Helper molecule reverses degeneration of muscle in mouse model of tissue aging, wasting

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Enzymes in the NAD salvage pathway 'handing off' molecules to the front runner, representing fully formed NAD leading the pack in terms of muscle function. Credit: Artwork by Mary Leonard and courtesy of Joe Baur, Perelman

Maintaining proper levels of an essential helper molecule is crucial for optimal muscle function, according to a study led by Joseph Baur, PhD, an assistant professor of Physiology in the Perelman School of Medicine at the University of Pennsylvania. Some athletes are already taking supplements to increase synthesis of this compound, called NAD, with the hopes of reversing the natural decay associated with aging of the mitochondria, the cell's powerhouses. However, this is the first study to directly investigate the consequences of NAD deficiency on muscle function. The Penn team published their findings this week in the cover article of *Cell Metabolism*.

Oversight of the natural products industry is much looser than that of regulated drugs, and supplements to boost NAD are available over the counter. "Finding out whether strategies to enhance the production of NAD will have any impact on muscle function in healthy individuals is a subject of much speculation," Baur said. "However, answering this question will have to wait for controlled clinical trials."

Baur and colleagues examined the role of NAD precursor molecules on mitochondria by specifically disrupting the "NAD salvage pathway," in mouse skeletal muscle. This pathway consists of a series of enzymes that recycles building block molecules to make fresh NAD to power reactions throughout the cell, and especially within the mitochondria, the cell component that makes energy for the body from ingested food. Chemical reactions involving NAD are fundamental to metabolizing all fats and carbohydrates, yet NAD is degraded in response to such physiological stresses as DNA damage, and its concentration declines in several tissues over the natural course of aging.

Lead author David W. Frederick, PhD, a postdoctoral fellow in the Baur lab, and the team generated mice in which they could restrict the amount of NAD in specific tissues in order to simulate this aspect of normal aging in otherwise healthy mice. Surprisingly, young knockout mice were found to tolerate an 85 percent decline in intramuscular NAD content without losing spontaneous activity or treadmill endurance. However, when these same mice hit early adulthood (three to seven months of age), their muscles progressively weakened and their muscle fibers atrophied.

"Their muscle tissue looked like that of Duchene's muscular dystrophy [DMD] patients," Baur said. "The genes that were turned on and the presence of inflammatory immune cells in the muscles lacking NAD looked very similar to what we see in DMD."

The team next sought to test whether a dietary NAD precursor might remedy the muscle pathology in the mice. The muscle decline was completely reversed by feeding the mice a form of vitamin B3, called nicotinamide riboside (NR), obtained from natural products company ChromaDex, a study collaborator.

"At first we were surprised by how rapidly NR was able to reactivate dormant mitochondria in muscle, despite being largely consumed by other cell types," Frederick said. "It appears that a relatively small enhancement in muscle NAD can have profound functional consequences in this setting."

Additionally, the team found that induced lifelong overexpression of Nampt, an enzyme important in making NAD, prevented the natural decline in NAD and partially preserved exercise capacity in aged mice. "This was supporting evidence that strategies to enhance muscle NAD synthesis might help to combat age-associated frailty," says Frederick, emphasizing the need for more studies to confirm the long-term safety

of such interventions.

Baur plans to follow up on the unexpected muscular dystrophy finding, asking if NAD is also depleted in some forms of dystrophy and if restoring NAD might help ameliorate certain features of the disease. Though the Baur lab previously found that enhanced NAD synthesis does not benefit muscle performance in young mice, these new findings suggest that it may be useful for combating age-related declines in muscle function.

Provided by Perelman School of Medicine at the University of Pennsylvania