Transporting Antibodies Across the Blood–brain Barrier to Treat Alzheimer's Disease

2023-03-12
Researchers led by Tokyo Medical and Dental University (TMDU) find that antibody fragments encapsulated in nanomicelles cross the blood–brain barrier and reduce the levels of toxic Aβ species in the brain of an Alzheimer's disease model mouse.

Sometimes the best things in life come by chance, when we happen to be in the right place at the right time. Now, researchers from Japan have found a way to ensure that new medications are delivered to the right place in the body and at the right timepoint in disease progression, so that they have the best effect.

In a study published recently in the Journal of Nanobiotechnology, researchers led by Tokyo Medical and Dental University (TMDU) have revealed that a novel delivery system delivers treatment to where it is needed most in a mouse model of Alzheimer's disease (AD).

AD is a common neurodegenerative disease that causes dementia. It is characterized by the accumulation of a protein called amyloid β (Aβ) in the brain, and a number of different toxic forms of Aβ have been identified that impair brain function, notably Aβ oligomers (AβOs).

"Multiple clinical trials have attempted to use an anti-Aβ antibody to treat AD, but the results have been unsatisfactory," says lead author of the study Akiko Amano. "One potential explanation for this is that the blood–brain barrier (BBB) prevents most full-length antibodies from entering the brain."

To address this challenge, the researchers previously developed glucosylated (sugar-linked) polymeric nanomicelles (PMs), which are tiny, hollow balls that could successfully cross the BBB via transcytosis in mouse brain capillary endothelial cells; this process was mediated by

glucose-transporter-1 and induced by an increase in blood glucose levels after the mice experienced fasting conditions. In this study, Takanori Yokota and colleagues filled PMs with fragments of an anti-AβO antibody, injected them into a mouse model of AD, and assessed the effects on the brain and on behavior.

"The results were very clear," explains senior author Nobuo Sanjo. "Administration of anti-AβO antibody fragments through PMs significantly reduced the amounts of various toxic Aβ species. In addition, the Aβ plaques that did form were smaller and less dense than those seen in untreated mice."

Next, the researchers analyzed the behavior of the mice and found that the mice treated with the antibody fragment-filled PMs had better learning and spatial memory than untreated mice. "Our findings suggest that delivering sufficient levels of antibodies to the brain using PMs can reduce toxic Aβ species and slow AD progression in mice," says Amano.

Peripheral administration of nanomicelle-encapsulated anti-Aβ oligomer fragment antibody reduces various toxic Aβ species in the AD model mouse brain.

Given that the failure of anti-Aβ antibodies to improve cognitive function in human clinical trials was likely because of an insufficient supply of the antibodies in the brain, PM-encapsulated antibody fragments could represent an effective way to prevent AD progression. In addition, new candidates for AD treatment that degrade toxic Aβs and reduce their toxic effects could also be delivered to the brain using the same PM-based system.

The newly developed antibody 6H4 fragments (Fabs) specific to Aβ oligomers, encapsulated in the polymeric nanomicelles (PMs), were peripherally administrated to AD model mouse for 10 weeks. In mice that were administered anti-AβO 6H4 Fabs in the PMs, various toxic Aβ species (Aβ oligomers, Aβ42s, N3pE Aβs, Aβs with toxic conformer) and the presence of Aβ plaques with dense cores in the brain were significantly reduced. Additionally, suppression of

the progression of pathological processes of AD was supported by the prevention of cognitive-behavioral decline in the spatial memory tests.

Read the original article on Tokyo Medical and Dental University.