Ethanol-induced Retinal Defects are Rescued by Retinoic Acid Supplement in Developing Zebrafish Embryos

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Fetal Alcohol Spectrum Disorder (FASD) is caused by prenatal alcohol exposure, producing a spectrum of defects including facial abnormalities, sensory (visual and auditory) deficits, impaired fine motor skills and learning deficits including mental retardation. Our laboratory has used a zebrafish model for FASD that exposes embryos to ethanol during early development (midblastula transition through somitogenesis). Children diagnosed with FASD frequently show severe eye defects ranging from small eyes, underdeveloped optic nerve, and cataract. Zebrafish embryos exposed to ethanol showed defects similar to human eye birth defects. Presence of ethanol affected the differentiation of many retinal cell types including, retinal ganglion cells and photoreceptors. We hypothesize that ethanol may affect retinal patterning by competing with Retinaldehyde dehydrogenase (Raldh), reducing retinoic acid (RA) synthesis and signaling. Co-treatment of embryos with ethanol and 10^{-9} M RA could rescue the photoreceptor and retinal ganglion cell differentiation defects in the retina. RA plays a crucial role in the dorso-ventral patterning of the retina, and the enzymes involved in RA biosynthesis are expressed in the ventral retina during mid-somitogenesis stage. Our experiments showed that ethanol exposure during that critical time window when Raldh is expressed in the ventral retina causes severe defects in retinal cell specification. No defects were induced by ethanol exposure at the earlier stages. Presence of RA during photoreceptor differentiation could rescue ethanol-induced photoreceptor differentiation defects. Future work will dissect molecular mechanisms underlying ethanol defects, including retinoic acid-mediated eye development mechanisms. Determining the effects of ethanol exposure on retinal morphogenesis and differentiation will help identify potential therapeutic targets for ocular defects in this regrettably frequent birth defect syndrome.

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