

Transplantation of new brain cells reverses memory loss in Alzheimer's disease model

July 16 2014



Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

A new study from the Gladstone Institutes has revealed a way to alleviate the learning and memory deficits caused by apoE4, the most important genetic risk factor for Alzheimer's disease, improving cognition to normal levels in aged mice.

In the study, which was conducted in collaboration with researchers at UC San Francisco and published today in the *Journal of Neuroscience*, scientists transplanted inhibitory neuron progenitors—early-stage brain cells that have the capacity to develop into mature [inhibitory neurons](#)—into two mouse models of Alzheimer's disease, apoE4 or apoE4 with

accumulation of amyloid beta, another major contributor to Alzheimer's. The transplants helped to replenish the brain by replacing cells lost due to apoE4, regulating brain activity and improving learning and memory abilities.

"This is the first time transplantation of inhibitory neuron progenitors has been used in aged Alzheimer's disease models," said first author Leslie Tong, a graduate student at the Gladstone Institutes and UCSF.

"Working with older animals can be challenging from a technical standpoint, and it was amazing to see that the cells not only survived but affected activity and behavior."

The success of the treatment in older mice, which corresponded to late adulthood in humans, is particularly important, as this would be the age that would be targeted were this method ever to be used therapeutically in people.

"This is a very important proof of concept study," said senior author Yadong Huang, MD, PhD, an associate investigator at Gladstone Institutes and associate professor of neurology and pathology at UCSF.

"The fact that we see a functional integration of these cells into the hippocampal circuitry and a complete rescue of learning and [memory deficits](#) in an aged model of Alzheimer's disease is very exciting."

A balance of excitatory and inhibitory activity in the brain is essential for normal function. However, in the apoE4 model of Alzheimer's disease—a [genetic risk factor](#) that is carried by approximately 25% of the population and is involved in 60-75% of all Alzheimer's cases—this balance gets disrupted due to a decline in inhibitory regulator cells that are essential in maintaining normal brain activity. The hippocampus, an important memory center in the brain, is particularly affected by this loss of inhibitory neurons, resulting in an increase in network activation that is thought to contribute to the learning and memory deficits

characteristic of Alzheimer's disease. The accumulation of amyloid beta in the brain has also been linked to this imbalance between excitatory and inhibitory activity in the brain.

In the current study, the researchers hoped that by grafting inhibitory neuron progenitors into the hippocampus of aged apoE4 mice, they would be able to combat these effects, replacing the lost cells and restoring normal function to the area. Remarkably, these new inhibitory neurons survived in the hippocampus, enhancing inhibitory signaling and rescuing impairments in learning and memory.

In addition, when these inhibitory progenitor cells were transplanted into apoE4 mice with an accumulation of amyloid beta, prior deficits were alleviated. However, the new inhibitory neurons did not affect [amyloid beta](#) levels, suggesting that the cognitive enhancement did not occur as a result of amyloid clearance, and amyloid did not impair the integration of the transplant.

According to Dr. Huang, the potential implications for these findings extend beyond the current methods used. "Stem cell therapy in humans is still a long way off. However, this study tells us that if there is any way we can enhance inhibitory neuron function in the hippocampus, like through the development of small molecule compounds, it may be beneficial for Alzheimer disease patients."

Provided by Gladstone Institutes

Citation: Transplantation of new brain cells reverses memory loss in Alzheimer's disease model (2014, July 16) retrieved 28 April 2024 from <https://medicalxpress.com/news/2014-07-transplantation-brain-cells-reverses-memory.html>

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