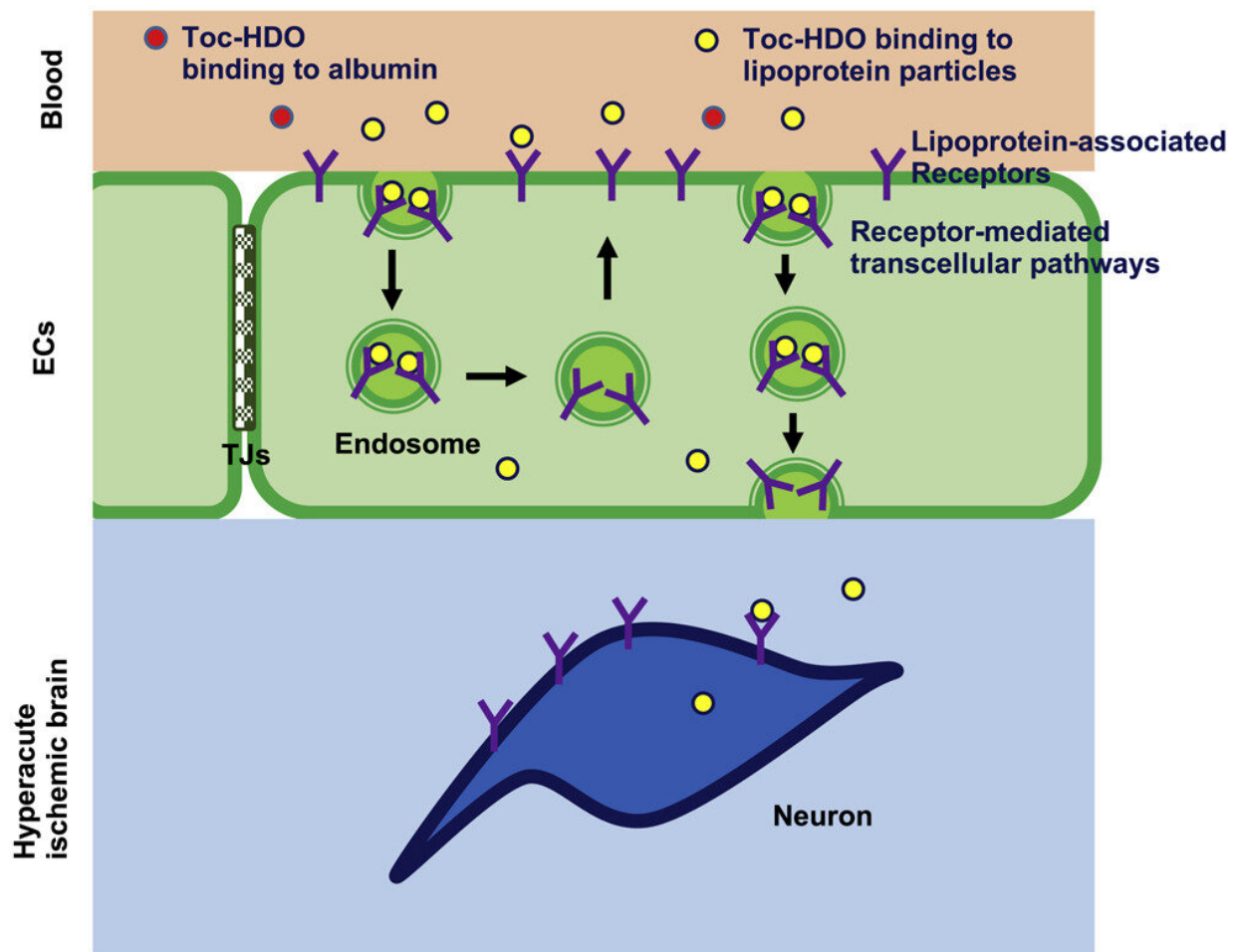


Lipid molecules may help get stroke therapies into the brain

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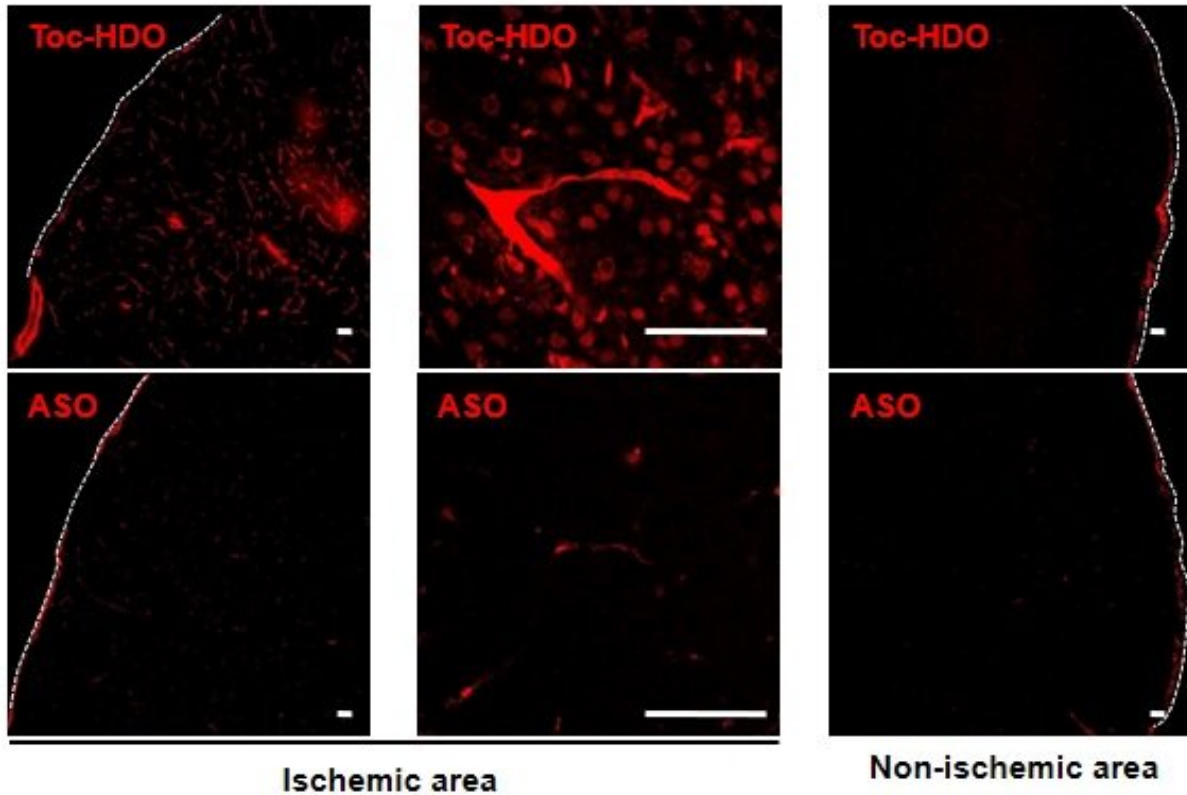


Graphical abstract. Credit: *Molecular Therapy* (2023). DOI: 10.1016/j.ymthe.2023.01.016

To get therapies into the brain after a stroke, researchers are increasingly making use of the blood–brain barrier, which allows only certain molecules to pass from the blood into the brain. In a study published earlier this year in *Molecular Therapy*, Japanese researchers have found that antisense oligonucleotides—specialized molecules that can modulate RNA and alter protein production—are preferentially taken up from the blood into areas of stroke damage when they're linked to a specific kind of lipid known as α -tocopherol (TOC).

Current stroke therapies are only effective if they are delivered within a short window of time, which limits their effectiveness in many patients. Many new therapies are being investigated that can be applied outside this short window of opportunity.

One such therapy involves the use of antisense oligonucleotides, which can be targeted to increase the production of beneficial proteins after a stroke, for example, or to decrease the production of harmful proteins. However, getting these molecules into the right area at the right time can be difficult, something that the researchers at Tokyo Medical and Dental University wanted to address.



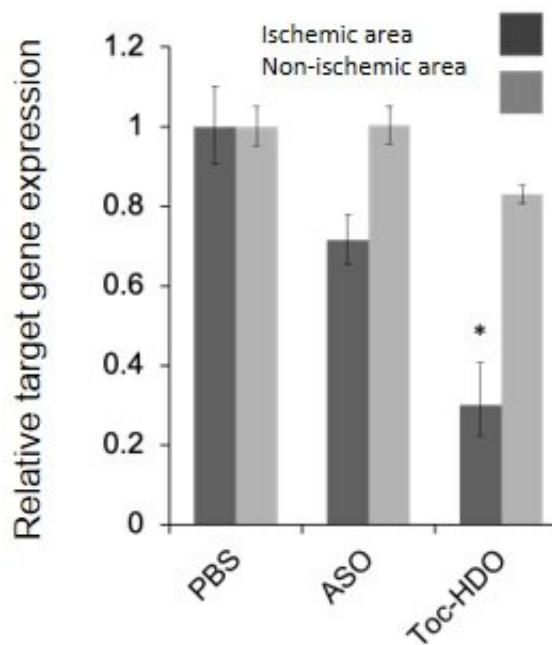
Toc-HDO, but not ASO, could be effectively delivered into ischemic brain regions, in the hyperacute phase of ischemic stroke. Credit: Department of Neurology and Neurological Science, TMDU

"We've recently developed an [antisense oligonucleotide](#) known as a DNA/RNA heteroduplex oligonucleotide, or HDO," says senior author of the study Takanori Yokota. "To see how different lipids affect the uptake of HDO in the brain, we linked it to either cholesterol or TOC and then injected it into the blood of mice who had been given an experimentally induced stroke in just one side of the brain."

Unexpectedly, the TOC-linked molecules were observed at very high levels in the stroke-lesioned side of the brain only, whereas the cholesterol-linked molecules were high in both sides of the brain. This

suggests that TOC specifically increases HDO uptake after stroke, while cholesterol does not.

Furthermore, because HDO can be tailored to target different genes, it was used to silence a gene known to be beneficial in stroke. As expected, the researchers observed greater areas of stroke-related damage in the mice treated with this TOC-linked HDO.



Toc-HDO showed significantly greater silencing effect of Target gene in ischemic brain regions. Credit: Department of Neurology and Neurological Science, TMDU

"Together, our findings suggest that TOC-linked HDO is safe to use and is preferentially taken up and incorporated into cells in areas of stroke damage," says Yokota. "This [delivery method](#) is potentially very useful for the targeted up- or down-regulation of protein expression after

stroke."

Given the relative lack of stroke therapies targeting the pathological processes that happen after a stroke, the current findings are very important. Increasing anti-inflammatory proteins and/or lowering inflammatory proteins in the stroke-lesioned brain is a promising way to avoid secondary damage to the [brain](#) after a stroke has occurred, and will lead to reductions in stroke-related disabilities.

More information: Fuying Li et al, Preferential delivery of lipid-ligand conjugated DNA/RNA heteroduplex oligonucleotide to ischemic brain in hyperacute stage, *Molecular Therapy* (2023). [DOI: 10.1016/j.ymthe.2023.01.016](#)

Provided by Tokyo Medical and Dental University

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