Smart Life Forum

Bruce Ames, PhD

Delaying (or Accelerating) the Mitochondrial Decay of Aging

Thursday, September 21, 2006
7:00 PM

Cubberly Community Center
4000 Middlefield Road, Room H1, Palo Alto, California

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FMBR Meeting

Friday, September 29, 2006, Dr. Beverly Rubik will discuss the measurement of subtle energy effects in biology and medicine. See their website www.fmbr.org for more information.

Meet Bruce Ames

Dr. Bruce N. Ames is a Professor of the Graduate School in Molecular and Cell Biology, University of California, Berkeley, and a Senior Scientist at Children's Hospital Oakland Research Institute (CHORI).

Originally a native of New York City, Ames obtained his bachelor's degree in chemistry from Cornell University and his PhD in biochemistry from the California Institute of Technology. During Dr. Ames' distinguished career, he has published over 500 scientific articles, resulting in his being among the few hundred most-cited scientists in all fields. He has also been the recipient of numerous prestigious awards, including the National Medal of Science "for changing the direction of basic and applied research on mutation, cancer, and aging."

Ames established that many cancer-causing chemicals are also mutagens, and devised a simple, inexpensive test for environmental and natural mutagens. Commonly called "the Ames test," it has been widely used in research institutes, industry and regulatory agencies around the world to screen for environmental carcinogens and mutagens and weed out mutagenic chemicals before they are introduced into commerce.

He has also identified the causes and effects of oxidative DNA damage and translated these findings into intelligible public policy recommendations on diet and cancer risk for the American people. Specifically, he concluded that degenerative diseases of aging, such as cancer, cardiovascular disease, cataracts and brain dysfunction, are in good part due to oxidative damage. Dietary antioxidants, such as Vitamin C and E and carotenoids, play a major role in minimizing this damage, he argues.

Dr. Ames' ongoing research focuses on identifying mutagenic agents that damage human DNA and the defenses against them. He is also working to elucidate the consequences of

DNA damage for cancer and aging. Ames discovered that deficiency of certain micronutrients -- such as vitamins B12, B6, C, E, folate, and niacin, and the minerals iron and zinc -- appear to mimic radiation in damaging DNA. Such micronutrient deficiency may explain why the quarter of the population that eats the fewest fruits and vegetables has double the cancer rate for most types of cancer when compared with the quarter that consumes the most fruits and vegetables.

MAIN PRESENTATION

Poor nutrition has long been linked to an increased risk of many diseases, including cancer, heart disease, and diabetes. The human diet requires both macronutrients (fat, carbohydrate, protein) and micronutrients (about 40 essential minerals, vitamins, fatty acids, and amino acids). Based on his research and that of others, Dr. Ames concludes that far too little attention has been given to the importance of optimizing the intake of micronutrients, which are required for virtually all metabolic and developmental processes. The leading dietary sources of energy in the United States are abundant in carbohydrate and fat calories but deficient in micronutrients (i.e., are energy dense and nutrient poor). Such foods are inexpensive and tasty and as a consequence are consumed excessively, particularly by the poor. Thus, even in wealthy countries such as the United States, some vitamin and mineral inadequacies from diet are common (Table 1). Micronutrient malnutrition often accompanies caloric excess and may be the norm in obesity and contribute to its numerous associated pathologies.

Significant chronic metabolic disruption may occur if a micronutrient deficiency is at a level between that which causes clinical symptoms and the current recommended daily allowance (RDA) . When one component of the metabolic network is inadequate, there may be repercussions in metabolism that could accelerate degenerative diseases. The optimum intake of any micronutrient to maximize a healthy lifespan remains to be determined and could even be higher than the current RDA, particularly for some populations. For example, folic acid intakes above the RDA appear to be necessary to minimize chromosome breaks.

Micronutrient Deficiencies May Accelerate Mitrochondrial Decay and Degenerative Diseases of Aging, Such as Cancer

1. Mitochondrial decay

Mitochondrial decay appears to be a major contributor to aging and associated degenerative diseases. Oxidative damage to DNA, RNA, proteins, and lipids in mitochondrial membranes contributes to this decay and leads to a functional decline of mitochondria, cells, and organs such as the brain with accompanying loss of ambulatory activity and cognition.

The importance of optimizing metabolic function to prevent mitochondrial decay is illustrated by feeding the mitochondrial metabolites acetyl carnitine (ALC) and lipoic acid (LA) to old rats, which appears to reverse much of the decay process, rejuvenating the mitochondria and improving brain and other functions . Carnitine is used for transporting fatty acid fuel into the mitochondria; the main form of carnitine in the plasma is ALC. LA is a mitochondrial coenzyme, and is reduced in the mitochondria to a potent antioxidant. LA is also an effective inducer of about 200 phase 2 antioxidant enzymes, including those required for glutathione synthesis .ALC and LA together, in some cases synergistically, restore much of the lost mitochondrial function in old rats.

Below, mitochondrial decay-promoting effects of several micronutrient deficiencies are discussed as well as the association of deficiencies with degenerative disease, DNA damage, or cancer.

2. Magnesium deficiency

Magnesium intakes for ~56% of adults in the U.S. are below the Estimated Average Requirement (EAR). Intakes are below the EAR particularly among the poor, teenagers, the obese, African-Americans, and the elderly : 78% of 14-18 year old males and 91% of 14-18 year old females, and 81% of the elderly. Preliminary experiments have shown that mitochondrial DNA is a major target of magnesium deficiency in primary human cells in culture. In these cells, magnesium deficiency leads to mitochondrial DNA damage, accelerated telomere shortening, activation of cell cycle arrest proteins, and premature senescence [Killilea et al., in preparation]. Magnesium deficiency in rats leads to chromosome breaks and cancer. In humans, magnesium deficiency has been associated with colorectal and other cancers , hypertension, and the metabolic syndrome . In a study of 4035 men followed for 18 years, the highest quartile of magnesium compared to the lowest had a 40% decrease in all-cause mortality and cardiovascular disease and a 50% decrease in cancer deaths [Leone et al., Epidemiology, 2006]. A standard MVM supplement

would help, but does not contain sufficient magnesium and calcium, as it would make the pill too bulky.

3. Other vitamin and mineral deficiencies associated with chronic degenerative diseases, DNA damage, or cancer

Vitamin D deficiency could account for 29% of cancer mortality and in many studies has been strongly associated with colon, breast, and prostate cancer and other long latency diseases. African-Americans as a group are unusually deficient in vitamin D because of their dark skin, though inadequacy is prevalent in Caucasians as well. It has been suggested that efforts to improve vitamin D status by supplementation could reduce cancer incidence and mortality at low cost, with few or no adverse effects. Calcium deficiency is common and has been associated with chromosome breaks and diabetes in humans and colon cancer in mice . Selenium deficiency in mice induces genes linked to DNA damage and oxidative stress and suggestive evidence that selenium is protective against cancer has been reviewed. Omega-3 fatty acid deficiency has been associated with melanoma and other cancer as well as cognitive dysfunction . Vitamin B12 deficiency is common in the population and causes chromosome breaks , as does folate deficiency, which has also been associated with several human cancers. Marginal thiamine deficiency in rats induces the formation of colonic aberrant crypt foci, a preneoplastic lesion in a model for detecting colon carcinogens. Thiamine deficiency is also associated with brain dysfunction and diabetes. Niacin deficiency in cellular and animal studies appears to be genotoxic. Choline deficiency in humans increases DNA damage in lymphocytes and has been associated with brain dysfunction in rats. Choline deficiency in rats or rat cells causes oxidant release and mitochondrial damage. We and others have discussed t he need to set micronutrient requirements high enough to minimize DNA and mitochondrial damage.

4. Heme deficiency may play a central role in how seven micronutrient deficiencies accelerate mitochondrial decay, DNA damage, and cell senescence

[Editor's note: According to Wikipedia, "hemes" are iron-containing components of conjugated proteins of which there are several biologically important types. For example, heme-B, the most abundant heme, is contained in hemoglobin, the oxygen transport protein in blood.]

Seven micronutrients are required for heme synthesis in mitochondria (Table 2) and their deficiency causes a deficit of heme and therefore of complex IV, of which heme-A is an

essential component . The normal complement of complex IV minimizes oxidants, and deficits result in oxidant leakage, DNA damage, accelerated mitochondrial decay, and cellular aging.

Iron. Iron deficiency is the most common micronutrient deficiency in the world, and anemia is widespread in poor countries . Iron intake in U.S. menstruating women is low: ~16% are below the EAR . Hispanic women and the obese are at greater risk. Iron deficiency anemia is associated with poor cognitive development in toddlers, suggesting that if iron deficiency occurs in humans during critical periods of development, it results in harm to the developing brain.

Functional iron deficiency also has been associated with accelerated aging, diminished immune function, and neuromuscular abnormalities. The primary measure used to identify iron deficiency in most human populations is a reduction in hemoglobin concentration to the point of anemia (malaria, HIV, and other nutrient deficiencies may also lead to anemia). The effects of iron deficiency occur along a continuum and subclinical iron deficiency may have deleterious effects on heme biosynthesis. Dietary iron deficiency in the absence of anemia decreases aerobic capacity and physical work performance, which are improved by iron supplementation . Iron deficiency has not been well studied as a risk factor for cancer and the results are discordant. However, many studies are looking for a monotonic relationship and do not take into account that one might expect cancer at levels of iron that are both too low and too high, as in hereditary hemochromatosis, a risk factor for cancer.

Zinc. Zinc deficiency is not uncommon in adults, ~12% of whom are below the EAR . In human cells in culture, zinc deficiency causes heme deficiency and the release of oxidants, resulting in significant oxidative damage to DNA. Zinc deficiency also causes chromosome breaks in rats and is associated with cancer in both rodents and humans . Zinc deficiency in human cells also inactivates other zinc-containing proteins such as the tumor suppressor protein p53 and the DNA base excision repair enzyme apyrimidinic / apurinic endonuclease with a resulting synergistic effect on genetic damage.

Biotin. Biotin deficiency is more common than previously thought; ~40% of pregnant women who do not take a multivitamin show metabolic signs of deficiency . Biotin deficiency induced in normal human lung fibroblasts in culture caused a 40–50% decrease in heme content and premature senescence, though the relationship to human intake is unclear.

Should People Take a Multi-Vitamin / Mineral (MVM) Supplement for Insurance ?

1. Multi-vitamin / mineral supplement The National Health and Nutrition Examination Surveys (NHANES) indicate that the diets of many in the United States do not provide the intakes of all the vitamins and minerals recommended by official bodies as being adequate (Table 1). From NHANES and Table 1 it seems likely that intakes of various micronutrients are not only inadequate for the poor, teenagers, menstruating women, the obese, and the elderly, but for much of the rest of the population as well. These deficiencies would clearly be removed if only everyone would eat a healthy diet. However, decades of public health efforts to improve the American diet have not been very successful, particularly among the poor. Why not recommend that a MVM pill be added to a healthy lifestyle? An approach that focuses on micronutrient undernutrition in addition to continuing efforts to improve diet might be more successful in improving health. It may be easier to convince people to take an inexpensive and safe MVM pill than to markedly change their eating habits. Some evidence is accumulating that a MVM supplement is good insurance and would improve health—reducing heart disease, cancer, and cataracts and improving immune function, particularly for those who consume inadequate diets . Other studies showed a limited combination of micronutrients to be efficacious. Though consuming too high a dose of many of the minerals, such as iron, zinc, copper, and selenium, and some of the vitamins, such as vitamin A, is toxic, taking a daily standard MVM pill should not be of concern, as the amounts are not close to the upper limit (UL) for the micronutrients.

Despite the lack of definitive proof of efficacy, it is simply common sense to recommend that people take a MVM pill in addition to leading a healthy lifestyle: there are widespread deficiencies; an impressive array of evidence for supplementation; and the absence of realistic safety concerns. If this simple change could be widely implemented, and particularly if multivitamins could be made available to the poor, a marked decrease in the prevalence of micronutrient intakes below the RDA would ensue, and the evidence discussed herein suggests this could be accompanied by significant long-term health benefits.

2. Other possibly useful supplements Another useful supplement may be omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oil; inadequate intakes of omega-3 fatty acids are widespread and appear to be important for

brain function . Inadequate fiber intakes, both soluble and insoluble, are widespread and important ; fiber supplementation is inexpensive. Also worth noting is the widespread prevalence of magnesium and calcium intakes below the levels recommended, and the insufficient amounts in a standard MVM. Fortification of food, such as folate fortification, is another approach that has been shown to improve health. Fortification, however, might not be sufficient for population sub-groups that may have special needs. For example, most African-Americans are unusually low in vitamin D despite milk fortification, and it seems prudent for them to take a vitamin D or multivitamin supplement.

Advice to take MVM, fiber, and omega-3 fatty acids supplements should always be coupled with advice to eat a good diet, as we also need other nutrients and probably phytochemicals that may not be present in supplements.

3. Variable optimal requirements The elderly may need more or less of certain vitamins and metabolites compared to younger people, but this issue has not been seriously examined. For example, approximately 25% of Dutch adults over 70 years of age showed mild to severe vitamin B12 deficiency, most likely due to malabsorption rather than low-dietary intakes. Vitamin B12 intakes at levels ~200 times the RDA reversed the deficiency . Menstruating women need more iron than men or older women, some of whom may be getting too much. Most smokers have inadequate intake of vitamin C, as 76% are < EAR . The optimal intake of micronutrients and metabolites can also vary with genetic constitution . A variety of MVM pills have been developed that reflect different needs depending on one's age and gender—more are likely to be developed with new knowledge.

4. An excess of certain vitamins and minerals also can be toxic or carcinogenic In mice both low (one-third of normal) intake of a mixture of vitamins and a 5-fold excess supplementation caused an increase in intestinal neoplasia. In rats, both too little and too much iron intake caused mitochondrial damage, release of oxidants, and DNA damage. The percentage of the population consuming more than the upper limit (UL) is very low compared to the percentage consuming less than the EAR. Thus, micronutrient deficiencies are likely to be a far more important public health problem than excess consumption. This conclusion is supported by many epidemiological and other human studies. Nevertheless, increasing consumption of supplements and increasing fortification emphasize the need for vigilance to prevent over-consumption of certain micronutrients.

In Table 1, below : * EAR = Estimated Average Requirement. Less than the EAR is used as a measure of inadequacy in populations. The Recommended Daily Allowance (RDA) is defined as two standard deviations above the EAR. Data are from Moshfegh et al., What We Eat in America, NHANES 2001-2002, U.S. Dept. of Agriculture 2005: Agriculture Research Service.

Table 1: Selected micronutrient inadequacy in the U.S .

Nutrient	Population Group	% Ingesting < EAR From Food*
Minerals		
Iron	Women 14 – 50 y	16%
Magnesium	All	56%
Zinc	All	12%
Vitamins		
B6	Women > 71 y	49%
Folate	Adult Women	16%
E	All	93%
C	All	31%

Table 2: Micronutrient deficiency and heme: effects on human cells in culture

Micronutrient Deficiency	Heme Deficit	Complex IV Deficit	Oxidative Stress	DNA Damage	Early Senescence
Pyridoxine	[√]				
Zinc	√		√	√	
Riboflavin					
Iron	√	√	√	√	
Copper	[√]	√	[√]		
Biotin	√	√	√	√	√
Pantothenate	[√]	[√]			
√ = Atamna/Ames unpublished, [√] Literature					

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