SCIENCE BRIEF

Even Low Levels of Alcohol During Pregnancy Can Affect Fetal Brain Development

A review of a recent study in mice shows that consuming even small doses of alcohol during fetal development can alter the rate of development of neurons in the brain.

Each Science Brief summarizes the findings and implications of a recent study in basic science or clinical research. Studies are selected for review based on their scientific merit and contributions to understanding early development. No single study is definitive, of course. Understanding of early development is based on many studies that, taken together, permit broad conclusions and human applications. Generalizing to human children the results of studies with animals, for example, must be done cautiously and confirmed by research with children and their families. The National Scientific Council rests its work on a rigorous discussion of the validity of many studies like these conducted over many years and using different methodologies and samples. For more information, go to www.developingchild.net

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Why was the study done?

Alcohol consumption during pregnancy can have profound detrimental effects on overall fetal and brain development—Fetal Alcohol Syndrome (FAS) is a well-known outcome of large consumption of alcohol, resulting in severe to moderate disturbances in brain architecture and chemistry, leading to long-lasting intellectual disabilities. However, the impact of low levels of alcohol consumption during fetal development has been studied far less. This study focused on the impact of low levels of ethanol consumption by pregnant mice—as the active ingredient in the alcohol consumed by humans, ethanol is used by scientists to mimic the human use of alcoholic beverages in mice. In particular, this study focused on the formation of "inhibitory" neurons that use a neurotransmitter known as GABA. Neurons in the brain either excite or inhibit each other, and the balance of excitation and inhibition is critical for the maturation of complex functions such as learning and emotional regulation. Too many or too few inhibitory neurons can lead to deficits in brain function. For example, more inhibitory neurons than normal, even during brief periods of development, can lead to early maturation of brain architecture, reducing the ability of later experiences to help connections stabilize properly. Previous work has shown that high levels of ethanol exposure reduce the number of these inhibitory neurons in adult animals, leading to seizures because there is not enough control over the excitatory neurons. The current study focused on how low levels of ethanol exposure might interfere with inhibitory neuron development, and whether even such mild exposure might also lead to imbalances in excitation and inhibition.

What did the study find?

Indeed, imbalances in excitation and inhibition occurred. Unexpectedly, however, exposing pregnant mice to low levels of ethanol *accelerated* the production of inhibitory neurons in their fetuses' brains,

and these inhibitory neurons migrated almost twice as quickly to their final destination in the neocortex. Prenatally, there was an almost doubling of the number of inhibitory neurons in the neocortex in the fetuses exposed to low levels of ethanol—an effect that is reversed in adulthood, when *fewer* inhibitory neurons were measured. Thus, the developmental trajectory of maturing excitation-inhibition was disrupted (too much inhibition), leading to over-compensation that appears to cause a final imbalance in the other direction (too little inhibition in the adult). Additional experiments showed that the ethanol exposure caused changes in the expression of GABA receptors on the migrating neurons, resulting in a greater sensitivity of the inhibitory neurons to the very neurotransmitter that they produce and release as they migrate. Further, the authors partially reversed the accelerated rate of migration by using a drug that blocks the ability of inhibitory neurons to respond to GABA. Therefore, they concluded, it is ethanol's effects on how neurons respond to GABA that leads to an imbalance in the developing brain architecture.

How was the study conducted?

Doses of ethanol were provided to pregnant mice one day after mating and resulted in blood levels three times *lower* than what is considered legal intoxication for human adults in the United States. A liquid diet containing 1-2% ethanol was used, with animals having free access to the food, control animals having access to the liquid diet but without ethanol, and a third group that was fed a diet to match food intake of the ethanol-exposed mice (to control for the unrelated effects of reduced calories that can occur in animals that ingest ethanol). The investigators used standard anatomical methods to monitor the movement of developing GABA-producing inhibitory neurons. This allowed them to count the number of inhibitory neurons that had been produced prenatally, and those that had reached their final destination in the neocortex during fetal brain development. To examine how rapidly the inhibitory neurons migrated, the authors used a video camera and microscope trained on tissue samples. The authors calculated the rate of movement over the time period that the tissue was monitored. To determine how sensitive the inhibitory neurons were to GABA, the authors recorded electrical responses when the neurotransmitter was applied to the cells, or they monitored how rapidly the inhibitory neurons migrated when GABA was applied to the tissue in the plastic dish.

What do the findings mean?

The results of this study indicate that even exposure to low levels of alcohol during pregnancy can initiate a cascade of atypical development that results in distinct imbalances of excitation and inhibition during postnatal development and in the adult. This imbalance can be detrimental because the excitation and inhibition signals are critical for the maturation of brain circuits that control important functions. Moreover, while there is an imbalance of excitatory to inhibitory neurons during prenatal development, this actually reverses in the adult, as the number of inhibitory neurons decrease below normal. The authors suggest that the initial accelerated development sets into motion corrective action by the neocortex to attain a normal balance of excitation and inhibition. Instead of correction, there appears to be an over-compensation. These data indicate that the detrimental influences on the brain of even low levels of ethanol exposure for the fetus, though probably subtle, are nonetheless of concern because the exposure sets in motion changes in brain architecture that may have functional implications during and after maturation.

Study Title and Authors

Cuzone, V.C., Yeh, P.W.L., Yanagawa, Y., Obata, K. & Yeh, H.H. (2008). Effects of prenatal alcohol exposure on GABAergic neurons. *Journal of Neuroscience,* 28:1854-1864.