New hope for treating common form of inherited neuromuscular disease

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Treatments that ramp up production of the tiny "motors" that power cells may have promise for treating one of the most common forms of inherited neuromuscular disease, according to a report in the September *Cell Metabolism,* a Cell Press publication. Neuromuscular disorders caused by defects in those mitochondrial motors affect a large number of children and adults worldwide, but today remain without treatment, the researchers said.

The researchers now show in mice with a muscular defect in mitochondria function that treatments designed to increase the number of mitochondria can improve symptoms of muscle weakness and enhance survival. Those treatments work by enhancing the activity of so-called peroxisome proliferator-activated receptor ? (PPAR?) coactivator a (PGC-1a), a master regulator of metabolism known to play an important role in the production of mitochondria.

" The idea was that in the mice and in patients with these disorders, there is still residual activity of the defective mitochondrial enzymes," said Carlos Moraes of the University of Miami School of Medicine. "If per cell there were more mitochondria, each with that same residual activity, would it improve clinical symptoms?," he asked.

"That's exactly what happened in the mice," he said. "With more mitochondria, the myopathy was milder and the mice lived longer without symptoms." Myopathy refers to any neuromuscular disease in which muscle fibers fail to function properly, resulting in muscle

weakness.

In the mice with mitochondrial myopathy, the researchers induced mitochondria production in two ways: through genetic modifications that increased PGC-1a in skeletal muscle and by giving them a drug called bezafibrate that is already FDA-approved for the treatment of metabolic disorders, including elevated lipids (hyperlipidemia), diabetes and metabolic syndrome. Bezafibrate activates PGC-1a along with other peroxisome proliferator activated receptors (PPARs).

Both treatment approaches resulted in longer life span for the mice and delayed the onset of their disease, they report. That effect most likely stemmed from an increase in mitochondria. In some cases they found mitochondria in the muscle increased by as much as four or five times, Moraes said.

Mice with the impaired mitochondria typically live only three or four months, he said. The transgenic PGC-1a mice lived for about one year and some for as long as 22 months. Those treated with bezafibrate therapy lived for at least six months, they found.

The treated animals also showed stronger performances on a treadmill. Untreated mice with the mitochondrial defect begin to fall on treadmill tests at three months of age. The PGC-1 a transgenic mice with myopathy didn't show signs of falling until seven months. Those taking the drug showed a better treadmill performance at six months than the untreated mice did at three months.

" Controlling the expression of PGC-1a and the PPARs might offer a novel treatment strategy not only to mitochondrial myopathies, but also other mitochondrial diseases," the researchers conclude from their findings. "The promising results with the bezafibrate-fed myopathy mice

clearly identify small-molecule PPAR agonists, already used in humans with metabolic disorders as a treatment option for mitochondrial diseases."

While the results are promising, Moraes cautioned that there are potential side effects of bezafibrate that need to be examined. He said he hopes a clinical trial to find out how well they might work in patients with mitochondrial disorders will begin soon. They are also doing studies to test whether a similar treatment might have potential for treating mitochondrial disorders of the brain as well.

Source: Cell Press