'Rejuvenating' the Alzheimer's brain

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Alzheimer's disease is the main cause of dementia and current therapeutic strategies cannot prevent, slow down or cure the pathology. The disease is characterized by memory loss, caused by the degeneration and death of neuronal cells in several regions of the brain, including the hippocampus, which is where memories are initially formed.

Researchers from the Netherlands Institute for Neuroscience (NIN) have identified a small molecule that can be used to rejuvenate the brain and counteract the memory loss.

New cells in old brains

The presence of adult-born cells in the hippocampus of old people was recently demonstrated in scientific studies. It suggests that, generally speaking, the so-called process of adult neurogenesis is sustained throughout adulthood. Adult neurogenesis is linked to several aspects of cognition and memory in both animal models and humans, and it was reported to sharply decrease in the brains of patients with Alzheimer's disease. Researchers also found that higher levels of adult neurogenesis in these patients seem to correlate with better cognitive performance before death. "This could suggest that the adult-born neurons in our brain may contribute to a sort of cognitive reserve that could later on provide higher resilience to memory loss," says Evgenia Salta, group leader at the NIN. Therefore, researchers from the NIN investigated if giving a boost to adult neurogenesis could help prevent or improve dementia in Alzheimer's disease.

A small molecule with big potential

Salta states, "Seven years ago, while studying a small RNA molecule that is expressed in our brain, called microRNA-132, we came across a rather unexpected observation. This molecule, which we had previously found to be decreased in the brain of Alzheimer's patients, seemed to regulate homeostasis of neural stem cells in the central nervous system." Back then, Alzheimer's was thought to be a disease affecting only mature neuronal cells, so at first glance this finding did not seem to explain a possible role of microRNA-132 in the progression of Alzheimer's.

In this study, the researchers set out to address whether microRNA-132 can regulate adult hippocampal neurogenesis in healthy and Alzheimer's brains. Using distinct Alzheimer's mouse models, cultured human neural stem cells and post-mortem human brain tissue, they discovered that this RNA molecule is required for the neurogenic process in the adult hippocampus. "Decreasing the levels of microRNA-132 in the adult mouse brain or in human neural stem cells in a dish impairs the generation of new neurons. However, restoring the levels of microRNA-132 in Alzheimer's mice rescues neurogenic deficits and counteracts memory impairment related to adult neurogenesis," Sarah Snoeck, technician in the group of Salta, explains.

These results provide a proof-of-concept regarding the putative therapeutic potential of bringing about adult neurogenesis in Alzheimer's. Salta concludes, "Our next goal is to systematically assess the efficacy and safety of targeting microRNA-132 as a therapeutic strategy in Alzheimer's disease."

More information: Hannah Walgrave et al, Restoring miR-132 expression rescues adult hippocampal neurogenesis and memory deficits in Alzheimer's disease, *Cell Stem Cell* (2021). DOI: 10.1016/j.stem.2021.05.001

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