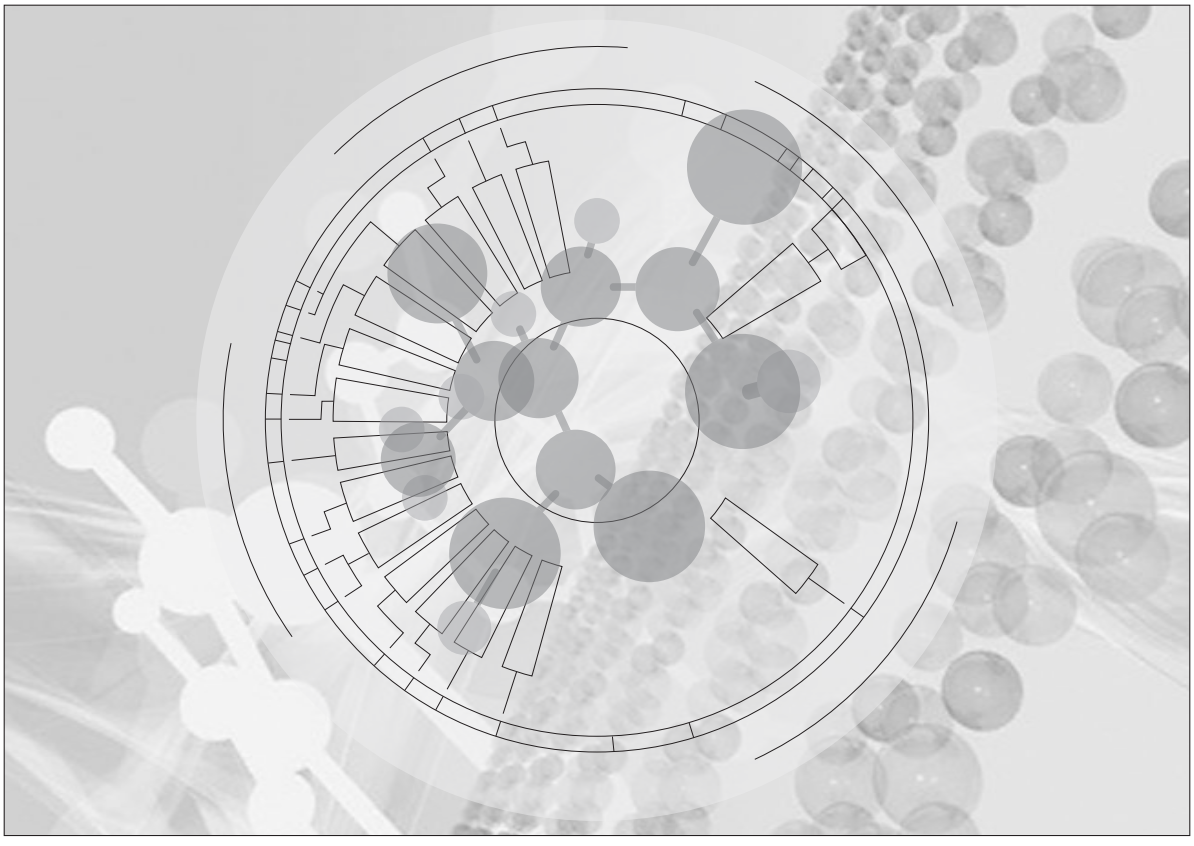

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Boosting Supply of Key Brain Chemical Reduces Fatigue in Mice

Researchers at Vanderbilt University have "engineered" a mouse that can run on a treadmill twice as long as a normal mouse by increasing its supply of acetylcholine, the neurotransmitter essential for muscle contraction.

The finding, reported this month in the journal Neuroscience, could lead to new treatments for neuromuscular disorders such as myasthenia gravis, which occurs when cholinergic nerve signals fail to reach the muscles, said Randy Blakely, Ph.D., Director of the Vanderbilt Center for Molecular Neuroscience.

Blakely and his colleagues inserted a gene into mice that increased the production of a protein called the choline transporter at the neuromuscular junction.

The choline transporter is vital to the capacity for muscle contraction -- including the ability to breathe -- because it regulates the supply of choline, the precursor to acetylcholine. "We reasoned that giving more of this protein might enhance muscle function and reduce nerve-dependent fatigue," Blakely said.

Other researchers have manipulated the gene for the muscle tissue growth factor myostatin to produce animals with greater strength and endurance, but Blakely said this may be the first time "neural endurance" was enhanced by manipulating the nerves that innervate muscle.

Drugs that increase choline transporter activity "could represent a novel therapeutic strategy" for myasthenia gravis and a wide range of other disorders that involve cholinergic signaling deficits, Blakely said.

These disorders include muscular dystrophy, congestive heart failure, depression, schizophrenia, Alzheimer's disease and Attention-deficit Hyperactivity Disorder (ADHD). "The brain uses acetylcholine for a wide variety of functions, including the ability to sustain attention," Blakely noted.

Last year, Blakely and his colleagues reported that a variation in the choline transporter gene is associated with the "combined" type of ADHD, which is characterized by both inattention and hyperactivity/impulsivity.

With funding from the National Institutes of Health, the researchers are developing choline transporter-targeted agents that could lead to new medications for these conditions.

D. Lund, A.M. Ruggiero, S.M. Ferguson, J. Wright, B.A. English, P.A. Reisz, S.M. Whitaker, A.C. Peltier, R.D. Blakely. Motor neuron-specific overexpression of the presynaptic choline transporter: impact on motor endurance and evoked muscle activity. Neuroscience, 2010; 171 (4): 1041 DOI: 10.1016/j.neuroscience.2010.09.057