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GLUTATHIONE PEPTIDE

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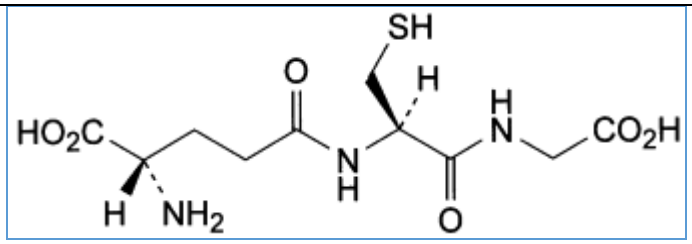
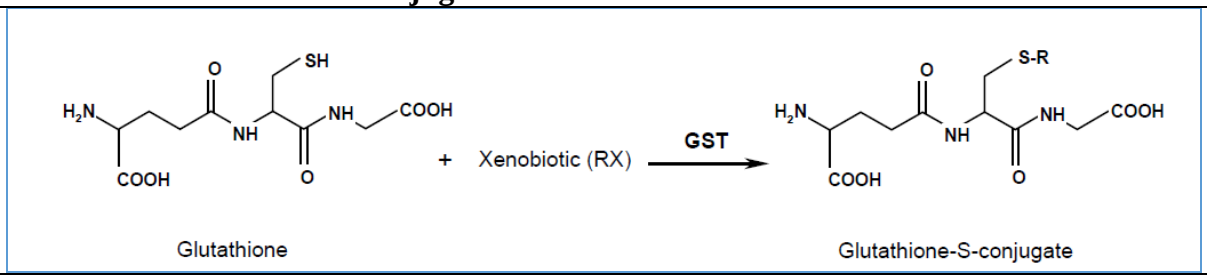
ABSTRACT

In this review article would selected and talk in some sides related to Glutathione and highlights the some points as general. Glutathione (γ-glutamyl-cysteinylglycine) is an endogenous peptide with antioxidant plays many useful functions in human body and therefore determination of this small molecule is very important for present-day medicine and pharmacy. General multiple functions of GSH **A**. Reducing agent, antioxidant **B**. Detoxification of xenobiotic **C**. Metabolic regulation. GSH levels in human tissues normally range from 0.1 to 10 millimolar (mM). Glutathione plays a central role in the maintenance of tissue antioxidant defenses and in the regulation of redox sensitive signal transduction. Glutathione transferases (GST) are essentially known as enzymes that catalyze.

Glutathione[1-30] *(Ph Eur monograph 1670)* *70-18-8*	 307.3
General Notices	$C_{10}H_{17}N_3O_6S$
Definition	L-g-Glutamyl-L-cysteinylglycine. Fermentation product.
CHARACTERS	
Appearance	White or almost white, crystalline powder or color less crystals.
Solubility	Freely soluble in water, very slightly soluble in ethanol (96 per cent) and in methylene chloride, and in dichloromethane. Protect from light.

Formation of Glutathione Conjugate[7]



INTRODUCTION

Glutathione (γ-glutamyl-cysteinylglycine) plays many useful functions in human body and therefore determination of this small molecule is very important for present-day medicine and pharmacy. It is synthesized in every prokaryotic and eukaryotic cell because it takes part in protection against oxidative stress, plays important role in detoxification and immunity modulation. Thanks to the glutathione, the body is able to protect itself against different infections, cancer development, the liver has ability to detoxify heavy metals, toxins, and other xenobiotic and cells are not subject of continuous destruction. Characteristic element of glutathione structure is thiol group (-SH), which is responsible for biological functions of this compound. Because of the presence of this group, glutathione can occur in several forms. The most important forms are reduced (GSH) and oxidized (GSSG) glutathione. Other widespread forms are S-nitrosoglutathione and conjugates of GSSG and proteins.[21]

Glutathione in every cell in the body, from three amino acids - glycine, cysteine, and glutamic acid or glutamate.[30] Its main function is to give its electrons away to other molecules in need and will continually regenerate its electrons. Glutathione's ability to fill a vital role in the chemical, mechanical, and electrical functions. Glutathione is an extremely large molecule. Many studies have shown the ingestion of Glutathione in a pill or liquid form, or even inject it into the blood stream intravenously, very little, if any of it, will make it into the cells and so it will have a nominal effect.[18]

Glutathione is an endogenous peptide with antioxidant and other metabolic functions. Glutathione and glutathione sodium are used to prevent neurotoxicity associated with cisplatin or oxaliplatin; they have also been used to prevent other adverse effects of antineoplastic and radiation therapy, as well as in a wide range of other disorders including poisoning with heavy metals and other compounds, liver disorders, corneal disorders, and eczema. Glutathione has also been tried in idiopathic pulmonary fibrosis and peripheral vascular disorders.[2]

Many of these reactions to which we return later are crucial to cell survival, so much so that glutathione has been termed ‘‘the most important non-protein thiol’’. Probably, there is no contradiction in further widening its role: glutathione is a key factor for cellular survival. One hypothesis has even suggested that glutathione is responsible for the origin of life. While this latter view seems likely to reflect a certain level of scientific hyperbole, it may be difficult to overestimate the central importance of this molecule in the biochemistry of living cells.[5]

The immune system works best if the lymphoid cells have a delicately balanced intermediate level of glutathione. Even moderate changes in the intracellular glutathione level have profound effects on lymphocyte functions. Certain functions, such as the DNA synthetic response, are exquisitely sensitive to reactive oxygen intermediates and, therefore, are favored by high levels of the antioxidant glutathione. Certain signal pathways, in contrast, are enhanced by oxidative conditions and favored by low intracellular glutathione levels.[26]

GENERAL MULTIPLE FUNCTIONS OF GSH[5,17]

Reducing agent, antioxidant

Free-radical scavenger.

Protection of cell membranes.

Protection against oxidative stress and lipid peroxidation (elevated level of oxidized glutathione (GSSG)).

Protection against radiation and UV light; DNA repair.

Maintenance of the SH groups of proteins and other molecules.

Destruction of hydrogen peroxide, other peroxides and free radicals.

Detoxification of xenobiotics

Conjugation.

Transport of metals between ligands.

Determination of drug resistance.

Reservoir and transfer of cysteine.

Metabolic regulation

Cofactor and substrate.

Protein and nucleic acid synthesis.

Leukotriene synthesis.

Amino acid transport.

Ca^{2+} homeostasis (protection of –SH in ATPase's).

Mitogenesis, cell-cycle regulation.

Immune functions.

Thermotolerance.

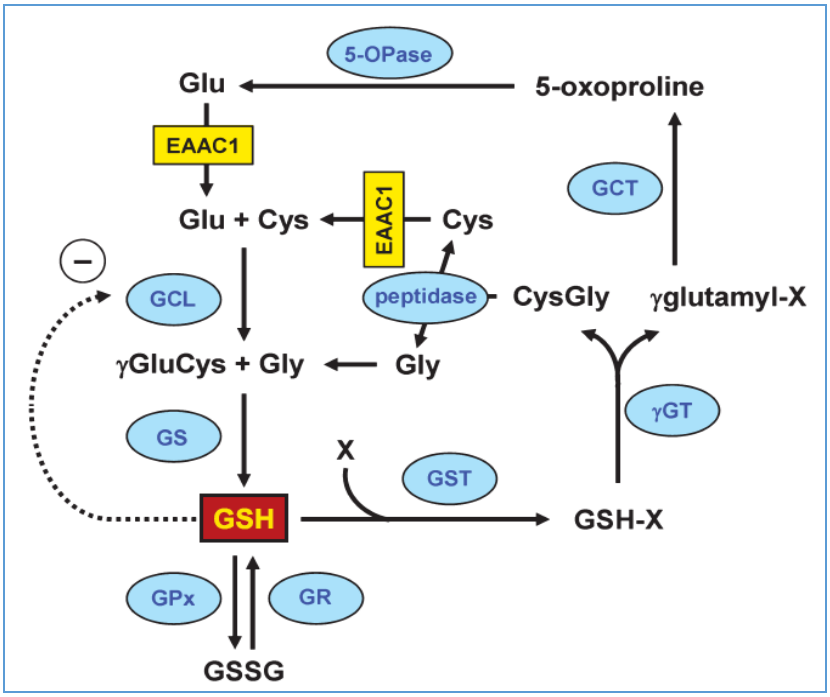
Glutathione's Role as an Antioxidant

Glutathione is currently one of the most studied antioxidants. This is likely due to it being endogenously synthesized all throughout the body and it is found in all cells, sometimes in rather high concentrations. Investigations have highlighted many roles in which it is used including antioxidant defense, detoxification of electrophilic xenobiotics[13], modulation of redox regulated signal transduction, storage and transport of cysteine, regulation of cell proliferation, synthesis of deoxyribonucleotide synthesis, regulation of immune responses, and regulation of leukotriene and prostaglandin metabolism.[12]

Glutathione in Human

GSH levels in human tissues normally range from 0.1 to 10 millimolar (mM), most concentrated in the liver (up to 10 mM) and in the spleen, kidney, lens, erythrocytes, and leukocytes. Plasma concentration is in the micromolar range (approx. 2-20 μM).[29] Oxidative stressors that can deplete GSH include ultraviolet and other radiation; viral infections; environmental toxins, household chemicals, and heavy metals; surgery, inflammation, burns, septic shock; and dietary deficiencies of GSH precursors and enzyme cofactors.[8]

The new[11] (High-Performance Liquid Chromatography) HPLC-validated procedure for the determination of Glutathione (γ-glutamyl-cysteinyl-glycine, GSH) in micro-volumes of blood, that were collected by finger stick in humans, sample volumes as low as 0.5 μL are suitable for analysis. Being minimally invasive, the finger stick method can be used to monitor frequently Glutathione (GSH) concentrations while avoiding the dis-comfort and possible adverse events associated with phlebotomy. This method is likely to be equally suitable for Glutathione (GSH) measurement in blood from small experimental animals by minimally invasive techniques, which improve the chance of survival in long-term studies. The new procedure simplifies Glutathione (GSH) analysis in blood by eliminating the need for the use of blanks but it also improves accuracy of the analysis because it avoids artefactual oxidation of Glutathione (GSH) during sample manipulation. Moreover, this method, with minor-modifications, can also be applied to the analysis of Glutathione (GSH) in red blood cells.[4]



Schematic: Metabolism of glutathione (GSH). GSH synthesis requires three amino acids (glutamate, cysteine, and glycine) and two enzymatic steps involving ATP. In neurons, glutamate/cysteine uptake is mediated by EAAC1. GCL catalyzes the first, i.e., the ratelimiting enzymatic, step in GSH synthesis. GSH regulates its own synthesis via feedback inhibition of GCL (dotted arrow). Abbreviations are as follows: **Glu**: glutamate, **Cys**: cysteine, **Gly**: glycine, **γGluCys**: γ-glutamylcysteine, **CysGly**: cysteinylglycine, **GSSG**: glutathione disulfide, **X**: compounds that can form conjugates with GSH, **GCL**: γ-glutamylcysteine ligase, **GS**: glutathione synthase, **GPx**: glutathione peroxidase, **GR**: glutathione reductase, **GST**: glutathione-S-transferase, **γGT**: γ-glutamyltransferase, **GCT**: γ-glutamylcylotransferase, **5-OPase**: 5-oxoprolinase.[23]

Glutathione transferases (GST)

Glutathione transferases (GST) are essentially known as enzymes that catalyze[22,28,30] the conjugation of glutathione to various electrophilic compounds[24,25,28,30] such as chemical carcinogens, environmental pollutants, and antitumor agents.[10] As it was mentioned, GST plays an important role in plant resistance against biotic and abiotic stresses.[16] However, this protein family is also involved in the metabolism of endogenous compounds, which play critical roles in the regulation of signaling pathways. For example, the lipid peroxidation product 4-hydroxynonenal (4-HNE) and the prostaglandin 15-deoxy-Δ12,14-prostaglandin J_2 (15d-PGJ_2) are metabolized by GSTs and these compounds are known to influence the activity of transcription factors and protein kinases involved in stress response, proliferation,

differentiation, or apoptosis. Furthermore, several studies have demonstrated that GSTs are able to interact with different protein partners such as mitogen activated protein kinases (i.e., c-jun N-terminal kinase (JNK) and apoptosis signal-regulating kinase 1 (ASK1)) which are also involved in cell signaling. New functions of GSTs, including S-glutathionylation of proteins by GSTs and ability to be a nitric oxide (NO) carrier have also been described. Taken together, these observations strongly suggest that GST might play a crucial role during normal or cancer cells proliferation or apoptosis.[10]

Antineoplastic toxicity

Glutathione has been reported to reduce the incidence of neurotoxicity induced by cisplatin therapy. In a double-blind, randomized trial1 in 50 patients receiving cisplatin for advanced gastric cancer, glutathione significantly reduced the incidence of neuropathy assessed within one week of completing cisplatin therapy. There did not appear to be any reduction in cytotoxic activity.[2]

Glutathione and Alzheimer's disease

GSH is a major endogenous enzyme-catalyzed antioxidant that plays a fundamental role in detoxification of reactive oxygen species (ROS)[27] and regulates the intracellular redox environment. It is present at high concentrations of 1–2mM within the brain, and its intracellular equilibrium has been shown to be important for health and function of brain cells.[19]

Mild cognitive impairment (MCI) represents an at-risk state for Alzheimer's disease in which underlying pathophysiological mechanisms could be delineated. Oxidative stress has been implicated in Alzheimer's disease and can be measured by levels of the antioxidant glutathione. Shantel L.et.al assess in vivo levels of glutathione via proton magnetic resonance spectroscopy in patients with MCI and to determine how glutathione relates to cognitive decline. Was shown for the first time that MCI is associated with increased glutathione in the cingulate, which in turn relates to neuropsychological performance. Higher levels of anterior cingulate glutathione were related to neuropsychological decrements on tests of executive functions. Elevated posterior cingulate glutathione was associated with poorer memory consolidation. This finding may be indicative of an early compensatory or neuro-protective response, and the role of glial cells and glutathione enzymes requires delineation. Longitudinal studies examining the utility of glutathione as a marker for cognitive decline are now required.[3]

Lung disorders

Glutathione is an important extracellular antioxidant[12,29] in the lung and high concentrations are found in lung epithelial lining fluid. A deficiency of glutathione may contribute to the epithelial damage that occurs in various lung disorders, and treatment with nebulized glutathione has therefore been investigated. Small studies have found beneficial biochemical results in patients with cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis) and in cystic fibrosis, but the clinical effects of these changes are not clear. Another study in cystic fibrosis found no effect on oxidative markers after treatment for 2 weeks, but there was a small improvement in lung function. Benefit has also been reported in a patient with emphysema. However, in a study of patients with mild asthma, inhalation of glutathione solution was associated with bronchoconstriction, leading to cough or breathlessness in some patients, possibly due to sulfite formation.[2]

Dietary Supplementation of Glutathione

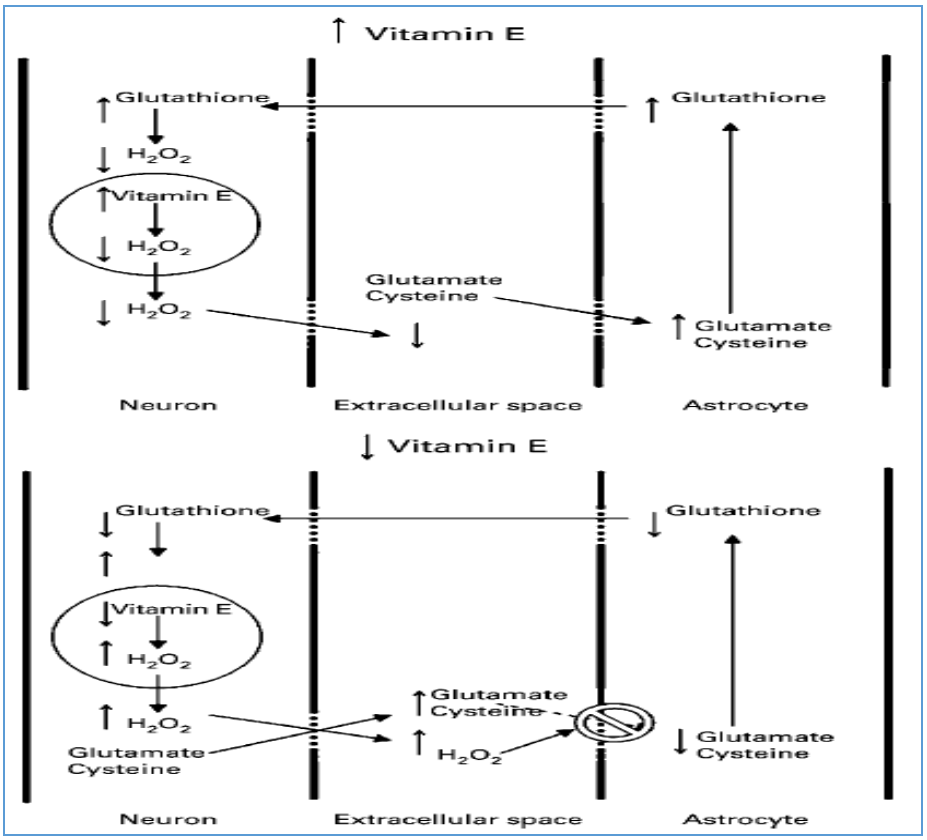
Glutathione plays a central role in the maintenance of tissue antioxidant defenses and in the regulation of redox sensitive signal transduction. Physical exercise may cause oxidation of GSH in tissues such as the blood, skeletal muscle and liver. N-acetyl-L-cysteine (NAC) and α-lipoic acid (LA) are two antioxidant dietary supplements that are able to enhance cellular GSH levels. Because LA can be recycled to its potent dithiol form, dihydrolipoate, by enzymes present in the human cell it has a clear advantage over NAC.[15]

In study by J. Hyeong K. et al. has revealed the effects of Glutathione (GSH) on Holstein neonatal calves. Body Weight (BW) gain, total Dry Matter Intake (DMI), feed efficiency, and breathing rate did not differ between groups. Mean diarrhea and enteritis frequency were less in calves fed milk with Glutathione (GSH) supplementation. Moreover, higher mean corpuscular volume (MCV) and lower Red blood cell Distribution Width (RDW) were found in calves fed milk with GSH supplementation. Red blood cell Distribution Width (RDW) and Mean Corpuscular Volume (MCV) are highly sensitive blood cell parameters in the differentiation of iron deficiency anemia. Higher Lactate dehydrogenase (LDH) enzyme is related to the generation of frequent anemia and diarrhea. In the present study, Lactate dehydrogenase (LDH) values were lower in calves fed GSH. With the results obtained, supplementation of Glutathione (GSH) is highly recommended.[6]

Glutathione and vitamin E deficiency

Vitamin E is an antioxidant that has been demonstrated to improve insulin action. Glutathione, another natural antioxidant, may also be important in blood pressure and glucose homeostasis, consistent with the involvement of free radicals in both essential hypertension and diabetes mellitus.[20]

Vitamin E deficiency increases H_2O_2 levels. H_2O_2 is scavenged by glutathione. Glutathione deficiency allows H_2O_2 to rise. High concentrations of H_2O_2 can block the uptake of glutathione precursors, glutamate and cysteine, into astrocytes. Without glutathione precursors, astrocyte glutathione synthesis drops. Neural glutathione is derived from astrocytes. Reducing astrocytic glutathione synthesis reduces glutathione levels in neurones for protection from H_2O_2. An imbalance of this homeostatic cycle can be introduced at any point: vitamin E, glutathione, glutamate or H_2O_2. Vitamin E, glutathione, glutamate and H_2O_2 levels in this cycle are all affected by many factors.[14]



Schematic representation of glutathione and vitamin E metabolism in astrocytes and neurons. Reactive oxygen species homeostasis in the neuron depends upon the relationship between vitamin E and glutathione that is produced in astrocytes. (○), Mitochondria; (▌), cell walls.[14]

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