Targeting P-glycoprotein in a Mouse Model of Alzheimer's Disease: Insights from a Long-Term Study

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Accumulation of amyloid beta (Aβ) in Alzheimer's disease (AD) is due, in part, to impaired clearance of Aβ across the blood-brain barrier. P-glycoprotein (P-gp) is a blood-brain barrier efflux transporter that is critical for clearing Aβ from the brain. In AD, however, P-gp is substantially reduced, which contributes to impaired Aβ clearance. Despite the importance of P-gp for Aβ clearance, there is currently no strategy available to restore P-gp.

The current 2-year cross-sectional study with a longitudinal component was designed to 1) restore P-gp levels by activating the nuclear receptor PXR and 2) evaluate the therapeutic benefit of this strategy on reducing Aβ brain load and slowing cognitive decline. To that end, 3-month old hAPP mice (over-expressing human amyloid precursor protein; Tg2576 model) received a diet containing the PXR activator pregnenolone-16α-carbonitrile (PCN; 50 mg/kg). Age-matched wild-type (WT) and hAPP control mice received purified diet alone. In the cross-sectional study, mice underwent a battery of motor and cognitive testing at 3, 9, 12, 15, and 18 months of age. A subsection of mice from the cross-sectional study were used for the longitudinal component and received testing at 15, 18, and 21 months of age. After testing, we isolated brain capillaries to determine P-gp expression and transport activity levels .

Cross-Sectional Data: Prior to treatment with PCN, 3-month old hAPP mice had significantly reduced brain capillary P-gp activity levels compared to WT mice. Within 6 months of treatment and until the completion of the study at 18 months of age, brain capillary P-gp activity levels in PCN-treated hAPP mice were comparable to those in WT mice. However, PCN treatment had no significant effect on cognition.
Longitudinal Data: At 21 months of age, brain capillary P-gp activity levels were similar between WT and PCN-treated hAPP mice, and both of which these levels were higher than those in hAPP mice. PCN treatment selectively alleviated deficits in behavioral flexibility and memory that manifested as an increase in accuracy under a reversal-learning paradigm in the 8-arm radial water maze.

The data suggest that restoring blood-brain barrier P-gp via PXR activation may offer select neurobehavioral protection from Aβ neurotoxicity.