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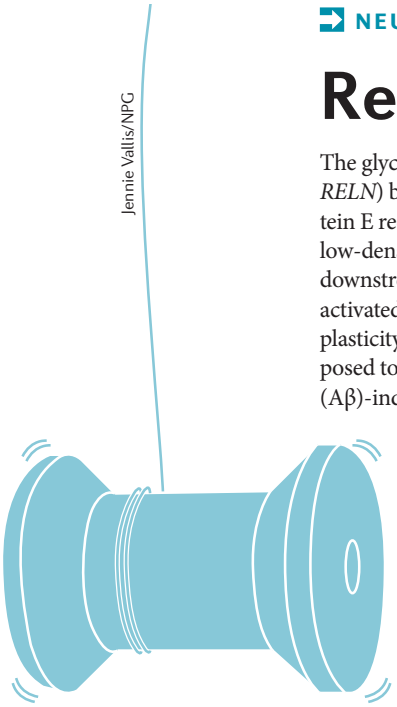

Jennie Vallis/NPG

NEURODEGENERATION

Reelin' from loss

The glycoprotein reelin (encoded by *RELN*) binds to neuronal apolipoprotein E receptor 2 (APOER2) and very low-density lipoprotein receptor, and downstream signalling from these activated receptors promotes synaptic plasticity. This effect has been proposed to protect against the amyloid-β (Aβ)-induced inhibition of long-term potentiation (LTP) that drives Alzheimer disease (AD). However, it has been difficult to obtain evidence of a protective effect of reelin *in vivo*, because *Reln*-knockout mice exhibit developmental and motor defects. Now, Herz and colleagues show that, in the adult CNS, reelin protects against Aβ-induced synaptic and behavioural deficits.

> Aβ may have a more deleterious impact on the plasticity of synapses lacking reelin

To differentiate the role of reelin in the adult brain from its developmental functions, the authors generated inducible conditional *Reln*-knockout mice ($Reln^{CKO}$ mice) that, when treated with tamoxifen, exhibited a brain-wide loss of reelin expression. Tamoxifen-treated $Reln^{CKO}$ mice had no severe phenotype, indicating that the deleterious effects of germline *Reln* knockout may owe to the deficiency of reelin during development.

Electrophysiological recordings of neurons from the hippocampal CA1 region in acute slices from $Reln^{CKO}$ mice that had been treated with tamoxifen at 2 months of age ($Reln^{2mCKO}$ mice) revealed that these animals show increases in the late burst-induced LTP of field excitatory postsynaptic potentials compared with controls, indicating that adult loss of reelin affects synaptic plasticity. Although this result may be unexpected (given the fact that *Reln*-knockout mice have been shown to have impaired LTP), the authors suggest this increase in LTP with reelin loss may reflect the involvement of reelin in inhibitory synapses, glutamate receptor trafficking and/or transcription.

To investigate whether the adult loss of reelin and the resulting changes in synaptic plasticity affect Aβ toxicity, the authors crossed $Reln^{CKO}$ mice with Tg2576(APPSwe) mice, which overexpress an AD-associated mutant form of human amyloid precursor protein (APP; from which Aβ is derived) and exhibit increasing brain concentrations of Aβ with age. Whereas 7-month-old Tg2576(APPSwe) mice (which exhibited a small increase in levels of Aβ oligomers but no Aβ plaque pathology) still performed as well as wild-type mice in a test of learning and memory, 7-month-old $Reln^{2mCKO}$;Tg2576(APPSwe) mice performed poorly. Moreover, the increase in hippocampal LTP observed in $Reln^{2mCKO}$ animals was abrogated in $Reln^{2mCKO}$;Tg2576(APPSwe) mice, indicating that Aβ may have a more deleterious impact on the plasticity of synapses lacking reelin, and thus impair hippocampus-dependent learning and memory.

Overall, this study provides evidence for a protective role of reelin against Aβ in the adult CNS. The authors propose that the ability of reelin to protect synapses from Aβ is diminished by the ε4 allele of the gene encoding APOE (APOE4) — the most common risk allele for AD in humans — as APOE4 impairs APOER2 signalling downstream of reelin.

Natasha Bray

ORIGINAL RESEARCH PAPER
Lane-Donovan, C. *et al.* Reelin protects against amyloid β toxicity *in vivo*. *Sci. Signal.* **8**, ra67 (2015)