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Nutrition *Invited Editorial*

Amplifying the human body's innate "rapid response" systems to inflammation and oxidative stress

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Inflammation is a key contributor to host defense against infection. A prime example is the rapid neutrophil response to bacterial infection during which neutrophils generate reactive oxygen species to kill ingested bacteria. While this powerful mechanism is vital to maintaining health, it can go awry and damage organs and tissues in the absence of infection. Ideally, the human body should have a remarkable ability to rapidly respond to and combat both inflammation and oxidative stress when it develops with or without the presence of infection. Inadvertent inflammation and oxidative stress may originate from a wide variety of metabolic, chemical, environmental, physical, disease, drug, and even emotional factors and at times when there is no infection. Unfortunately, the intrinsic ability of the body to rapidly respond to such challenges is limited in an increasingly significant number of individuals by certain genetic factors, metabolic dysfunction, dietary limitation, and lifestyle.

An important goal, therefore, is to restore optimal or near optimal functionality to critical mechanisms that counteract potentially detrimental inflammation and oxidative stress that occurs in the absence of infection. This concept forms an often overlooked foundational starting point as part of every rational program seeking to improve nutrition-based health and well-being.

Even in the most modern advanced countries, the potential to achieve optimal health by improving the responses to inflammation and oxidative stress is either limited or virtually absent. Moreover, regrettably, nutritional programs are based more on "the next big thing" rather than establishing a strong foundation based on organically or biodynamically grown and minimally processed nutrient-dense whole foods coupled with targeted supplementation. This type of supplementation is likely needed in certain individuals. Appropriately and rationally based supplementation that focuses on three limited or missing elements that when provided in unison and on a consistent basis could support and amplify the body's rapid response to inflammation and oxidative stress deserves consideration.

The critical importance of the multiple body "systems" that must function both as separate systems and in harmony with all the other body systems to maintain a fully functional organism is well recognized. The entire human biological system includes cardiovascular, respiratory, endocrine, reproductive, digestive, immune, and nervous systems. No system is one dimensional and no system functions independently. Absent the coordination of these systems, we cease to be able to continue living. Moreover, of course, there is no such thing as the "next big system." That is why recognition, restoration, and maintenance of the "rapid response system" that provides the ability

to deal effectively with both inflammation and oxidative stress caused by a myriad of environmental, physiological, pathological, and emotional challenges emerges as a vitally important consideration. Further, it is also why approaches relying on a dietary supplement program that relies on single compounds in a never-ending variety are essentially limited at best as the needed way to provide sufficient protection against excessive inflammation and oxidative stress [Figure 1].

The purpose of this brief opinion is to identify critical elements that can respond rapidly to an acute inflammatory and oxidative stress response and to suggest how these key elements can be supplemented in unison to improve the efficacy of any one pathway individually. This review will focus on three nutritional elements – ascorbate, L-ergothioneine, and glutathione.

First, the ability to produce ascorbate (Vitamin C) [Figure 2] in the human liver in response to oxidative stress and inflammation is absent in humans due to a genetic anomaly that makes l-gulonolactone oxidase unavailable to transform glucose in the liver. This enzyme deficiency is a suspiciously problematic genetic characteristic of humans since this enzyme deficiency is common only in a very small number of animals (monkeys, apes, fruit bats, guinea pigs, and a few varieties of birds). At present, approaches to optimize the availability of ascorbate in humans, including the recommended level of daily intake set forth by the U.S. Government, focus only on providing sufficient Vitamin C, with an added safety factor, to protect against the development of scurvy. Approaches that profess to provide benefit from higher levels of ingested ascorbic acid are questioned with respect to safety and efficacy for the claimed benefits. This impression is based in part on the intermittent requirement for ascorbate by the body and in part because the acid form of ascorbate must be neutralized by a variety of compounds, including minerals, before efficient use by the body.[1-23]

Next, the human body, by design, has a unique gene (SLC22A4) that is specifically responsible for the utilization of a unique sulfur compound called L-ergothioneine [Figure 3]. This gene codes for an ergothioneine transporter, OCTN1, which is produced in response to an increase in oxidative stress and inflammation that exceeds the body's ability to respond with available antioxidant resources, including vitamins and plant-derived polyphenols. Ergothioneine is a unique molecule, first discovered in 1909, that is produced in the soil by microorganisms, including fungi and bacteria, as part of nature's natural recycling of deteriorated plant and animal matter. Neither plants nor animals can produce it. Ergothioneine can only be passed on by way of what is produced by these microorganisms and taken up by plants that pass it on directly to animals or humans. Accordingly, plants then pass it on to animals and, in turn, then to humans. As a result, and because of the nature of the typical American diet, the amount of ergothioneine consumed is highly variable and either extremely limited or absent altogether. Ergothioneine has some unique characteristics. For example, it acts as an independent antioxidant, but may also amplify and extend the activity of other antioxidants, including Vitamin C and Vitamin E. The half-life of ergothioneine is 30 days, compared to only minutes or seconds of other antioxidants. Notably, ergothioneine has been suggested to be an essential vitamin by leading scientific authorities, including Dr. Bruce Ames and Dr. Solomon Snyder. Ergothioneine is concentrated in humans in the brain, eyes, kidneys, skin, and the reproductive organs – ostensibly sites that are particularly prone to damage from inflammation and oxidative stress. Further, the relatively little amount of ergothioneine that is present in younger individuals diminishes with age, a phenomenon that has prompted some experts in the scientific community to suggest a role for ergothioneine in the aging process.[24-30]

Finally, glutathione is known as the body's "master antioxidant" and a key component of the glutathione redox cycle. Like ergothioneine, glutathione is a sulfur-containing molecule present in every cell of the body. Human cells are designed to maintain glutathione homeostasis as the third part of the body's rapid response to oxidative stress. Glutathione is produced by a series of enzymatic actions that initially link the amino acids cysteine and glutamate and then ultimately to the amino acid glycine. This process requires not only adequate levels of the three amino acids but also a fully functioning suite of enzymes at every stage of the process. Most importantly, glutathione in its finished form cannot be taken up by the cells of the body due to an unfavorable concentration gradient. Rather, cells rely on a constant internal supply of the immediate precursor, gamma-glutamylcysteine (GGC) [Figure 4]. GGC is then linked to glycine in a continuously operating system designed to maintain glutathione homeostasis in response to oxidative stress and inflammation. Unfortunately, for a variety of reasons, including most notably aging, inadequate levels of glutathione develop, most likely because of deficiencies in the required enzymes and dietary limitations. Consequently, the homeostatic glutathione maintenance system may not be fully functional, leaving the body at elevated risk of a variety of health challenges directly related to unresolved oxidative stress and inflammation. GGC is present in a small number of foods, such as undenatured (heat processed) whey, but is impossible to obtain from the diet in a clinically useful amount. In addition, consuming pre-formed glutathione is an inefficient way to raise cellular levels of glutathione since published clinical studies demonstrate that it may take weeks or months to impact cellular levels when elevated levels are most needed acutely.[31-43]

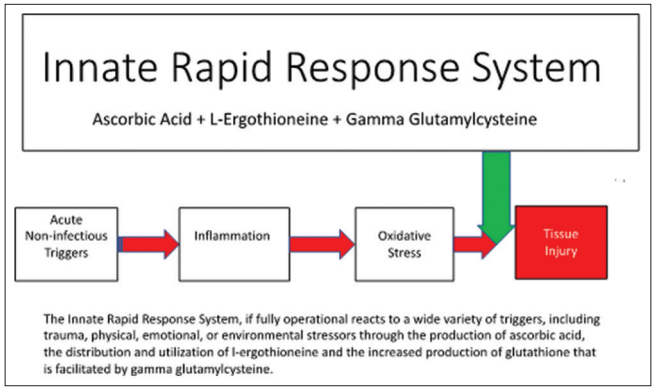

Figure 1: Amplifying the human body's innate "rapid response" systems to inflammation and oxidative stress.

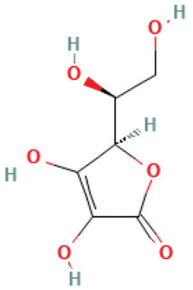

Figure 2: Chemical structure of Ascorbic Acid.

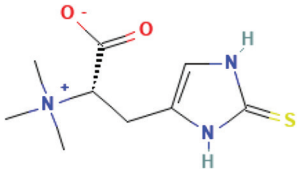

Figure 3: Chemical structure of L-Ergothioneine.

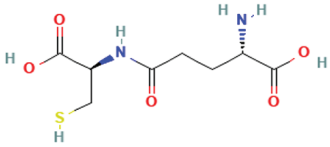

Figure 4: Chemical structure of Gamma-glutamylcysteine.

While each of these compounds is individually available and known to have an established safety profile, administration of any one of these, and even more so, taking them in unison in a timely fashion is rarely, if ever, incorporated into a clinical regimen or daily supplement regimen. Significantly, the combination is never taken together during an unwarranted inflammation or oxidative stress exacerbation. Perhaps, this concept should be considered and tested using this approach in conjunction with measuring blood biomarkers that reflect individual and pathway proteins that correspond to inflammation and oxidative stress.

Taken together, this combination of dietary supplements could represent the first opportunity for humans to potentially and simultaneously activate three critical rapid response capabilities in unison that combat inflammation and oxidative stress. Moreover, because of the detrimental effects of inflammation and oxidative stress and reductions in these and other anti-inflammatory and antioxidant protective mechanisms during aging, supplementing one's diet on a daily basis with all three of these agents as part of a health maintenance regimen might be warranted and well advised. A potential concern is whether amplifying this rapid response system in this way could limit host defense mechanisms that are needed intermittently during a response to infection. However, that potential concern should be evaluated as part of a continuing research focus on addressing the negative and potentially catastrophic effects of out of control inflammation and oxidative stress when it is not needed for host defense.

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