

## **Bexarotene and astaxanthin modulate cholesterol and amyloid-beta metabolism in cerebrovascular endothelial cells**

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**Background/Aims:** This study investigated the effects of a pharmacologic retinoid-X receptor (RXR) agonist, bexarotene, and a PPAR- $\alpha$  agonist and strong antioxidant, astaxanthin, on pathways of cellular cholesterol metabolism, APP processing, A $\beta$  production and transfer at the BBB. **Methods:** Primary, porcine brain capillary endothelial cells (pBCEC) were incubated with Bex [ $\leq 100$  nM] or Asx [ $\leq 10$  nM] for 24 h. *ApoA-I*, *ABCA1*, *LRP1*, and *BACE1* mRNA expression and ABCA1, apoA-I, and A $\beta$  oligomer protein levels were determined by RTQ-PCR and immunoblotting. *In vivo* effects on cerebrovascular endothelial cells were investigated using 3xTg AD and non-TG mice gavaged with 100 mg/kg Bex, 80 mg/kg Asx, or vehicle control (7d). **Results:** cerebrovascular endothelial cells isolated from 3xTg AD mice treated with Bex, revealed elevated mRNA expression of apoE, ABCA1, and LRP1, whereas Asx treatment resulted in increased LRP1 mRNA expression. Both, Bex and Asx reduced BACE1 mRNA expression as compared to cells isolated from untreated and from non-Tg, treated animals. Bex or Asx treatments dramatically reduced levels of soluble A $\beta$  oligomers in brain and mBCEC of 3xTg AD mice. Bex treatment of mice further revealed up-regulated ABCA1, apoE and LRP1 as well as down-regulated BACE1 mRNA expression detected in brain homogenates. **Conclusion:** Our results strongly suggest that these two different nuclear receptor agonists exert beneficial effects on cholesterol and A $\beta$  metabolism in cerebrovascular endothelial cells.