Transcriptomic and Metabolomic Analyses of Acetaminophen Exposure in a Stem Cell Model: Potential Mechanisms Explaining Epidemiological Associations Between Prenatal Acetaminophen Exposure and Increased Risk of Autism Spectrum Disorder

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Background

- 1 in 54 children diagnosed with Autism Spectrum Disorder (ASD)

- Underlying mechanisms remain unknown

- Likely multifactorial etiology

https://www.cdc.gov/ncbddd/autism/data/index.html#data
Background

Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study

Zeyan Liew, Beate Ritz, Jasveer Virk, Jørn Olsen

Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms

JAMA Pediatrics | Original Investigation

Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood Evidence Against Confounding

Evie Stergiakouli, PhD; Anita Thapar, FRCPsych, PhD; George Davey Smith, MD, DSc

• ≈65% of pregnant women take Acetaminophen (APAP)
• In vitro studies show high APAP concentrations induce cell death
Objectives

• Study APAP exposure in human stem cells with a systems-level approach

• Identify mechanistic links between APAP exposure and ASD

• Establish a model and methods to evaluate the safety of substances with consideration to neurodevelopment
Methods

• Neural Progenitor Cell differentiation from induced Pluripotent Stem Cells (iPSCs)
• 6-day exposure to APAP
• Dose-response assessment in iPSCs
• Selection of therapeutic (0.16 mM) and toxic (0.32 and 0.48 mM) APAP concentrations
• RNA-sequencing
• Metabolomics with LC-MS
Methods

• RNA-seq → DESeq2 → Qlucore Omics Explorer
• Metabolomics → MetaboAnalyst
• RNA-seq + Metabolomics → Ingenuity Pathway Analysis
Results

• Concentration-dependent decreases in expression for COBL, CYP2B6, FZD5, GPC4, NCALD and FGFBP3, and increases in expression for ATP1A2, PROS1, HES1 and NRIP1
Results

- Differential regulation of metabolites involved in aminoacyl-tRNA biosynthesis, as well as valine, leucine and isoleucine biosynthesis.
Results

• Canonical pathways of interest:
  ○ Nuclear factor erythroid 2-related factor 2 (NRF2) mediated oxidative stress
  ○ Serotonin receptor signaling
Discussion

• Biological impacts of APAP parallel those in ASD
• Highlight potential mechanisms between prenatal exposure to APAP and ASD

• Limitations:
  o Low power due to low APAP concentrations
  o Effects at *in vivo* level are inferred via an *in vitro* model
Public health implications

• Connects APAP exposure with established ASD literature and elucidates new perspectives for future research
• Present approach as tool for future research regarding chemicals of neurodevelopmental concern
• Implications for precision medicine
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