Long-term aerobic exercise prevents age-related brain changes

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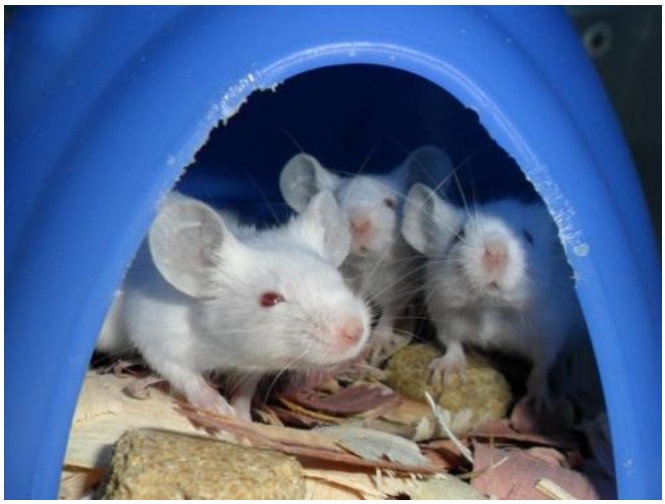

Credit: Martha Sexton/public domain

A study of the brains of mice shows that structural deterioration associated with old age can be prevented by long-term aerobic exercise starting in mid-life, according to the authors of a research article publishing in the Open Access journal *PLOS Biology* on October 29th. Gareth Howell, Ileana Soto and their colleagues at The Jackson Laboratory in Bar Harbor, Maine (USA) found that structural changes that make the blood-brain barrier leaky and result in inflammation of brain tissues in old mice can be mitigated by allowing the animals to run regularly, so providing a potential explanation for the beneficial effects of exercise on dementia in humans.

Old age is the major risk factor for Alzheimer's disease, like many other diseases. Age-related cognitive deficits are due partly to changes in neuronal function, but also correlate with deficiencies in the blood supply to the brain and with low-level inflammation. In this study, the authors set out to investigate the changes in the brains of normal young and aged laboratory mice by comparing by their gene expression profiles using a technique called RNA sequencing, and by comparing their structures at high-resolution by using fluorescence microscopy and electron microscopy. The gene expression analysis indicated age-related changes in the expression of genes relevant to vascular function (including focal adhesion, vascular smooth muscle and ECM-receptor interactions), and inflammation (especially related to the complement system, which clears foreign particles) in the brain cortex.

These changes were accompanied by a decline in the function of astrocytes (key support cells in brain) and loss of pericytes (the contractile cells that surround small capillaries and venules and maintain the blood-brain barrier) and of major components of the basement membrane, which forms an integral part of the blood-brain barrier, as well as an increase in the density and functional activation of the immune cells known as microglia/monocytes, which scavenge the brain for infectious agents and damaged cells. Dr. Soto, lead author on the study, says: "Collectively, our data suggests that normal aging causes significant dysfunction to the cortical neurovascular unit, including basement membrane reduction and pericyte loss. These changes correlate strongly with an increase in microglia/monocytes in the aged cortex,"

Physical activity is already known to ameliorate the cognitive decline and sensorimotor deficits seen in old age in humans as well as in mice. To investigate the impact of long-term physical exercise on the brain changes seen in the aging mice, the researchers provided the animals with a running wheel from 12 months old (equivalent to middle aged in humans) and assessed their brains at 18 months (equivalent to ~60yrs old in humans, when the risk of Alzheimer's disease is greatly increased). Young and old mice alike ran about two miles per night, and this physical activity improved the ability and motivation of the old mice to engage

in the typical spontaneous behaviors that seem to be affected by aging. This exercise significantly reduced age-related pericyte loss in the brain cortex and improved other indicators of dysfunction of the vascular system and blood-brain barrier. Exercise also decreased the numbers of microglia/monocytes expressing a crucial initiating component of the complement pathway that others have shown previously to play are role in age-related cognitive decline. Interestingly, these beneficial effects of exercise were not seen in mice deficient in a gene called Apoe, variants of which are a major genetic risk factor for Alzheimer's disease. The authors also report that Apoe expression in the brain cortex declines in aged mice and this decline can also be prevented by exercise.

Numerous studies have correlated the development of Alzheimer's disease with vascular dysfunction during aging. This study suggests that this dysfunction might be driven by astrocyte dysfunction and/or pericyte loss leading to a breakdown of the blood-brain barrier. But further work will be required to establish the mechanism(s): what is the role of the complement-producing microglia/macrophages, how does Apoe decline contribute to age-related neurovascular decline, does the leaky blood-brain barrier allow the passage of damaging factors from the circulation into the brain?

Previous studies showing that exercise is beneficial for the human brain suggest the effects on mice are relevant for human health. The authors conclude that, "Our data, supported by data from human studies, point towards focusing efforts on understanding the impact of aging and lifestyle choices on neurovascular unit decline and neuroinflammation, particularly astrocyte and pericyte dysfunction. Dr. Howell believes as a society we need to work hard to ensure we maintain an active lifestyle wherever possible. "In this day and age, with so many distractions and conveniences, it is easy to fall into a lifestyle that does not include enough exercise. With an aging population, I hope our study helps in encouraging a healthy lifestyle that includes exercise." He goes on to say that: "For those that are unfortunately unable to exercise, our study provides insight into a possible mechanism by which exercise may benefit the aging brain and may one day lead to improved treatments for age-related cognitive decline, Alzheimer's disease and other neurodegenerative disorders."

More information: Soto I, Graham LC, Richter HJ, Simeone SN, Radell JE, Grabowska W, et al. (2015) APOE Stabilization by Exercise Prevents Aging Neurovascular Dysfunction and Complement Induction. *PLoS Biol* 13(10): e1002279. DOI: 10.1371/journal.pbio.1002279

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