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Glutathione and Oxidative Stress - Part II
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Antioxidants are the body's premier resource for protection against free radicals and other oxidative stressors to which it invariably becomes exposed. Glutathione is a central constituent of the antioxidant system. Nowhere is its presence more important than in the mitochondria which is the "energy producing part of the cell."

Source of Free Radicals in the Body

Originating within the mitochondria of aerobic cells is a steady supply of oxygen free radicals, unavoidably generated from the processes that utilize oxygen to make adenosine triphospate (ATP), the energy storage molecule in the body. The complex system of enzyme pathways by which the mitochondria use oxygen to produce ATP is called oxidative phosphorylation. As oxidative phosphorylation takes place in the mitochondria, single electrons escape, leaking out of the oxidative phosphorylation complex to react with oxygen and generate oxygen free radicals.

This oxygen radical leakage both wastes energy and poses a potential toxic risk to the body. An estimated 2-5 percent of the electrons that pass through the oxidative phosphorylation system are converted into superoxide and other oxygen radicals. Since oxidative phosphorylation processes at least 95 percent of all the oxygen used by the body, this production of oxygen free radicals is significant

Free Radicals Produce Oxidative Stress

These free radicals creates oxidative stress in human tissues. Superoxide, peroxide, hydroxyl radical, and other free radicals derived from oxygen are highly reactive and therefore threatening to:

1. DNA
2. RNA
3. Enzymes
4. Other proteins
5. Phospholipids responsible for cell membrane integrity

The aerobic cell is continually challenged to neutralize these oxygen-generated-free-radical time bombs before they can initiate free radical reactions that could cause the cell's disintegration. Healthy cells oppose free radicals through the use of antioxidants.

Oxidative Challenge Inescapable

With our reliance on oxygen, humans cannot escape this ongoing oxidative challenge. It may be the ultimate challenge of being alive. An ever more impressive body of evidence indicates that the cumulative damaging effects of oxygen radicals and other oxidants are principal contributors to:

degenerative diseases
progressive loss of organ functions that we recognize as aging
In the face of this oxidative burden, the formidable reducing power of the GSH/GSSG couple is a profound asset for the aerobic organism. Perhaps equally as significant for lifespan is that Glutathione also helps protect against exogenous (external to the body) oxidative insults, which are (or ought to be) potentially more controllable.

Glutathione is Depleted by Exogenous Stressors

Oxidative stress originating from outside the body is a feature of life in the modern world. First, the tens of thousands of confirmed toxic substances in our external environment are invariably sources of free radicals or related oxidants. Add to this substantial burden the many negative aspects of the modern, Westernized lifestyle and a picture emerges of the human organism burdened by chronic disease and threatened with a shorter lifespan than might otherwise be possible. The most important of the exogenous oxidative stressors are:

Cigarette smoke contains thousands of different chemical species, and a single puff of cigarette smoke contains trillions of free radicals. Cigarette smoke literally burns away the antioxidant vitamins C and E, as well as other nutrients. The cigarette tars are long-lived free radical generators and potent carcinogens.
Many pharmaceutical products are oxidants capable of depleting GSH from the liver, kidneys, heart, and other tissues. The popular over-the-counter drug acetaminophen is a potent oxidant. It depletes Glutathione from the cells of the liver, and by so doing renders the liver more vulnerable to toxic damage. The anticancer drug Adriamycin has been used in animal experiments as a "model" for free radical-induced tissue damage; its foremost threat is to the heart.

The halogenated hydrocarbons (halocarbons) are potent oxidants. Halocarbons are ubiquitous, being used in the plastics industry, as industrial and dry cleaning solvents, as pesticides and herbicides, and as refrigerants. The chlorofluorocarbons that currently threaten the ozone layer are one type of halocarbon. Halocarbons currently contaminate much of the ground water of the United States, and can now be detected in adipose tissue

of humans from around the globe. They are potent free radical generators in the liver and they effectively deplete liver Glutathione.

Strenuous aerobic exercise can deplete antioxidants from the skeletal muscles, and sometimes also from the other organs. Exercise increases the body's oxidative burden by calling on the tissues to generate more energy. Making more ATP requires using more oxygen, and this in turn results in greater production of oxygen free radicals. Studies in humans and animals indicate Glutathione is depleted by exercise, and that for the habitual exerciser supplementation with Glutathione precursors may be a prudent policy.
Some of the other exogenous factors known to deplete tissue Glutathione include:

Dietary deficiency of methionine, an essential amino acid and Glutathione precursor. The liver uses 70 percent of the total dietary intake. As an essential amino acid methionine cannot be synthesized in the body, but has to be obtained through diet. Food sources of methionine include beans, garlic, lentils, onions, soybeans and seeds. Other excellent food sources are beef, chicken, fish, pork, soybeans, eggs, cottage cheese, liver, sardines, yogurt, pumpkin seeds, and sesame seeds. The range of human need for methionine is estimated at between 800 and 3,000 milligrams per day.

- Ionizing radiation, whether as X-rays or ultraviolet from sunlight.
- Tissue injury, as from burns, ischemia and reperfusion, surgery, septic shock, or trauma.
- Iron overload, as in hemochromatosis and transfusional iron excess. Surgery can cause iron release from damaged tissue, and unbound iron catalyzes free radical generation via several putative mechanisms.
- Bacterial or viral infections, including HIV.
- Alcohol intake is toxic through a number of differing pathways, some of which are free radical/oxidative in character.

The following negative lifestyle factors converge with environmental stressors to attack the body through related oxidative pathways.

1. smoking
2. alcohol consumption
3. legal or illegal drug use
4. emotional stress and
5. "life in the fast lane"

Sustained oxidative stress from a heavy cumulative burden of oxidants may deplete the body's Glutathione and other antioxidant reserves to a point of "distress," beyond which the individual's antioxidant defenses are overwhelmed. The negative antioxidant balance, featuring an excess of free radical challenge over antioxidant defense capabilities, begins to compromise life functions on a successively wider scale.

The consequences of sustained Glutathione depletion are grim. As cellular Glutathione is depleted :

1. Individual cells die in those areas most affected
2. Then zones of tissue damage begin to appear
3. Those tissues with the highest content of polyunsaturated lipids and/or the most meager antioxidant defenses are generally the most vulnerable.
4. Localized free-radical damage spreads across the tissue in an ever-widening, self-propagating wave.
5. If this spreading wave of tissue degeneration is to be halted, the antioxidant defenses must be augmented. Repletion of Glutathione appears to be central to meeting the challenge of sustained (or acute) oxidative stress.

Increasing Glutathione Levels in the Body

If glutathione is manufactured within the body, what can we do to maintain or increase Glutathione levels? Some pharmaceutical drugs can do it, and so can some natural sources. Eating glutathione cannot. There are many ideas about how to raise Glutathione levels in the body but only a few actually work --- and some of them have side effects.

The following "co-factors" are important to the production and/or function of Glutathione:

- Vitamin B-1
- Vitamin B-2
- Vitamin B-6
- Vitamin B-12
- Vitamin C
- Vitamin E
- Folic Acid
- Selenium
- Magnesium
- Vanadium
- Zinc

Many of these are antioxidants in their own right. The key ingredient to the increasing of Glutathione levels in the body is a nutritional source of cysteine in a form which can be used by the body. It must be in a form that can survive the trip from our mouths to our cells. Unfortunately, merely eating either Glutathione or the free amino acid cysteine does not give the cell what it needs to manufacture Glutathione.

N-acetyl-cysteine (NAC) is commonly used in critical care medicine, toxicology, and pulmonary medicine. It has been the most researched of the GSH-promoting modalities, and newer clinical applications are being developed all the time.

Many natural products exert some of their positive effects by supporting or directly raising Glutathione levels. Undenatured whey proteins are an exciting development. A

whey protein isolate, Immunocal, has recently been patented to augment Glutathione levels and enhance immune function.

Recommendation

Supplements are medicines and should not be taken carelessly. Before beginning any serious program of supplements, you should discuss your plans with your healthcare provider. If he/she is unfamiliar with supplements and their benefits and cautions, consult a healthcare provider who is. Once you have your healthcare providers advice, being the following:

1. Vitamin C -- at least 1000 mg a day
2. CoQ10 -- at least 100 mg a day and up to 400 mg a day if you are diabetic or have heart disease.
3. Alpha Lipoic Acid (in the R-form) -- at least 200 mg a day and up to 400-600 mg a day if you have a diabetic neuropathy.
4. Vitamin E - 400 IU daily
5. Glutathione -- Add at least 1000 mg of NAC to your diet, and at least one scoop of a high quality whey to your diet each day and 1000 mg of Methionine daily.

At present Glutathione supplements do not appear to be effective, but taking the precursors of Glutathione increases your body's production of Glutathione.
Next week, we will discuss whey. What is it and how does it help you?

Remember, it is your life and it is your health.