BIOLOGY  AGING

AGE Breakers
Rupturing the body's sugar-protein bonds might turn back the clock

LONDON—For all the promise of anti-aging creams and therapies, nothing has ever restored the vigor of youth or even delayed the inevitable process of growing old. Researchers now claim to have developed a compound that might rejuvenate hearts and muscles—by breaking the stiff sugar-protein bonds that accumulate as we get older.

Anthony Cerami of the Kenneth S. Warren Laboratories in Tarrytown, N.Y., suspected some 30 years ago that sugar affects how the body ages, based on observations of diabetics, who age rapidly. Sugars are an essential source of energy, but once in circulation they can act as molecular glue, attaching themselves to the amino groups in tissue proteins and cross-linking them into hard yellow-brown compounds known as advanced glycation end products, or AGEs.

Indeed, after years of bread, noodles and cakes, human tissues inevitably become rigid and yellow with pigmented AGE deposits. For the most part, piling on dark pigments in the teeth, bones and skin is harmless. But where glucose forms tight bonds with the long-lived protein collagen, the result is a constellation of changes, including thickened arteries, stiff joints, feeble muscles and failing organs—the hallmarks of a frail old age. (Diabetes age prematurely because sugar-driven damage acquires breakneck speed, raising their levels of AGE-infused collagen to those of elderly people.) “The evidence that sugar cross-linking increases as we age is persuasive,” comments Jerry W. Shay of the University of Texas Southwestern Medical Center at Dallas. “There are diseases associated with increased glycation, which are directly related to increased age.” Sugar's connection with AGE formation may be one reason caloric restriction might delay aging.

Cerami's quest has been to find an “inhibitor”—a compound that by tying up reactive glucose might keep it away from susceptible proteins. To his surprise, the food industry had the answer. Since 1912 chemists have known that in the heat of an oven sugars and amino acids form tight chemical bonds—a reaction that turns roasted turkey, toast and coffee to a tasty golden brown. This Maillard chemistry, as it is known in food circles, is the same sugar-protein bonding that stiffens our tissues. Crucially, food chemists also discovered that adding sulfites prevents browning and hardening and keeps food and beverages looking fresh.

Exploiting this culinary knowledge, Cerami’s team showed in the mid-1980s that aminoguanidine lowered diabetics’ urine albumin—an indicator of kidney malfunction—and delayed AGE-related damage to the retina. Perhaps more exciting is Cerami’s recent discovery of a molecular “breaker”—a drug that may actually reverse the aging process by cracking sugar-protein links once they form. “Instead of looking for prevention, we can now administer a compound to reduce the stiffness we see in diabetes and aging,” Cerami reported at a recent Novartis Foundation symposium in London. The breaker, dimethyl-3-phenacylthiazolium chloride, or ALT-711, can tear tough AGE bonds apart. Diabetic animals, old dogs and elderly rhesus monkeys given the compound daily for three weeks yielded spectacular results. “The heart and major arteries, which were quite stiff, became more pliable and elastic. So the heart could pump more blood—similar to what you’d see in a young animal,” Cerami stated.

Cerami envisions multiple uses for breakers in pathologies wherein tissues lose flexibility. In glaucoma, for example, increasing the elasticity of the draining canal would prevent the buildup of pressure in the eye. ALT-711 could also renew declining lung elasticity and soften an enlarged and hardened prostate. But it will be at least 10 years until such drugs, currently undergoing clinical trials, are approved for humans.

Will breakers stop aging in its tracks? After all, the field of antiaging drugs is littered with compounds that failed to live up to their hype or were hardly more than snake oil [see SCIENTIFIC AMERICAN PRESENTS: The Quest to Beat Aging; Summer 2000]. A single fountain-of-youth elixir is highly unlikely, says Tamara Harris of the National Institute on Aging, because other activities, such as free-radical oxidation and possibly telomere shortening, also contribute to the body’s slow decline. Moreover, AGE-related research tends to be slow: Harris points out that there is no easy, well-validated way to measure AGE in the body, a shortcoming that complicates trials. To Harris, however, AGE breakers remain an appealing option. “This is a nice approach because it is multifocal, aimed at a basic process that occurs in multiple systems. But,” she warns, “there won’t be one silver bullet.”

—Lisa Melton

FOOD FOR THOUGHT: A roasted turkey may hold the clues to reversing aging.

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