# New method delivers Alzheimer's drug to the brain

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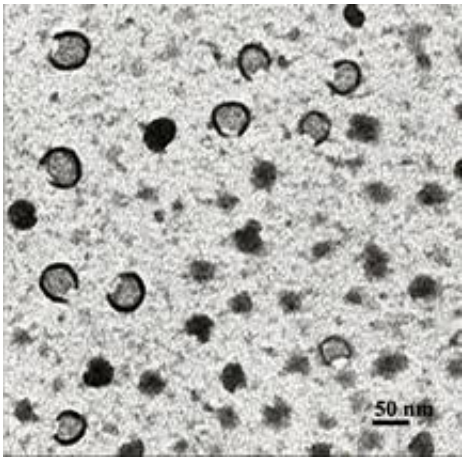


Exosomes, as shown in this electron microscope image, are tiny capsules that are produced by most cells in the body.

(PhysOrg.com) -- Oxford University scientists have developed a new method for delivering complex drugs directly to the brain, a necessary step for treating diseases like Alzheimer's, Parkinson's, Motor Neuron Disease and Muscular Dystrophy.

These diseases have largely resisted attempts to over the last 50 years develop new treatments, partly because of the difficulty of getting effective new drugs to the brain to slow or halt disease progression.

The team has successfully switched off a gene implicated in Alzheimer's

disease in the brains of mice by exploiting exosomes – tiny particles naturally released by cells. The exosomes, injected into the blood, are able to ferry a drug across the normally impermeable blood-brain barrier to the brain where it is needed.

Although this is a significant and promising result, there are a number of steps to be taken before this new form of drug delivery can be tested in humans in the clinic. The study, partly funded by the Muscular Dystrophy Campaign, is published in Nature Biotechnology.

"These are dramatic and exciting results. It's the first time new 'biological' medicines have been delivered effectively across the blood-brain-barrier to the brain," says Dr. Matthew Wood of the Department of Physiology, Anatomy and Genetics at the University of Oxford, who led the work.

Exosomes are small capsules that are produced by most cells in the body in varying amounts. These natural nanoparticles are thought to be one of the ways cells communicate with each other and the body's immune system. When exosomes break off from the outer walls of cells, they can take various cellular signals and genetic material with them, transporting this material between different cells.

This led the Oxford University researchers to wonder whether exosomes could be adapted for delivering drugs to different cells and tissues of the body.

"This is the first time this natural system has been exploited for drug delivery," says Dr. Wood.

Novel drugs based on antibodies, peptides or more recently RNA molecules have been developed on many occasions to target specific parts of disease pathways. While these have shown good results in the

lab, too often it has proved difficult to get the drugs to the right part of the body to see any effect in humans.

Currently, delivering any such type of therapy to the brain would have to involve neurosurgery. Nothing delivered intravenously would be able to cross from the blood into the brain.

"The major barrier for these drugs is delivery," explains Dr. Wood. "This problem becomes even greater when you want to reach the brain. The blood-brain barrier – which stops most things in the blood stream from crossing to our brains – is much too great an obstacle."

The Oxford University team set out to adapt naturally occurring exosomes to deliver a gene therapy. They used an RNA sequence – RNA is a molecule related to DNA that also caries genetic information – that switches off a gene that's implicated in Alzheimer's disease.

To be able to make the approach work, they would need to be able to load the exosomes with the RNA, the drug. But they would also need to be able to target the right tissues in the body.

First of all, they produced and purified exosomes from mouse cells. They then developed and patented new methods to both insert RNA molecules into the exosomes and add protein elements into the exosome coat that would target nerve cells.

The exosomes, injected intravenously into mice, crossed the blood-brain barrier and ended up in the brain. Once there, the RNA was able to switch off a gene implicated in the build up of malformed protein in Alzheimer's disease. This resulted in a 60% decrease in the brain of the problem enzyme encoded by the gene.

"We've shown that a natural system could be exploited to deliver drugs

across the blood-brain barrier," says Dr. Wood. "We believe we can use this same technology for Alzheimer's, motor neuron disease, Parkinson's and Huntington's. All we need is a different RNA each time.

"The next steps are to test the exosomes in a mouse model of Alzheimer's disease to see if it makes a difference to disease progression," Dr. Wood explains.

He also notes that other steps would be needed before exosomes could be tested in humans, including safety tests and scaling up the procedures.

"Many of these diseases have not been possible to treat in the last 50 years using standard drugs. New drugs have been developed based on complex biological molecules – antibodies, peptides, and RNA – but all require new ways of delivering the drugs," he says.

"These natural nanoparticles would be administered intravenously, or perhaps even orally, and would still reach the brain."

Provided by Oxford University