Name: Ramji Bhandari Email: bhandarir@missouri.edu

Paternal THC Exposure Effects on Their Fertility and Offspring Reproductive Health

Yashi Feng, Sourav Chakraborty, Santosh Anand, Su Men, Ramji K. Bhandari

Division of Biological Sciences, University of Missouri

Delta-9 tetrahydrocannabinol (THC) can induce epigenetic alterations (epimutations) in the sperm's DNA. Nevertheless, it is not clearly understood whether the preconception THC-induced alterations in the germline epigenome can be passed on to the offspring, causing transcriptional profiles of abnormal reproductive health phenotypes in the subsequent generations. The present study, therefore, examined pre-conceptional paternal (F0) THC exposure effects on the DNA methylome of the paternal germline and transcriptional profiles of the F1 offspring testis using medaka fish as an animal model. Reproductively active male medaka fish to four different concentrations of THC (0, 30, 120, 600 ug/L) for 21 days and determined their fertilization efficiency, including the DNA methylation profile of their sperm (P0) and transcriptome profile of the derived offspring (F1) reproductive tissues at adulthood. Low-concentration paternal THC exposure reduced the fertilization efficiency of the F0 father and F1 offspring. Direct paternal THC exposure resulted in differentially expressed genes (DEGs) related to metabolism, neuron-specific RNA splicing mechanism, and myocyte formation in the testis (F0). Differentially methylated regions (DMRs) of paternal F0 sperm predicted dysregulation in the transcriptome profile of the F1 offspring testis. Among the pathways, metabolism, neuron signaling, and immune pathways were dysregulated in the F1 testis. THC exposure induced a 25% increase in fertility defects in males with a pre-existing history of ancestral bisphenol A exposure. Overall, THC can cause harmful, heritable effects in reproductive tissues if exposure occurs during the pre-conception period of male germline development.