BRUCE N. AMES - CHILDREN'S HOSPITAL OAKLAND RESEARCH INSTITUTE / UNIVERSITY OF CALIFORNIA, BERKELEY

April 21 at 6:00 p.m. in the Garren Auditorium, Basic Science Building
Sponsored by the Sam & Rose Stein Institute for Research on Aging, UCSD

Delaying Aging and Optimizing Health with Supplements & Diet

Inadequate intakes of vitamins and minerals (<50% of the RDA) are very common (often 10% of the population for each) and can lead to DNA damage, mitochondrial decay, and other pathologies. Inadequate intake of folate, B12, or B6 leads to uracil incorporation into DNA and chromosome breaks ---a radiation mimic. Inadequate zinc in human cells causes release of oxidants, DNA oxidation, and inactivation of p53 and other zinc enzymes involved in oxidant defense and DNA damage repair. Inadequate iron intake (2 billion women in the world; 25% of U.S. menstruating women) inactivates Complex IV in mitochondria, which causes oxidant release and mitochondrial decay; in the brain complex IV inactivation mimics the neurodegeneration of aging.

***High dose B vitamins can counteract a poorer Km*.** As many as one-third of mutations in a gene result in the corresponding enzyme having an increased Km (decreased binding affinity) for a coenzyme, causing a lower rate of reaction. About 50 different human genetic diseases due to a poorer binding affinity of the mutant enzyme for its coenzyme can be remedied by feeding high dose B vitamins, which raise levels of the corresponding coenzyme; many polymorphisms also result in a lowered affinity of enzyme for coenzyme and thus may be in part remediable.

***Mitochondrial decay with age due to oxidation of RNA/DNA, proteins, and lipids*,** is a major contributor to aging, and can be ameliorated by feeding old rats the normal mitochondrial metabolites acetyl carnitine (ALCAR) and lipoic acid (LA) at high levels. The principle behind this effect appears to be that with age increased oxidative damage to protein causes a deformation of structure of key enzymes, with a consequent lessening of affinity (Km) for the enzyme substrate. The effect of age on the enzyme binding affinity can be mimicked by reacting it with malondialdehyde (a lipid peroxidation product). Feeding the substrate (acetyl carnitine) with lipoic acid, a mitochondrial antioxidant, restores the velocity of the reaction, Km for acyl carnitine transferase, and mitochondrial function. In old rats (vs. young rats) mitochondrial membrane potential, cardiolipin level, respiratory control ratio, and cellular O2 uptake are lower; oxidants/02, neuron RNA oxidation, and mutagenic aldehydes from lipid peroxidation are higher. Ambulatory activity and cognition declines with age. Feeding old rats acetyl carnitine and lipoic acid for a few weeks restores mitochondrial function; lowers oxidants, neuron RNA oxidation, and mutagenic aldehydes; and increases rat ambulatory activity and cognition (as assayed with the Skinner box and Morris water maze).

An optimum intake of micronutrients and metabolites, which varies with age and genetics, should tune up metabolism and markedly increase health at little cost, particularly for the poor and elderly.