NEUROLOGICAL HEALTH

How Exercise Might "Clean" the Alzheimer's Brain

Hints at potential treatments for age-related dementia and memory loss

By Jonathan D. Grinstein on October 16, 2018

Credit: Getty Images

For the 50 million individuals worldwide ailing from Alzheimer's disease, the announcements by pharmaceutical giants earlier this year that they will end research on therapeutics were devastating. The news is even more devastating considering projections that 100 million more people will be diagnosed with Alzheimer's disease across the globe by 2050, all potentially without a medical means to better their quality of life.

As it happens, though, the pursuit of a therapeutic has been given a lifeline. New research shows that physical exercise can "clean up" the hostile environments in the brains of Alzheimer's mice, allowing new nerve cells in the hippocampus, the brain structure involved in memory and learning, to enable cognitive improvements, such as learning and memory. These findings imply that pharmacological agents that enrich the hippocampal environment to boost cell growth and survival might be effective to recuperate brain health and function in human Alzheimer's disease patients.

The brain of an individual with Alzheimer's disease is a harsh place filled with buildups of harmful nerve cell junk—amyloid plaques and neurofibrillary tangles—and dramatic loss of nerve cells and connections that occur with severe cognitive decline, such as memory loss. Targeting and disrupting this harmful junk, specifically amyloid plaques, to restore brain function has been the basis of many failed clinical trials. This futility has led to a re-evaluation of the amyloid hypothesis—the central dogma for Alzheimer's disease pathology based on the toxic accumulation of amyloid plaques.

At the same time, there have been traces of evidence for exercise playing a preventative role in Alzheimer's disease, but exactly how this occurs and how to take advantage of it therapeutically has remained elusive. Exercise has been shown to create biochemical changes that fertilize the brain's environment to mend nerve cell health. Additionally, exercise induces restorative changes relevant to Alzheimer's disease pathology with improved nerve cell growth and connectivity in the hippocampus, a process called adult hippocampal neurogenesis. For these reasons, the authors Choi et al. explored whether exercise-induced effects and hippocampal nerve cell growth could be utilized for therapeutic purposes in Alzheimer's disease to restore brain function.

The researchers found that exercised animals from a mouse model of Alzheimer's had greatly enhanced memory compared to sedentary ones due to improved adult hippocampal neurogenesis and a rise in amounts of a specific molecule that promotes brain cell growth called BDNF. Importantly, they could recover brain function,

specifically memory, in mice with Alzheimer's disease but without exercise by increasing hippocampal cell growth and BDNF levels using a combination of genetic —injecting a virus—and pharmacological means. On the other hand, blocking hippocampal neurogenesis early in Alzheimer's worsened nerve cell health later in stages, leading to degeneration of the hippocampus and, subsequently, memory function. This provides preclinical proof of concept that a combination of drugs that increase adult hippocampal neurogenesis and BDNF levels could be disease-modifying or prevent Alzheimer's disease altogether.

With this work, things don't look promising for the amyloid hypothesis—that Alzheimer's disease is caused by the deposition of amyloid plaques. In this study, it was shown that eliminating amyloid plaques were not to necessary to ameliorate memory defects, which is consistent with evidence that plaques can also be found in the brains of healthy individuals. On the contrary, we may be looking at a new and improved fundamental theory for Alzheimer's disease based on promoting a healthier brain environment and adult hippocampal neurogenesis.

However, this inspiring news should be taken with an important caution—mouse

models of Alzheimer's are notorious for failing to translate into humans such that treatments that have worked to remedy mice have failed for humans. Besides, even if

these findings translate into humans, it may apply to a fraction of Alzheimer's individuals with relevant genetic components to the mouse model utilized. Future studies will need to replicate these results in mouse models emulating the range of known Alzheimer's disease genetic milieus and, more importantly, prove its medical relevance to human disease.

Before translating these findings into human patients, there remains significant research to establish that a medication or drug could mimic the effects of exercise—exercise mimetics—by "cleaning up" the brain with BDNF and stimulating neurogenesis to combat Alzheimer's disease. Currently, the method for administering BDNF to animals in the lab—by direct injection into the brain—is not ideal for use in people, and a hippocampal neurogenesis stimulating compound remains elusive.

Future attempts to generate pharmacological means to imitate and heighten the benefits of exercise—exercise mimetics—to increase adult hippocampal neurogenesis in addition to BDNF may someday provide an effective means of improving cognition in people with Alzheimer's disease. Moreover, increasing neurogenesis in the earliest

stages of the disease may protect against neuronal cell death later in the disease, providing a potentially powerful disease-modifying treatment strategy.

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