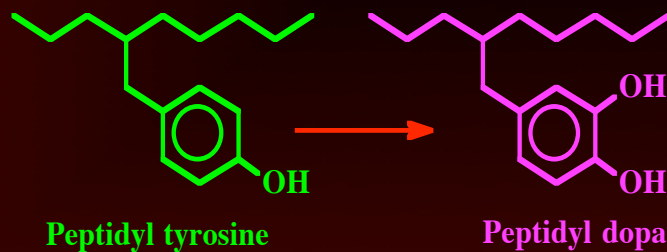
1. 3-chloro (bromo, or iodo) tyrosines
2. 3,5-dichloro (bromo, or iodo) tyrosines.
3. 3-chloro, 5-bromo tyrosine.

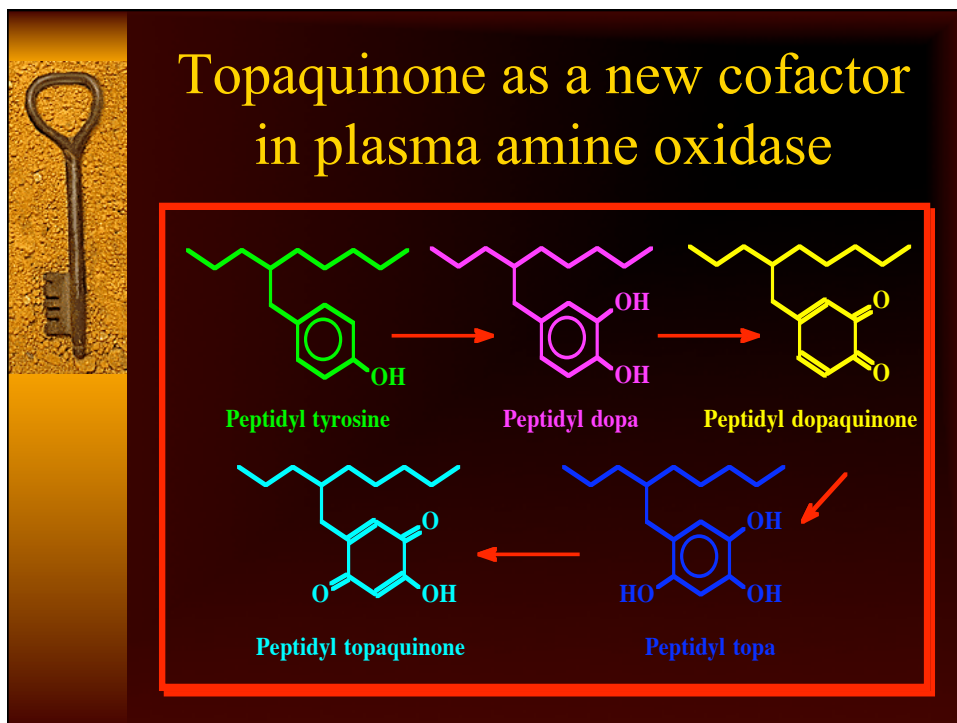
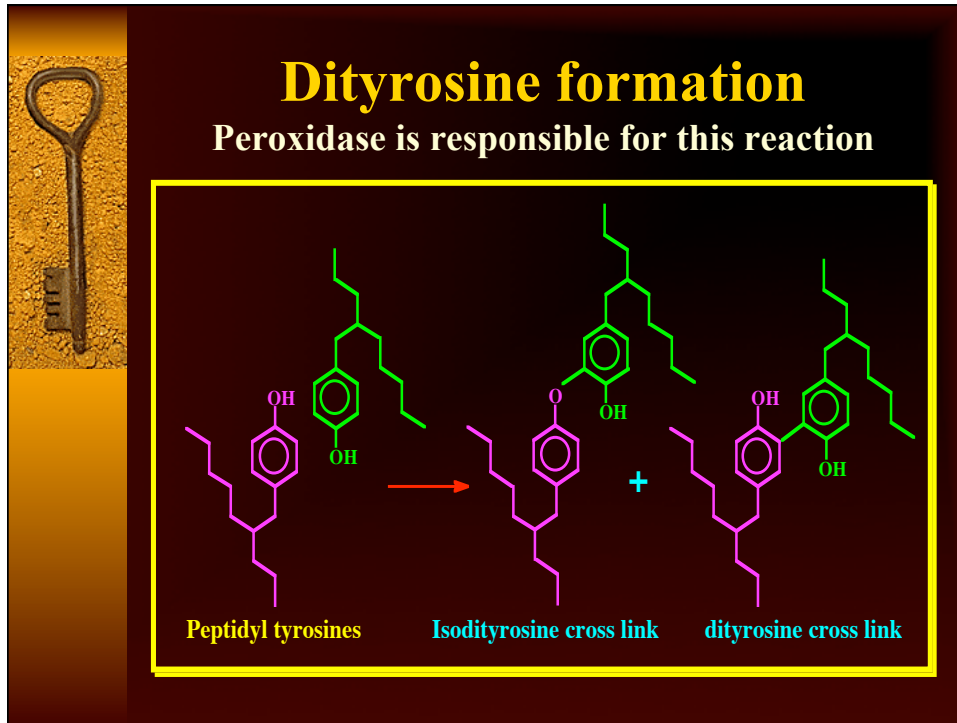
- ◆ Complex halogenation: (hormone)
- ◆ 1,3,5,3'-triiodothyronine
- ◆ 2,3,5,3',5'-tetraiodothyronine (thyroxin)

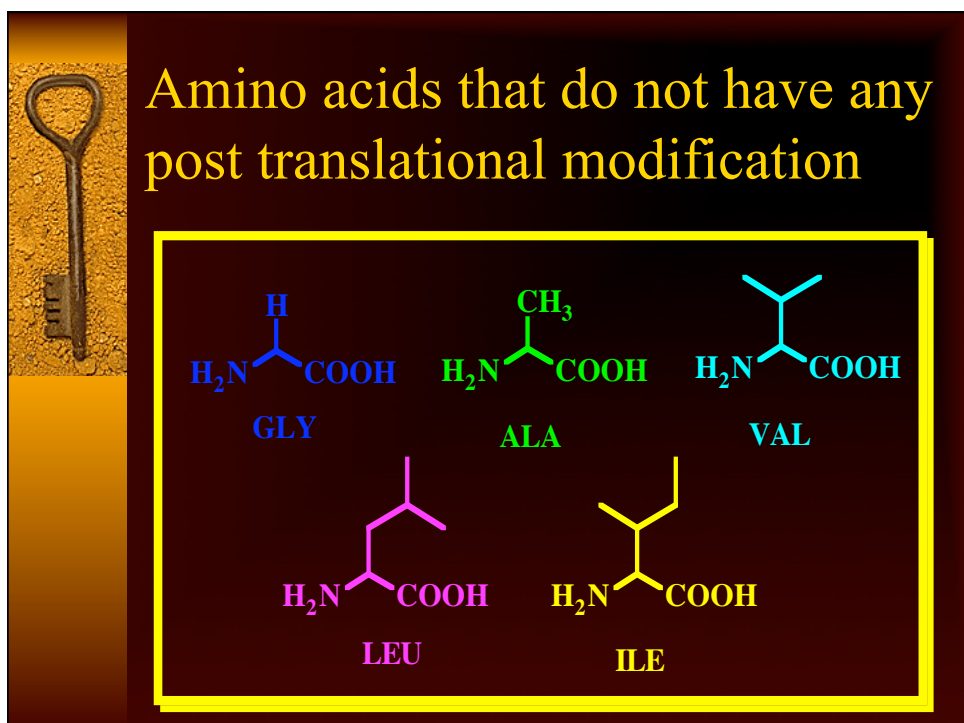
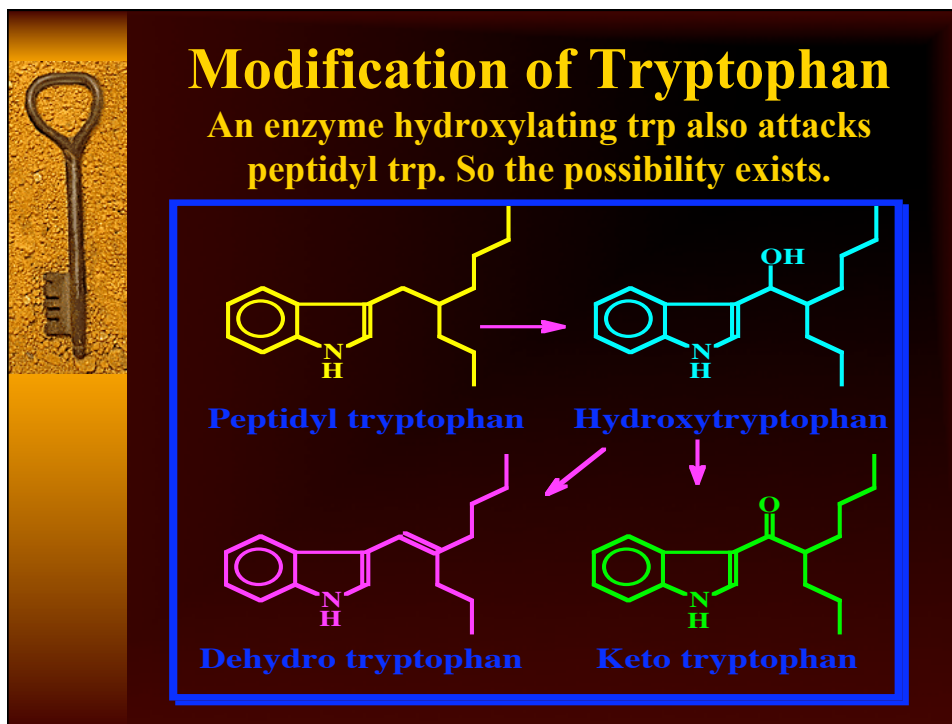



Tyrosine Hydroxylation

Although tyrosinase performs this reaction, the existence of a separate hydroxylase cannot be ruled out in some cases.









Nonspecific modification of all modifiable amino acids

(Bulk of the work was from our lab)

In insects as well as most other arthropods, hardening of their exoskeleton is achieved by nonspecific arylation of all modifiable amino acids. The mechanisms are shown in next slide. It is vital for the survival of most arthropods.

CATECHOLS

↓

PHENOL OXIDASE

↓

REACTIVE INTERMEDIATES

↓

CHITIN PROTEINS

↓

SCLEROTIZED CUTICLE

