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Role of formate in methanol-induced exencephaly in CD-1 mice

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ABSTRACT

Mouse embryos develop exencephaly when dams are exposed by inhalation to high concentrations (≥10,000 ppm) of methanol on gestational day 8 (GD8; copulation plug = GD0). The present study examined the role of formate, an oxidative metabolite of methanol, in the development of methanol-induced exencephaly in CD-1 mice and cultured mouse embryos. The pharmacokinetics and developmental toxicity of sodium formate (750 mg/kg by gavage), a 6-hr methanol inhalation (10,000 or 15,000 ppm), or methanol gavage (1.5 g/kg) in pregnant CD-1 mice on GD8 were determined. Gross morphological evaluations for neural tube closure status in embryos or exencephaly in near-term fetuses were performed. Decidual swellings and maternal plasma were analyzed for methanol and formate. The mean (± S.E.M.) end-of-exposure plasma methanol concentration was 223 ± 23 mM following the 6-hr, 15,000 ppm methanol inhalation. There were no changes in blood or decidual swelling formate concentrations under any of the methanol exposure conditions. Peak formate levels in plasma (1.05 ± 0.2 mM; control 0.5 ± 0.3 mM) and decidual swelling (2.0 ± 0.2 mM; control 1.1 ± 0.2 mM) from pregnant mice (GD8) given sodium formate (750 mg/kg, po) were similar to those observed following a 6-hr methanol inhalation of 15,000 ppm (plasma = 0.75 ± 0.1 mM; decidual swelling = 2.2 ± 0.3 mM) but did not result in exencephaly. In cultures of neurulating mouse embryos explanted on GD 8, the incidence of cephalic dysraphism observed on GD 9 + 6 hr was significantly increased relative to appropriate controls after a 12-hr exposure to 375 mM methanol or to formate concentrations (40 mM) that exceeded those observed in vivo. These results suggest that exencephaly is a direct result of the effects of the parent compound methanol, administered at high concentrations, rather than the accumulation of formate. © 1995 Wiley-Liss, Inc.

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