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NUTRITIONAL AND METABOLIC ASPECTS OF GLUTATHIONE

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INTRODUCTION AND DEFINITIONS

Glutathione is a ubiquitous tripeptide composed of glutamic acid, cysteine, and glycine (Figure 1). Because the peptide bond between glutamic acid and cysteine involves the γ rather than the α carboxyl group of glutamate, the

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tripeptide is resistant to peptidase, and its metabolism is unique. In its reduced form glutathione has a free sulfhydryl group and is designated GSH. Glutathione disulfide consists of two glutathione molecules joined by a disulfide bond at the cysteine sulfhydryl groups; this oxidized form of glutathione is designated GSSG.

Glutathione is of interest to the nutritionist for several reasons: (*a*) the levels of two of the enzymes important in glutathione metabolism and that of GSH itself can be markedly influenced by diet; (*b*) glutathione may be involved in amino acid transport through the γ-glutamyl cycle; and (*c*) GSH is enzymatically conjugated to electrophilic xenobiotics and plays an important role in their detoxification. Figure 2 shows some of the important reactions in which glutathione plays a role, including the γ-glutamyl cycle (95).

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SYNTHESIS

The synthesis of glutathione proceeds in two steps (39, 94). Unlike in the synthesis of larger peptides, no RNA template is involved. First, γ-glutamylcysteine synthetase catalyzes the formation of a peptide bond between the γ-carboxyl group of glutamic acid and the amino group of cysteine, thereby forming γ-glutamylcysteine (85, 86) (Figure 2, reaction 5). Next, glycine is joined to γ-glutamylcysteine by a reaction catalyzed by glutathione synthetase, to form GSH (85, 160) (Figure 2, reaction 6). Both reactions require the presence of ATP, which is dephosphorylated to ADP in the process. The strong inhibitory influence that GSH has on the first enzyme, γ-glutamylcysteine synthetase, acts as an effective feedback control for the regulation of glutathione synthesis. Indeed, when the second reaction is inoperative because of a hereditary deficiency in glutathione synthetase, copious amounts of γ-glutamylcysteine accumulate, are catabolized to 5-oxoproline, and are excreted in the urine (68, 90).

REDUCTION

Since most of the functions of glutathione require its reduced form, an active enzymatic mechanism exists for the reduction of GSSG to GSH. This reduc-

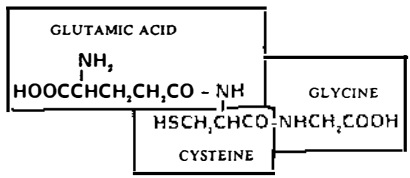

Figure 1 The structure of reduced glutathione. The tripeptide is composed of glutamic acid, cysteine, and glycine.

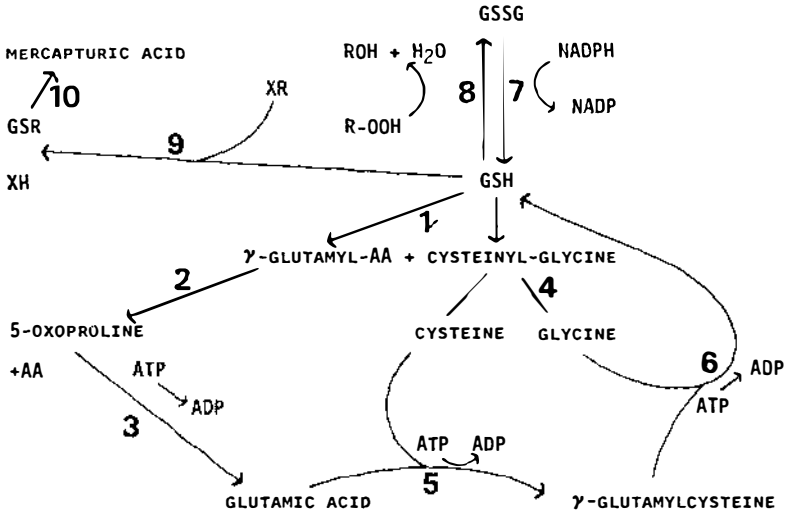

Figure 2 Some of the reactions of glutathione: 1) γ-glutamyl transpeptidase; 2) cyclotransferase; 3) oxoprolinase; 4) peptidase; 5) γ-glutamylcysteine synthetase; 6) glutathione synthetase; 7) glutathione reductase; 8) glutathione peroxidase; 9)glutathione-S-transferase; 10) formation of mercapturic acid from glutathione conjugates.

tion is achieved through the catalytic properties of glutathione reductase (Figure 2, reaction 7) (32, 54, 57, 147), an enzyme that preferentially utilizes reduced nicotinamide adenine dinucleotide phosphate (NADPH) as a hydrogen donor but that can also utilize reduced nicotinamide adenine dinucleotide (NADH). Because glutathione reductase is a flavin enzyme, its activity is markedly influenced by riboflavin intake (see below).

FUNCTION

Maintenance and Protection of Sulfhydryl Groups

Many proteins require their sulfhydryl groups to be maintained in the reduced (-SH) form if they are to function normally. GSH participates in several different reactions that serve to prevent oxidation of -SH groups or to reduce them once they have become oxidized. Through the enzyme glutathione peroxidase (Figure 2, reaction 8), GSH removes peroxides that could oxidize sulfhydrils. The substrate specificity of this enzyme is quite broad, so that it may serve to detoxify both hydrogen peroxides and organic peroxides (48). GSH may also serve to reduce oxidized sulfhydryl groups nonenzymatically. The enzyme thioltransferase, however, serves to catalyze the exchange of disulfides from proteins to form GSSG (54, 87). Another enzyme, glutaredoxin (82, 83), utilizes GSH as a hydrogen donor for the reduction of ribonucleotide reductase.

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Detoxification

One of the oldest known functions of glutathione is as a coenzyme for the enzymes that catalyze the glyoxylase reaction. Glyoxylase I (lactoylglutathione lyase; E.C. 4.4.1.5) catalyzes the formation of a complex between methylglyoxal and GSH. Glyoxylase II (hydroxyacylglutathione hydrolase; E.C. 3.1.2.6) hydrolyses a variety of hydroxyacylglutathiones, including the conjugate with methylglyoxal formed in the glyoxylase I reaction. The final product of the reaction is D,L-lactate. The glyoxalase reaction protects the cell against the mutagenic effect of 2-oxoaldehydes, which may arise during intracellular oxidation processes. This reaction formed the basis of one of the earliest, highly specific assays for glutathione.

Formaldehyde is the toxic product of methanol oxidation. A GSH-dependent formaldehyde dehydrogenase catalyzes the first of two reactions that lead to the conversion of formaldehyde to formic acid, reactions that are somewhat analogous to the glyoxalase reaction (153, 154). The enzyme is widely distributed in both plant and animal tissues.

The glutathione-S-transferases catalyze the formation of thioethers between electrophilic compounds and GSH. Potentially toxic substances such as benzo[α]pyrene derivatives (98, 127), 1-chloro-2,4-dinitrobenzene (5), and products of acetaminophen metabolism (130) are substrates for this reaction, and the conjugate formed is degraded to a relatively harmless mercapturic acid (Figure 2, reaction 10).

Transport of Amino Acids

The γ-glutamyl group of GSH is readily transferred by γ-glutamyl transpeptidase to form the γ-glutamyl derivatives of free amino acids in the first reaction of the putative γ-glutamyl cycle (93) (Figure 2, reaction 1). Since γ-glutamyl transpeptidase is usually membrane bound, it has been suggested that this reaction might serve to capture amino acids from one side of the membrane so that the dipeptide might be translocated to the other surface. Although some support for such a mechanism comes from studies in patients with defects of glutathione synthesis (49, 60, 90), there is by no means agreement that GSH plays an important role in amino acid transport in general (8, 56, 164).

Leukotrienes

Glutathione is required in the synthesis of leukotrienes. Glutathione-S-transferase forms a thioether bond between leukotriene A_4 and glutathione to form leukotriene C_4. The glutamic acid is removed from the glutathione moiety by γ-glutamyl transpeptidase, thereby forming leukotriene D_4. Removal of glycine by a peptidase leaves only the cysteine, forming leukotriene E_4. In this way, glutathione plays a major structural role in the synthesis of these important mediators of inflammation (3, 51, 118).

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CATABOLISM

Glutathione is in a constant state of metabolic turnover. Since it is actively synthesized, it must also be degraded. How this degradation occurs is incompletely understood; the mechanism probably varies considerably among tissues.

In red blood cells the half-time of turnover has been estimated to be approximately 4 days in man (37), and there is a broad range of turnover rates in various animal species (131). The suggestion (107) that the γ-glutamyl cycle is active in red cells and that GSH turnover is a function of the transpeptidase is invalid, since γ-glutamyl transpeptidase is not present in mature erythrocytes (22, 138, 164). Erythrocyte turnover seems rather to be a function of active, ATP-requiring outward transport of GSSG from the interior or the cell to the plasma (11, 81, 111, 131, 139). This transport system seems to be of physiologic importance. Its activity correlates with the rate of turnover of GSH in red cells of various species (131). The transport enzyme is inhibited by pyrimidine nucleotides (64). In pyrimidine-5'-nucleotidase deficiency, when the levels of pyrimidine nucleotides in red cells increase greatly, the steady-state levels of GSH are also increased (106). Two GSSG-stimulated ATPases have been isolated from red cell membranes (65), and they presumably account for GSSG transport. The same transport system appears to transport the conjugates of glutathione and electrophilic xenobiotics formed by the action of glutathione-S-transferase (5, 20, 21); one of the physiologic roles of this transport system might be to allow the red cell to serve as a scavenger of toxic materials in the circulation (11).

The same GSSG transport system found in red cells is probably also operative in the liver (2, 38, 125, 126), with the excretion of GSSG into the bile. The GSSG-dependent ATPase that is presumably responsible for this transport has been isolated and partially characterized (104). In contrast to the red cell, where only GSSG is transported, there is also evidence for the transport of GSH across liver (7, 58, 75, 105), kidney (47) cell membranes.

HEREDITARY DEFECTS OF GLUTATHIONE METABOLISM

γ-Glutamylcysteine Synthetase Deficiency

Human γ-glutamylcysteine synthetase (Figure 2, reaction 5) deficiency is extremely rare. Only two affected families have been described (66, E. Beutler & C. West, unpublished observations, 1988). The levels of GSH in the patients' red cells were very low, which caused nonspherocytic hemolytic anemia. Decrease of enzyme activity and GSH in other tissues was modest or not documented, but in one of the families spinocerebellar degeneration was

present in both sibs who had the enzyme deficiency and absent from other family members (115).

In Tasmanian Merino sheep, mild γ-glutamylcysteine deficiency is common. These sheep manifest a polymorphism characterized by low GSH levels that is associated with a deficiency of the enzyme (133, 165).

Glutathione Synthetase Deficiency

Deficiency of the second enzyme of glutathione synthesis, glutathione synthetase (Figure 2, reaction 6), is uncommon but not nearly as rare as defects in the first enzyme. Two forms of this type of enzyme deficiency have been described. In some cases, the only manifestation of the deficiency is hemolytic anemia (14, 25, 26, 97, 112, 113). In others, there is excretion of large amounts of 5-oxoproline (pyroglutamic acid) and neurologic defects usually associated with mild hemolytic anemia (40, 50, 59, 68, 69, 88–90, 136, 137, 159). The former type is probably caused by a mutation that results in enzyme deficiency primarily limited to the erythrocytes, while the latter probably is the result of a more systemic defect (10, 89).

Glutathione Reductase Deficiency

Only a single family with severe inherited glutathione reductase (Figure 2, reaction 7) deficiency has been reported (79). Although the deficiency of GSH in the red cells of the affected family members was very severe, anemia occurred only after ingestion of fava beans. Mild glutathione reductase deficiency has sometimes been reported to occur on a hereditary basis (100, 158); a deficiency of this enzyme is usually a result of riboflavin deficiency, as indicated below.

Glutathione Peroxidase Deficiency

Modest deficiency of glutathione peroxidase (Figure 2, reaction 8) is a common, asymptomatic polymorphism among Mediterranean populations (15, 16, 46). Earlier reports suggesting a cause-and-effect relationship between this enzyme and hemolytic anemia (27, 28, 96, 101, 102, 144, 161) are not creditable, considering the lack of hematologic effects of this enzyme deficiency, which occurs either as a polymorphism or as a result of selenium deficiency (see below).

Glutathione-S-Transferase Deficiency

Only a single case of glutathione-S-transferase (Figure 2, reaction 9) deficiency, presumed to be hereditary, has been reported (13). Only approximately 10% of the normal level of the enzyme was found in the red cells, but other tissues examined seemed relatively spared. Mild hemolysis was noted, but a cause-and-effect relationship could not be established between this

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finding and the enzyme deficiency because no family members were available for examination.

γ-Glutamyl Transpeptidase Deficiency

γ-Glutamyl transpeptidase (Figure 2, reaction 1) deficiency is very rare; only two families have been identified (121, Wright et al, *J. Inherit. Metab. Dis.* 2:3–7). The absence of the enzyme resulted in glutathionuria, a finding consistent with the proposed role of this enzyme in glutathione transport in the γ-glutamyl cycle (93).

GSSG-Dependent ATPase Deficiency

No deficiencies of GSSG-dependent ATPase, presumably important in the transport of GSSG from tissues, have been found.

EFFECT OF DIETARY CONSTITUENTS ON GLUTATHIONE METABOLISM

Effect on Enzymes

GLUTATHIONE REDUCTASE Glutathione reductase plays a central role in maintaining glutathione in the reduced state (Figure 2, reaction 7). Deficiency of this enzyme in red blood cells of humans was first described in the late 1950s (36) and assumed to be hereditary (18, 19, 67). Glutathione reductase is a flavin enzyme with a flavin-adenine-dinucleotide (FAD) prosthetic group (57, 122, 142, 162). Erythrocytes of rats deficient in riboflavin, the vitamin precursor of FAD, had decreased activity of glutathione reductase, and FAD corrected the deficiency (45). These results were soon extended to humans (6, 9, 17), and a relationship was found between the degree of in vitro stimulation that could be achieved with FAD and the dietary intake of riboflavin (17). True genetic deficiencies of glutathione reductase are by comparison very rare (76, 79). The stimulatory effect of FAD on glutathione reductase has thus become a simple, relatively reliable method for assessing riboflavin nutriture (34, 43, 44, 55, 120).

The functional effect of riboflavin deprivation on glutathione metabolism is much less clear, however. The central question is whether the degree of glutathione reductase depletion is sufficient to exert a functional effect on the reduction of GSSG to GSH. Most data are derived from studies in red cells, and they suggest that GSH homeostasis is not affected. The degree to which the hexose monophosphate shunt of rat red cells could be stimulated, a sensitive measurement of the rate of glutathione reduction, was not impaired (108). Red cells of riboflavin-deficient rats have been subjected to in vivo oxidative stress by the administration of nitrofurantoin or phenylhydrazine (17). No difference in red cell lifespan was found. Administration of nitrofu-

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rantoin to a riboflavin-deficient volunteer did not result in hemolysis (17). The remarkably good health of the rare individuals who manifest a total lack of glutathione reductase in their erythrocytes (36), too, militates against the idea that the relatively moderate partial deficiency of this enzyme that occurs with riboflavin deficiency is likely to result in any adverse metabolic effects.

In the case of the lens of the eye, however, riboflavin deficiency may affect cataract formation in the presence of other stresses such as galactose feeding of rats (140, 141). In humans, little evidence indicates that riboflavin deficiency alone plays a role in cataract formation (128, 129). Although there is no evidence that this effect is mediated through the glutathione reductase reaction, such mediation could occur, since the integrity of GSH plays a central role in protection against galactose cataracts and other cataracts (29, 63, 80). Lenses of riboflavin-deficient rats, however, manifest only minimal decreases in the levels of GSH and other thiols (141).

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GLUTATHIONE PEROXIDASE In contrast to glutathione reductase, which serves to reduce GSSG to GSH, glutathione peroxidase is the catalyst for the oxidation of GSH to GSSG, during which it uses GSH to remove unwanted and potentially toxic peroxide from the cell (Figure 2, reaction 8). Glutathione peroxidase is a selenium-containing enzyme that has selenocysteine at its active site (1, 4, 42, 117). Interestingly, selenocysteine itself has glutathione peroxidase activity; incorporation into the protein vastly increases the rate of reaction (12). The question of how selenocysteine becomes incorporated into a protein has been a puzzle that has recently yielded a fascinating solution. During the cloning and sequencing of glutathione peroxidase cDNA the triplet UGA, usually a "stop" codon, was found to specify the position of selenocysteine (31, 143, 146). Contrary to earlier work, it now seems likely that serine is incorporated into this position and altered to selenocysteine (146), instead of the translational incorporation of selenocysteine into the polypeptide (52). The reason for the ambiguity in reading UGA is not yet clear; presumably it is related to the conformation of the mRNA at this point due to the sequences that surround it.

Considering that glutathione peroxidase contains selenium, it is not surprising that a deficiency of selenium results in decreased levels of glutathione peroxidase in erythrocytes, platelets, muscle, and liver (53, 61, 72, 73, 77, 78, 92, 99, 103, 110, 123, 124, 135, 148–152, 155, 156). Silver intoxication also decreases the levels of glutathione peroxidase in rat red cells and liver, and this effect is mitigated by supplementation with selenium (157). Several studies suggest that iron deficiency decreases the glutathione peroxidase activity of red blood cells (30, 84, 109, 116) by an unknown mechanism.

The functional significance of selenium deficiency with respect to glutathione metabolism and the protection of tissues from peroxidatic attack is

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unclear. The putative occurrence of liver necrosis and Heinz body hemolytic anemia (99) as consequences of selenium deprivation are consistent with the view that a deficiency of this enzyme exposes the tissues to peroxidatic attack. In humans, however, a common polymorphism of glutathione peroxidase activity, lowering the enzyme activity of the red cells of homozygotes to half of normal (16), is unassociated with any clinical findings; remarkably low levels of glutathione peroxidase as a result of prolonged selenium deprivation produced minimal clinical consequences (61). Since glutathione peroxidase catalyzes the oxidation of GSH, a functional deficiency of the enzyme might be expected to increase GSH levels. The actual level of GSH in the tissues of selenium-deficient humans and experimental animals has only rarely been measured, however. The tissue GSH levels were unaffected by selenium deficiency in rats, but a high–vitamin E intake increased tissue GSH levels (123, 124). Similarly, in selenium- and vitamin E–deficient chicks, liver GSH levels are increased (163). However, challenge of glutathione peroxidase–deficient red cells by incubating them with azide (an inhibitor of catalase) failed to reveal increased methemoglobin production (77).

Effect on Substrates

The substrates for the synthesis of GSH are the three amino acids glutamic acid, cysteine, and glycine. To the extent that GSH is degraded through the γ-glutamyl transpeptidase (Figure 2, reaction 1) and dipeptidase (Figure 2, reaction 4) reactions, these amino acids are readily available in the cell for the resynthesis of GSH. To the extent that GSH is transported out of the cell in the form of GSSG or as a thioether of an electrophile, a source of these amino acids must be present.

Studies in rats (33, 35, 145) and chicks (24, 163) fed a protein-poor diet have shown that the decrease in GSH contents of various tissues is prevented by the addition of cysteine or methionine. In Finnish Landrace sheep, a low-erythrocyte-GSH polymorphism has been attributed to defective amino acid transport that affects, in particular, the entrance of cysteine into erythrocytes (165). In burn patients with increased demand for sulfur amino acids, decreased levels of leukocyte GSH were documented (91).

Although these investigations indicate that, at the level of the whole organism, sulfur amino acids are the only limiting substrate for glutathione synthesis, studies in red cells indicate that intracellular availability of glutamate may also be important. Studies in GSH-deficient sheep and in rabbits also indicate a limiting role for glutamate in the levels of the tripeptide in red cells. Treatment with methylene blue increases the red cell GSH levels of rabbits (23); this dye may exert its effect by increasing red cell glutamate levels (134). The increase in the glutathione content of anemic sheep red cells has also been attributed to a dramatic increase in red cell glutamate as well as

glycine and ATP levels (132). Human red cells are quite impermeable to glutamic acid (41, 165), but nevertheless have higher concentrations of this amino acid than are present in the plasma (74). Therefore, one suggestion was that glutamine entered the cell and was converted subsequently to glutamic acid by glutaminase (114). The subsequent demonstration that red cells were actually devoid of this enzyme (62, 119) led to another proposal that small glutamate-containing peptides might enter the red cells and serve as a source of glutamic acid for glutathione synthesis (62). Contrary to earlier reports, however, red cells were shown to be quite impermeable to α-glutamyl dipeptides (166) and so could not serve as a source of glutamic acid. Thus, the source of intracellular glutamate required for glutathione synthesis in red cells remains a mystery.

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