NEURODEGENERATIVE DISEASE

Orphan receptor coupled to Aβ production

The purpose of many compounds developed as potential treatments for Alzheimer's disease in recent years is to reduce the accumulation of amyloid-β peptide (Aβ) in the brain, a hallmark of the disease. However, some of the most popular targets, such as γ-secretase, which has a key role in processing the amyloid precursor protein (APP) to form Aβ, have presented considerable challenges owing to their effects on multiple substrates. Now, in a collaborative study, Merchier and De Strooper's research groups have identified the orphan G protein-coupled receptor GPR3 as a potential new therapeutic target for Alzheimer's disease as it specifically activates APP processing by γ-secretase.

The authors carried out a functional genomics screen of a library of adenoviruses, encoding nearly 2,000 potential targets, for modulators of Aβ production. In addition to confirming previously identified targets, such as APP, the serotonin receptor HTR2C and the prostaglandin receptor PTGER2, they found new regulators of Aβ secretion in HEK293 cells expressing APP. The authors chose to focus their efforts on GPR3 as its gene has been mapped to a chromosomal locus that is associated with increased risk of Alzheimer's disease and is highly expressed in regions of the brain that are affected as the disease progresses.

RNA interference-mediated knockdown of GPR3 reduced Aβ secretion by 50% without affecting the general secretion and transport mechanisms of the cell. Aβ results from the sequential cleavage of APP by β- and γ-secretases, but immunoprecipitation and mass spectrometry analyses revealed that both the levels and the activity of β-secretase were unaffected by GPR3 expression. Instead, GPR3 is likely to exert its effects by promoting the cleavage of APP by γ-secretase, as co-expression of the γ-secretase substrate APP-C99 and GPR3 in hippocampal neurons substantially increased Aβ release. Consistent with this finding, GPR3 expression increased the formation and cell surface localization of the mature γ-secretase complex, and treatment with a selective γ-secretase inhibitor abolished the effects of GPR3 on Aβ secretion.

The authors also showed that GPR3 expression in mouse hippocampus increased Aβ production whereas, in hippocampal neurons of *Gpr3*$^{-/-}$ mice, both mature γ-secretase complex formation and Aβ release were markedly decreased. Moreover, when GPR3 was genetically ablated in a mouse model of Alzheimer's disease, the levels of Aβ were dramatically reduced. Importantly, γ-secretase-mediated processing of Notch, another key substrate of the enzyme, was unaffected in these mice and when GPR3 was overexpressed in cells.

Together, these findings highlight the key role of GPR3 in Aβ production and reveal a new level of specificity in γ-secretase processing, suggesting that identifying GPR3 modulators might be a new approach to drug discovery for Alzheimer's disease.

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ORIGINAL RESEARCH PAPER Thathiah, A. *et al.* The orphan G protein-coupled receptor 3 modulates amyloid-beta peptide generation in neurons. *Science* **323**, 946–951 (2009)