Two amyloid-beta antibodies found to cause neuronal dysfunction in mice

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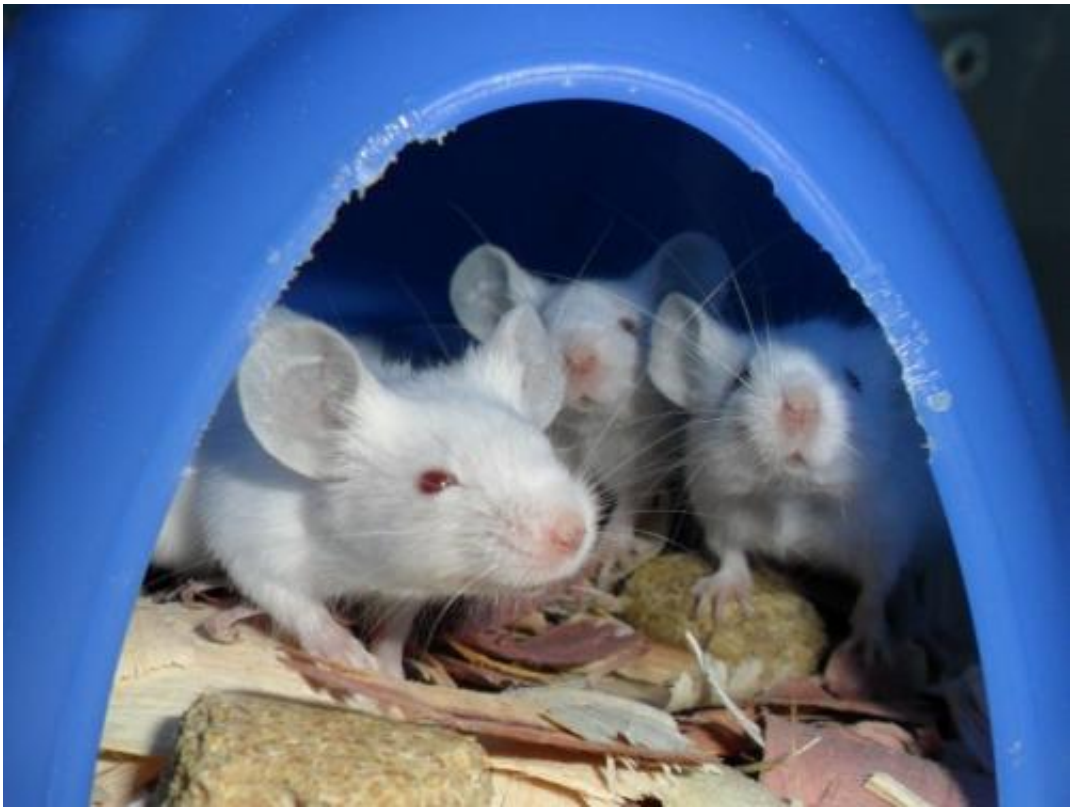

Credit: Martha Sexton/public domain

(Medical Xpress)—A team of researchers working in Germany has found that giving two different types of amyloid-β antibodies to mice genetically engineered to have Alzheimer's type symptoms caused them to develop a type of neuronal dysfunction in their brains. In their paper published in the journal *Nature Neuroscience*, the team described the

studies they undertook of the impact of the antibodies on mouse brains and what it could mean for the development of such antibodies for use in treating human patients.

Scientists believe that a buildup of plague (known as amyloid-β) in the brain is at the root of Alzheimer's disease, and because of that have been hard at working looking to find ways to reduce such buildup to prevent the onset of the disease—one promising area has been using antibodies that have been shown to reduce such buildup, even though it is not really known how they do it. But, for a variety of reasons, few such antibodies have worked as hoped, with many failing to even reach clinical trials. In this new research, the group looked at two such antibodies to see if they could determine why they had failed.

To test the antibodies, the researchers genetically altered test mice to cause amyloid-β to build up in their brains, mimicking Alzheimer's disease. They then administered one of the antibodies, bapineuzumab, to both genetically altered and non-altered mice to see what impact it had. In vivo two-photon imaging revealed that the antibody did indeed reduce plague in the mice's brains, but it also caused an increase in cortical hyperactivity—the rapid firing of neurons. In contrast, there was no such increase in mice that had not been genetically altered. The team repeated the test on mice that had been altered in the same way but had not yet developed plague buildup, and found the same increase in neuronal firing. The group then conducted the same type of tests on the antibody A-beta and found the same results.

Because they found the same results in two different antibody tests, the researchers believe that they have found a connection between amyloid-β and antibody use leading to cortical hyperactivity, though they note that their work does not show the same would be true in humans.

More information: Marc Aurel Busche et al. Decreased amyloid-β

and increased neuronal hyperactivity by immunotherapy in Alzheimer's models, *Nature Neuroscience* (2015). DOI: 10.1038/nn.4163

Abstract

Among the most promising approaches for treating Alzheimer´s disease is immunotherapy with amyloid-β (Aβ)-targeting antibodies. Using in vivo two-photon imaging in mouse models, we found that two different antibodies to Aβ used for treatment were ineffective at repairing neuronal dysfunction and caused an increase in cortical hyperactivity. This unexpected finding provides a possible cellular explanation for the lack of cognitive improvement by immunotherapy in human studies.