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Drug candidate leads to improved endurance

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An international group of scientists has shown that a drug candidate designed by scientists from the Florida campus of The Scripps Research Institute (TSRI) significantly increases exercise endurance in animal models.

These findings could lead to new approaches to helping people with conditions that acutely limit exercise tolerance, such as obesity, chronic obstructive pulmonary disease (COPD) and congestive heart failure, as well as the decline of muscle capacity associated with aging.

The study was published July 14, 2013, by the journal *Nature Medicine*.

The drug candidate, SR9009, is one of a pair of compounds developed in the laboratory of TSRI Professor Thomas Burris and described in a March 2012 issue of the journal Nature as reducing obesity in animal models. The compounds affect the core biological clock, which synchronizes the rhythm of the body's activity with the 24-hour cycle of day and night.

The compounds work by binding to one of the body's natural molecules called Rev-erb?, which influences lipid and glucose metabolism in the liver, the production of fat-storing cells and the response of macrophages (cells that remove dying or dead cells) during inflammation.

In the new study, a team led by scientists at the Institut Pasteur de Lille in France demonstrated that mice lacking Rev-erb? had decreased skeletal muscle metabolic activity and running capacity. Burris' group

showed that activation of Rev-erb? with SR9009 led to increased metabolic activity in skeletal muscle in both culture and in mice. The treated mice had a 50 percent increase in running capacity, measured by both time and distance.

"The animals actually get muscles like an athlete who has been training," said Burris. "The pattern of gene expression after treatment with SR9009 is that of an oxidative-type muscle— again, just like an athlete."

The authors of the new study suggest that Rev-erb? affects muscle cells by promoting both the creation of new mitochondria (often referred to as the "power plants" of the cell) and the clearance of those mitochondria that are defective.

More information: "Rev-Erb? Modulates Skeletal Muscle Oxidative Capacity by Regulating Mitochondrial Biogenesis and Autophagy" DOI: 10.1038/nm.3213

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