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FACTS FOR HEALTH PROFESSIONALS ABOUT SETRIA® GLUTATHIONE*

Definition

Glutathione (GSH), a small peptide comprised of three common amino acids, is one of the primary protective molecules in the body. Its scientific name is N-(N-L-gamma-Glutamyl-L-cysteinyl)glycine. Its constituent amino acids -- glutamate, cysteine and glycine -- are connected together in a unique way that allows GSH to be made and broken down independently of the systems that maintain the bodyís protein.

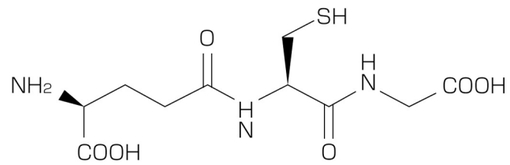
GSH exists in four common forms in the body:
1. a reduced thiol form (GSH)
2. an oxidized disulfide form (GSSG)
3. a form with cysteine (CySSG0)
4. a protein-bound form (PrSSG)

Under many circumstances, the balance of these forms (redox balance) is more important than the absolute amount of GSH.

Chemistry

Molecular formula: $C_{10}H_{17}N_3O_6S$

Structural formula:



Sources and metabolism

Glutathione is provided both through the diet and through endogenous synthesis. The best food sources are fresh fruits and vegetables and freshly prepared meats[1]. Most methods of food processing destroy glutathione; therefore, processed foods, dairy foods and grain products are poor sources. Glutathione is also available in dietary supplements under the name Setria® Glutathione, a highly pure and stable form of reduced glutathione manufactured by Kyowa Hakko Bio Co., Ltd.

Internal synthesis occurs in all cells via ATP-dependent reactions. Synthesis increases when glutathione levels decrease and/or demands increase. The rate of synthesis is determined by the availability of the precursor amino acids, principally cysteine, as well as other amino acids including methionine and glutamate. It is estimated that humans are likely to secrete about 25-50 milligrams of glutathione during digestion of a meal.[2]

Because of endogenous synthesis, glutathione it has not been considered an essential nutrient and no recommended intake level has been established. Moreover, the variable levels of glutathione in different tissues and organs present a challenge both to measuring status and estimating needs. Early studies did not find an appreciable increase in plasma levels after supplementation, and thus it was thought that oral glutathione was not bioavailable. However, over the past 20 years numerous studies have demonstrated that plasma levels are not indicative of levels in other tissues and that oral glutathione is bioavailable.[3,4,5,6,7,8] Animal evidence suggests that it may be delivered preferentially to specific sites of high demand such as the lungs and intestines.[3]

Oral glutathione enters tissues by three routes: (1) it can be absorbed intact in the intestines and taken up by tissues; (2) it can be broken down in the GI tract to its constituent amino acids, which are then absorbed and GSH is resynthesized in tissues; (3) it can be taken up directly into GI tissues by cells that line the GI tract.[9]

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GSH is present in all tissues and body fluids, both inside and outside of cells. The entire body pool is made and degraded daily through a continuous turnover of both cellular and extracellular glutathione. In most cases GSH is released from cells and converted to precursor amino acids, which are absorbed and recombined to make new GSH. Cells of the intestinal tract, lung, kidney and possibly brain have specific transport systems to take up intact glutathione, but the liver and most other sites take up the individual amino acids and re-synthesize them to GSH.[2,6,10]

Glutathione is unevenly distributed throughout the body. The highest levels are found in the liver and kidneys to support detoxification functions. Other major organ systems including the brain, heart, lungs, intestines, skeletal muscle, skin and immune system also have high levels. Cellular levels are much higher than extracellular levels. In all there are about 15 grams of GSH in the body, of which about 4 grams are in the liver.[2]

Biochemical roles

Glutathione plays multiple roles. It provides a reserve of cysteine that is used for protein synthesis and metabolic homeostasis under conditions of nutritional deficiency.[2] Under more normal circumstances of protein adequacy, glutathione is used for protective functions.

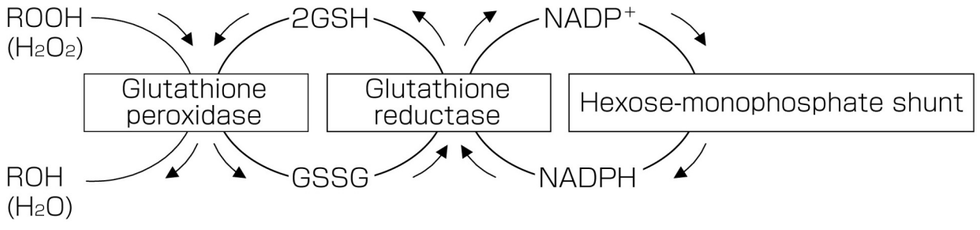
Chemically it is adept at sharing and donating electrons, making it ideal for reducing toxic oxidants and intercepting reactive DNA-damaging chemicals. GSH has been shown to support the bodyís natural detoxification process by removing hundreds of potentially harmful chemicals that are inhaled and ingested, to reduce oxidative stress and to maintain the redox balance of cellular proteins. Interorgan transport of glutathione is part of a homeostatic control system that helps maintain the primordial chemical environment that is essential for life.[2]

Unstable and reactive compounds that are produced by the liver during drug metabolism are detoxified by glutathione through enzymatic conjugation the action of glutathione S-transferase and through nonenzymatic conjugation to stable glutathione conjugates.

Glutathione in extracellular fluids also plays important protective roles, and levels are high in mucosal secretions. In the gastrointestinal tract it serves as a first line of defense by conjugating with electrophilic compounds and ingested toxins before they can be absorbed.[9] Similarly, there are high amounts in the lung lining fluid to eliminate airborne oxidants, maintain mucus fluidity and maintain the function of pulmonary macrophages.[2]

As an antioxidant, glutathione acts as a hydrogen donor in the reduction of hydrogen peroxide and lipid peroxides. The reaction is catalyzed by glutathione peroxidase containing selenium.

Antioxidant Action of Glutathione



Roles in health

The central roles of glutathione in maintaining redox balance and in detoxifying compounds suggest protective roles in all conditions related to oxidative stress. Although large-scale clinical trials still need to be conducted, many observational and laboratory studies suggest:

- Glutathione decreases with aging, beginning in midlife and plunging precipitously after age 60[11,12] and healthy elders have high blood glutathione concentrations.[13]
- Higher glutathione status in older individuals has been correlated with multiple indices of good health -- better overall health and vitality, higher levels of self-rated health, normal cholesterol, lower body mass index and normal blood pressure -- as compared to older individuals with lower glutathione levels.[14]
- Higher glutathione status and/or dietary intakes have been correlated with good cardiovascular,[15] oral,[16,17] and eye health.[18,19]
- Glutathione supplementation may help increase levels of glutathione in certain circumstances associated with low glutathione status including cigarette smoking, heavy drinking, use of large numbers of prescription and non-prescription medications,[2] and chemotherapy.[2]
- Glutathione supplementation may help increase levels of glutathione in conditions associated with low glutathione status including obesity, type 2 diabetes, cardiovascular disease, kidney disease, Parkinson disease, lung disease, AIDS and other diseases.[2]

Potential benefits of oral supplementation

A strong case can be made for oral supplementation with glutathione based on the following reasoning:

- Modern diets are often devoid of glutathione due to the excessive intake of processed foods. Dietary intakes of glutathione among Americans have been measured in at least two studies. In the first, intakes ranged from a low of 3 milligrams per day to a high of about 150 mg per day, with a mean intake of 35 mg per day.[1] Another study found an even wider range of intakes among men -- from 5 milligrams to 242 mg per day ñ and 7 to 96 mg per day in women, with most people regardless of gender falling below 60 mg per day.[17] If the best diets provide close to 250 mg per day and the mean intake is only 35 mg, there is a considerable gap in much of the population.
- Glutathione levels fluctuate diurnally with lowest levels found in the morning, which may present a window of vulnerability that could be addressed through increased oral intake. The morning shortfall becomes even lower with advancing age.[22]
- Many millions of Americans have one or more dietary, lifestyle or physical factors that may increase their risk for low glutathione levels:[23]
  - 77 million consume fewer than five fruits or vegetables a day,
  - 91 million are aged 55 and over,
  - 59 million currently smoke cigarettes,
  - 74 million have diabetes,
  - 110 million are overweight or obese, and
  - 15 million chronically consume excessive amounts of alcohol.

Safety

There have been no reported adverse reactions to supplemental glutathione taken orally, inhaled or used intramuscularly or intravenously.[24] Doses of three grams have been used experimentally with no adverse effects.[25] Less is known about chronic supplementation, but dosages of about 150-200 mg per day to close the dietary gap would appear to be rational. One theoretical exception would be for individuals who have or are at greater risk for cancer, since glutathione could potentially provide a growth advantage to cancer cells.[2]

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