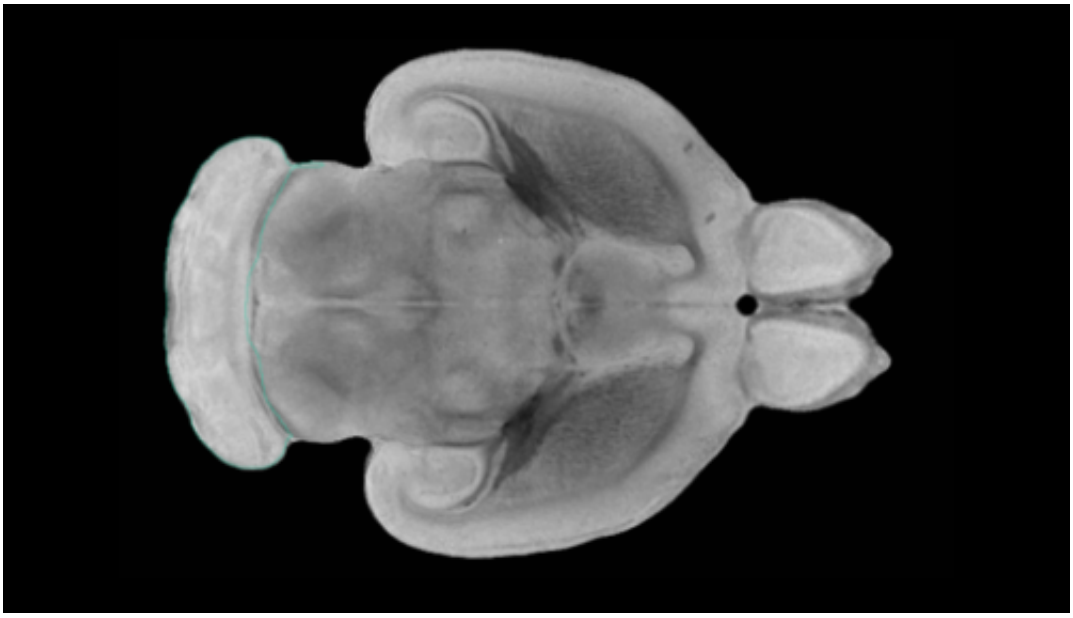
Mice on wheels show scientists how exercise benefits their brains

June 2 2016



Cerebellum of CIVM postnatal rat brain atlas. Credit: Neurolex

The relentless desire by mice to run on cage "exercise" wheels has helped explain at a molecular level how exercise benefits a mammal's brain.

Scientists from NYU Langone Medical Center behind the related research say their latest findings not only add evidence to the value of exercise for humans looking to keep their brains fit, but also suggest new strategies to ward off neurological disease.

In a study to be published in the journal *eLife* online June 2, researchers report measuring the natural buildup of certain chemicals in the brain during the rodents' exercise, substances that kick-start production of a protein called brain-derived neurotrophic factor, or BDNF. Since the protein's discovery in the 1980s, BDNF has been labeled as "Miracle-Gro" for the brain because of its role in enhancing memory and the growth of nerve cells.

"We believe that our study shows a precise biological mechanism behind increased BDNF production in mammals due to exercise," says study senior investigator and cell biologist Moses Chao, PhD. "Unraveling the mysteries of BDNF is important as we seek more ways to naturally keep mammalian brains healthy, including those of people," says Chao, a professor at NYU Langone and its Skirball Institute of Biomolecular Medicine.

"Our latest findings suggest how we might boost production of BDNF as studies have confirmed that doing so protects the brain," says Chao, who notes that studies in people have already linked exercise, increased BDNF levels, and lower rates of dementia. Still other studies have shown that BDNF levels in the brains of people with Alzheimer's or Huntington's disease are, on average, half that of people without either brain-damaging disease.

Among the key findings of the current study was that a ketone, a chemical naturally produced in the liver called beta-hydroxybutyrate (DBHB), triggers biological reactions that activate the BDNF gene to produce more of its protein. DBHB has long been known to build up in the body and brain with exercise. Ketones are "by-product" chemicals made when animals break down fat as an alternative energy source after having drained more readily available sugar stores during exercise.

Specifically, Chao says, the researchers found that DBHB prevents other

proteins in the brain known as histone deacetylase complexes, or HDACs, from suppressing BDNF production by altering the environment of the BDNF gene. HDACs are among the epigenetic, chemical mechanisms that turn gene action up and down by controlling access to the gene through protein modifications.

Using commercially available psychiatric drugs already known to stabilize mood and prevent seizures by inhibiting HDACs, the researchers found that they could "open up" the otherwise "closed" BDNF gene, making it easier to trigger its action and increase BDNF production by as much as 50 percent.

According to Chao and his colleagues, their study shows that DBHB naturally mimics the action of HDAC inhibitors in the brain.

For the study, researchers compared the brains of mice that had been allowed to run at will on a cage wheel for a month with the brains of mice that did not run. Chemical analyses were later performed on the animals' brain cells in the lab to determine molecular changes in BDNF production from exposure to HDAC inhibitors and DBHB. Genetic testing was used to determine which genes were more active than others.

Chao and his research colleagues next plan to investigate what parts of the brain are most affected by ketone buildup and what factors promote or discourage HDAC activity.

More information: *eLife* , DOI: 10.7554/eLife.15092

Provided by New York University School of Medicine