Study may explain exercise-induced fatigue in muscular dystrophies

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A University of Iowa study suggests that the prolonged fatigue after mild exercise that occurs in people with many forms of muscular dystrophy is distinct from the inherent muscle weakness caused by the disease.

The research, which is published in *Nature* Advance Online Publication Oct. 26, identifies a faulty signaling pathway that appears to cause exercise-induced fatigue in mouse models of muscular dystrophy. Moreover, the study shows that Viagra can overcome the signaling defect and relieve the fatigue. The findings suggest that targeting the signaling pathway may lead to therapies for this type of fatigue.

"This is an exciting finding and our research suggests that there probably are many different neuromuscular conditions where fatigue could be treated by targeting this newly discovered pathway," said Kevin Campbell, Ph.D., UI professor and head of molecular physiology and biophysics and a Howard Hughes Medical Institute investigator, who holds the Roy J. Carver Chair of Physiology and Biophysics.

Using animal models, the researchers showed that if an enzyme called neuronal nitric oxide synthase (nNOS) is not present at its normal location on the muscle membrane, then blood vessels that supply active muscles do not relax normally and the animals experience post-exercise fatigue.

Early clues about the role of nNOS came from observing that the significant inactivity of dystrophic mice following mild exercise was

very similar to the fatigue experience by muscular dystrophy patients after a short period of walking.

"A clinician colleague said, 'Those mice behave just like my patients with Becker muscular dystrophy.' As soon as he said that we knew what might be going on, because Becker patients have mislocalized nNOS," Campbell said.

Working with mouse models of muscular dystrophy and normal mice engineered to lack nNOS, the UI team, including lead study author Yvonne Kobayashi, Ph.D., UI research associate in molecular physiology and biophysics, showed that mice with misplaced or missing nNOS exhibited prolonged fatigue after mild exercise.

"The mice without nNOS have normal muscles and can exercise quite well, but after just mild exercise, we found that they had the intense fatigue response," Kobayashi said.

Blood vessel imaging of these mice showed post-exercise constriction of the blood vessels supplying muscle. Blocking nNOS activity in normal mice also produced post-exercise fatigue and narrowed blood vessels to the muscles.

The team also found that although gene therapy could restore the structure and function of an important component of muscle membranes in mice with muscular dystrophy, this treatment did not alleviate the post-exercise fatigue. Further analysis showed that although the muscle membrane complex was intact, nNOS was still not correctly localized to the membrane, and blood vessels supplying skeletal muscle were abnormally constricted after mild exercise.

"The signaling pathway probably maintains blood flow into the muscle during exercise and keeps the blood flow going after exercise. But when

nNOS is missing or mislocalized, this pathway breaks down," Campbell explained. "The mice with mislocalized nNOS are able to exercise, but after exercise that reduced blood flow to the recovering muscles produces the fatigue."

To determine if nNOS was affected in humans with muscular dystrophy, Steven Moore, M.D., Ph.D., UI professor of pathology and study co-author, examined muscle biopsies from 425 patients with many different forms of muscular dystrophy. He found that nNOS was missing or reduced in most cases, suggesting a common mechanism of fatigue.

"Our findings could lead to a better understanding of fatigue under other physiological conditions in which muscle nNOS expression, localization, or activity is affected," Kobayashi added.

The enzyme nNOS makes a signaling molecule called nitric oxide, which stimulates production of a chemical called cGMP that causes smooth muscle around blood vessels to relax thereby increasing blood flow.

This nitric oxide signaling pathway is turned off by phosphodiesterase (PDE), an enzyme that breaks down cGMP. Viagra, a drug designed to increase blood flow, inhibits PDE and prolongs the existence of the cGMP molecules that promote blood vessel dilation.

The researchers showed that Viagra could alleviate fatigue in mice with mislocalized nNOS.

"The mice that have the nNOS mislocalized still have some nitric oxide signaling, but the Viagra enhances that signal by inhibiting PDE and preventing breakdown of cGMP," Campbell said.

Source: University of Iowa