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Rodents with trouble walking reveal potential treatment approach for most common joint disease

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Maintaining the supply of a molecule that helps to nourish cartilage prevented osteoarthritis in animal models of the disease, according to a report published in *Nature Communications* online May 11.

The study is the first, say its authors, to provide evidence that adenosine, a biochemical at the heart of human cellular function, plays another crucial role—keeping on hand a steady number of healthy chondrocytes, the cells that make and sustain cartilage.

Important to the study's implications, adenosine is derived from adenosine triphosphate (ATP), the molecule that stores the energy needed by the body's cells until they break it up to use it. Scientists have known that both inflammation and aging lead to diminished ATP production (and so lower adenosine levels) in chondrocytes. Until now, they had not linked diminished adenosine levels to osteoarthritis, the commonplace, "wear-and-tear" form of arthritis.

Led by researchers at NYU Langone Medical Center, the study found that maintaining high levels of adenosine in rats with damage to the anterior cruciate ligament (ACL), which is known to lead to osteoarthritis in humans, prevented the rats from developing the disease. If the finding proves to be true in humans, the study authors say adenosine replacement therapy could potentially delay the onset of osteoarthritis and the need for joint replacements.

"We found that if adenosine levels decrease, or if the capacity to respond to adenosine diminishes, cartilage starts to degenerate," says study senior investigator Bruce Cronstein, MD, the Dr. Paul R. Esserman Professor of Medicine at NYU Langone. "Our study suggests that diminished ATP and adenosine production are likely contributing factors to the development of osteoarthritis in aging individuals," says Cronstein, who also serves as the director of the Clinical and Translational Science Institute (CTSI), and chief of the Division of Translational Medicine at NYU Langone.

The findings suggest that reductions in the number of cartilage-producing cells, and greater risk for osteoarthritis, may be driven not just by lower adenosine levels but also by lower levels of the protein on the surface of chondrocytes designed to receive and pass on adenosine's signal. Adenosine helps to sustain such cells by fitting into a protein called the A2A adenosine receptor on their surfaces, like a key into a lock. Cronstein and colleagues observed that mice lacking the A2A adenosine receptor did not move (walk) as easily or as well as mice with the receptor. Radiologic examination of the knees of mice without the receptor confirmed that they had osteoarthritis.

Cronstein and his team also found that levels of adenosine A2A receptors went up on rat chondrocytes when osteoarthritis was present, in what the researchers say was a "failed attempt" to compensate for the loss of adenosine from the energy-processing (metabolic) changes underlying the inflammation. Additional tests in tissue samples from osteoarthritic patients who had joint replacements at NYU Langone found similarly increased levels of adenosine A2A receptors on chondrocytes.

When researchers treated mouse chondrocytes with a molecule called IL-1beta, which contributes to the development of osteoarthritis, they found that 39 percent less ATP was produced by the inflamed

chondrocytes. They also found 80 percent less expression of ANKH, a molecule that exports ATP, in the IL-1beta-treated cells. Finally, they found that lacking the enzyme involved in turning ATP into adenosine diminished adenosine levels, which led to osteoarthritis in mice. The lack of the enzyme in humans is also known to lead to the disease.

When the team administered adenosine packaged in lipid bubbles into rats' ACL injuries, researchers found that the excess adenosine, as mediated by the adenosine A2A receptor, prevented the development of osteoarthritis in the animals.

Cronstein says related future therapies, if successful, would prevent or delay the need for some of the million or so joint replacements performed each year, numbers of which are growing in part thanks to obesity, which puts more pressure on joint structures.

"Because joints may have to be replaced again and again, if we can put off the need for joint replacement until later in life, odds are that patients will only have to have this done once," says Cronstein.

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