

Ionophore reverses Alzheimer's within days in mouse models

9 July 2008

Scientists report a remarkable improvement in Alzheimer's transgenic mice following treatment with a new drug. The study, published by Cell Press in the July 10th issue of the journal *Neuron*, provides the first demonstration that an ionophore, a compound that transports metal ions across cell membranes, can elicit rapid and pronounced improvement in neuropathology and cognitive function in mouse models of Alzheimer's Disease (AD).

Recent research has implicated dysregulation of metal ions in the brain, particularly copper and zinc, in the pathogenesis of AD and the damaging accumulation of amyloid beta (A β) protein that is characteristic of this devastating disease. The ionophore clioquinol (CQ), an 8-hydroxyquinoline, has been shown to increase intracellular copper and zinc levels and decrease A β levels in cultured cells and in the brains of transgenic (Tg) AD mice. However, further studies in mice and humans demonstrated that brain entry of CQ was quite limited.

Dr. Ashley I. Bush from the Mental Health Research Institute of Victoria in Australia, with Dr. Paul A. Adlard and colleagues examined the therapeutic potential of PBT2, a second generation 8-hydroxyquinoline designed for easier synthesis, higher solubility and increased blood-brain barrier permeability, in two well established Tg mouse models of AD. The Tg mice examined in the study overexpress the precursor protein for A β and possess mutations that cause AD in humans. One of the Tg models also expresses the human presenilin deletion mutation that also causes AD.

"Both types of Tg mice exhibit progressive spatial learning deficits that are accompanied by increasing A β levels and plaque formation. Demonstrating benefits of PBT2 treatment in the two separate models was both a stringency test, increasing confidence that PBT2 is more likely to show benefit in clinical trials, and also allowed us

to determine whether specific forms of A β change in register with cognitive improvement in both strains. This is significant as cognitive loss in AD is not just a simple product of rising A β levels," explains Dr. Bush.

PBT2 was shown to be a superior ionophore when compared to CQ and the researchers went on to test A β levels and cognitive outcomes after oral treatment with PBT2. "We found that oral treatment with PBT2 induced a dramatic improvement in learning and memory in both Tg models of AD, accompanied by a marked inhibition of AD-like neuropathology. These outcomes were rapid, with reduction of soluble interstitial A β occurring within hours, and significant cognitive benefits seen within days of first administration of the compound," says Dr. Bush.

These results encourage further testing of compounds that target synaptic metals as a possible treatment of AD. Further, recent clinical trials in AD patients taking oral PBT2 have been promising and support PBT2 as a viable treatment for AD.

Source: Cell Press

APA citation: Ionophore reverses Alzheimer's within days in mouse models (2008, July 9) retrieved 17 September 2022 from <https://medicalxpress.com/news/2008-07-ionophore-reverses-alzheimer-days-mouse.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.