Androgens and Prenatal Alcohol Exposure

McGivern et al. (1) reported that altered nonreproductive, sexually dimorphic behavior is associated with exposure of rats to ethanol during development. They concluded that the results were evidence of a direct effect of ethanol on testicular or adrenal function. There have been many studies of monamine control, direct and indirect, of neuroendocrine function (for example, inhibition of prolactin release by dopamine) which, in turn, may influence sexually dimorphic behaviors. In 1974 I reported that nonreproductive, sexually dimorphic behaviors could be altered by treating pregnant rats early during gestation with drugs that affect the synthesis or storage of such monoamine transmitters (2), so I am not questioning the observations of McGivern et al. (1). However, there are alternative interpretations of their results.

Caution should be used when data from other laboratories, based on studies with different experimental designs, are used to support one’s own experimental design decisions or interpretation of results. For example, if other laboratories had studied the same behavioral variables and reported that cross-fostering has no effect on that measure of behavioral teratogenicity in fetal alcohol-exposed (FAE) animals, then McGivern et al. could use such studies to defend their decision not to remove the pups from their biological mothers at term. The early experience literature supports the possibility that residual ethanol effects (more likely withdrawal) in the dams may have affected the outcome of the experiment. Furthermore, neonatal withdrawal might also have acted alone or in concert with altered maternal behavior to contribute to or be responsible for the outcome. It would have been preferable to cross-foster half of each litter to pair-fed dams and the other half to ethanol-fed dams to clarify this issue.

While perinatal birth weights are not given for experiment 1, McGivern et al. report a significant reduction in body weight of day-old ethanol-exposed males and females, weights being not significantly different from controls at 35 or 90 days of age in experiment 2. Even if greater malnutrition did not occur on succeeding days, when maternal or neonatal withdrawal might have been more severe, the fact that a significant weight differential existed at this early stage is problematic.

The suggestion that adrenal steroids may be responsible for at least the masculinization of adult FAE females, because others have reported increased brain and plasma levels of corticosterone in 1-day-old pups after prenatal alcohol exposure, begs the question related to the contribution of perinatal withdrawal and malnutrition and its associated stresses. We have recently reported such a potential source of epiphenomena in studies of the effects of opiates during development (3). We used opiate-naïve subjects, rendered neonatally undernourished to an extent essentially identical to some and less severe than others exposed to opiates during development (4). These subjects showed significant differences in basal body temperature and in hyperthermic and behavioral responses to morphine administration later in life compared to fully nourished littermates. Similar results have been offered by others as evidence of a direct perinatal opiate effect in mature subjects whose body weights were even more severely reduced at the time of testing. While it may be necessary to include an isocarboxylic pair-fed group as a control, it is not a sufficient control if significant body weight differences of offspring emerged during the perinatal period, unless the data are interpreted within a framework that includes the concept that exposure to ethanol prenatally invariably leads to undernutrition or running in offspring and that this effect is part of the fetal alcohol syndrome. Thus it may be premature to attribute to testosterone the effects observed by McGivern et al. until there is evidence that identical behavioral outcomes can be obtained in subjects with testicular hormone production suppressed in some other manner.

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References


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Our work demonstrating long-term alterations in saccharin preference and maze performance of animals exposed to alcohol in utero was based on the hypothesis that an alcohol-induced inhibition of fetal testicular steroidogenesis would feminize adult male behaviors that are organizationally dependent on perinatal androgen concentrations (1). Both saccharin preference and maze behavior are such behaviors. Moreover, alcohol is well known to inhibit testicular steroidogenesis in adult rats and humans (2). Our results revealed a clear feminization of both behaviors in adult fetal alcohol exposed (FAE) males. Our pair-fed control dams received the same number of calories during pregnancy as the alcohol-fed dams, but no alcohol. Offspring from these control dams showed the normal sex differences reported by numerous investigators over the past 20 years [see

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