How Exercise May Bolster the Brain

Exercise prompts the liver to pump out a little-known protein that appears to rejuvenate the brain, a new study found.

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Exercise may help change exercisers' brains in surprising ways, according to a new study of physical activity and brain health. The study, which included both mice and people, found that exercise prompts the liver to pump out a little-known protein, and that chemically upping the levels of that protein in out-of-shape, elderly animals rejuvenates their brains and memories. The findings raise provocative questions about whether the brain benefits of exercise might someday be available in a capsule or syringe form — essentially "exercise in a pill."

We already have considerable evidence, of course, that physical activity protects brains and minds from some of the declines that otherwise accompany aging. In past rodent studies, animals that ran on wheels or treadmills produced more new neurons and learned and remembered better than sedentary mice or rats. Similarly, older people who took up walking for the sake of science added tissue volume in portions of their brains associated with memory. Even among younger people, those who were more fit than their peers tended to perform better on cognitive tests.

But many questions remain unanswered about how, at a cellular level, exercise remodels the brain and alters its function. Most researchers suspect that the process involves the release of a cascade of substances inside the brain and elsewhere in the body during and after exercise. These substances interact and ignite other biochemical reactions that ultimately change how the brain looks and works. But what the substances are, where they originate and how they meet and mingle has remained unclear.

So, for the new study, which was published this month in Science, researchers at the University of California, San Francisco, decided to look inside the minds and bloodstreams of mice. In past research from the same lab, the scientists had infused blood from young mice into older ones and seen improvements in the aging animals' thinking. It was like "transferring a memory of youth through blood," says Saul Villeda, a professor at U.C.S.F., who conducted the study with his colleagues Alana Horowitz, Xuelai Fan and others.

Those benefits were a result of the donor animals' young age, though, not their exercise habits. The scientists suspected that exercise would spark additional changes in the bloodstream that might be transferable, whatever an animal's years.

So, as a first step in the new study, they had both young and elderly mice run for six weeks, then transfused blood from both groups into elderly, sedentary animals. Afterward, those aged mice performed better on cognitive tests than equally elderly controls, whether their transfusions had come from young runners or old. They also showed spikes in the creation of new neurons in their brains' memory centers. It was the donors' activity that had mattered, not their age.

Intrigued, the scientists next set out to find what differed in the exercisers' blood. Using sophisticated mass spectrometry and other techniques, they separated out and enumerated various proteins in the running animals' blood that were not seen in similar profusion in blood from inactive mice.

They then zeroed in on one little-studied protein known as GPLD1 (its scientific name is long and unpronounceable). The slightly mysterious protein is known to be produced mostly in the liver, an organ not usually thought to have much interplay with the brain. But levels of the protein were elevated enough after exercise to justify more investigation.

So, the researchers now employed genetic engineering to amplify the release of GPLD1 from the livers of old, inactive mice. Afterward, those animals performed almost like young mice on tests of learning and memory, and their brains teemed with far more newborn neurons than in other old mice. In effect, they gained the brain benefits of exercise without the effort of actually exercising.

To ensure that this reaction was not purely rodent-based, the scientists also checked blood drawn from elderly people. The older men and women who habitually walked for exercise showed higher levels of GPLD1 in their bloodstreams than those who did not.

The combined upshot of these findings seems to be that exercise improves brain health in part by prompting the liver to pump out extra amounts of GPLD1, Dr. Villeda says, although it is not yet clear how the protein then changes the brain. Subsequent experiments by the scientists showed that the protein probably does not breach the blood-brain barrier and act directly on the brain, Dr. Villeda says. Instead, it is likely to incite alterations in other tissues and cells elsewhere in the body. These tissues, in turn, produce yet more proteins that have effects on other tissues that eventually lead to direct changes to the neurotransmitters, genes and cells in the brain itself that undergird cognitive improvements.

Dr. Villeda believes that if further experiments show that GPLD1, in isolation, helps to initiate this molecular chain reaction, then it is at least conceivable that infusions of the substance might offer the brain benefits of exercise to people who are too frail or disabled for regular physical activity.

This experiment principally involved mice, though, not people, and does not tell us anything about the systemic effects of extra GPLD1, which in high amounts might be undesirable. More fundamentally, the findings highlight the pervasive, intricate, whole-body effects of exercise, with the liver, in this case, somehow changing minds and brains after workouts. At the moment, it is impossible to know if the same synchronized, interwoven processes all would occur in response to a GPLD1 exercise pill and, if not, whether it could be considered an exercise pill at all.

Dr. Villeda is quick to agree that pharmaceutical GPLD1, even if effective for brain health, "would not recapitulate the benefits of exercise." There would be none of the usual fat burning, muscle building or cardiovascular improvements, he points out. But he hopes that, if future experiments in his lab with animals and people show consistent results, the substance might eventually help people who find moving difficult to think better.