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Competition for glutathione precursors between the immune system and the skeletal muscle: pathogenesis of chronic fatigue syndrome

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Summary The chronic fatigue syndrome (CFS) is typically associated or follows a recognized or presumed infection.

Abnormalities of both humoral and cellular immunity have been demonstrated in a substantial proportion of patients with CFS. The most consistent findings are of impaired lymphocyte responses to mitogen. As an antioxidant, glutathione (GSH) is essential for allowing the lymphocyte to express its full potential without being hampered by oxiradical accumulation. Hence, protracted challenge of the immunocytes may lead to cellular GSH depletion. Because GSH is also essential to aerobic muscular contraction, an undesirable competition for GSH precursors between the immune and muscular systems may develop.

It is conceivable that the priority of the immune system for the survival of the host has drawn to this vital area the ever-diminishing GSH precursors, thus depriving the skeletal muscle of adequate GSH precursors to sustain a normal aerobic metabolism resulting in fatigue and eventually myalgia. © 1999 Harcourt Publishers Ltd

Mammalian cells have evolved numerous mechanisms to prevent or treat injurious events that can result from normal oxidative byproducts of cellular metabolism. The "glutathione (GSH) antioxidant system" is foremost among these endogenous protective systems because GSH participates directly in the destruction of reactive oxygen compounds and maintains in reduced active form vitamins C and E, which also exert an antioxidant effect (1). In addition, GSH detoxifies foreign compounds (2). For these reasons, cellular GSH plays a central role in body defense against infection, free radicals and carcinogens. It is not surprising that the liver, which is the major organ involved in the detoxification and elimination of toxic materials, has the greatest concentration of GSH (3).

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HOW GSH IS FORMED: THE CELL'S OWN ANTIOXIDANT

The sulfhydryl (thiol) group (SH) of cysteine is responsible for the chemical properties of the whole GSH molecule (L-γ-glutamyl-L-cysteinylglycine). As systemic availability of oral GSH is negligible in man (4) and because there is no evidence for transport of GSH into cells (2,3), GSH has to be synthesized intracellularly. Though the inflow of cysteine, glutamate, and glycine (components of GSH) may prove somewhat limiting under selected circumstances, numerous observations have shown that cysteine tends to be the rate-limiting event in GSH synthesis.

A number of conditions may coexist, each of which places on the body a demand for GSH. Such conditions include:

- production of endogenous oxiradicals during immune activity and strenuous muscular exercise (oxidative stress);

- detoxification of foreign pollutants;
- protection against radiation.

GSH AND THE IMMUNE SYSTEM

It has been demonstrated that the ability of lymphocytes to offset oxidative damage (during their oxygen-requiring clonal expansion and following that expansion in the production of antibodies) is measured by determining the capacity of these cells to regenerate intracellular stores of GSH, therefore allowing them to respond more fully to the antigenic stimulus (5,6). More evidence for the involvement of GSH in the modulation of immune function comes from studies related to HIV infection. Staal et al. showed that HIV-infected individuals have lower GSH concentrations in their blood lymphocytes (7). Moreover, a recent study indicates that the more GSH the patients carry in their CD4 helper T-cells – the cells primarily targeted by the HIV virus – the longer these patients are likely to survive (8).

GSH AND STRENOUS MUSCULAR ACTIVITY

Free radicals are formed in the course of energy production. Thus, it is not surprising that oxidative stress can occur during exercise in healthy individuals (9,10). Furthermore, while the causes of muscular fatigue are multifactorial, the evidence for oxidative stress playing a role in such fatigue is based on:

1. the demonstration that skeletal muscle can generate oxygen free radicals at rest (11) and during stimulation (12);
2. this free radical production increases with muscular fatigue (11,13);
3. augmenting antioxidant defenses with N-acetylcysteine diminishes fatigue (14).

Interest has focused on the glutathione system because of its pivotal antioxidant role. Supplementation with N-acetylcysteine, a pro-glutathione agent, slows the onset of fatigue in healthy humans and spares exercise-induced glutathione oxidation (14), while glutathione deficient rats have remarkedly reduced muscular endurance (15).

Hence it appears that the aerobic muscular activity which generate oxygen-derived free radicals requires the antioxidant property of GSH in as much as the lymphocyte needs GSH to fully express its immune response.

In our current polluted environment, trace amounts of GSH precursors found in an otherwise adequate diet may not be sufficient to allow for full GSH replenishment because GSH is also a major detoxifying agent. In the development of this function, GSH binds through the transferases to the xenobiotics and leaves the body with them.

This results in highly undesirable competition for GSH precursors developing among different systems. For example: the chronic fatigue syndrome often follows a recognized or presumed infection (16). In fact abnormalities of both humoral and cellular immunity have been demonstrated in a substantial proportion of patients with chronic fatigue (17). It is conceivable that the priority of the immune system for the survival of the host has drawn to this vital area the ever-diminishing GSH precursors, thus, depriving the skeletal muscle of enough GSH precursors to sustain a normal aerobic metabolism hence fatigue and eventually myalgia . Some evidence for this assumption comes from observing what happens when skeletal muscles are performing beyond their normal activity. Professional athletes following extreme prolonged exercise are often susceptible to infections (18) and the effectiveness of their immune system can be impaired (19,20).

The increased GSH demand of the skeletal muscle imposed by excessive exercises deprives the immune cells of the capacity to replenish their cellular GSH, an essential prerequisite of an optimal immune status. Competition for GSH precursors between these two demanding systems can thus create a state of imbalance leading to chronic muscular fatigue in one instance or short term immune deficiency following excessive muscular stress. If one looks at the animal kingdom for natural wisdom, the word moderation comes to mind, a concept at odds with the current compulsion to increase performance with a view to the next Olympic Games.

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