REVIEW

EXPERIMENTAL MODELS USED TO MEASURE DIRECT AND INDIRECT ETHANOL TERATOGENICITY

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Abstract — The teratogenic effects of ethanol have been widely studied in a variety of experimental models. In humans, ethanol teratogenicity results from both direct and indirect effects. This paper reviews the differences between direct and indirect effects of ethanol on the developing fetus. Experimental paradigms are discussed that attempt to differentiate between direct and indirect effects. For the purpose of this review, direct effects of ethanol are caused by ethanol interacting with the fetal cell. Indirect effects of ethanol teratogenicity are defined as any perturbation of the developing fetus resulting from ethanol exposure but not caused by ethanol’s interacting with the fetal cell. Indirect effects of ethanol teratogenicity include: ethanol-induced maternal undernutrition; ethanol-induced placental dysfunction and acetaldehyde teratogenicity.

INTRODUCTION

Exposure to ethanol in utero can result in a multitude of biochemical and physiological alterations in the developing fetus. The teratogenic effects of ethanol on human fetuses were first reported in 1968 (Lemoine et al., 1968). In 1973, the term fetal-alcohol syndrome (FAS) was first used to describe a constellation of physiological abnormalities seen in infants exposed to ethanol in the womb (Jones et al., 1973; Jones and Smith, 1973). The teratogenicity of ethanol may not be caused simply by ethanol’s direct interaction with the developing fetal cells. Ethanol may cause damage by many indirect means, such as by causing maternal undernutrition or adversely affecting placental function. Some of the teratogenic effects of ethanol may in fact be due to the teratogenicity of acetaldehyde, the direct product of ethanol oxidation. Ethanol causes such a wide variety of pathophysiological responses that the underlying causes of ethanol teratogenicity lie somewhere among the many individual changes wrought by ethanol exposure on the developing fetus. Experimental models are needed to define more clearly the molecular mechanisms of ethanol teratogenicity.

Animal, cell culture and organ culture models are the means currently used to differentiate between direct and indirect ethanol teratogenicity. Often, the use of experimental models to study the direct effects of ethanol is justified by the fact that other drugs, such as cocaine or nicotine, are often present in humans who drink. The only way to analyse the effect that ethanol exerts is to control the conditions. But even in experimental models, where ethanol is the only drug to which a developing fetus is exposed, the direct effect of ethanol may be difficult to determine. If using a mammalian model to study ethanol teratogenicity, for example, maternal undernutrition must be accounted for by using appropriate controls. But even when maternal undernutrition is adequately controlled for, the direct effects of ethanol exposure are still difficult to differentiate from the indirect effects, because of the presence of a placenta and because ethanol is metabolized to acetaldehyde.

Because this paper deals primarily with the

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