

## Original Article

### Dimebon alters hippocampal amyloid pathology in 3xTg-AD mice

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**Abstract:** A double blind, placebo-controlled phase II study revealed that the antihistamine, Dimebon® (dimebolin, latrepirdine) improved cognition in Alzheimer disease (AD) patients compared to placebo controls. However, the Phase III CONNECTION trial failed to demonstrate significant differences between dimebon and placebo treatments. Despite the controversial therapeutic outcomes in the treatment of AD, dimebon's mechanism(s) of action within the brain remain unclear. In the present study, we evaluated the effects of dimebon upon  $\beta$ -amyloid (A $\beta$ ), tau and astrocytes in the hippocampus of triple transgenic (3xTg-AD) mice, which develop AD-like pathology in an age-dependent manner. At age 6.5 months, prior to the development of A $\beta$  plaques in the hippocampus, male and female 3xTg-AD mice, received a daily intraperitoneal injection of 0.1 % dimebon or saline for 1.5 months. At 8 months, quantitative immunohistochemistry revealed a significant reduction in hippocampal/subicular APP/A $\beta$  in dimebon-treated mice, whereas protein bioassay found no change in full length APP, soluble A $\beta$ 1-40 and A $\beta$ 1-42, A $\beta$  oligomers, BACE1 and GFAP levels between groups. Interestingly, the number of the hippocampal APP/A $\beta$  plaques in female and male dimebon-treated mice was higher compared to gender-matched control mice. Dimebon did not alter hippocampal tau levels. Furthermore, dimebon protects SH-SY5Y neurons against A $\beta$  toxicity and promotes GFAP expression in primary mouse astrocyte cultures. Our findings demonstrate that dimebon in vivo modifies hippocampal APP/A $\beta$  pathology and in vitro protects against A $\beta$  toxicity promoting cell survival and activates astrocytes. (IJPPP1208006).

**Keywords:** Alzheimer's disease, amyloid, dimebon, hippocampus, plaques, tangles, tau, transgenic mice

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