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Glutathione and Exercise

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During exercise the increase in whole body oxygen consumption of 10-20 fold causes a severe disturbance of various biochemical pathways. The oxygen flux in individual muscle fibers is believed to increase by as much as 100-200 fold. This tremendous increase in oxygen consumption results in an increased leakage of electrons from the mitochondrial respiratory chain, forming various one-electron oxygen intermediates, such as superoxide anion, hydrogen peroxide and hydroxyl radicals. These reactive oxygen species are capable of triggering a chain of damaging reactions in the cell, such as lipid peroxidation, inactivation of certain enzymes, alteration of cellular oxidoreductive status, and oxidative damage to proteins and DNA.

Reactive oxygen species are removed constantly in the cell by scavengers known as antioxidants. The most important antioxidants are vitamin E (α-tocopherol), vitamin C (ascorbic acid), β-carotene, and glutathione (GSH). In addition, specialized enzymes catalyze the metabolism of reactive oxygen species preventing them from causing further damage. It is the

balance between the production of reactive oxygen species and the levels of antioxidants that determines the oxidative stress induced by exercise.

Biochemistry and Function of Glutathione

Glutathione (L-γ-glutamyl-L-cysteinyl-glycine; GSH) is a tripeptide found in virtually all animal cells. It has been the subject of much research since its discovery by Rey-Pailhade in 1888. Rey-Pailhade named the structure *philothione* (Greek for love and sulfur) because of its spontaneous reaction to sulfur. Eventually it was found that the molecule itself contained sulfur, and Hopkins named the structure glutathione. The elucidation of its structure was not resolved until around 1930. Initially it was thought to be a dipeptide containing glutamate and cysteine. The later elucidated tripeptide structure was hypothesized to be a reducing agent that maintains enzymes in an active state, and was involved in keeping various compounds like dehydroascorbate (vitamin C) and α-tocopherol (vitamin E) in the reduced state. The many enzymes involved in GSH metabolism and function were discovered in the following years. Now the studies of GSH and related enzyme systems have become an important area of biochemistry, nutrition, and pharmacology. Much of the work regarding the function, metabolism and regulation of GSH have been carried out in Cornell University by Professor Alton Meister and his colleagues.

Although GSH is essential for normal cell function, most organs and tissues cannot synthesize GSH by themselves. Instead, GSH has to be taken up from extracellular source and imported into the cell. This process encompasses seven enzymes and crosses the cell membrane. The modern concept of GSH metabolism is depicted in Figure 1. The synthesis and degradation of GSH involve two separate pathways which form an interrelated cycle to maintain intracellular GSH homeostasis. This cycle is referred to as the γ-Glutamyl Cycle. The majority of the various amino acids needed for the intracellular synthesis of GSH are transported into the cell. This first involves the degradation and transport of GSH at the cell membrane. The first enzyme involved in the cross-membrane transport of GSH is γ-glutamyltranspeptidase (GGT). This enzyme cleaves the extracellular GSH into a glutamate amino acid bound to either a cystine or other available amino acid. The resulting peptide is then easily transported into the cell. The remaining cysteinylglycine (CysH-Gly) of the GSH molecule is transported into the cell and further cleaved into CysH and Gly. GGT is predominately an external membrane-bound enzyme but various isoenzymes could exist inside the cell. The transport of GSH is largely dependent on the availability of GSH outside of the cell.

The synthesis of GSH in the cell involves a series of reactions requiring a total of 2 ATP. The two major enzymes responsible for this synthesis are γ-glutamylcysteine synthetase (GCS) and glutathione synthetase (GS), the former

being rate-limiting. If the receptive amino acid is cystine, the so-formed γ-glutamylcystine can bypass the GCS reaction and derive GSH directily via the GS reaction. Otherwise the imported γ-Glu-AA is further metabolized to 5-oxoproline and then glutamate, which along with cysteine is a substrate for GCS. Feedback inhibition of GSH regulates the activity of GCS which seldom operates at maximal flux. Genetic deficiencies in GSH synthesizing enzymes may lead to life-threatening acidosis because of the accumulation of 5-oxyproline, a cytotoxic compound, which is formed by 5-oxyprolinase reaction.

GSH has a broad spectrum of functions which include: (1) detoxification of exogenous and endogenous compounds, such as reactive electrophiles and peroxides with glutathione S-transferase and glutathione peroxidase; (2) reducing disulfide linkages of enzymes and proteins, thereby maintaining the essential thiols at a reduced status; (3) functioning as a nontoxic reservoir of cysteine and forming a vehicle for the transport of cysteine to all organs; (4) being actively involved in leukotriene and prostaglandin metabolism. (5) playing an important role in the reduction of ribonucleotides to deoxyribonucleotides, and (6) serving as a scavenger of certain free radicals. Figure 2 shows the major mechanism by which GSH removes hydroperoxides (including xenobiotic organic peroxide and lipid hydroperoxide). By accepting an electron from the peroxide (or donating a hydrogen ion), GSH is oxidized to half of a disulfide (GSSG) . This reaction is catalyzed by the Se-containing enzyme GSH peroxidase (GPX).

The GSSG formed from these oxidizing reactions can be reduced back to GSH by the flavin-containing enzyme glutathione reductase (GR). This important intracellular step requires NADPH which is supplied by a reduction of NADP+, a relatively abundant cellular reducing power, via the hexose monophosphate pathway or an isocitrate dehydrogenase catalyzed reaction. Together, these reactions make GSH a "recyclable" antioxidant in the cell. In the liver, GSH S-transferase (GST) catalyzes the conjugation of GSH with a wide variety of xenobiotic toxins to form water-soluble compounds, thereby reducing oxidative stress inflicted by the metabolism of these prooxidants. When GPX activity is low, such as under Se-deficiency, the importance of GST may rise due to its ability to remove certain organic peroxides.

Recent evidence show that GSH is an efficient scavenger of hydroxyl radicals and singlet oxygen. In addition, GSH may be involved in the recycling of vitamin E radicals. When there is an excessive production of free radicals or reactive oxygen species under various physiological and pathological conditions, the concentration of GSH will fall whereas GSSG will rise, resulting in a decreased GSH/GSSG ratio. This dynamic alteration is indicative of an oxidative stress.

Cellular Concentration of Glutathione

GSH is the most abundant short-chain peptide and the most important non-protein thiol source in the body. Its

concentration in the cell is in the millimolar range for most tissues. However, there is a great variability in GSH content in different body tissues depending on their function and oxidative capacity. The eye lens has the highest GSH concentration of approximately 10 mM among all tissues, probably due to its essential role to protect against photoradiation in this tissue. The concentration of GSH in the liver is between 5-7 mM. It is mainly synthesized within the hepatocytes. Kidney has about 3 mM and Heart about 2 mM, whereas the muscle has about 1-2 mM depending on fiber type. Red oxidative tissue e g. red vastus lateralis has 2 fold higher contents of glutathione (2 mM) then the white vastus lateralis. Skeletal muscles are highly heterogeneous in a variety of metabolic properties, such as oxidative potential, pattern of fuel utilization, and antioxidant enzyme activity. Therefore, the levels of GSH and GSSG as well as the ratio of GSH/GSSG, reflect these differences in metabolic characteristics. Concentration of GSH in the red blood cell is relatively high (~2 mM) compared to that of blood plasma (< 0.05mM). Since the red blood cell carries oxygen directly and hemoglobin contains large amount of iron, an important catalyst for free radical formation, high levels of GSH in the red blood cell is needed for adequate protection against potential oxidative damage. Most of the glutathione in the cell is kept in the reduced state in vivo, giving a high GSH/GSSG ratio. Fluctuations occurs when the cell is under

oxidative stress, making the GSH/GSSG ratio a sensitive marker of cellular redox status.

Transport of Glutathione

Although a number of cells are capable of synthesizing GSH, liver by far is the most important organ for synthesize and transport of GSH de novo. It is estimated that 90% of the plasma GSH comes from hepatic origin, where the various amino acids (Glu, Cys, Gly) from the portal blood are synthesized to GSH. The majority of the GSH synthesized is exported via exocytosis across the sinusoidal membrane into plasma whereas the remaining is excreted into the bile. Damage to the liver like cirrhosis will lead to a decreased efflux of GSH. Use of GSH by the liver is usually small but it's importance rises when free radicals are produced in metabolizing xenobiotic drugs. Furthermore, import of GSH is rather limited because of the low activity of GGT. Although human liver contains significantly higher amounts of sinusoidal GGT compared to other species such as rat, the amount is still not sufficient for significant import of GSH. The kidney on the other hand is the major consumer of plasma GSH. Anywhere from 70-90% clearance from the plasma occurs during first-pass extraction of GSH. It is also a high capacity system due to a large volume of rennin blood flow. It has been demonstrated that exogenously administered GSH is rapidly cleared within a short period of time, keeping plasma GSH within a narrow range. The

constituent amino acids are taken up by cells of the proximal tubule and used for resynthesis of GSH, or returned to the liver and other organs. The lung and intestine also significantly contribute to plasma GSH turnover, because of the recent finding that a high concentration of GGT is present in the lung. Although muscle contains low activity of GGT as well as synthesizing enzymes of GSH, its large mass makes it also a potential consumer of circulating GSH, particularly when the muscle is under oxidative stress and extra antioxidant protection is required. Thus uptake of GSH by different organs and tissues is primarily dependent on the activity of GGT in the cell membrane. This is clearly demonstrated by the finding that an inhibitor of GGT can lead to a marked increase in GSH in blood and eventually the urine (glutathionuria). Humans with an inborn GGT deficiency also experience glutathionuria. Thus, glutathione is subject to constant turnover in the body, with the liver, kidney, lungs, heart, intestine, and muscle being the main organs responsible for GSH homeostasis (See Figure 3).

In addition to supplying GSH for interorgan transport, the export of GSH through the membrane appears to also protect the cell membrane of the exporting tissues against oxidative and other types of damage. This is accomplished by maintaining thiols and other antioxidants (e.g. α-tocopherol) required for membrane integrity in the reduced state. The interorgan transport of glutathione is primarily in its reduced form (i.e. GSH) rather than GSSG. However, tissues do export GSSG

when GSSG production is drastically increased and exceeds the reducing capacity of GSSG reductase. For example, liver excretes large amounts of GSSG into the bile duct when a large dose of prooxidant xenobiotic drug is metabolized, thereby alleviating the oxidative stress the liver is exposed to. Increased levels of GSSG are deleterious and will disturb intracellular redox status and cause cross-linkage of proteins and nucleotides to form mixed disulfide. These alterations of cell structure can result in functional impairment of the cell, such as energy production and replication. In addition to liver, several other tissues also exhibit such active export of GSSG, including erythrocytes, eye, and heart, resulting in an increase in plasma GSSG. Plasma GSSG and the ratio of GSH/GSSG are therefore often used as an indicator of total body oxidative stress. It is hypothesized that during intense exercise ATP pool is markedly decreased thereby hampering the export of GSSG and eventually causing an increase of GSSG in the cell. This has been postulated as a potential factor for muscle fatigue.

Dietary Requirement and Absorption of GSH

It is known that GSH is an important anti-carcinogens and antioxidant in the mammalian cells. It detoxifies a variety of carcinogens and chemical toxins in the gastrointestinal tract. This makes GSH a little-known but important nutrient in the diet. Glutathione is present in many food sources like fresh

fruits, vegetables, and meats. It is estimated that a daily human diet high in these food sources contain approximately 150 mg of GSH. At this time there is no dietary requirement of GSH in the US, but in Japan and some other countries GSH is nutritionally supplemented to provide an additional protection against xenobiotics in the diet. The additional GSH also provide an increased antioxidant level in the intestinal cells and in the blood.

GSH absorption in the GI tract with GSH supplemented diets is studied quit extensively. Although the results show an increase in GSH in the blood after dietary supplementation, there is still some debate on the extent of the absorption. Scientists in the US have found significant increases in blood plasma concentration of GSH after oral GSH supplementation, indicating that transepithelial transport of intact GSH occurs in the small intestine, and that there might exist a tripeptide transport channel in the intestinal membrane. It is also well known that the bile excretes GSH into the small intestine to assist in detoxification. This process may allow dietary or billary derived GSH to be utilized directly by various organs via circulating blood. Moreover, it has been shown that oral administration of GSH may be therapeutically useful in instances of oxidative stress.

Although GSH can be absorbed by the GI track relatively efficiently, the uptake of GSH by the cell is limited by the cross-membrane transport systems and ultimately by the activities of the various enzymes involved. Thus, other

possible route of GSH supplementation has been explored. It has been demonstrated that GSH monoethyl ester can be taken up by many types of cells as well as organelles, such as mitochondria, far more efficiently than GSH. Once absorbed, GSH is deesterified and GSH levels are increased inside the cell. This provide an efficient way to raise intracellular GSH concentration in cells which are deprived of GSH or exposed to an excessive oxidative stress.

GSH exhibits a pronounced circadian rhythm. GSH synthesizing enzymes are highly active after a meal; the highest levels of GSH are reached 6 to 7 hours post absorption. This enhancement of GSH synthesis depends on the nutritional composition of the meal and the activity of the enzymes involved.

Glutathione as an Antioxidant during Exercise

In order to understand the role of GSH in protection against exercise-induced oxidative injury, we need first to understand why exercise can cause an oxidative stress to the body. There are a variety of mechanisms which may contribute to tissue and cell damage during strenuous aerobic exercise and intense physical training. Each of them likely plays an important role in the etiology of cell injury, but oxygen derived free radicals seem to cross link most of the mechanisms involved. The following are the most relevant processes occurring during and after an acute bout of

strenuous exercise. (1) increased oxygen flux through the mitochondrial electron transport chain causing excessive leakage of one-electron reductants of oxygen, such as superoxide radicals; (2) direct mechanical damage to muscle protein and ligament stimulating activation of the lysosomal system and attracting polymorpho neutrophils at the site of damage, producing superoxide and hydrogen peroxide. This may contribute to the delayed injury and muscle soreness after exercise; (3) disruption of calcium homeostasis and activation of Ca^{2+} dependent proteases causing further tissue damage; (4) increased oxidation of intracellular thiols and glutathione leading to altered redox status and possible inactivation of certain enzymes; (5) certain types of exercise may cause redistribution of blood flow and local ischemic conditions resembling that of a heart ischemia-reperfusion induced injury. At present there is no clear consensus as to whether oxygen free radicals are the causes or results of the above-mentioned episodes, however, it is not difficult to perceive that a highly efficient antioxidant system is critical in protection against the oxidative processes and stopping the vicious cycles occurring during and after heavy exercise.

A major role of GSH in protecting tissues from the exercise-induced oxidative damage is to serve as a substrate for the Se-containing enzyme GSH peroxidase (GPX). It has been shown that under Se deficiency wherein GPX activity in muscle and liver tissues are reduced to minimum, increased lipid peroxidation occurs despite a normal level of GSH. The

biochemical reactions involved in the GSH antioxidant function are summarized in Figure 2. During moderate exercise, the formation of GSSG as a result of the removal of hydroperoxide can be reversed by the GSSG reductase reaction, at the expense of NADPH. Since most cells have relatively abundant sources of reducing power (NADPH), accumulation of GSSG does not occur and the GSH/GSSG ratio is maintained at a high level (estimated to be 50-100). These mechanisms make GSH a "rechargeable" antioxidant. However, the balance can be disrupted if (1) hydroperoxide production is excessive, such as during exhaustive exercise; (2) GR-catalyzed reaction is impaired due to a lack of flavin protein (essential for GR synthesis) or when GR is inhibited by GSSG or $NADP^+$. In addition to these enzymatically catalyzed functions, GSH is also an efficient scavenger to "quench" superoxide ($O_2\cdot^-$) and hydroxyl radical ($\cdot OH$), which can be formed during exercise. These processes are illustrated in the following equations.

$$O_2\cdot^- + 2GSH \rightarrow 2GS\cdot + H_2O_2$$

$$\cdot OH + GSH \rightarrow GS\cdot + H_2O$$

Finally, GSH is capable of scavenging singlet oxygen ($^1O_2$). Because of the significant role of GSH in cellular protection against reactive oxygen species (a term used to include oxygen radicals and other toxic oxygen intermediates not qualified to be called free radicals), numerous studies have been conducted to elucidate its response, regulation and

adaptive changes during acute and chronic exercise. For purposes of discussion, we will summarize these findings in the following categories: (1) an acute bout of exercise; (2) chronic training; and (3) GSH depletion and supplementation.

An Acute Bout Of Exercise

As early as 1985, GSH status (a term used to address the concentrations of GSH and GSSG, and the ratio of GSH/GSSG) of various body tissues was measured in rats following an acute bout of exhaustive exercise. It was found that GSSG was significantly increased after exercise in skeletal muscle, liver, and plasma. The investigators proposed that GSSG is an useful indicator of oxidative stress in the body. GSH was slightly decreased in the liver and muscle whereas it was increased in plasma. The total glutathione levels (GSH+GSSG) in the blood was consistently higher after exercise. They hypothesized that the increase of blood GSH was due to an increase in GSH efflux from the liver. It was further suggested that GSH export from the liver could be stimulated by vasopressin, a hormone released during physical exercise. These authors later showed that during an acute bout of exhaustive exercise in rats, running time correlated significantly ($r = -0.79$) with the GSH content in the liver and that depletion of hepatic GSH under these conditions was approximately 20%.

The findings in the above-mentioned study have been confirmed by a number of subsequent studies in principle,

although some discrepancies have also been generated. These controversies were primarily caused by the fact that different exercise intensities and durations were used by various investigators, causing the tissue responses to be different. It is now clear that, at least in skeletal muscle, GSH oxidation to GSSG is proportional to work load and there seems to be a threshold beyond which significant accumulation of GSSG in tissue can occur. This finding seems to be consistent with the scenario of GSH-GSSG recycle mechanism and the higher tissue GSSG reflects the inability of the cycle to cope with the excessive amount of hydroperoxide produced during exercise. Exercise duration seems to be an important factor in determining whether oxidative stress will take place. It was demonstrated in humans that maximal graded bicycle exercise lasting 10-15 min did little to alter blood GSH status, whereas sub maximal exercise at ~65% VO_2max caused a significant increase in blood GSSG and a decrease in GSH. These findings were confirmed by experiments in rats.

Consistent with the scenario that liver is exporting GSH during prolonged exercise, the authors laboratory has found that skeletal muscle content of GSH was increased along with a significant increase in GSSG, and that this increase in GSH was proportional to exercise intensity. It was hypothesized that exercising muscle takes up GSH from circulation to cope with an increased oxidative stress in muscle cells. To further support this notion, the authors showed that the ingredient amino acid of GSH, e.g. glutamate and cysteine, were also

significantly elevated in muscle. GSH and GSSG responses to exercise also seemed to differ in various muscle fiber type, with the slow-twitch oxidative (type 1) muscle being more resistant to oxidation than the fast-twitch oxidative (IIa) fibers. This fiber-specific pattern may be related to the higher intrinsic GSH concentration in the former (~3 mM) compared to the latter (1-2 mM). Recruitment pattern during exercise may also play a role as the fast-twitch glycolytic (IIb) does not show substantial alteration of GSH during prolonged exercise despite its low GSH level (<1 mM).

In order to investigate the possible mechanisms involved in the regulation of hepatic and blood GSH status, an experiment was carried out in the authors' laboratory wherein human subjects rode on a bicycle to exhaustion with or without carbohydrate supplementation. It was found that subjects who had repeated oral glucose ingestion had blunt blood GSH response, whereas the controls demonstrated elevated GSH during the two and a half hour ride. Glucose supplemented subjects also had higher blood antioxidant enzyme activity and showed signs of greater oxidative stress. It was hypothesized that carbohydrate supplementation probably altered the normal hormonal responses during prolonged exercise, such as an increased glucagon and decreased insulin levels, thereby disrupting hepatic export of GSH into the blood.

Although these studies provided evidence that interorgan GSH transport may occur during prolonged heavy exercise, two crucial pieces of information remain to be identified: (1)

there is an activation of membrane transport of GSH, e.g., an increased GGT activity or a decreased Km for GSH, or both, during acute exercise; and (2) the elevated GSH in muscle cells is indeed of hepatic origin. So far there is little data to substantiate these hypothesis. It also has to be pointed out that some investigators believe that muscles export GSH into the plasma, instead of importing GSH from the plasma, during exercise to assist coping with the oxidative stress in the body . This hypothesis was supported by the notion that muscle and liver both have low GGT activity, and by their findings that plasma GSH levels were sustained during prolonged exercise in hepectomised rats. Given the large volume of muscle mass, this hypothesis seems to be attractive. However, the mechanism to export GSH from muscle cells has not been postulated and the signals stimulating muscle GSH efflux remain to be identified in this scenario.

Chronic Training

The effect of chronic exercise training on tissue GSH status and regulation has not been studied extensively and data in this topic is rather limited. Although the already published research suggests that training may have a profound impact on GSH status in various individual tissues and total body GSH homeostasis, the conclusions drawn from these studies were not consistent.

Our previous studies show that highly trained human subjects, both in males and females, do not demonstrate

significant disturbance in blood GSH status during prolonged exercise. This is in contrast with the results with less trained or untrained individuals who had increased GSSG and decreased GSH/GSSG ratio. Similar results have been found in the rats wherein GSH levels in various major organs were better preserved in response to an acute bout of submaximal treadmill running after 10 weeks of training. It seems plausible that training has induced some mechanisms in the body which can maintain GSH homeostasis under acute oxidative stress. Because trained individuals have a higher rate of hepatic blood flow at a given work intensity compared to untrained individuals, a greater hepatic release of GSH is one of the most likely reason. An increase in GSH synthesis in the liver and a decrease of GSH consumption by other organs have also been postulated, but these explanations are largely speculative.

With regard to skeletal muscle GSH status, an early study indicates that GSH concentration is significantly increased as a result of training in the red but not in the white skeletal muscle in rats. Recently, it has been reported that in Beagle dogs GSH content increased substantial in several muscle types after a rigorous training program (55 weeks). Consistent with these findings was an elevation of muscle GGT activity, an indication of enhanced GSH transport, and an increase in GSH synthesizing enzymes in the exercised skeletal muscle.

The effect of training on muscle GSH status has recently been investigated in our laboratory. Using young, adult and

old rats, we found GSH response to training was muscle fiber specific. The deep portions of the vastus lateralis muscle (type IIa) showed a significant adaptations of GPX and SOD activities and had no change in GSH content or GSH/GSSG ratio. Soleus muscle, on the other hand, showed a significant decrease of GSH content and the GSH/GSSG ratio, associate with a significant reduction of GGT activity with training. The discrepancies between our data and the others are not readily explainable, however, it points out the possibility that muscles involved in high intensity chronic exercise may have a deficit of GSH and that supplementation of GSH or analogs may be advisable in physically active individuals.

Glutathione Depletion And Supplementation

Because of the important role of GSH in the total body antioxidant function, depletion of GSH would be expected to exacerbate oxidative stress during prolonged exercise. Several methods are currently available to deplete the body GSH pool, each involving a different mechanism. The most effective one which has the least side effect is to use buthionine sulfoximine (BSO), developed initially by Dr. Meister. BSO inhibits the rate-limiting enzyme of GSH synthesis, i.e. γ-glutamylcysteine synthetase thereby dramatically decreasing GSH output by the liver . In a recent study in our laboratory, mice were injected i.p. with BSO (2 mmol/kg body wt) for 12 days along with 20 mM BSO in their drinking water. These

treatment were found to deplete GSH content in liver, kidney, heart, and muscle to 23, 15, 10, and 7% of the normal values, respectively. The GSH-depleted mice and GSH adequate mice were then subjected to an acute bout of swimming to exhaustion. GSH content in the GSH adequate mice was decreased as a function of time in all tissues studied except quadriceps muscle which showed a slight increase. In the GSH depleted mice, exercise further lowered GSH levels in all tissues, accompanied with a higher MDA level than the GSH adequate mice. Furthermore, GPX activity was significantly elevated in the skeletal muscle of the GSH-depleted mice compared to the controls, whereas GST and GGT activity were significantly decreased with glutathione depletion. These alterations show that GSH-depletion can exacerbate the vulnerability of exercising muscle to reactive oxidants, while adaptations occur in related antioxidant system to compensate the loss of GSH.

Since exercise decreases the reduced thiol pool in the body, including GSH, it might be beneficial to supplement thiols during acute or chronic exercise. Indeed, several compounds have been widely used in protecting ischemia-reperfusion caused myocardial oxidative damage and hyperoxia mediated lung injury, among these are N-acetylcysteine (NAC), GSH acetyl monoester and free GSH. Acute GSH injection i.p. at the dosages of 250-1000 mg/kg body wt has been reported to increase endurance time by 120-140% in swimming mice, although the level of oxidative stress was not determined in the study. NAC supplemented orally to human subjects for two days (total

dose 2.4 g) was found to decrease GSSG levels provoked by an acute maximal exercise test. Regardless of the mechanisms in the mentioned studies, supplementation of exogenous thiol source may have potential merit in reducing oxidative stress during exercise.

Conclusions

Although the role of GSH in the biological systems has been studied extensively, its significance in relation with exercise physiology and sport medicine has not been fully appreciated until recently. From the available evidence accumulated in the past decade, it is now known that GSH is an important antioxidant protecting the cell against reactive oxygen species produced during aerobic exercise. The effectiveness of protection depends on both the concentration of tissue GSH and the capacity of the GSH-GSSG redox cycle under oxidative challenge. When there is an excessive production of hydroperoxide or when GSH content is deprived in the cell, GSH/GSSG ratio will decrease markedly. This is indicative of an oxidative stress often accompanied with increased lipid peroxidation and disturbance of antioxidant enzyme systems.

GSH is subject to constant turnover in the body. The liver exports GSH into the plasma whereas other organs and tissues take up GSH from the circulation. This interorgan transport facilitates the local needs of GSH to cope with a

potential oxidative stress. There is evidence that skeletal muscle and heart increases its utilization of GSH during acute and chronic exercise, and that GSH efflux into plasma from the liver is enhanced. These regulatory mechanisms, however, can be interrupted by physiological, pharmacological, and nutritional interventions. Therefore, supplementation of GSH at appropriate levels and with proper means seems advisable in physically active individuals.

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Figures Legends

Figure 1. The γ-Glutamyl-Cycle. AA, amino acids; GGT, γ-glutamyltranspeptidase; GGC, γ-glutamylcyclotransferase; 5-OP, oxoprolinase; GCS,γ-glutamylcysteine synthetase; GS, glutathione synthetase; GSHT, glutathione transporter.

Figure 2. Antioxidant function of glutathione. SOD, superoxide dismutase; GPX, glutathione peroxidase; GR, glutathione reductase; ICDH, isocitrate dehydrogenase; G6PDH, glucose-6-phosphate dehydrogenase; GST, glutathione S-transferase; GS·, glutathione thiyl radical; X, compounds that react with GSH to form conjugates.

Figure 3. Postulated outline of interorgan transport of glutathione. GS·, glutathione thiyl radical; ROOH, hydrogen peroxide; ROH, alcohol; GGT γ-glutamyltranspeptidase.