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Strategy discovered to prevent Alzheimer's-associated traffic jams in the brain

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Amyloid beta (Aβ) proteins, widely thought to cause Alzheimer's disease (AD), block the transport of vital cargoes inside brain cells. Scientists at the Gladstone Institute of Neurological Disease (GIND) have discovered that reducing the level of another protein, tau, can prevent Aβ from causing such traffic jams.

Neurons in the brain are connected to many other neurons through long processes called axons. Their functions depend on the transport of diverse cargoes up and down these important pipelines. Particularly important among the cargoes are mitochondria, the energy factories of the cell, and proteins that support cell growth and survival. Aβ proteins, which build up to toxic levels in the brains of people with AD, impair the axonal transport of these cargoes.

"We previously showed that suppressing the protein tau can prevent Aβ from causing memory deficits and other abnormalities in mouse models of AD," explained Lennart Mucke, MD, GIND director and senior author of the study. "We wondered whether this striking rescue might be caused, at least in part, by improvements in axonal transport."

The scientists explored this possibility in mouse neurons grown in culture dishes. Neurons from normal mice or from mice lacking one or both tau genes were exposed to human Aβ proteins. The Aβ slowed down axonal transport of mitochondria and growth factor receptors, but only in neurons that produced tau and not in neurons that lacked tau. In the absence of the Aβ challenge, tau reduction had no effect on axonal

transport.

"We are really excited about these results," said Keith Vossel, MD, lead author of the study. "Whether tau affects axonal transport or not has been a controversial issue, and nobody knew how to prevent Aβ from impairing this important function of neurons. Our study shows that tau reduction accomplishes this feat very effectively."

"Some treatments based on attacking Aβ have recently failed in clinical trials, and so, it is important to develop new strategies that could make the brain more resistant to Aβ and other AD-causing factors," said Dr. Mucke. "Tau reduction looks promising in this regard, although a lot more work needs to be done before such approaches can be explored in humans."

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