

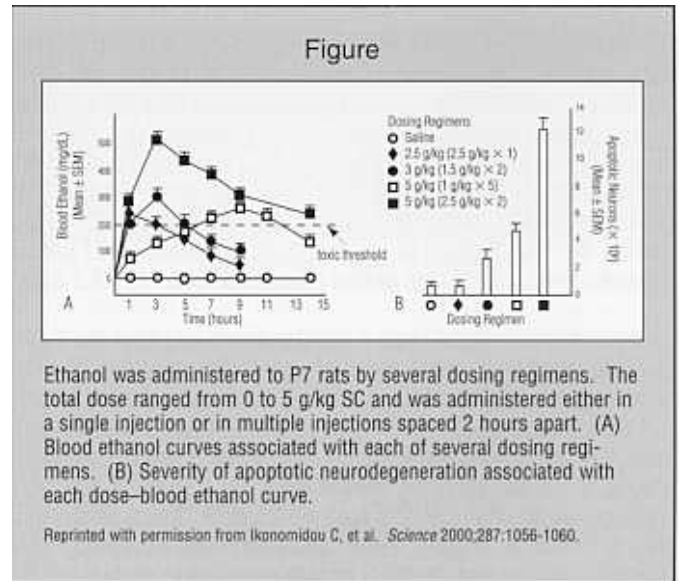
## Fetal Alcohol Syndrome and Brain Receptors

Intrauterine exposure of the human fetus to ethanol damages the developing brain, producing fetal alcohol syndrome (FAS) or fetal alcohol effects (FAEs), depending on severity. The primary manifestations are neurobehavioral disturbances, ranging from hyperactivity and learning disabilities to depression and psychosis. Patients severely affected also exhibit characteristic facies and growth deficiency. It long has been suspected that sensitivity to ethanol correlates with the time when synapses form, which is greatest during the last trimester of gestation for humans. A study headed by John Olney and colleagues provides an explanation for this correlation and identifies a probable mechanism that contributes to FAS/FAEs.

This work was done in rats, in whom the period of synaptogenesis occurs postnatally. Ethanol exposure of 1-week-old rats leads to a generalized loss of brain mass and a specific loss of cerebellar and hippocampal neurons. The authors had previously observed that transient blockade of *N*-methyl-D-aspartate (NMDA) glutamate receptors during the period of synaptogenesis causes widespread apoptosis of neurons in the infantile rat brain. Since ethanol is a known NMDA antagonist, Olney and colleagues explored the possibility that apoptosis is the mechanism by which ethanol causes neuronal loss (Figure).

Examination of brains 1 day after exposure to a control injection of saline revealed a low level of apoptosis consistent with the normal process by which biologically redundant neurons are deleted during brain development. However, after ethanol exposure, apoptosis was extensive. When quantitated by neuronal density, degenerating neurons comprised 0.13% to 1.55% of the total neurons in controls compared with 5% to 30% in ethanol-exposed brains. The extent of apoptotic degeneration varied by region. Dosing experiments revealed a threshold for apoptotic changes; blood ethanol concentration had to remain above 200 mg/dL for 4 hours to induce apoptosis. Exposures beyond this threshold led to progressively more severe apoptotic degeneration. They also found a time window from near the end of gestation to 2 weeks of age during which neurons in the forebrain showed transient sensitivity to ethanol. The period of vulnerability varied slightly among different populations of neurons, but coincided with the time when synapses were being formed.

The authors also screened for other drugs that could induce apoptosis of neurons. They found that drugs that block the NMDA receptor for glutamate, which is an excitatory neurotransmitter, or those that activate receptors for the inhibitory neurotransmitter,  $\gamma$ -aminobutyric acid (GABA), trigger apoptosis of neurons during the time of synaptogenesis. The most relevant drugs in this category were benzodiazepines and barbiturates. The authors



caution that even though the window of greatest sensitivity in humans to ethanol and other drugs that block NMDA glutamate receptors or activate GABA receptors is the last trimester of pregnancy, synapses continue to form for several years after birth. They point out that prolonged use of these drugs as anticonvulsants in infants could pose a risk to the developing brain.

Ikonomidou C, et al. *Science* 2000;287:1056-1060.

Barinaga M. *Science* 2000;287:947-948. News.

**Editor's comment:** This paper provides new insight into the mechanism by which ethanol harms the developing fetus. It offers potential explanations for why binge drinking, with its sustained high levels of ethanol, as well as drinking in late pregnancy, after organogenesis is largely completed, can have such severe consequences on the developing brain. A potential danger of misinterpretation in this article is to conclude that drinking small amounts of ethanol in the early and middle stages of pregnancy is not harmful. This is unwarranted given the many aspects of the mechanism uncovered here that remain poorly understood, and the substantial differences in nervous system development between rats and humans. Knowing how ethanol disturbs neuronal development provides the first step to devising ways to prevent or minimize its harmful effects on the unborn.

William A. Horton, MD

## A Novel Subtype of Type 1 Diabetes Mellitus Characterized by a Rapid Onset and an Absence of Diabetes-Related Antibodies

Type 1 diabetes mellitus is classified as type 1A (autoimmune) or idiopathic (type 1B). The second is less frequent, and little is known concerning the entity. This article deals with type 1B, which in turn may be 2 different diseases, as elucidated by these investigators. Imagawa et al classified 56 consecutive Japanese

adults with type 1 diabetes according to the presence or absence of glutamic acid decarboxylase (GAD) antibodies as a marker of autoimmunity. Thirty-six of 56 patients had GAD antibodies, indicative of type 1A diabetes; 20 patients did not. On the basis of elevated versus low glycosylated hemoglobin values, the 20