CONTRASTING PHENOTYPES OF FETAL ALCOHOL SYNDROME, TOLUENE EMBRYOPATHY AND MATERNAL PHENYLKETONURIA
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In utero exposure to neurotoxic exogenous substances or to endogenous compounds that accumulate because of genetic mutations often results in undesirable modification of the fetal central nervous system (CNS).

Ethanol is one of the best recognized human neuroteratogens. Fetal alcohol syndrome (FAS) has been defined as a triad including prenatal and postnatal growth impairment, unique facial anomalies, mental retardation and behavioral dysfunction in children of alcohol abusing mothers. FAS is considered to be a leading cause of mental retardation in the general population.

Abuse of toluene, an occupational and recreational chemical, by pregnant women can lead to an embryopathy known as fetal solvent syndrome (FSS). Unlike FAS, the evidence here is based on cases of neonates born to toluene-abuse mothers, displaying low birth weight, microcephaly, low-set ears, flat nasal bridge, short palpebral fissures, micrognathia, and neurodevelopmental delay, phenotypic characteristics similar to FAS.

Phenylketonuria (PKU) is a genetic defect in an enzyme that converts phenylalanine (Phe) to tyrosine. Women with uncontrolled high plasma levels of Phe or its metabolites may deliver offspring with maternal PKU (mPKU) syndrome. These children have severe CNS dysfunction, microcephaly, facial dysmorphology, congenital heart disease, and growth retardation. In fact, there is very close resemblance in the facial changes of mPKU to those of FAS. Whether Phe itself, or one of its metabolites, is responsible for the CNS dysfunction associated with mPKU is unknown. Also, the mechanisms of ethanol and toluene teratogenicity are not yet clearly defined.

Thus, the authors refer to the evidence that exposure to two unrelated substances (ethanol and toluene), and a genetic defect can all lead to developmental effects which display very similar phenotypes. They state that understanding of the mode of action of these developmental effects would be of great interest, as it may draw attention to possible therapeutic intervention. The term “mode of action” is introduced to describe events supported by scientific knowledge, which provide a biologically plausible explanation of causality of the toxic effects considering the dose, duration of exposure, and susceptibility of the target tissue. In contrast, the term “mechanism of action” identifies all of the key events from the molecular to the organism level. The authors believe that identification of similar teratogenic modes of action may improve the assessment process when the knowledge of possible mechanisms of action of a more studied substance (as in case of ethanol) may be applied to substances with limited information available, such as toluene and mPKU.

Developmental neurotoxins may affect neurogenesis, gliogenesis, neuronal migration, cell differentiation and synaptogenesis, potentially leading to structural abnormalities and impaired neurobehavioral functioning.

While in vitro and in vivo studies have shown that ethanol can cause neuronal death, no such evidence is available for toluene or Phe and/or its metabolites. On the other hand, inhibition of the proliferation and maturation of the astroglial cells that were found in vitro...
in each of these conditions may represent a potential common mode of action for at least some of the CNS effects found in FAS, mPKU, and FSS.

The authors suggest that focusing on these two mechanisms of action (which can be studied also in vitro), may offer a starting point for assessing whether a common mode of action exists among these three syndromes, and testing the theory that glial cells play a central role in the developmental neurotoxicity of FAS, FSS, and mPKU. It may also offer a working hypothesis for the design of studies on possible common modes of action. Further in vivo and in vitro studies should validate this hypothesis and determine target cellular population.

While the paper analyzes cellular mechanisms in some depth, its starting point of “similar phenotypes” to the three entities is superficial at best. While the complex neurobehavioral phenotype of FAS has been described by many, there is almost nothing on neurobehavior of children with mPKU. Based on what is known, children with mPKU do not display the pervasive behavior of FAS. While the similar facial features of FAS and mPKU are very compelling, the inclusion of toluene in this analysis is problematic. The “Toluene Syndrome” is still just a suggestion. Moreover, most toluene abusers also abuse ethanol and the “phenotype” of toluene may reflect FAS, partial FAS, or a genuine syndrome contaminated with FAS.

REFERENCES