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Disposition of Ethanol and Acetaldehyde in Maternal Blood, Fetal Blood, and Amniotic Fluid of Near-Term Pregnant Rats

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Alcohol consumption in Japan increase annually, especially alcohol consumption by young women (Omoto 1985). Women's drinking has ill effects not only on the women themselves but also on their fetuses during pregnancy, causing the fetal alcohol syndrome (Jones et al. 1973; Rosett and Weiner 1985; Yamamoto and Tanimura 1986). Although the pharmacokinetics of ethanol during pregnancy have been elucidated for multiple-dose ethanol in several mammalian species, the disposition of ethanol and its metablite, acetaldehyde, in the maternal-fetal unit is not known for maternal administration of a single dose of ethanol on one day.

The objectives of the present study were to investigate in rats the transplacental distribution of ethanol and acetaldehyde into the amniotic fluid and to determine the time course of ethanol and acetaldehyde in maternal and fetal blood and amniotic fluid following the maternal ingestion of a single dose of ethanol.

MATERIALS AND METHODS

Female Wistar rats, weighting 200-250 g were mated with male of the strain. Day 0 of pregnancy was established by observing their vaginal plug. Six pregnant rats were orally administrated with 2 g of ethanol/kg maternal body weight on day 20 of pregnancy. The pregnant rats were sacrificed at each of the following experimental time after a single administration of ethanol:1, 2, 3, 4, 5, 6, 7 and 8 hours. Maternal blood was taken from the vena cava inferior. The gravid uterus was exposed and incisions in the uterine horns were made to expose each fetus sequentially. Amniotic fluids were obtained prior to removing each fetus and blood samples from each fetus were collected from

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the jugular vein using heparinized capillary tubes. Simultaneously, the maternal and fetal liver removed.

Blood and amniotic fluid were added to 3 ml of ice-cold 0.6 N perchloric acid (PCA) containing 20 mM thiourea and deproteinized. The mixture was then centrifuged and 0.5 ml of the supernatant was subjected to analysis. One gram of liver powdered with liquid nitrogen was added to 3 ml of 0.6 N PCA. After centrifugation, quantitatively for ethanol and acetaldehyde using the head-space technique on a Shimazu 6 A gas chromatograph. Statistical comparison of the ethanol and acetaldehyde was analyzed by the Mann-Whitney test.

RESULTS AND DISCUSSION

The ethanol concentration-time curves for maternal blood and fetal blood and amniotic fluid are presented in Fig. 1. The maximum concentration of maternal blood and fetal blood was 1.930 mg/ml and 1.732 mg/ml, respectively. This occurred at 2 hours. The ethanol concentration of liver was higher in the fetus than in the mother throughout the time period studied, but not significantly (Fig. 2). During the 1- to 8-hour elimination phase, the ethanol concentration-time curves in maternal and fetal blood or liver was virtually identical (Fig. 1 and 2), which demonstrated that there rapid equilibrium distribution of ethanol in the maternal and fetal compartments. There was a time lag in the appearance of ethanol in amniotic fluid compared with its appearance in maternal and fetal blood or liver. The maximum amniotic fluid ethanol concentration was 1.192 mg/ml, and this occurred at 5 hours. In the third trimester of pregnancy, the major contribution of fluid into the amniotic cavity is fetal urine. In view of this and the relative delay in the appearance of ethanol in amniotic fluid compared with fetal blood, fetal urinary excretion would appear to be the major route of transfer of ethanol into the amniotic fluid. Elimination of ethanol from the amniotic fluid may occur by fetal swallowing of amniotic fluid and subsequent absorption of ethanol from the gastrointestinal tract into the fetal circulation. In this study, the concentration of ethanol in amniotic fluid was higher than the concentrations in maternal and fetal blood throughout the 4- to 8-hour interval. This indicated that the amniotic fluid might serve as a reservoir for ethanol in utero, thereby reulting in exposure of the fetus to ethanol form both the maternal and amniotic fluid compartments, as has been proposed previously for second-trimester pregnant

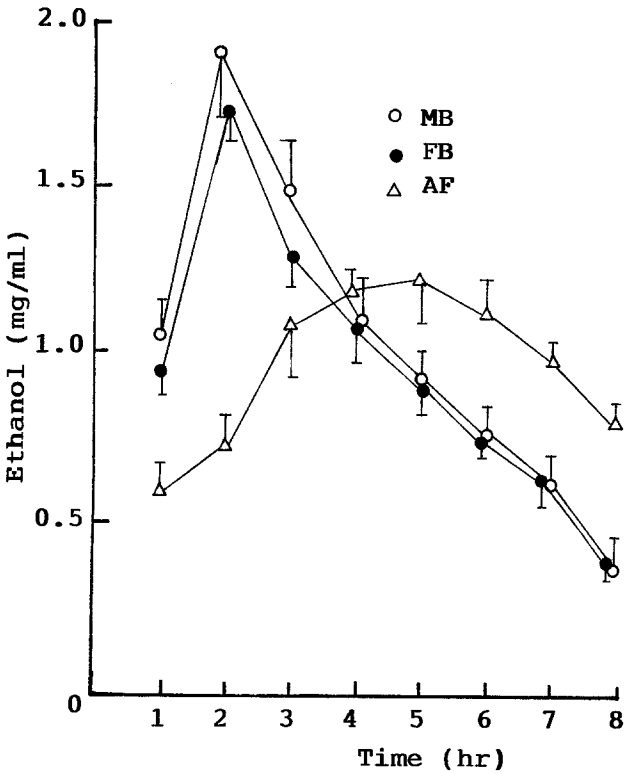

Figure 1. Mean(±SD) ethanol concentration-time curves in maternal blood (MB), fetal blood (FB) and amniotic fluid (AF) of six pregnant rats following oral administration of a single dose of 2 g/kg maternal blody weight.

women (Brien et al. 1983), third-trimester pregnant ewes (Brien et al. 1985), and third-trimester pregnant guinea pig (Clarke et al. 1985, 1986).

The role of acetaldehyde in the actions of ethanol is controversial and evidence exists that both supports (Yamamoto et al. 1986) and refutes (Keaniemi and Sipple 1975) the proposed involvement of acetaldehyde in the fetal alcohol syndrome.

The acetaldehyde concentration-time curves of the maternal blood, fetal blood and amniotic fluid are presented in Fig. 3. The acetaldehyde concentrations were at least 1000- to 1500-fold less than the respective ethanol concentration, which indicated that only samll amounts of acetaldehyde escaped from the acetaldehyde-oxidizing capacity of the maternal liver (Khanna and Israel 1980). The lower concentration of acetaldehyde in fetal blood ($p<0.02$) compared with that in maternal blood during the elimination phase indicated that

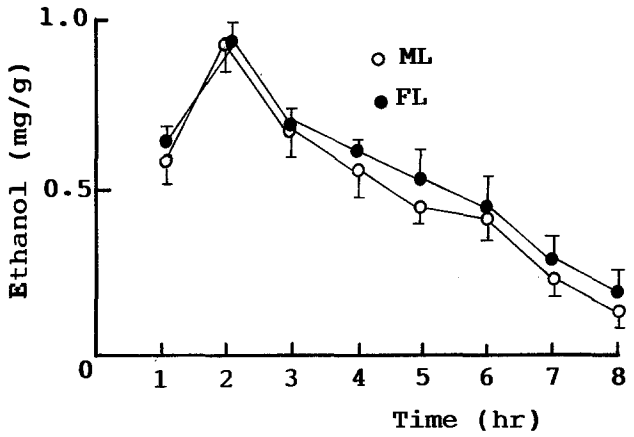

Figure 2. Mean(± SD) ethanol concentration-time curves in maternal liver(ML) and fetal liver(FL) of six pregnant rats following oral administration of a single dose of 2 g/kg maternal body weight.

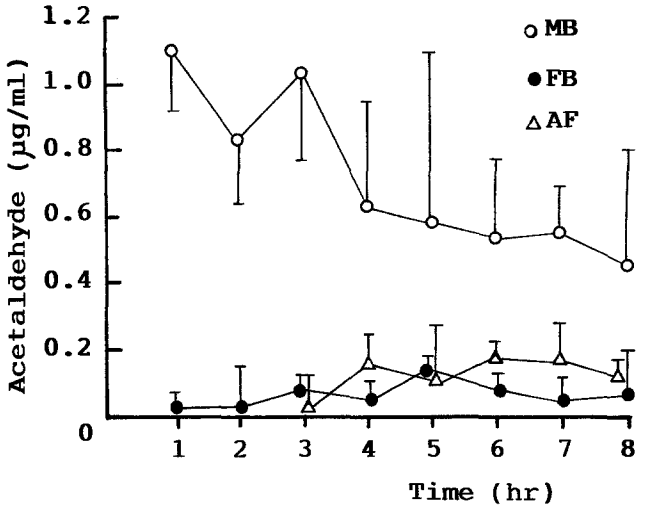

Figure 3. Mean(± SD) acetaldehyde concentration-time curves for maternal blood(MB), fetal blood(FB) and amniotic fluid(AF) of six pregnant rats following oral administration of a single dose of 2 g/kg maternal body weight.

it was the extrahepatic acetaldehyde-oxidizing capacity which regulated the transfer and accumulation of this active metabolite in the fetus. Since maternal and fetal ethanol clearance rates are similar, and the mean fetal liver alcohol dehydrogenase activity

is about 10 % of maternal liver activity (Khanna and Israel 1980; Cummin et al. 1985), the fetus must rely on maternal metabolism for the elimination of ethanol, and elimination occurs primarily from the mother. The mechanism by which acetaldehyde accumulates in amniotic fluid is unclear, but it would appear that fetal metabolism of ethanol would not be important because of the low ethanol-oxidizing capacity of the fetal liver.

The data of the present study indicate that there is differential disposition of ethanol in maternal blood and amniotic fluid following maternal administration of acute, single-dose ethanol during near-term pregnant rats. Thus the fetus could be exposed to significant ethanol concentration in amniotic fluid for a longer period of time than would be predicated by the ethanol concentration in maternal blood.

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