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ALZHEIMER DISEASE

Could anti-amyloid-β immunotherapy do more harm than good?

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Anti-amyloid-β (Aβ) immunotherapy has been shown to effectively remove Aβ plaques from the brain, but this apparent success has failed to translate into cognitive improvement in patients with Alzheimer disease (AD). This inconsistency might be explained by a new mouse study published in *Nature Neuroscience*, which indicates that anti-Aβ antibodies worsen rather than reverse the neuronal dysfunction that results from Aβ accumulation in the brain.

"On the basis of earlier work that we had performed in mouse models of AD, we had quite a good picture of disease-related neuronal impairments *in vivo*," explains Arthur Konnerth, who led the new study. "We knew that in the diseased brain, there is coexistence of neurons that are too active ('hyperactive neurons') and neurons that are inactive ('silent neurons'), and we wondered how the immunotherapy would affect these neuronal impairments."

For the study, the researchers employed the PDAPP and Tg2576 mouse models of AD, which were treated with the monoclonal antibodies 3D6 (the mouse equivalent of bapineuzumab) and β1, respectively. Control mice were treated with an isotype-matched antibody that did not target Aβ. *In vivo* two-photon imaging was used to monitor the function of neuronal circuits in the brains of the mice.

In the PDAPP mice, 3D6 treatment reduced the Aβ burden in the brain. In comparison with control mice, however, the 3D6-treated mice exhibited a substantial increase in the proportion of hyperactive neurons in the cortex.

The aggravation of neuronal hyperactivity by anti-Aβ antibodies was confirmed in the Tg2576 mice. Intriguingly, the Tg2576 mice did not display a marked reduction in Aβ burden in response to immunotherapy, suggesting that the effects of this treatment on neuronal dysfunction are independent of its capacity to elicit plaque clearance.

The authors argue that functional *in vivo* assays should be incorporated into protocols for preclinical testing of new treatment strategies for AD. "In our future studies, we will try to implement an effective platform for *in vivo* testing of candidate drugs in AD models, and intensify our efforts towards an understanding of the mechanisms underlying the impaired neuronal function," concludes Konnerth.

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ORIGINAL ARTICLE Busche, M. A. *et al.* Decreased amyloid-β and increased neuronal hyperactivity by immunotherapy in Alzheimer's models. *Nat. Neurosci.* http://dx.doi.org/10.1038/nn.4163