NEURODEGENERATIVE DISEASE

# RXR agonist reverses Alzheimer's disease

The accumulation of amyloid-β (Aβ) in the brain is postulated to initiate a cascade of events leading to Alzheimer's disease (AD). However, therapeutic approaches that aim to reduce Aβ production or aggregation have so far been unsuccessful. Now, writing in *Science*, Cramer and colleagues demonstrate that a retinoid X receptor (RXR) agonist rapidly stimulates Aβ clearance, improving cognitive and behavioural deficits in mouse models of AD.

Clearance of Aβ from the brain is normally facilitated by the cholesterol transport protein apolipoprotein E (APOE), through the formation of high-density lipoprotein (HDL) particles that promote the proteolytic degradation of soluble Aβ. APOE expression is transcriptionally regulated by the ligand-activated nuclear receptors peroxisome proliferator-activated receptor-γ (PPARγ) and liver X receptors (LXRs), which form heterodimers with RXRs. Previously, chronic administration of PPARγ or LXR agonists has been shown to reduce Aβ levels and improve cognitive function in mouse models of AD. With this in mind, Cramer and colleagues hypothesized that an RXR agonist would exert similar beneficial effects.


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To test their hypothesis, the authors used bexarotene (Targretin; Ligand Pharmaceuticals/Eisai) — a selective blood–brain barrier-permeant RXR agonist that is currently approved by the US Food and Drug Administration to treat cutaneous T cell lymphoma. In primary microglia and astrocytes, the compound stimulated expression of APOE and its lipid transporters, ATP-binding cassette transporter A1 (ABCA1) and ABCG1, and promoted the secretion of highly lipidated HDL particles, thereby facilitating degradation of soluble Aβ in a PPARγ-, LXR- and APOE-dependent manner.

Next, they assessed the effects of the RXR agonist in several mouse models of AD. In 2-month-old mice expressing mutated amyloid precursor protein (APP) and presenilin 1 (PSEN1), known as *APP/PSEN1* mice, a single oral dose of bexarotene significantly decreased levels of soluble Aβ in the brain interstitial fluid by 25% within just 6 hours of administration, an effect that lasted for over 70 hours. Furthermore, acute 14-day administration of bexarotene to 6-month-old *APP/PSEN1* mice progressively enhanced the expression of APOE, ABCA1 and ABCG1, and elevated HDL levels in the hippocampus and cortex, in conjunction with a sustained 30% reduction in soluble Aβ levels, a 40% reduction in insoluble Aβ levels and a 75% reduction in Aβ plaque area. Chronic 90-day treatment similarly reduced soluble Aβ levels by 30%. Bexarotene was also effective in older 11-month-old *APP/PSEN1* mice and in *APPPS1-21* mice (an aggressive model of amyloidosis, also expressing mutated forms of APP and PSEN1), in which acute treatment reduced plaque numbers by 50% and 35%, respectively.

Importantly, rapid significant improvements in cognitive and behavioural deficits were also observed. Acute or chronic bexarotene treatment restored cognition and memory in 6- or 11-month-old *APP/PSEN1* mice and in *APPPS1-21* mice, as assessed by contextual fear conditioning and Morris water maze performance. In addition, 72 hours of bexarotene restored nest construction (an affiliative social behaviour) and odour habituation behaviours in Tg2576 transgenic mice (which express mutated APP), through improvements in neural network function.

Based on these findings, the authors have founded ReXceptor Inc., which plans to begin a small proof-of-concept trial of bexarotene in healthy volunteers within the next few months.

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**ORIGINAL RESEARCH PAPER** Cramer, P. E. *et al.* ApoE-directed therapeutics rapidly clear β-amyloid and reverse deficits in AD mouse models. *Science* 9 Feb 2012 (doi:10.1126/science.1217697)