Effects of Endocrine Disrupting Chemicals (EDCs) on Human Developing Neurons in Vitro and Their Potential Connection in Autism

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Background: Endocrine Disrupting Chemicals are exogenous substance that may impact normal synthesis, secretion, transport, binding, action or elimination of natural hormones responsible for the maintenance of homeostasis, reproduction, development and differentiations of developing fetal brains. We normally encounter myriad of chemicals in our daily live (i.e. perfumes, freshener, moisturizers, fragrances, makeup product, plastic product, sunscreen etc.) that can be harmful to the developing fetal brain neurons. These chemicals have potential of getting stored in adipose tissue and alter the hormonal and homeostatic system, and thus affect the metabolism, sexual development, growth, stress response, insulin production, gender behavior, reproduction and fetal development. Autism Spectrum Disorders (ASD) is developmental disabilities that can cause significant social, communication and behavioral challenges. We have proposed that some EDCs like Benzyl Benzoate, Benzyl Salicylate, DEP (Diethyl phthalate), Eugenol, Musk Ketone, Octinoxate, and other androgenic and estrogenic present in our environment that can interfere in normal neurodevelopment, especially in a developing fetus if exposed EDCs during the early gestational periods (i.e. week 8-24).

Methods: In this study we exposed neuroblastoma cell lines (NBC) of male and female origins (CRL 2267 and CRL 2266 respectively), representing developing human brain neurons, to seven most commonly encountered chemicals, found in regularly used household products to three different concentration of chemicals; (i.e., 62.5µg/ml (high), 31.25µg/ml (medium) and 15.625µg/ml (low) for 3-5 days and evaluated for the morphological, and receptor expression modulations by immunologic and molecular methods (qPCR) to determine their effects on potential role in development of neuromodifications in fetal brain. We carried out morphological analyses by determining the degree of central chromatolysis, axonal length and thinning, degeneration and syncytia formation in exposed NBCs and compared to unexposed controls. We also analyzed the expressions levels of oxytocin (OXY) and Arginine-vasopressin receptors (AVPR) in controls *versus* EDC–exposed NBCs. Finally, we utilized gene expression analysis by qRT-PCR for *RORA*, *Aromatase* (*CYP19A*), *Estrogen and Androgen receptors* in cells exposed to EDCs Vs controls.

Results: These NBCs exposed to EDCs at various concentrations exhibited significant neuromodifications. The morphologic analyses showed significant differences in axonal length and axonal degeneration in EDCs exposed NBCs from both genders. Furthermore, there was significant downregulation in oxytocin receptor expression in cell lines that were exposed to EDCs at all level of concentrations as compared to controls in both male and female cell lines.

qRT-PCR analyses showed dysregulation of *RORA, Aromatase, Estrogen, Androgen receptor* expressions in both the neuronal cell lines exposed to 7-EDCs.

Conclusion: We concluded that exposures to EDCs, at very low concentration levels, induce significant neuromodifications as evaluated by neurohistologic, immunologic and molecular levels, suggesting that these chemicals may play an important role in neurodevelopment of a fetal brain if exposed during early stages of gestation.