Alcohol and Cell Adhesion: Rewiring the Brain before Birth

M.E. Charness

Alcohol and drug exposure during brain development may increase the risk for alcohol and substance use disorders (SUD) during adulthood. One developmental period that deserves special attention is gestation. Prenatal alcohol exposure modifies neurogenesis, neuronal cell migration, axon pathfinding, and synaptogenesis. Some of these actions alter the structure and function of the brain in ways that might predispose to addiction.

Results: Our laboratory has studied the effects of ethanol on the L1 neural cell adhesion molecule, which regulates diverse developmental events. Brain lesions of children with mutations in the gene for L1 resemble those of children with fetal alcohol spectrum disorders (FASD). Alcohol inhibits L1-mediated cell adhesion by interacting with an alcohol binding pocket in the L1 extracellular domain. Furthermore, drugs that block the effects of alcohol on L1 also prevent teratogenesis in mice. The sensitivity of L1 to ethanol is modified by phosphorylation of discrete residues in the L1 cytoplasmic domain, and the activity of signaling pathways that phosphorylate L1 differ in clonal cell lines or mouse strains that are sensitive or insensitive to ethanol. Preliminary work suggests that polymorphisms in genes for some of these pathways are associated with facial dysmorphology, brain structure, and executive function in children heavily exposed to ethanol during pregnancy.

Discussion: If alcohol rewires the developing brain through interactions with developmentally critical molecules, what might be the impact on the development of SUDs? Some of the cognitive and behavioral features of FASD include impaired executive function, externalizing behaviors, impulsiveness, poor self-regulation, heightened stress responses, and impaired social adaptation – known risk factors for SUDs. Conceivably, prenatal alcohol exposure increases the risk of SUDs by increasing the probability of risky behaviors. Because FASD encompasses a spectrum of effects, early recognition of FASD becomes imperative for identifying children at risk for poor school performance, impaired social functioning, and SUD. The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) is using novel methods to recognize mild facial dysmorphology and abnormal brain development. The larger challenge is to develop effective interventions that rewire the still developing brain of children and adolescents and mitigate the effects of prenatal alcohol exposure on cognition, behavior, and social adaptation. In this way, a non-genetic, transgenerational, cycle of risk might be broken.

References: Valenzuela, C. F., Morton, R. A., Diaz, M. R. & Topper, L. *Trends Neurosci.* **35**, 284 292 (2012).Arevalo, E. *et al. Proc. Natl. Acad. Sci. U. S. A.* **105**, 371-375 (2008).
Wilkemeyer, M. F. *et al. Proc. Natl. Acad. Sci. (U.S.A.)* **100**, 8543-8548 (2003). Dou, X. *et al. Proc. Natl. Acad. Sci. U. S. A.* **110**, 5683-5688,(2013). Kable, J. A. *et al. Child Psychiatry Hum. Dev.*(2015). Miller, M. W. & Spear, L. P. *Alcohol. Clin. Exp. Res.* **30**, 1466-1469 (2006). Suttie, M. *et al. Pediatrics* **131**, 2012-1371 (2013).

Funding provided by NIAAA R01AA12974 and U24 AA014811 (CIFASD) and VA 5101BX002374 - the Medical Research Service, Department of Veterans Affairs