Glutathione content as a potential mediator of the vulnerability of cultured fetal cortical neurons to ethanol-induced apoptosis.

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Ethanol ingestion during pregnancy elicits damage to the developing brain, some of which appears to result from enhanced apoptotic death of neurons. A consistent characteristic of this phenomenon is a highly differing sensitivity to ethanol within specific neuron populations. One possible explanation for this "selective vulnerability" could be cellular variations in glutathione (GSH) homeostasis. Prior studies have illustrated that ethanol elicits apoptotic death of neurons in the developing brain, that oxidative stress may be an underlying mechanism, and that GSH can be neuroprotective. In the present study, both multiphoton microscopy and flow cytometry demonstrate a striking heterogeneity in GSH content within cortical neuron populations. Ethanol differentially elicits apoptotic death and oxidative stress in these neurons. When neuron GSH content is reduced by treatment with butathione sulfoxamine, the ethanol-mediated enhancement of reactive oxygen species is exacerbated. Sorting of cells into high- and low-GSH populations further exemplifies ethanol-mediated oxidative stress whereby apoptotic indices are preferentially elevated in the low-GSH population. Western blot analysis of the low-GSH subpopulations shows higher ethanol-mediated expression of active caspase 3 and 24-kDa PARP-1 fragments compared with the high-GSH subpopulation. In addition, neuronal content of 4-hydroxynonenal adducts is higher in low-GSH neurons in response to ethanol. These studies suggest that GSH content is an important predictor of neuronal sensitivity to ethanol-mediated oxidative stress and subsequent cell death. The data support the proposition that the differences in proapoptotic responses to ethanol within specific neuron populations reflect a heterogeneity of neuron GSH content.

Low Antioxidant Level May Damage Fetal Neurons

ScienceDaily (Jan. 3, 2008) — Fetal neurons that have low levels of a vital antioxidant, glutathione, are the first to die when exposed to alcohol in cell culture and possibly in the living brain, according to new research from the laboratory of George Henderson, Ph.D., professor of medicine and pharmacology at The University of Texas Health Science Center at San Antonio.

The researchers examined brain tissue from immature rats and neurons from rat fetuses.

Why do only some neurons die quickly?

“The scope of the study was to document, in a convincing manner, why only some neurons within a specific brain area are extremely sensitive to alcohol exposure and die very fast, while adjacent neurons are resistant and able to survive the same insult,” said
D., the lead author and assistant professor of medicine. “A deficiency in glutathione might explain it.”

Normal growth of the fetal brain in animals as well as humans requires that approximately half of the newly formed neurons die by a process called apoptosis. However, when fetal brains are exposed to alcohol, this neuron death is increased. There is evidence that this may be caused by oxidative stress similar to what may also occur in neurodegenerative diseases such as Alzheimer’s and Parkinson’s diseases.

When alcohol is involved, 3 percent to 5 percent more neurons die. “Typically when the fetal rat brain is exposed to alcohol, we have observed a 3 percent to 5 percent increase in neuron death that depends on the amount of alcohol and length of exposure,” Dr. Maffi said.

The answer could provide preventive therapies.

Knowing how some of the neurons escape apoptotic death during alcohol exposure could tell researchers how to provide therapies to prevent at least some of the devastating consequences of fetal exposure to alcohol. These studies confirm previous findings that neurons can be protected from alcohol by supplementing their glutathione content.

The scientists noted a 37 percent increase in oxidative stress and a 23 percent drop in glutathione levels in exposed tissues.

One in 100 live births in Texas suffers from a fetal alcohol spectrum disorder. Of 370,000 live births in the state annually, 3,700 babies are affected, said Carolyn A. Smith, executive director of the Texas Office for Prevention of Developmental Disabilities. “Each child may need $1 million to $2 million worth of supportive services during his lifetime,” Smith said. “You can see that this is an expensive problem in human and economic terms.”

- The study is published in the Journal of Neuroscience Research. Dr. Henderson’s co-authors, all from the Health Science Center, are Drs. Rhoda Hamby-Mason, Mary Rathinam, Priscilla Cherian, William Pate, Steven Schenker and Dr. Maffi.

- Support for the study was from the National Institute on Alcohol Abuse and Alcoholism to an established investigator (Dr. Henderson) and the Executive Research Committee at the Health Science Center to a new investigator (Dr. Maffi).

- Adapted from materials provided by University of Texas Health Science Center at San Antonio