Effect of Valproate on Zinc Metabolism in Fetal and Maternal Rats Fed Normal and Zinc-Deficient Diets

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ABSTRACT

Pregnant Wistar rats fed control and Zn-deficient diets received daily oral doses of 0, 100, and 300 mg/kg sodium valproate from d 16 to 20 of gestation. Only the highest valproate doses induced a small reduction in fetal body weight in the normally fed group. Zinc deficiency caused a drastic reduction in maternal and only a small reduction in fetal serum Zn concentrations. Valproate treatment had no effect on maternal and fetal serum Zn concentrations.

Valproate reduced fetal liver Zn content only in the normally fed group. The reduction of liver Zn content resulted from the reduction of Zn-metallothionein. Valproate did not affect total Zn and Zn-metallothionein in kidneys. Three percent of the Zn-deficient fetuses developed hydronephrosis and hydrops. Valproate treatment drastically enhanced the occurrence of fetal hydronephrosis and hydrops. Valproate induced fetal liver necroses, independent of Zn nutrition.

Index Entries: Zn-metallothionein; effect of valproate and Zn deficiency on hydronephrosis; induction by Zn deficiency and valproate; hydrops, induction by Zn deficiency and valproate; fetal liver; fetal kidney.

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INTRODUCTION

Valproic acid, an anticonvulsant drug, can induce various malformations, preponderantly defects of the neural tube and other toxic effects, e.g., hepatotoxicity (1,4).

Zinc deficiency produces similar malformations (5). Several side effects of valproic acid are similar to those observed after zinc or selenium deficiency, and administration of valproic acid to adult rats reduces plasma Zn and Se concentration and liver Se content (6,7). Therefore, an interaction of Zn and valproate or its metabolites is suggested. However, in adult rats, hepatotoxicity of valproic acid does not appear to be caused by Zn deficiency, but probably by an interaction with coenzyme A (CoASH) (8). The teratogenic effects of valproate are as yet unexplained. Therefore, we investigated fetal and maternal Zn metabolism of normal and Zn deficient rats treated with valproate. As in similar experiments with salicylate (9), the drug was given from d 16 to 20 of gestation, when most of the fetal rat body mass is synthesized.

MATERIALS AND METHODS

Pregnant Wistar rats, weighing 200 g, were fed a control or Zn-deficient diet and distilled water ad libitum from d 0 to 21 of gestation. For preparing the diets, a commercial diet (Ssniff, Soest, FRG) without ZnCO₃ and MgSO₄ in the mineral mix was used. Casein, separately received, was extracted with 1% EDTA (disodium salt) for 4 h and 0.5% EDTA for 3 h with stirring, and washed twice with distilled water by suction. The Zn-deficient diet was supplemented with MgCl₂ to 100 ppm Mg. Its Zn content was measured after ashing by atomic absorption spectrophotometry and amounted to 1.5 ± 0.2 ppm Zn. Control rats were fed the same diet supplemented with ZnCl₂ to 100 ppm Zn. Food intake by the control and Zn-deficient rats was measured daily. [For more details see ref. (10).]

From d 16 to 20, the rats in both dietary groups received daily oral doses of 0, 100, or 300 mg/kg sodium valproate. Other authors (6,7) gave 300 (6) or up to 750 mg/kg (7) valproic acid (VPA) for 7 d to nonpregnant rats. Thus, our doses were somewhat lower, although the elimination of VPA is increased during pregnancy (11). Daily therapeutic doses of VPA are lower (4) than those applied in experiments with rats. However, the elimination rate of VPA in rats is higher than in humans because of the lower binding of VPA to rat serum proteins (12).

At d 21, the uteri were dissected under nembutal anesthesia (50 mg/kg sc). Blood was taken from the fetal hearts by means of heparinized capillaries and from the mothers by heart puncture and was centrifuged for 5 min at 1300g. Fetal and maternal livers were removed and cleaned in cold 10% sucrose. Sections (0.5 g) of livers were used for preparing a