

Histidine Metabolism and Function

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ABSTRACT

Histidine is a dietary essential amino acid because it cannot be synthesized in humans. The WHO/FAO requirement for adults for histidine is $10 \text{ mg} \cdot \text{kg body weight}^{-1} \cdot \text{d}^{-1}$. Histidine is required for synthesis of proteins. It plays particularly important roles in the active site of enzymes, such as serine proteases (e.g., trypsin) where it is a member of the catalytic triad. Excess histidine may be converted to *trans*-urocanate by histidine ammonia lyase (histidase) in liver and skin. UV light in skin converts the *trans* form to *cis*-urocanate which plays an important protective role in skin. Liver is capable of complete catabolism of histidine by a pathway which requires folic acid for the last step, in which glutamate formiminotransferase converts the intermediate N-formiminoglutamate to glutamate, 5,10 methenyl-tetrahydrofolate, and ammonia. Inborn errors have been recognized in all of the catabolic enzymes of histidine. Histidine is required as a precursor of carnosine in human muscle and parts of the brain where carnosine appears to play an important role as a buffer and antioxidant. It is synthesized in the tissue by carnosine synthase from histidine and β -alanine, at the expense of ATP hydrolysis. Histidine can be decarboxylated to histamine by histidine decarboxylase. This reaction occurs in the enterochromaffin-like cells of the stomach, in the mast cells of the immune system, and in various regions of the brain where histamine may serve as a neurotransmitter. *J Nutr* 2020;150:2570S–2575S.

Keywords: carnosine, histamine, histidase, formiminoglutamate, urocanate, 3-methylhistidine

Introduction

Histidine was first isolated from salmon protamine by Albrecht Kossel in 1896 (1). He chose the name histidine from the Greek word *histon* meaning “tissue.” It is a basic amino acid with an imidazole side chain. The pK for the side chain of the free amino acid is 6.0 so that both the neutral and protonated forms are present at physiological pH. The imidazolium side chain of histidine provides functions which are unavailable to other amino acids, such as general base catalysis in the catalytic triad of serine proteases (2). The proximal and distal histidines of the β -globin chains of hemoglobin also play essential roles in the oxygenation, rather than oxidation, of hemoglobin under physiological conditions (3).

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Abbreviations used: ECL, enterochromaffin-like; FIGLU, N-formiminoglutamate; FTCD, formimidoyltransferase cyclodeaminase; HDC, histidine decarboxylase; PEPT, oligopeptide transporter; THF, tetrahydrofolate; UROC1, urocanate hydratase 1.

The content of histidine in different proteins can vary from 73% of total amino acids in the histidine-rich protein of *Plasmodium lophurae* (4) to virtually no histidine in some mammalian elastins (5). Histidine is one of the least abundant amino acids in whole body protein in humans. Tessari (6) calculated the total body protein content of various amino acids in humans. The most abundant were proline (1328 g) and glycine (1247 g), both important in structural proteins, whereas there were only 245 g histidine, second only to tryptophan at 88 g.

In addition to free and protein-bound histidine in the diet, histidine can be obtained from proteolysis of endogenous protein and from hydrolysis of histidine-containing peptides in the diet (Figure 1). Besides its role in protein synthesis, it can be converted to histamine or to carnosine and excess can be catabolized. All of these pathways of histidine will be reviewed.

Histidine Catabolism

Figure 2 shows the metabolic pathway for histidine metabolism. Histidase (histidine ammonia lyase) is the first and principal regulatory enzyme in the pathway, producing ammonia and *trans*-urocanate. It is a cytosolic enzyme, principally found in skin and liver, with a K_m for histidine in the 1–4 mM range (7). Liver and skin histidases are expressed from the same gene (8). Histidase contains an unusual modified amino acid, dehydroalanine, which is produced from serine (9). *Trans*-urocanate is nonenzymically converted to *cis*-urocanate in skin by UV light (270–320 nm), which has led to the suggestion

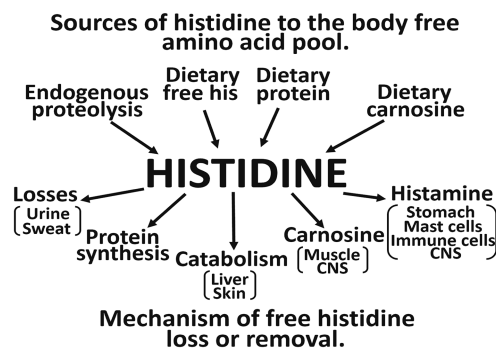


FIGURE 1 Fates of histidine in the human body. CNS, central nervous system.

it may serve as a natural protector against sunlight (10). Alternatively, it may play a role in UV-induced immunosuppression (11). A report suggests that *cis*-urocanate acts on human keratinocytes by generating reactive oxygen species, which in turn result in a transient modulation of epidermal growth factor receptor signaling, followed by induction of PGE₂ synthesis and increased apoptotic cell death (12).

Patients with histidinemia have blood histidine concentrations which range from 290 to 1420 μM , compared with control subjects who have 70–120 μM histidine (8). When the plasma and tissue histidine concentrations become supraphysiological, histidine can be transaminated to imidazolepyruvic acid which can be detected in the urine of these patients (13). It was thought that there was a specific histidine transaminase, but it has not been possible to isolate such an enzyme; the activity has been reported to copurify with glutamine transaminase in kidney (14) and with serine transaminase in liver (15). Products of histidine transamination are only detected in urine if the histidine concentration is very high, such as in patients with histidinemia.

Trans-urocanate is hydrolyzed in the liver by urocanase to give 4-imidazolone-5-propionate which, in turn, is converted to formiminoglutamate (FIGLU). Urocanase has a high affinity for its substrate; the human enzyme has a K_m of $\sim 2.2 \mu\text{M}$ for urocanate (7). The next step involves one-carbon metabolism as the formimino group of FIGLU is transferred to tetrahydrofolate (THF) to produce 5',10'-methenyl-THF, glutamate, and ammonia. This step couples histidine catabolism to one-carbon metabolism because the 5,10-methenyl-THF formed by histidine catabolism may be metabolized to a variety of products. 5,10-methenyl-THF may be reduced to 5,10-methylene-THF which may be used for synthesis of thymidine

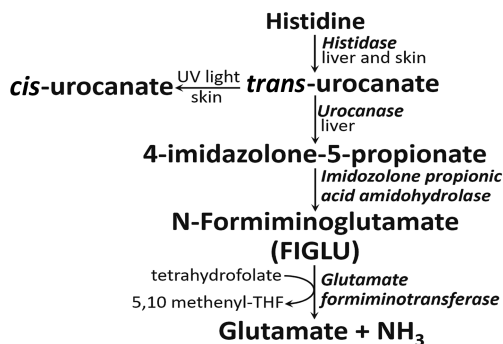


FIGURE 2 Histidine catabolism in skin and liver. FIGLU, N-formiminoglutamate; THF, tetrahydrofolate.

or which, in turn, may be reduced to 5-methyl-THF which may methylate homocysteine to methionine. This methionine may be converted to S-adenosylmethionine, the body's principal donor of methyl groups for transmethylation reactions. 5,10-methenyl-THF may also be oxidized to 10-formyl-THF which is used directly for synthesis of purines, such as ATP and GTP (16). The requirement of THF as a substrate for glutamate formiminotransferase implies that folate deficiency could limit histidine catabolism. Evidence for this idea is provided by the increased urinary FIGLU excretion that is found in folate-deficient individuals (17). Glutamate, the other product of glutamate formiminotransferase, is used for many functions, including gluconeogenesis.

In common with many enzymes of amino acid catabolism (18, 19), liver histidase is hormonally regulated. Histidase activity is not apparent in rat liver until 4 d postpartum; thereafter it increases until puberty (8). Sexual maturation in female rats is accompanied by an estrogen-driven doubling in hepatic enzyme activity. Both glucocorticoids and glucagon induce the synthesis of liver histidase (20), as does a high-protein intake or a histidine load (8).

Some thoughts on the relative importance of histidine to one-carbon metabolism

The total flux of one-carbon groups into the canonical 3 products of one-carbon metabolism has been estimated to be $\sim 26 \text{ mmol/d}$ (purines, 5.5; thymidylate, 6.2; methyl groups, 14.5 mmol/d) in humans (16). By comparison, the daily histidine intake is ~ 19 and $\sim 13 \text{ mmol/d}$ in men and women, respectively. In the steady state, the flux of amino acids to protein equals that of proteolysis and, assuming that flux of histidine to other products is relatively minor, it might be tempting to conclude that histidine catabolism could provide $\leq 75\%$ of the necessary one-carbon groups. There are a number of other sources of one-carbon groups, however, of which serine is thought to be the most significant (21). The one-carbon pool should be viewed as being continuously filled from a variety of sources and used for metabolic purposes, with excess one-carbon units being oxidized to carbon dioxide (16). Thus it is likely that histidine contributes a relatively small proportion of the one-carbon groups that go to homocysteine remethylation and synthesis of purines and thymidylate.

Inborn errors of histidine catabolism

Genetic mutations have been reported in 3 enzymes of the histidine catabolic pathway in liver: histidase, urocanase, and glutamate formiminotransferase. All 3 disorders are thought to be relatively benign, although many of the patients have been reported to have mental retardation which may be independent of the enzyme defects.

Histidinemia is the most frequent inborn metabolic error in Japan with an incidence of 1:8400 (22). It is characterized by increased concentrations of histidine in the blood and urine and decreased concentrations of urocanate in blood and skin. It results from decreased activity of the histidase protein. The initial characterization of the condition included mental retardation and speech impairment but it is now apparent that these are diverse phenotypes of this disease, ranging from a benign phenotype in the majority of subjects to classical features, including mental retardation, in the minority of subjects. The original subjects were identified by newborn screening. However, screening for histidinemia is no longer carried out in many countries, including Japan (23), which means that "benign" histidinemia is now very rarely identified

(24). Kawai et al. (22) investigated a group of subjects who were identified before screening for histidinemia was eliminated. They identified a number of mutations, including 4 missense mutations and 2 exonic and 2 intronic polymorphisms, in the *histidase* gene.

Urocanic aciduria is caused by a defect in the enzyme urocanase, which is coded for by the gene urocanate hydratase 1 (*UROCI*). Kalafatic et al. (25) reported on 2 sisters with normal hepatic histidase activity but who demonstrated urocanase deficiency. The few early cases that were reported all showed mental retardation of unknown etiology (26). Recently, Grinton et al. (27) employed untargeted metabolomics to identify adult siblings with urocanic aciduria; in this case there was no sign of mental retardation. Both subjects were found to be compound heterozygotes for missense variants in *UROCI*. These authors suggest that urocanase deficiency is a benign disease, unrelated to developmental delay.

Formiminoglutamic aciduria is characterized by increased excretion of FIGLU, due to deficiency of glutamate formiminotransferase (28), coded for by the formimidoyltransferase cyclodeaminase (*FTCD*) gene. This enzyme is a bifunctional protein (formiminotransferase-cyclodeaminase) in which the first domain releases glutamate and the second domain produces ammonia and 5,10-methenyl-THF. Patients present with various degrees of severity, ranging from mental and physical retardation (29) to relatively mild outcomes (30). Hilton et al. (30) observed 2 missense mutations (R135C; R299P) in the *FTCD* gene in each of 2 siblings; the mutations both occurred in the first domain of the enzyme. The resultant enzyme activity was ~60%, which effectively blocked the histidine catabolic pathway and resulted in FIGLU excretion in the urine, even in the absence of supplemental histidine. Because THF is a required cofactor for glutamate formiminotransferase, its activity is very low in patients with folate deficiency and FIGLU consequently also appears in the urine.

In all of these inborn errors, a histidine-deficient diet was tried but the diets did not seem to matter for the relatively benign disorders. In addition, the diets were difficult for caregivers to manage so no dietary treatment is recommended (22). The lack of a specific treatment of histidinemia is the reason newborn screening was stopped some years ago (23).

Methylation of Histidine Residues in Peptide Linkage

The imidazole side chain of histidine in proteins, such as actin, may be methylated in the N-3 position, using S-adenosylmethionine as methyl donor. Recently, Wilkinson et al. (31) isolated an enzyme, SET domain-containing protein 3, which can carry out this methylation and showed that this posttranslational modification was important for smooth muscle contraction. Until now, no function was known for 3-methylhistidine residues. When the modified protein is degraded, the 3-methylhistidine is released intact and is excreted in the urine, providing a useful estimation of muscle protein degradation (32).

Histidine-Containing Dipeptides

Skeletal muscle of most vertebrates contains significant amounts (1–16 g/kg wet muscle) of ≥ 1 of the histidine-containing dipeptides (carnosine, anserine, and ophidine/balentine) (33).

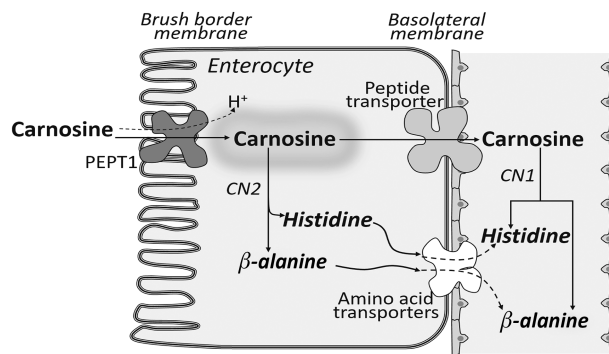


FIGURE 3 Intestinal handling of dietary histidine-containing dipeptides. CN1, carnosinase 1 in plasma; CN2, carnosinase 2 in cytoplasm of intestinal cells; PEPT1, peptide transporter in brush border of intestine.

The only one present in human muscle is carnosine, β -alanine-L-histidine, but most other mammals also contain 1 of the methylated derivatives, anserine or ophidine/balentine. There are significant quantities of histidine-containing dipeptides in most of the meat or fish that humans eat. Histidine-containing dipeptides are not hydrolyzed by regular (di)peptidases, but are hydrolyzed by their own specific hydrolytic enzymes, the carnosinases. Carnosinase 1 occurs in human serum, but not in serum from most other animals. Carnosinase 2 is located intracellularly in intestinal and kidney cells (33). As Figure 3 shows, dietary carnosine is transported into the apical side of intestinal cells by oligopeptide transporter 1 (PEPT1) where it can remain unchanged and enter the blood or it can be hydrolyzed by carnosinase 2 to give histidine and β -alanine. Transporters on the basolateral side of the membrane must be facilitated (passive) because the sodium gradient works in the wrong direction. The transporter for carnosine is unknown (34); PEPT1 is sodium-dependent and is only present on the apical side of the membrane so it cannot transport carnosine on the basolateral side (35). Amino acid transporters most likely come from the solute carrier family, member 7A, but most amino acids are transported by >1 transporter (36). In the kidney tubule, carnosine is transported by oligopeptide transporter 2 (PEPT2), then it is hydrolyzed by carnosinase 2 and the products enter the blood. Very little histidine or β -alanine escape in the urine. If intact carnosine reaches the blood, it will be rapidly hydrolyzed there by carnosinase 1 so that there is minimal carnosine circulating in the human body (34). Most of the carnosine in the human occurs in skeletal muscle where it is synthesized from β -alanine and histidine by the cytoplasmic enzyme carnosine synthase, at the cost of ATP hydrolysis. It is believed that β -alanine, not histidine, is the limiting substrate for carnosine synthesis (37). There is more carnosine in type II or fast-twitch muscle fibers. Definitive functions of carnosine are not known but it has been suggested that the histidine-containing dipeptides may act as intracellular buffers, metal-ion chelators, antioxidants, and/or free radical scavengers (37). It has been reported that β -alanine supplements will increase carnosine in human muscle and improve exercise performance (38). Thus there is considerable interest in carnosine function in the sports fraternity. Adult men, on average, have 33 kg of muscle (39). Skeletal muscle in humans has ~1 g carnosine/kg wet muscle (33), so the adult male would contain ~33 g carnosine in his skeletal muscle, which would represent ~99% of his total body carnosine (33). There is very little, if any,

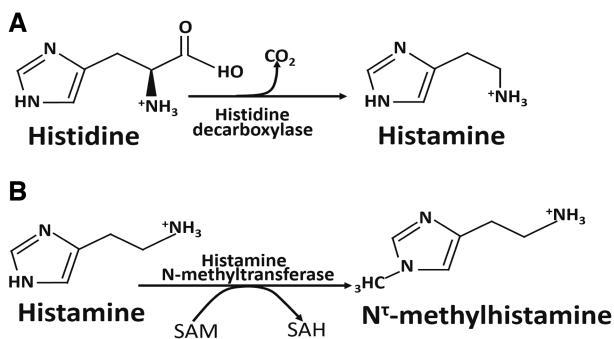


FIGURE 4 Histidine can be decarboxylated to histamine which may be subsequently methylated to N¹-methylhistidine. (A) Conversion of histidine to histamine by histidine decarboxylase. Pyridoxal phosphate is the cofactor. (B) Inactivation of histamine by histamine N-methyltransferase in brain. The methyl donor is SAM, which is converted to SAH. SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine.

carboxinase activity in muscle (40) so carnosine would need to be transported out of the muscle to the plasma before it could be hydrolyzed to histidine and β -alanine. Proton-coupled oligopeptide transporter 1, a member of the proton-coupled oligopeptide transporter family, is expressed in human skeletal muscle (40) but it is not yet clear how readily it transports carnosine out of muscle (33). When humans are carnosine loaded, loss of carnosine from muscle is slow (2–4%/wk) (41).

Histidine is A Dietary-Essential Amino Acid

It has been reported that rats can grow normally in the absence of dietary histidine if they are supplied with carnosine containing an amount of histidine equimolar to that in a 20%-casein diet (42). Thus histidine can be recovered from carnosine and replace dietary histidine. Histidine was thought to be nonessential in adult humans because it was not possible to show a deficiency in humans who consumed a diet containing purified amino acids for 2 wk, although it was known that infant humans and adults of many other animals do require it (43, 44). It is possible that muscle carnosine gave rise to histidine to allow positive nitrogen retention for the 2 wk of no histidine in the diet. It is now known that histidine is a nutritional requirement for adult humans as well, because they are unable to synthesize it (45). The WHO/FAO requirement for adult men is 10 mg histidine \cdot kg body weight⁻¹ \cdot d⁻¹ (46) so the typical 70-kg individual would require 0.7 g histidine/d in some form in his/her diet.

Histamine

Histidine can be enzymatically decarboxylated to give histamine (Figure 4A). The enzyme involved is histidine decarboxylase (HDC) which requires pyridoxal phosphate as its essential cofactor. HDC has long been known to be localized to mast cells (47) in various tissues and enterochromaffin-like (ECL) cells of the oxyntic mucosa of the stomach (48), but more recently it has also been discovered in the central nervous system (49) and in immune cells (50). Histamine is known

as the quintessential inflammatory mediator, giving rise to all aspects of the “triple response” of Lewis (white line, red flare, wheal) in response to injury of the skin (51). Release of histamine from mast cells occurs in response to IgE binding to mast cell membrane receptors as part of the response to allergens. In stomach, histamine has been reported to increase hydrochloric acid secretion by parietal cells (52). HDC activity in ECL cells has been reported to be increased after gastrin treatment, as are histamine synthesis and release from these cells, followed by gastric acid secretion (52). It is not clear whether increased plasma histidine concentrations could lead to increased synthesis of histamine in ECL cells.

In addition to the role of histamine in gastric acid secretion and the immune response, it also serves as a neurotransmitter in specific regions of the brain (53). Histamine is synthesized in cells of the posterior hypothalamus which have projections in various brain regions (54). In brain of rats, the normal histidine content does not saturate HDC, so an increase in histidine would increase the rate of histamine synthesis (55). Brain histamine controls various functions, such as the sleep-wake cycle, appetite, memory, and stress response (56).

Histamine is removed from synapses by transport into cells and inactivated by histamine N-methyltransferase in the cytoplasm to give N-methylhistidine (Figure 4B). Too little histidine (57), loss-of-function mutation of the HDC gene (58), or too much histamine N-methyltransferase activity (59) would cause low histamine concentrations in brain and neurological symptoms such as anxiety in mice (57) or Tourette syndrome in humans (58). It has recently been suggested that an increase in brain histamine might contribute to the improvement of brain disorders (56).

Conclusion

Histidine metabolism has been studied since histamine was first discovered at the beginning of the previous century. The clinical and biochemical pictures were emphasized in the latter half of the century but there are still many questions to be answered. There is continuing disagreement over how much histidine an adult human needs or can safely ingest. Urinary excretion of 3-methylhistidine has been used as a measure of proteolysis for 50 y (32) but a possible role of the methylated protein has just recently been identified (31) and more work is needed on a possible mechanism. Many protective functions of *cis*-urocanate in skin have been proposed, but a recent article showed apoptotic cell death due to reactive oxygen species caused by *cis*-urocanate (12), so is it protective or harmful? Studies on the definitive role of carnosine in muscle (37) are still needed, as are those on a possible role of histamine in providing protection in several brain disorders (56). Thus histidine is a well-known, well-studied amino acid but there is still much to do.

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