Researchers breed a mighty mouse

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Case Western Reserve University researchers have bred a line of "mighty mice" (PEPCK-Cmus mice) that have the capability of running five to six kilometers at a speed of 20 meters per minute on a treadmill for up to six hours before stopping.

"They are metabolically similar to Lance Armstrong biking up the Pyrenees; they utilize mainly fatty acids for energy and produce very little lactic acid," said Richard W. Hanson, the Leonard and Jean Skeggs Professor of Biochemistry at Case Western Reserve and the senior author of the cover article that appeared in the *Journal of Biological Chemistry*, entitled "Over Expression of the Cytosolic Form of Phosphoenolpyruvate Carboxykinase (GTP) in Skeletal Muscle Repatterns Energy Metabolism in the Mouse."

These genetically engineered mice also eat 60 percent more than controls, but remain fitter, trimmer and live and breed longer than wild mice in a control group. Some female PEPCK-Cmus mice have had offspring at 2.5 years of age, an amazing feat considering most mice do not reproduce after they are one year old. According to Hanson, the key to this remarkable alteration in energy metabolism is the over-expression of the gene for the enzyme phosphoenolypyruvate carboxykinases (PEPCK-C).

Parvin Hakimi, the article's lead author and a researcher in the Hanson lab, developed this new line of PEKCK-C mice over the past five years as part of on-going research aimed at understanding the metabolic and physiological function of PEPCK-C in skeletal muscle and adipose

tissue.

The transgenic mice, which now number nearly 500, were derived from six founder lines that contain a chimeric gene in which a copy of the cDNA for PEPCK-C was linked to the skeletal actin gene promoter, containing the 3'-end of the bovine growth hormone gene. The skeletal actin gene promoter directs expression of PEPCK-C exclusively to skeletal muscle. Various lines of PEPCK-Cmus mice expressed PEPCK-C at different levels, but one very active line of PEPCK-Cmus mice had levels of PEPCK-C activity of 9 units/gram skeletal muscle, compared to only 0.08 units/gram in the muscles of control animals.

It was evident from the beginning that these mice were very different from average mice. Hakimi commented, "From a very early age, the PEPCK-Cmus mice ran continuously in their cages." She said she could identify which mice were from this new line by simply watching their level of activity in their home cage.

Animal behavior studies later demonstrated that the PEPCK-Cmus mice are seven times more active in their home cages than controls; in addition, the mice were also markedly more aggressive. "The enhanced level of activity noted in the PEPCK-Cmus mice extends well beyond two years of age; this is considered old-age for mice," the researchers said.

As part of this study, the researchers determined oxygen consumption, the production of carbon dioxide and changes in the lactate concentrations in the blood of the PEPCK-Cmus mice and controls during strenuous exercises on a treadmill, which was set at a 25-degree incline. The treadmill speed was increased by 2m/min every minute until the mice stopped running. The PEPCK-Cmus mice ran an average of 31.9 minutes, compared to 19 minutes for the control animals.

“What is particularly dramatic is the difference in the concentrations of lactate in the blood,” the researchers said. “At the beginning of exercise, the concentration of lactate was similar in two groups of mice, but by the end of the exercise period, the control group had elevated levels of blood lactate with little change in the levels in the PEPCK-Cmus mice.”

They added that this indicates that the PEPCK-Cmus mice relied heavily on fatty acids as a source of energy during exercise, while the control animals rapidly switched from fatty acid metabolism to using muscle glycogen (carbohydrates) as a fuel; this dramatically raised the blood lactate levels.

This new mouse line also has an increased content of mitochondria and high concentrations of triglycerides in their skeletal muscles, which also contributed to the increased metabolic rate and longevity of the animals.

“It is remarkable that the over-expression of a single enzyme involved in a metabolic pathway should result in such a profound alteration in the phenotype of the mouse,” Hakimi and Hanson said. “Understanding the biochemical mechanisms responsible for this repatterning of energy metabolism will keep us busy for some time to come.”

Source: Case Western Reserve University