Neuroprotectant delivered to brain in nanoparticles may improve stroke treatment, outcomes

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When NA1, a neuroprotectant, was delivered to the brain in nanoparticles, it reduced stroke severity and improved survival in a mouse model of stroke, according to preliminary research to be presented at the American Stroke Association's International Stroke Conference 2021.

In an earlier human trial (the ESCAPE-NA1 trial), NA1, a small peptide designed to save brain cells from death after stroke, showed mixed results when NA1 was administered to patients undergoing clot removal for severe stroke. Some patients in the trial also received the intravenous clot-busting medication tissue plasminogen activator (tPA), and these patients in particular showed a lack of improvement in functional outcomes from NA1.

"NA1 binds many organs, cells and proteins in the body. Without protection, it cannot get into the brain with high efficiency and specificity and may otherwise get into cells where we don't want it, or bind and deactivate other treatments, such as the clot-busting medicine tPA," said Jiangbing Zhou, Ph.D., co-senior author of the study and associate professor of neurosurgery and biomedical engineering at Yale University in New Haven, Connecticut.

To deliver NA1 precisely where it is needed, the research team in this study created stroke-targeting nanoparticles to encapsulate and deliver NA1 to portions of the brain being deprived of oxygen in a stroke mouse model.

In the mouse model study conducted from 2016 to 2020, researchers compared the ability of nanoparticles filled with NA1 and non-encapsulated NA1 to improve survival, reduce stroke size and reduce brain swelling. Both treatments contained the same dose of NA1 (50 micrograms) delivered intravenously to mice with blockage of a brain artery.

Researchers found:

- Stroke size was reduced 69.8% among mice treated with NA1-loaded nanoparticles, compared with 0.7% for those treated with NA1 that was not encapsulated.
- Brain swelling was reduced 60.3% among mice treated with NA1-loaded nanoparticles, compared with 3.3% for those treated with NA1 that was not encapsulated.
- Median days of survival were more than 14 days among mice treated with NA1-loaded nanoparticles (mice in this model usually survive significantly less than 14 days), compared to 6 days for those treated with NA1 that was not encapsulated.

"When delivered by nanoparticles, the same dose of NA1 that was not effective in an earlier study

reached the stroke area and provided a surprising degree of effectiveness. The use of nanoparticles in stroke treatment may open new doors to delivering NA1 and other promising therapies to the brain," said Kevin N. Sheth, M.D., co-senior author of the study and professor of neurology and neurosurgery at Yale University.

Since the nanoparticles themselves act as antioxidants and may improve stroke outcome, some of the mice were also treated with nanoparticles not containing NA1. Those mice had intermediate improvements: stroke size reduced by 52.2%, brain swelling reduced by 30.2% and a median survival of 10 days.

"We have not had any recent major advances in the delivery of brain-protective agents for stroke. These results suggest a significant effort to change that landscape," Sheth said.

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