



Glutathione in Health and Disease

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Glutathione (g-glutamylcysteinylglycine, GSH) is a water-soluble tripeptide composed of the amino acids glutamate, cysteine, and glycine. Present in all mammalian cells, it is widely distributed throughout the animal and plant kingdoms, underscoring its fundamental biological significance.

GSH is an endogenous antioxidant of great importance, as well as being a detoxicant of exogenous and endogenous toxic compounds. In addition, it plays a vital role in many other cell cycle-related events, including protein synthesis and gene expression. Not surprisingly, more than 25,000 medical articles on GSH have appeared over the last five years. A number of review articles have provided the basis for the material presented here.^{1,2}

BENEFITS OF GSH

GSH is a key antioxidant responsible for protecting the cell from damage by reactive oxygen species (ROS) such as peroxide, superoxide anion, and the hydroxyl radical.

GSH is responsible for detoxification of xenobiotics (eg, benzene compounds, acetaminophen), as well as endogenously produced potentially toxic metabolites such as prostaglandins and leukotrienes. Much of this detoxification occurs in the liver and kidneys. These substances are converted by GSH into inactivated water-soluble conjugates that can then be easily excreted.

GSH status plays an important role in innumerable cell functions, including gene expression, DNA synthesis and repair, protein synthesis, cytokine production, enzyme activation, and signal trans-

duction. This has a broad-reaching effect, one consequence being that GSH affects the ability of cells to proliferate in the body. It is perhaps for this reason that the immune system is particularly vulnerable to GSH deficiency since lymphocytes need to proliferate to develop an effective immune response.

GSH AND DISEASE

GSH plays crucial roles in antioxidant defense, detoxification, and the regulation of pathways essential for whole-body homeostasis. GSH deficiency contributes to oxidative stress and therefore appears to play a key role in the pathology of many diseases.

Patients with liver disease are GSH-depleted.³ Altomare et al,⁴ for instance, studied 35 chronic alcoholic patients and 20 nonalcoholic patients with liver disease (acute and chronic hepatitis, fatty liver, and cirrhosis) and observed decreased GSH in both groups when compared with control patients. These investigators postulated that the decreased GSH contributed to liver injury susceptibility. Thus, in patients with liver disease, GSH deficiency exists, which may predispose to further liver toxicity caused by the resultant inadequate defense mechanisms.

GSH deficiencies have been documented in a number of pulmonary diseases, including acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis (IPF), cystic fibrosis, and neonatal lung damage.⁵ GSH concentrations in the epithelial lining fluid (ELF) are only 25% of normal values in IPF, for example.⁶ The ELF normally contains 150 times more GSH than in other tissues,⁷ where it serves to protect the lungs against oxidative damage, environmental toxins, and atmospheric pollutants. Low levels of GSH lead to inflammation and oxidative stress with resultant damage to cell membranes, cellular proteins, and DNA.

The brain is highly susceptible to oxidative damage, and a depletion of antioxidants, including GSH, has been

reported in Parkinson's, Alzheimer's, and some other degenerative brain diseases.^{1,2,6} In Parkinson's disease, GSH levels are dramatically reduced in the substantia nigra (the area of the brain associated with this disease).^{10,11} In Alzheimer's disease, GSH is decreased in the cortical areas and the hippocampus.^{12,13} The cause-and-effect relationship between low GSH, oxidative stress, and neural cell death is strongly suggestive; however, it has not clearly been established as yet in these pathological states.

Low GSH values are found in cancer patients, especially in those with wasting in late-stage disease.^{1,14,16} Evidence suggests that GSH is important to protect the body against the development of malignancy and ameliorate the side effects of therapy. The intracellular depletion of GSH has been implicated, for example, in the development of skin cancers and renal and hepatic tumors.⁷ In addition, Ripple et al¹⁷ provided in vitro evidence that low GSH values may precede the development of cancer in the prostate. The antioxidant and detoxifying properties of GSH are important in protecting cells against abnormal intracellular levels of ROS and chemical carcinogens that can lead to cancer development.

It has been well-established that the GSH pool is unusually low in individuals with HIV/AIDS.^{1,2} This can be partially attributed to chronic oxidative stress.¹³ GSH deficiency in HIV/AIDS is an important issue, contributing to many of the complications of this disease, particularly the immune deficiency. Thus, many lymphocyte functions are compromised by low GSH, such as lymphocyte proliferation or the destruction of virally infected cells by "killer" lymphocytes. Furthermore, an imbalance of the GSH status indirectly results in upregulation of inflammatory cytokines (some of which promote wasting), increased viral replication, and increased apoptosis (death) of T lymphocytes.^{13,14} In 1997, Herzenberg et al¹⁵ directly demonstrated the critical importance of GSH by showing that HIV-positive individuals with higher GSH levels survived significantly better than those with lower values.

Pressure ulcers often fail to heal, one reason being lack of amino acids needed

for growth of new tissue.¹⁶ GSH deficiency is another important factor since most pressure ulcer patients are older and at the same time are suffering from many other medical conditions.¹⁶ The GSH system plays an important role in many of the processes involved in wound healing, such as opposing the oxidative stress associated with inflammation and infection, and participating in many of the processes associated with proliferation of cells to form new tissue. Direct evidence for the role of GSH in wound repair has been shown in experimental mouse¹⁷ and rat¹⁸ models.

When the amino acids (cysteine in particular) are not available to make GSH, these must be obtained from breakdown of lean muscle mass. This can lead to protein malnutrition and ultimately to wasting. This condition is seen, for example, in advanced cancer patients, older adults, and patients with pressure ulcers.

AGING

Popular theory holds that the process of aging is a function of "free radical damage."¹⁹ ROS accumulate in the tissues faster than they can be neutralized by the antioxidant capacity of the cells, thus implicating the GSH system. In support of this idea, a progressive loss of intracellular GSH has been observed in aged tissues. Thus, Lang et al¹⁹ found that 40 young subjects (aged 20 to 39) had a blood GSH value averaging 17% higher than 60 older subjects (aged 60 to 79). Julius et al²⁰ measured GSH concentrations in 33 people aged 60 to 79 and found a direct relationship between higher GSH values and increasing age with good health.

STRATEGIES FOR RESTORING GSH

Some GSH is obtained directly from the diet (averaging 150 milligrams per day), especially fruits and vegetables, but the majority of the body's GSH must be synthesized intracellularly. Much of this occurs in the liver. Approximately 80% of the liver GSH is exported to the plasma and is largely used by the kidneys for detoxification. A number of strategies exist for assisting the body in GSH repletion.

Oral administration of GSH is not effective, although intact aerosol GSH can be delivered directly into the lungs in pul-

monary disease to raise GSH levels in the epithelial lining fluid. Intravenous delivery is also effective but impractical.

GSH synthesis is limited by the availability of cysteine, so provision of this amino acid provides the means whereby GSH synthesis can be augmented. Free cysteine, however, is unsafe for routine oral administration since it readily auto-oxidizes in the circulation to form potentially toxic degradation products. Cysteine can be generated from methionine (via S-adenosylmethionine to homocysteine to cysteine), which is available as a dietary supplement, but this pathway may be inactive in neonates and adults with liver disease. Moreover, the body utilizes methionine in two other metabolic pathways as well.

A number of drugs exist that can be used orally to deliver cysteine precursors. Of these, N-acetyl cysteine appears to be the safest and most frequently used. Depending on the dose given, side effects have been reported, including nausea and other gastrointestinal problems, rash, and wheezing.

The best and most natural source of cysteine for GSH synthesis comes from dietary protein. It has recently been discovered that whey proteins provide the richest source of this amino acid. It is present as cystine (two molecules of cysteine linked by a disulfide bond), which is more stable than cysteine. The disulfide bond is pepsin- and trypsin-resistant but may be split by heat and mechanical stress. Thus, only whey proteins that have been prepared using very gentle processes retain cystine. Following digestion, the cystine is absorbed from the gut intact and only split into cysteine once it is safely inside the cell.

Nutritional strategies for raising GSH in patients with many of these conditions should prove highly beneficial.

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