Fighting diseases of aging by wasting energy

December 4 2007

By making the skeletal muscles of mice use energy less efficiently, researchers report in the December issue of *Cell Metabolism*, a publication of Cell Press, that they have delayed the animals' deaths and their development of age-related diseases, including vascular disease, obesity, and one form of cancer. Those health benefits, driven by an increased metabolic rate, appear to come without any direct influence on the aging process itself, according to the researchers.

The mitochondria powering the mouse muscles were made inefficient by increasing the activity of so-called uncoupling protein 1 (UCP1). UCP1 disrupts the transfer of electrons from food to oxygen, a process known as mitochondrial respiration, which normally yields the energy transport molecule ATP. Instead, the energy is lost as heat.

"When you make the mitochondria inefficient, the muscles burn more calories," a metabolic increase that could be at least a partial substitute for exercise, said Clay Semenkovich of Washington University School of Medicine in St. Louis. "There are a couple of ways to treat obesity and related diseases," he continued. "You can eat less, but that's unpopular, or you could eat what you want as these animals did and introduce an altered physiology. It's a fundamentally different way of addressing the problem."

Atherosclerosis, diabetes, hypertension, and cancer occur more frequently with increasing age, the researchers explained. These age-related diseases are distinct from the process of aging, a physiological decline that includes decreases in muscle strength, cardiopulmonary

function, vision, and hearing as well as wrinkled skin and graying hair. Thus, the researchers added, aging and age-related disease are associated but may not share the same mechanisms.

Given the difficulty of validating strategies to increase life span in humans and the possible dissociation between aging and age-related diseases, the researchers said, identifying a simple intervention affecting several age-related diseases is an attractive approach to decreasing the morbidity of growing old. They suspected that treatments designed to alter the efficiency of mitochondrial respiration might be one way to accomplish this.

Earlier studies had shown that young mice engineered to express modestly increased levels of UCP1 in skeletal muscle had a mildly increased metabolic rate, although they ate and grew normally. The animals' muscles otherwise functioned as usual. In the new study, Semenkovich's group used these mice to determine whether respiratory uncoupling in skeletal muscle—a tissue that adapts to altered heat production and oxygen consumption during exercise—can affect age-related disease.

They found that animals with increased UCP1 only in skeletal muscle lived longer. Altered female animals also developed lymphoma, a type of cancer that originates in white blood cells called lymphocytes, less frequently. In mice genetically predisposed to vascular disease, the increase in UCP1 led to a decline in atherosclerosis in animals fed a "western-type" high-fat diet. Likewise, mice predisposed to developing diabetes and hypertension were relieved of those ailments by increased UCP1 in skeletal muscle. The "uncoupled mice" also had less body fat (or adiposity) and higher body temperatures and metabolic rates, among other biochemical changes.

"The consequences of excess adiposity disproportionately affect older

individuals," the researchers concluded. "Excess adiposity can be treated through two simple approaches, decreasing energy intake or increasing energy consumption. Considerable effort is currently being devoted to the development of agents that decrease energy intake in hopes of decreasing adiposity and perhaps age-related disease. Our results indicate that increasing energy consumption in mice has beneficial effects on survival, vascular disease, elevated blood pressure, and diabetes. This intervention does not slow aging but may diminish susceptibility to pathology. Strategies to safely accelerate energy consumption specifically in skeletal muscle could decrease the impact of some common age-related diseases."

Source: Cell Press