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Mini review article

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Glutathione – a master antioxidant and an immune system modulator

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Abstract

The free radicals (oxidants) produced during cellular metabolism result in toxic effects that involve majority of diseases related to ageing, such as Alzheimer's, cataract, Parkinson's, arthritis, etc. which are inevitable. In contrast to age-related diseases, they also result in the destruction of DNA, clogging of arteries, etc. that can be prevented. In general, no individual is free from oxidative stress, as it is either the result of one's own cellular metabolism or the exposure to environmental toxins (such as air, food and water pollution). Hence, to combat these harmful unstable molecules, the body requires antioxidants of different varieties because each antioxidant targets certain type of damaging free radical. Each antioxidant does its own job in the body, and some even work together. One such antioxidant is Glutathione that provides greater antioxidant protection and recharges other antioxidants also within the body. Glutathione is termed as a master antioxidant by scientists, as it possesses the ability to maintain the exogenous antioxidants, such as vitamin C and E in their active form. Also, it plays a significant role in immune function. The biochemical reduction-oxidation state of Glutathione within our bodies is one of the best gauges of oxidative stress levels and overall health. Glutathione's deficiency is believed to lead almost every single disease, since it has its existence in every cell of the body. About such a special peptide molecule this review is, which represents its importance in human health apart from depicting its dietary sources and other beneficial aspects elaborately.

Keywords
Glutathione; *Antioxidant*; *Immunity*; *GSH*; *GSSG*; *Ageing*

Introduction

Glutathione (GSH), a tripeptide made of L-cysteine, L-glutamic acid and glycine, is a major free radical scavenger, immune booster and detoxifier of the body. Glutathione is not an essential nutrient, it is intracellularly synthesised and resists degradation by intracellular peptidases. Its antioxidant system is considered to be the foremost among the cellular protective mechanisms because it participates directly in the destruction of reactive oxygen species (ROS i.e. free radicals) through GSH peroxidase, and it also maintains the vitamins C and E in reduced active forms, which also exert an antioxidant effect.[1] Glutathione is produced naturally by almost every one of our innumerable cells and few studies reveal that, its level in the human body helps in predicting the life span. In fact, in HIV patients, the Glutathione levels are the sole predictor of death and there is also a hypothesis that, the mechanism responsible for AIDS could be reversed by the administration of reducing agents, especially those containing sulphydryl groups (SH).[2] In the body, Glutathione concentration is found to be the greatest, particularly in the liver, the organ which is involved in the detoxification and elimination of toxins[3] and in the lung epithelial lining fluid in case of chronic smokers and lung cancer patients.[4,5] Many studies have also shown that Glutathione synthesis is necessary for lymphocyte proliferation.[6]

This suggests how much Glutathione is important in the normal functioning of immune system. Its concentration in the human liver tissue is evaluated as 6,400 mmol/kg.[7] It detoxifies harmful compounds, for instance, Glutathione binds transitional metals, which is an important factor in their elimination.[8] The Glutathione levels are reported to decline consistently with old age.

It has been reported that, the erythrocyte Glutathione peroxidase activity was lower in elderly population than in young adults.[9] Some studies have shown that, correction of Gluathione deficiency in the ageing mosquito has shown to increase longevity,[10] and it was also found by research that, *in vitro* life span of human diploid fibroblasts could be extended or shortened with increased or decreased Glutathione levels.[11] Many disease states are characterised by low Glutathione levels. Therefore, optimum Glutathione levels are essential for healthy life.

Glutathione's chemistry

Glutathione's (GSH) IUPAC name is 2-amino-5-{[2-[(carboxymethyl) amino]-1-(mercaptomethyl)-2-oxoethyl] amino}-5-oxopentanoic acid, which is gamma-glutamyl cysteinyl glycine, a tripeptide. It contains an unusual peptide linkage between the amine group of cysteine and the carboxyl group of glutamate side chain.[12] In healthy cells and tissues, more than 90% of total Glutathione pool is in the reduced form (GSH) and less than 10% exists in the disulphide or oxidised form (GSSG). In fact, the ratio of reduced to oxidised Glutathione within the cells is often used scientifically as a measure of cellular toxicity.[13]

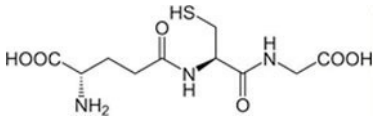

Fig. 1. Glutathione's structure

Glutathione's synthesis and mechanism

Glutathione has to be synthesised intracellularly, as there is no evidence for transport of GSH into cells. GSH is synthesised by two enzymes, namely γ-glutamyl cysteine synthetase, which is the rate-limiting enzyme and Glutathione synthetase.[14] Of the three building blocks (L-cysteine, L-glutamic acid and glycine) of Glutathione, the sulphydryl (thiol) group (SH) of cysteine serves as a proton donor, which is responsible for the biological activity of Glutathione and also acts as a limiting factor in Glutathione's biosynthesis. In the absence of reduced cysteine, the addition of an acetyl group to this amino acid (N-acetyl-cysteine, NAC) provides an ability for the molecule to cross the cell membrane and promote GSH biosynthesis inside the cell.[15]

GSH acts as electron carriers. When electrons are lost from GSH (i.e. on oxidation by ROS or Glutathione peroxidase), the molecule (GSH) becomes oxidised (GS-) and two such molecules become linked (dimerised) by a disulphide bridge to form Glutathione disulphide or oxidised Glutathione (GSSG). This linkage is reversible upon re-reduction.[15]

Beneficiaries of Glutathione

Glutathione is an important cell protectant. Besides antioxidation, immune enhancement and detoxification, it exhibits a fundamental role in numerous metabolic and biochemical reactions, such as DNA synthesis and repair, protein synthesis, prostaglandin synthesis, amino acid transport and enzyme activation. Glutathione supplementation may help to prevent or treat many conditions associated with impaired immune function due to elevated oxidative stress or ageing. These may include cancer, AIDS, asthma, heart disease, hepatitis, radiation poisoning, Parkinson's and Alzheimer's disease.[16] Few scientists have concluded on research that, the people suffering from schizophrenia, bipolar disorder, addiction and compulsive disorders could be benefitted by regulating Glutathione metabolism.[17] It has been also reported that, raising Glutathione levels in cells have reduced cancer growth by suppressing the activity of certain chemically-reactive oxygen molecules in the test tubes.[18] Few studies have revealed that, increasing Glutathione levels in breast, larynx, colon, lung and bone marrow cancer cells helped the cells to resist the effects of chemotherapy drugs. Glutathione plays a critical role in inhibiting carcinogenesis induced by a number of different mechanisms.[19]

Dietary sources of Glutathione

Glutathione is an intracellularly synthesised, abundant tripeptide. It is an endogenous antioxidant, which cannot be supplemented from food sources directly into the cells. Glutathione is readily available in fresh fruits, vegetables and meat but consuming them would transfer only a small (i.e. negligible) amount of reduced GSH in to the blood stream because most of it is lost in the digestive tract, which is not effective in raising the intracellular Glutathione level. Studies have revealed that, the circulating Glutathione could not be increased to a beneficial extent by oral administration.[20] Alternatively Johnson and coworkers[21] found that, blood Glutathione levels have increased nearly by 50% in healthy individuals who took 500 mg of vitamin C daily. In addition to that, dietary sources of Glutathione and several other nutritional compounds can help in increasing the Glutathione levels, which include N-acetylcysteine (NAC), alpha-lipoic acid, glutamine, methionine and undenatured whey protein.[22] Dietary consumption of foods rich in Vitamin B6, riboflavin and selenium are required for the manufacture of Glutathione. Foods rich in sulphur-containing amino acids are usually the best sources of Glutathione. Silymarin (a herb) has shown prevention of depletion of Glutathione that is induced by alcohol and other toxins and raise in the level of Glutathione in the liver cells.[23,24] In addition, curcumin may also be useful to increase tissue Glutathione levels.[25] Dietary Glutathione is in high amounts in fresh (uncooked) meat, moderate in certain raw fruits and vegetables and in small amounts or absent in grains and pasteurised dairy products.[26]

Although undenatured whey protein is one of the best precursors (building blocks) for Glutathione, it contains only moderate levels of naturally occuring Glutathione. Cooking and storage also have a great impact on foods' Glutathione content. To quote an example in support to this, in human breast milk that was put aside for later use by breast-fed babies, a 73–79% loss of Glutathione had occurred when the milk was kept at room temperature or refrigerated for two hours.[27]

Fresh fruits and vegetables provide excellent levels of Glutathione. Different fruits and vegetables containing Glutathione are represented in Table 1.

Table 1. Composition of Glutathione in different fruits and vegetables[26]

Food	Glutathione content in uncooked food (in mg per 100 g serving)
Apple	21.0
Carrot	74.6
Grapes	70.6
Spinach[28]	9.65
Tomato	169
Asparagus[28]	28.3
Avocado[28]	27.7
Purslane[28]	14.81

Commercial forms of Glutathione's precursors

Glutathione has no significant benefit when taken as a supplement. However, Glutathione synthesis could be enhanced by providing the precursors of Glutathione as supplements. Some of the commercial precursors include: S-adenosyl-methione, ornithine decarboxylase, procyteine and oxothiazolidine carboxylate.[29]

The familiar and mostly used drug is N-acetyl-cysteine (NAC), which is a powerful precursor of Glutathione. It works extremely quickly and is very effective.[29] On a wide variety of mental and physical disorders, the dietary supplements of NAC have been tested.[15] Immunocal® (or HMS90®) is a drug that contains undenatured, bio-active whey protein loaded with Glutathione precursors. Since it is a natural health supplement, there are no side effects.[29] It is clinically proven to raise Glutathione levels.[30] Essential GSH™ is a liquid formulation, which increases the systemic bio-availability of Glutathione through liposomal-based delivery. Because liposomes are made from the same material as the cell membranes, it fuses with cell membranes and permits absorption of Glutathione into the cells.[31]

Side effects

Glutathione's side effects are unknown. But S-adenosyl-methione can cause gastro-intestinal problems and NAC's several times

administration per day can cause toxicity. Oral NAC supplementation has been associated with cerebral symptoms, such as nausea, blurred vision and vomiting.

Conclusion

Poor diet, pollution, toxins, medications, stress, trauma, ageing, infections, radiation, etc. deplete the body's Glutathione levels. Since it is synthesised within the cell, a proper diet would be a correct approach to maintain a balanced Glutathione synthesis and prevent the body's cellular dysfunction. In addition, the Glutathione drugs (supplements), which target directly the cells, have to be researched with incorporation of nanoscience. This may be promising in the future for curing many diseases, especially those which are inevitable.

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