A vitamin could help treat Duchenne muscular dystrophy

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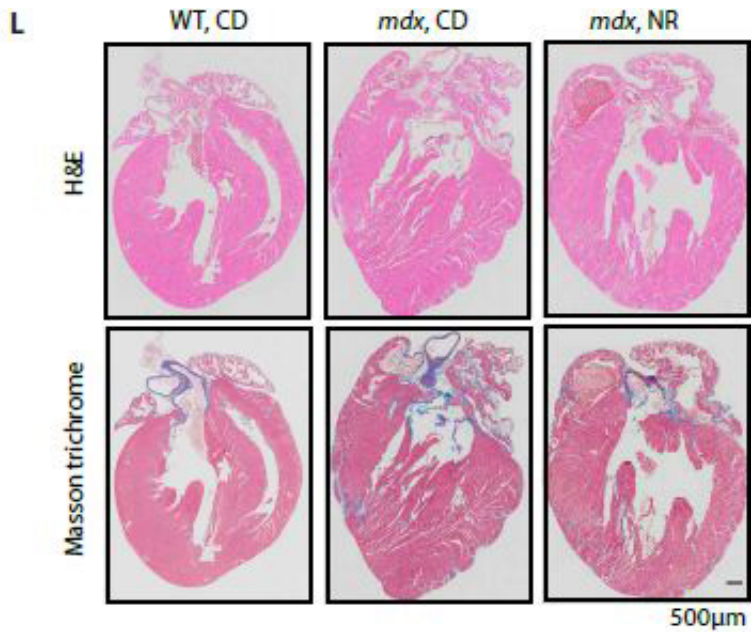

Hematoxylin and eosin and Masson's trichrome staining of hearts from control C57BL/10 and mdx male mice at 16 months of age with and without nicotinamide riboside (NR) treatment. Credit: Ryu et al., *Science Translational Medicine* (2016)

Duchenne is the most common and severe form of muscular dystrophy. Because of this genetic disease, one out of every 3,500 children spends their 12th birthday in a wheelchair. This disorder progressively leads to general paralysis, and most patients die of respiratory failure. The disease is caused by a genetic mutation that prevents a protein required

to keep muscle cells intact from being produced. While most research focuses on repairing the defective gene, researchers at EPFL have come up with a different strategy. As part of their work on nutrition and aging, they discovered that large doses of a vitamin called nicotinamide riboside were remarkably effective in countering the progress of the disease in animals. Their work has been published in *Science Translational Medicine*.

Patients suffering from Duchenne muscular dystrophy are unable to produce dystrophin. This protein is mainly responsible for connecting the various parts of muscle cells; without it, the cells cannot deform correctly. As a result, cell movement mechanically triggers an inflammatory response, which in turn gradually destroys the muscles.

A highly damaging second cycle

Johan Auwerx's team showed that the disease leads to a second cycle of events inside the cells, a series of reactions that exacerbate the disease's damaging effects.

Several processes are at work in the second cycle. First, the 'primary' inflammation overactivates a certain gene, which then consumes a large quantity of an essential component called NAD+.

This causes a shortage of NAD+ within the cell. But this component acts as a fuel for the powerhouse of cells, the mitochondria, which are especially important in muscle tissue. The NAD+ deficiency therefore weakens the muscle, an effect similar to that of mitochondrial deficiency in older people.

Yet the consequences are even worse than they appear. Deprived of energy, the dysfunctional mitochondria aggravate the inflammation that causes muscle loss. So much for what could have initially appeared to be

just a minor side effect of the disease.

Reversing course with a vitamin: nicotinamide riboside successfully tested on animals

What if it were possible to reduce muscle inflammation - and thus muscle loss - by providing the worn-out mitochondria with fuel? That would mean administering nicotinamide riboside, the vitamin precursor of NAD+. This is the hypothesis that the researchers wanted to test after having already successfully investigated this vitamin's effect on muscle aging in their work on nutrition.

They tried out their approach on animals, using C. elegans worms and mice that had been genetically modified to develop the disease. The effect was remarkable. When large doses of nicotinamide riboside were administered, the worms did not develop any of the disease's symptoms. The mice presented much lower muscular inflammation, and existing lesions were attenuated.

"We have good reason to think that humans will also respond to this treatment and that we'll be able to reduce inflammation," said Auwerx, the lead author. "But we don't know to what extent. It's important to remember that we're not going after the primary cause of the disease, dystrophin deficiency." Which means it is difficult to predict the treatment's effectiveness. "Regardless, it would still be quite an accomplishment if we can prolong the patient's life by several years and increase their comfort."

Clinical tests may be possible within two years

Nicotinamide riboside is a vitamin precursor to NAD+. This molecule is commercially available and presents no known toxicity, even in high

doses. The vitamin is water soluble, and any excess amount is evacuated in the urine.

According to Auwerx, because nicotinamide riboside is readily available and harmless, clinical tests could be possible in the very near future, maybe within two years. "We will need to test the doses," says the researcher. "In the animals that we tested, the quantities were so large they could not be administered through diet. To see if our strategy works on humans, we will have to use massive doses of synthetic molecules."

The genetic mutation that causes Duchenne muscular dystrophy was discovered 30 years ago. 2016 is thus an anniversary year, and it has already been marked by the FDA's recent approval of a promising treatment that partially corrects the defective gene in certain patients. "My hope is that we will give people suffering from Duchenne muscular dystrophy a second reason to celebrate in 2016," says Auwerx.

More information: "NAD+ repletion improves muscle function in muscular dystrophy and counters global PARylation," *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aaf5504

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