

Gene expression of arachidonic and docosahexaenoic acid cascade enzymes is coordinated within transcriptional modules in a hierarchical manner during human brain development and aging

Stanley I. RAPOPORT

Brain Physiology and Metabolism Section, National Institute on Aging, National Institute of Health, Bethesda, MD

Background: In brain, polyunsaturated arachidonic acid (ARA) and docosahexaenoic acid (DHA) participate in multiple functional and metabolic processes, including neurotransmission. Each is metabolized via distinct but interacting receptor-initiated phenotypic cascades. We hypothesized that mRNA expression levels for enzymes of the two cascades change cooperatively but with different trajectories during human brain Development and Aging, and that expression is coordinated within specific groups or modules in a hierarchical fashion.

Methods: Age changes in gene expression levels of thirty-four ARA- and DHA-cascade enzymes and related factors, downloaded from the publically available Brain Cloud database for normal human prefrontal cortex¹, were determined and correlated using hierarchical clustering and correlation matrices (heat maps).

Results: Brain mRNA expression patterns for the 34 genes were divided into Development (0 to 20 years) and Aging (21 to 78 years) periods. Expression of genes coding for cytosolic phospholipase A2 (cPLA2), cyclooxygenase (COX)-1 and -2, and other ARA cascade enzymes correlated closely with age within specific modules in a hierarchical manner during Development, less so during Aging². Expression of DHA cascade enzyme genes was less intercorrelated in each period, and often changed in the opposite direction to expression of ARA cascade genes.

Conclusions: Age changes in expression of genes coding for ARA and DHA cascade enzymes differ during human brain Development and Aging, underlying differences in the roles of the two phenotypic cascades during brain growth and homeostasis, respectively. Coordinated transcriptional changes in both intervals underlie integrated phenotypic changes in respective enzyme levels. Age-related coordinated gene expression probably is regulated by commonly acting miRNAs and transcription factors, and is influenced by gene proximity on similar chromosomal bands.

¹ Colantuoni *et al.* (2011) *Nature* 478: 519-523

² Ryan *et al.* (2014) *C PloS One* 9: e100858.