Antioxidant found in vegetables has implications for treating cystic fibrosis

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Scientists at the University of Pennsylvania School of Medicine discovered that a dietary antioxidant found in such vegetables as broccoli and cauliflower protects cells from damage caused by chemicals generated during the body's inflammatory response to infection and injury. The finding has implications for such inflammation-based disorders as cystic fibrosis (CF), diabetes, heart disease, and neurodegeneration.

Through cell-culture studies and a synthesis of known antioxidant biochemistry, Zhe Lu, MD, PhD , Professor of Physiology, Yanping Xu , MD, PhD , Senior Research Investigator, and Szilvia Szép , PhD, postdoctoral researcher, showed that the antioxidant thiocyanate normally existing in the body protects lung cells from injuries caused by accumulations of hydrogen peroxide and hypochlorite, the active ingredient in household bleach. These potentially harmful chemicals are made by the body as a reaction to infection and injury. In addition, thiocyanate also protects cells from hypochlorite produced in reactions involving MPO, an enzyme released from germ-fighting white blood cells during inflammation. They published their finding this week in the *Proceedings of the National Academy of Sciences*. Lu is also an Investigator of the Howard Hughes Medical Institute.

"Dr. Lu's work throws new light on how the genetic defect underlying CF leads to the lung illnesses that are the leading cause of death," said Bert Shapiro, Ph.D., who oversees membrane structure grants at the National Institutes of Health's National Institute of General Medical

Sciences (NIGMS). "His team's findings suggest that the lungs of people with the disease are more susceptible to the damaging effects of cellular oxidants. While the idea is tantalizing and creative, further testing is needed to confirm it."

The research team demonstrated that in three additional cell types used to extend their ideas to other inflammation-related conditions - cardiovascular disease, neurodegeneration, and diabetes - thiocyanate at blood concentrations of at least 100 micromolar (micromoles per liter) greatly reduces the toxicity of MPO in cells, including those lining blood vessels. Humans naturally derive thiocyanate from some vegetables and blood levels of thiocyanate in the general population vary from 10 to 140 micromolar.

This comparison raises the possibility, the authors point out, that without an adequate dietary supply of thiocyanate, hypochlorite produced by the body during inflammation would cause additional collateral damage to cells, thus worsening inflammatory diseases, and predisposing humans to diseases linked to MPO activity, including atherosclerosis.

Connection to CF

For over a decade Lu and colleagues have been exploring the inner workings of ion channels and how this knowledge relates to the pathology of such diseases as CF. The CF disease originates from mutations in the CF transmembrane conductance regulator (CFTR) protein, an ion channel protein in the cell membrane commonly thought to transport mainly chloride ions. It has, however, remained a mystery why a defect in a chloride-transporting channel leads to cystic fibrosis, a disease with exaggerated inflammation in both the lungs and the digestive system.

Lung injuries inflicted by excessive inflammation and recurring

infection cause about ninety percent of CF patients' symptoms and mortality. Although known as a chloride channel, CFTR also conducts thiocyanate ions, important because, in several ways, they can limit potentially harmful accumulations of hydrogen peroxide and hypochlorite, chemicals produced by the body to fight germs.

In CF patients, there is also a high incidence of diabetes, partly caused by damage to the pancreas. Type 2 diabetes is also associated with higher levels of MPO in the blood. The researchers found that the MPO-caused injuries to pancreas cells and endothelial cells used in their experiments can be greatly reduced by as little as 100 micromolar thiocyanate. Their finding raises the possibility that MPO, in the absence of adequate thiocyanate, contributes to diabetes.

In the cell-based experiments, thiocyanate at concentrations below 100 micromolar did not eliminate hypochlorite accumulation and did not fully protect against MPO toxicity. Conceivably, inadequate thiocyanate levels would aggravate MPO-produced injuries in patients suffering from inflammatory diseases, surmise the authors.

Links to Other Diseases

In other studies, MPO activity has been linked to lung cancers among smokers and also implicated in neurodegenerative diseases. Intriguingly, people with congenital MPO deficiency are less likely to develop cardiovascular diseases. The research team found that MPO-caused injuries to nerve cells, as well as to blood vessel-lining endothelial cells, can be greatly reduced by 100 micromolar thiocyanate.

Genetic defects in the CFTR predispose CF patients' lungs to excessive inflammation entangled with recurring lung infection. Defective CFTR channels would be expected to result in lower thiocyanate concentrations in the affected regions within the respiratory, as well as the digestive

systems, leaving tissues inadequately protected from accumulated hydrogen peroxide and overproduced hypochlorite.

Conceptually, delivering thiocyanate directly to the digestive and respiratory systems might be a therapy for CF disease, propose the researchers. As for the general population, individuals with low blood levels of thiocyanate may be at risk for chronic injuries by MPO, predisposing them to inflammatory or inflammation-mediated diseases. Many investigators have proposed developing drugs that specifically inhibit MPO-catalyzed hypochlorite production to combat these diseases, but natural thiocyanate not only decreases MPO-catalyzed formation of hypochlorite but also rapidly, once it is made, neutralizes it.

"In light of the obvious implications of this protective action of thiocyanate against the cell-damaging effect of MPO activity with regard to both CF disease and general population health, my colleagues and I will vigorously investigate the potential health benefit of thiocyanate," says Lu. He emphasizes though, "until the research community acquires a better understanding of both positive and negative impacts of thiocyanate on human health, it would be unwise for anyone to self-administer thiocyanate because like many other chemicals, thiocyanate has adverse side effects at improper doses and/or under inappropriate conditions."

Source: University of Pennsylvania School of Medicine (news : web)