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Application of human induced pluripotent stem cell-derived threedimensional cerebral organoids in modeling developmental brain disorders

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Maternal alcohol exposure during pregnancy can substantially impact the development of the fetus, causing cognitive dysfunction and psychiatric disorders, with the mechanisms largely unknown. Recently developed 3D human cerebral organoids from induced pluripotent stem cells are similar to fetal brains in the aspects of development and structure. These models allow more relevant in vitro systems for studying FASDs than animal models. We found that 50 mM alcohol exposure for 6 hours induced acute apoptosis on organoids. The apoptotic effects of alcohol depended on alcohol concentration and varied between cell types. Specifically, neurons were more vulnerable to alcohol-induced apoptosis than astrocytes. The alcohol-treated organoids also exhibit disrupted mitochondria cristae and decreased intensity of mitochondrial matrix. Additionally, alcohol resulted in metabolic stress in the organoids as evidenced by 1) decreased mitochondrial oxygen consumption rates being linked to basal respiration, ATP production, proton leak, maximal respiration and spare respiratory capacity, and 2) increase of non-mitochondrial respiration in alcohol-treated organoids compared with control groups. Furthermore, we found that alcohol treatment affected the expression of 199 genes out of 17,195 genes analyzed. Bioinformatic analyses showed the association of these dysregulated genes with 37 pathways related to clinically relevant pathologies. Collectively, this human organoid model allows in-depth analyses of alcohol neurotoxicity at cellular, subcellular, bioenergetic metabolism, and molecular levels. Our findings provide novel insights into alcohol-induced pathologic phenotypes in developing human brains and potential neuroprotective strategy by targeting affected mitochondrial metabolisms and molecular networks.

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