The Effects of Glutathione Depletion on the Immune System

In the immune system, complex networks of molecules are responsible for eliciting chemical signals that activate specific cells and tissues in order to protect the body from foreign pathogens that can cause illness and disease. One such molecule that plays an important role in this process is glutathione. Glutathione is an antioxidant that is present in high levels in every tissue and is important for metabolism as well as for the control and elimination of potentially harmful free radicals within the body (Perricone et al. 2009). During normal metabolic processes in the body, free radicals are formed as a natural by-product and glutathione eliminates them. Along with the detoxification and removal of radical species, glutathione is also involved with gene expression as well as cell production and death (Franco et al. 2007). Therefore, any fluctuation in the levels of glutathione in the body can adversely affect many of these processes.

Glutathione is normally found in its reduced and active form, GSH, and is found in particularly high levels in the liver (Perricone et al. 2009). GSH is a tripeptide composed of cysteine, glutamic acid, and glycine (Perricone et al. 2009). The reactive group on the molecule is the cysteine because of the sulfhydryl (-SH) group (Dilger and Baker 2007). In particular immunological diseases, supplementing with a cysteine precursor molecule has been shown to enhance the immune response of the body, even if the immune response has previously been more or less disabled. Many studies have shown that glutathione plays a crucial role in the function of the immune system and the severity of many diseases, including cystic fibrosis, influenza and AIDS.
Therefore, it is becoming common for people to supplement their diets with glutathione precursors, in order to increase the intracellular concentrations of this molecule in the body in order to gain its many disease-fighting and antioxidant benefits.

Although free radicals are a natural part of certain processes within the body, when their levels are not controlled and become too high, an organism will undergo oxidative stress. Often, poor nutrition will cause low intracellular glutathione, a condition that is exacerbated by oxidative stress (Ghezzi 2011). Oxidative stress is caused by an excess of reactive oxygen species (ROS), which are free radicals with unpaired electrons (Biswas and Rahman 2009). As a result of these unpaired electrons, these molecular species remain highly reactive and unstable and are able to cause many unwanted chemical reactions within the body, often leading to tissue damage and illness. In fact, many cells of the immune system, such as neutrophils, eosinophils, and macrophages, produce free radicals when they are activated (Biswas and Rahman 2009). During inflammation, neutrophils release ROS because they are a defensive mechanism of the innate immune system and are able to effectively destroy bacteria and other invading pathogens (Ghezzi 2011). Since this is a natural part of immune function, it is important that the body have mechanisms in place in order to diminish the number of ROS present. When these highly reactive, oxygen-containing molecules are produced in excess and for prolonged periods of time and when this becomes a chronic condition, it affects the “antioxidant defence system” of which glutathione is a major molecule (Perricone et al. 2009). Glutathione, in its reduced form (GSH), is able to act as a very good antioxidant which can donate electrons to free radicals. Its ability to do this comes from the free sulfhydryl group (-SH) on its molecular structure (Biwas and Rahman 2009).

However, when levels of glutathione in the body become depleted, ROS are not sufficiently removed as there is not enough active GSH to do so. The optimal level for intracellular glutathione is 20-30 nmol/mg protein, and this measurement is associated with a greater number of CD4 T-cells (Dröge and Breitkreutz 2000). However, if this level drops to just 10-20 nmol/mg, the concentration of CD4 T-cells can decrease by 30% (Dröge and Breitkreutz 2000). It appears, however, that this depletion is reversible by supplemental therapy with N-acetyl-cysteine (Dröge and Breitkreutz 2000). Unless the amount of GSH in the body is
increased, such as with supplemental therapy, there are many other disruptions that occur in the body as glutathione is a major factor in the function of numerous cells and pathways of the immune system.

**Glutathione plays a key role in both innate and adaptive immunity.** When faced with a foreign pathogen, the innate immune system responds by inducing an inflammatory response. This causes phagocytes to release ROS in order to directly attack the antigen and cytokines to attract other immune system cells (Ghezzi 2011). GSH also boosts innate immunity by aiding in the production of T-lymphocytes and dendritic cell function and affecting the ability of neutrophils to destroy foreign pathogens by phagocytosis (Ghezzi 2011). Glutathione is needed for dendritic cells to be able to produce interferon, which starts the cascade of attracting other cells and destroying mycobacteria in particular (Ghezzi 2011). All of these cells of the innate immune system are our bodies’ first lines of defense, and a deficiency in glutathione might be suspected if this initial response is unable to control an infection. Fortunately, the immune system has many other mechanisms for protecting us from invading pathogens. Generally, glutathione depletion normally inhibits the cell-mediated response and causes the humoral response to become activated (Peterson et al. 1998). When glutathione levels reach a very low threshold, the complement system may also be activated (Perricone et al. 2009). This would help protect the body from many pathogens, especially bacterial infections that are prevalent in people with diseases associated with glutathione deficiency.

The adaptive immune response involves cells that are able to recognize and respond to pathogens and remember them in order to mount a swifter defense in case of future infection. As an important component of the adaptive immune system, glutathione is essential in the process of antigen-presenting cells ingesting and breaking down the pathogen in order to display a piece of foreign peptide on their surface. Glutathione is essential in the process of breaking disulfide bonds in order to digest the pathogen into fragments that can then bind with the MHC and be displayed (Ghezzi 2011). When antigen-presenting cells such as macrophages and dendritic cells present the peptide and MHC on their surface, T-cells that are specific to that antigen recognize this and are then activated (Ghezzi 2011). Studies have shown not only that antigen-presenting cells can be inhibited in
their ability to present antigen to T-cells, but that low GSH levels inhibit cytokine production by Type 1 T helper cells and promote Type 2 T helper cells instead (Peterson et al. 1998). Other processes that depend on significant levels of glutathione for proper function include T-cell proliferation, specifically CD8 T-cells, and the actions of cytotoxic T-cells and natural killer cells (Dröge and Breitkreutz 2000). Depleted glutathione levels lead to lymphocytes, CD8 T-cells, and cytotoxic T-cells decreasing in activity, while having the opposite effect on CD4 T-cells (Perricone et al. 2009). The absence or non-functioning of T-cells is probably one of the most severe effects of glutathione depletion due to the variety of effective purposes they have in the immune system.

The immunological importance of GSH is demonstrated by a number of diseases that are associated with glutathione depletion. Patients with certain diseases are also often prone to secondary infections as a result of low GSH and the effects this has on the immune system. Depletion of GSH is associated with rheumatoid arthritis, Werner syndrome, muscular dystrophy, and Crohn’s disease (Perricone et al. 2009). Glutathione seems to prevent many of the detrimental effects of such conditions as tuberculosis, HIV, and cancers. In patients suffering from tuberculosis, glutathione levels are often so low that macrophage activity is inhibited, and they contract more bacterial infections as a result of being unable to kill the pathogens (Ghezzi 2011). Patients with HIV lack an abundant supply of cysteine, and they are also less able to synthesize it from its precursor methionine (Ghezzi 2011). Therefore, their intracellular glutathione levels are very low, and many of their immunological pathways are obstructed. It is possible that the GSH inhibits the replication of the human immunodeficiency virus, so being deficient in this GSH molecule increases the morbidity and mortality of the AIDS disease (Ghezzi 2011).

Specific studies have also recently shown the importance of glutathione in cancer patients. Ifosfamide is a drug used in chemotherapy that causes severe glutathione depletion in the body (Kuppner et al. 2008). This depletion, in turn, affects the ability of the patient’s natural killer cells to kill tumours or other virus-infected cells, although natural killer cells normally tend to have an extremely high level of glutathione, so a small depletion will not significantly affect their behaviour (Kuppner et al. 2008). Studies demonstrated how ifosfamide inhibits the ability of dendritic cells to activate T-cells and promote production of interleukins, but this deficiency is
completely reversible when glutathione concentrations in the dendritic cells are increased again (Kuppner et al. 2008).

The importance of glutathione is perhaps best shown by examining respiratory structures. The lungs are an area that are subjected to great oxidative stress as they are exposed to free radicals both from within the body itself as well as from exposure through inhalation of environmental toxins (Biswa and Rahman 2009). Glutathione depletion in the lungs is associated with respiratory diseases and inflammatory conditions such as chronic obstructive pulmonary disease, acute respiratory distress syndrome, pulmonary fibrosis, cystic fibrosis, and in HIV (Biswa and Rahman 2009). The lungs contain a secretion called the epithelial lining fluid, which provides protection against environmental toxins that may be inhaled, as well as from ROS released from neutrophil phagocytic activity in the lungs (Franco et al. 2007). When this fluid is tested, the glutathione levels are found to be very low in disorders such as pulmonary fibrosis and acute respiratory distress syndrome (Franco et al. 2007). The levels of glutathione are decreased in lung tissues as a result of reaction with toxins such as cigarette smoke and air pollution, creating an inflammatory response (Franco et al. 2007). Such inflammation can be the cause of severe lung damage. As many of these conditions have a fairly low treatment success rate, the importance of having a defensive system in place to avoid such infections is demonstrated. Glutathione is the building block upon which most of these preventative measures are built, and a deficiency in this molecule in the respiratory structures can have severe and fatal effects.

Now that the beneficial effects of glutathione have become well-known, many people are beginning to look for ways to increase the amount of GSH present in their body. This is often done for many other essential molecules, and levels of particular amino acids are often increased through ingestion of dietary supplements (Dilger and Baker 2007). However, it is not possible simply to administer glutathione orally itself in a dietary supplement as it is poorly absorbed and is completely broken down in the gastrointestinal tract. It is also incapable of crossing the blood-brain barrier in its full form and therefore would first have to be broken down into its individual amino acids, cross into cells, and then be re-synthesized (Franco et al. 2007). Thus, it is much more effective to simply
give the precursor molecules themselves. Although three components (cysteine, glutamate, and glycine) are needed to make glutathione, cysteine is the molecule that is the limiting factor and is normally present in the body in much smaller amounts (Franco et al. 2007). Therefore, in order to give the body the molecules that it needs to synthesize glutathione, it is important to supplement with extra cysteine. 

Unfortunately, cysteine is a very unstable molecule, due to the fact that it is such a good reducing agent. Even when it is oxidized, it remains very insoluble, and these factors make it unfeasible to take cysteine itself as an oral supplement (Dilger and Baker 2007). N-acetyl-cysteine (NAC) is a precursor molecule of cysteine that is completely metabolized to cysteine when taken orally (Dilger and Baker 2007). Studies have shown that HIV patients treated with NAC experience an increase in immune function, and in particular, all function is restored to natural killer cells (Dröge and Breitkreutz 2000). Although treating with NAC will increase T-cell numbers if they are low, their numbers will not necessarily increase if they were within a normal range to begin with (Dröge and Breitkreutz 2000). Therefore, this treatment actually seems best suited for immunocompromised individuals, rather than as a preventative measure. Along with NAC, NSAIDS and alpha-lipoic acid are also capable of increasing GSH levels (Perricone et al. 2009). There are other variations of cysteine compounds that can be stabilized for oral ingestion and in this manner it may become much more common to take a dietary supplement in order to increase intracellular GSH and help the immune system combat the effects of many diseases.

Glutathione has been shown to be an essential component of the immune system at the molecular level. A deficiency in this molecule has been associated with compromised immune function leading to many disorders such as respiratory diseases, cancers, and AIDS. In some cases, the low levels or absence of glutathione may somewhat directly cause illness especially by affecting the function of immune cells, while in other cases the disease itself may cause the deficiency in GSH and thus exacerbate the illness. Therefore it is important to ensure that the body has a sufficient level of glutathione precursor molecules present in order to synthesize this vital molecule whenever and wherever it is required. This can be done with nutritional supplementation of precursor molecules, especially cysteine, which many studies have shown to be a safe and effective measure. This is in no way an invasive practice as by supplementing the body with
glutathione we are simply providing the immune system with the basic building blocks that it needs to function optimally and are enabling the body to heal itself naturally, from within.

The use of "we" in the final paragraph is very engaging, but it only works because it is not used elsewhere in the paper.
References


