Name: Yingshi Ouyang, Ph.D. Email: YOUYANG@childrensnational.org

Xylazine exacerbates fentanyl-induced mitochondrial and transcriptional dysregulation in human trophoblasts

Illicit fentanyl exposure during pregnancy is associated with adverse pregnancy outcomes, but its impact on human trophoblasts and the underlying molecular mechanisms remain largely unknown. Alarmingly, xylazine, the α2-adrenergic agonists, are recently detected as adulterants in illicit fentanyl-containing products and have been linked to worsened clinical outcomes including more severe withdrawal syndrome and skin injury. To define trophoblast transcriptional responses to fentanyl alone or in combination with xylazine, we examined their impact on human trophoblast stem (TS) cells and differentiated syncytiotrophoblasts (STBs) by RNAseq-based gene expression and gene sets enrichment analyses. While fentanyl exposure led to modest transcriptional changes in TS cells, it induced significant downregulation of oxidative phosphorylation and metabolic processes in STBs, with attenuated suppression following prolonged exposure compared with short-term treatment. Co-exposure to xylazine resulted in marked mitochondrial pathway suppression in TS cells and further potentiated mitochondrial dysfunction in STBs. Together, these findings illuminate how fentanyl disrupts trophoblast development and function, and demonstrate that xylazine exacerbates fentanyl-induced transcriptional dysregulation, highlighting the increased risks of xylazine on fentanyl-exposed pregnancy.

Authors:
Submitter: Yingshi Ouyang, Assistant Professor, Developing Brain Institute, Center for Prenatal, Neonatal & Maternal Health Research, Children's National Hospital, Washington/D.C.
Keyi Huang, B., Children's National
Lei Liu, M.S., Children's National
Sheng Liu, Ph.D., Indiana University
Jiayu Meng, B.S., Magee-Womens Research Institute
Yoel Sadovsky, M.D., Stanford University

DRAFT