Cerebral cortex transcriptome responses to BPN-15606, a novel gamma secretase modulator

Authors: Carla D'Agostino[1], Amin Haghani[1], Mafalda Cacciottolo[1], Constantinos Sioutas[2], Rudolph E Tanzi[5], Todd E Morgan[1], Steven L Wagner[4], Caleb E Finch[1,3*]

1. Davis School of Gerontology, University of Southern California, Los Angeles, CA
2. Department of Civil and Environmental Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, CA
3. Department of Biological Sciences, Dornsife College, University of Southern California, CA
4. Department of Neurosciences, University of California, San Diego, La Jolla, CA
5. Genetics and Aging Research Unit, Department of Neurology, Massachusetts General Hospital, Charlestown, MA
*Corresponding author. Email cefinch@usc.edu.

Gamma-secretase is a critical target for AD drug development because of its key role in amyloid-β42 (Aβ42) generation. We examined cerebral cortex transcriptome responses to BPN-15606, a recently developed GSM (Wagner 2017 PMID 28416568), in young male and female wild type mice (C57BL/6J, male and female). After treatment with 9 weeks of chow fed BPN-15606, RNAseq showed altered expression of 1031 genes, which included 576 (55%) sex-specific gene responses. Analysis of upstream regulators by IPA identified presenilin-1 (Psen1), a component of the γ-secretase complex, as the top upstream regulator in both sexes. Drug treatment altered expression of genes associated with oxidative phosphorylation and other mitochondrial functions, protein ubiquitination, and sirtuin signaling. The top sex-specific responses included immune responses. Sex differing genes were enriched for SAPK/JNK, ILK, PI3K/AKT and B cell receptor signaling. Mitogen protein kinases were among the top upstream regulators of this GSM:Sex interactions. These pathways are highly responsive to many AD risk factors including air pollution. Ongoing experiments examine the combined effects of air pollution and BPN-15606 on neurotoxicity.

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