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Transplacental Passage of Methylmercury and Its Uptake by Primate Fetal Tissues[1] (38576)

W. ANN REYNOLDS AND ROY M. PITKIN

Department of Anatomy, University of Illinois at the Medical Center, Chicago, Illinois 60680 and Department of Obstetrics and Gynecology, University of Iowa, Iowa City, Iowa 52242

Organic mercury crosses the human placenta, as evidenced by its presence in blood (1) and urine (2) of newborns. Fetal death *in utero* and severe brain damage and other symptoms in liveborn infants have been noted with increased frequency in epidemics of methylmercury poisoning in Japan (3, 4) and Iraq (5). However, mortality rates among fetal victims of acute methylmercury poisoning appear to be lower than those for either children or adults (5, 6), suggesting the placenta may afford some degree of protection, at least initially, on the basis of limited permeability to organic mercury. Studies on rodents (7, 8) have indicated the extent to which organic mercury reaches fetal tissues in that species. However, information is needed on the rate and extent of movement of methylmercury across the hemochorial placenta in order to assess the risk of mercury poisoning in the human fetus. We have examined bidirectional placental transport of methylmercury in the rhesus monkey (*Macaca mulatta*), a species with placental structure and function similar to the human (9).

Materials and Methods. Maternal–fetal transfer of methylmercury was studied in five experiments and fetal–maternal transport in one. Pregnant macaques were obtained from commercial sources. The duration of gestation at the time of experimentation, determined retrospectively by comparing fetal weights and lengths and placental weights with normal growth charts (10), ranged between 135 and 165 days; length of gestation in this species is 168 days.

Following premedication with phencyclidine hydrochloride (1 mg/kg), each animal was anesthetized with halothane by inhalation. The maternal abdomen was opened, the uterus exposed and an interplacental vein catheterized (11) with a silastic T-tube, permitting repeated sampling from the fetal circulation with the fetus *in utero* and the amniotic sac intact. A catheter was inserted through the uterus for aspiration of amniotic fluid samples. Access to the maternal circulation was provided by a catheter inserted into the inferior vena cava through a saphenous vein.

Methyl-203-mercury chloride (New England Nuclear Corp., Boston, MA. sp act 1.5 mCi/mg) was administered in dosages of 45–100 μCi via an indwelling catheter into a maternal antecubital vein in five experiments. In the one experiment of fetal–maternal transfer, 15 μCi of the labeled compound was injected into the fetal circulation. Samples of 1 ml each were obtained at intervals from the maternal and the fetal circulations and from the amniotic sac over the ensuing 5–7 hr. Blood samples were collected in heparinized tubes and the separated plasma and red cells assayed separately for radioactivity. At the end of the experiment, the fetus was delivered by hysterotomy and killed with an overdose of pentobarbital. Fetal tissue samples in triplicate were assayed for gamma radioactivity in a well-type scintillation detector (Packard Instrument Corp., Downers Grove, IL). Corrections were made for background and decay. To permit comparison between different experiments, the results in radioactivity per ml (fluid samples) or g (tissue samples) were expressed as percentage of the administered dose.

Results and comment. As illustrated in Fig. 1a, methylmercury administered to the mother was present in the fetus within 10 min and fetal radioactivity levels increased progressively over the ensuing 5–6 hr. However, the maternal-fetal ratio remained high (10 or more) for both plasma and red blood cells. Minimal amounts of ^{203}Hg reached the amniotic fluid.

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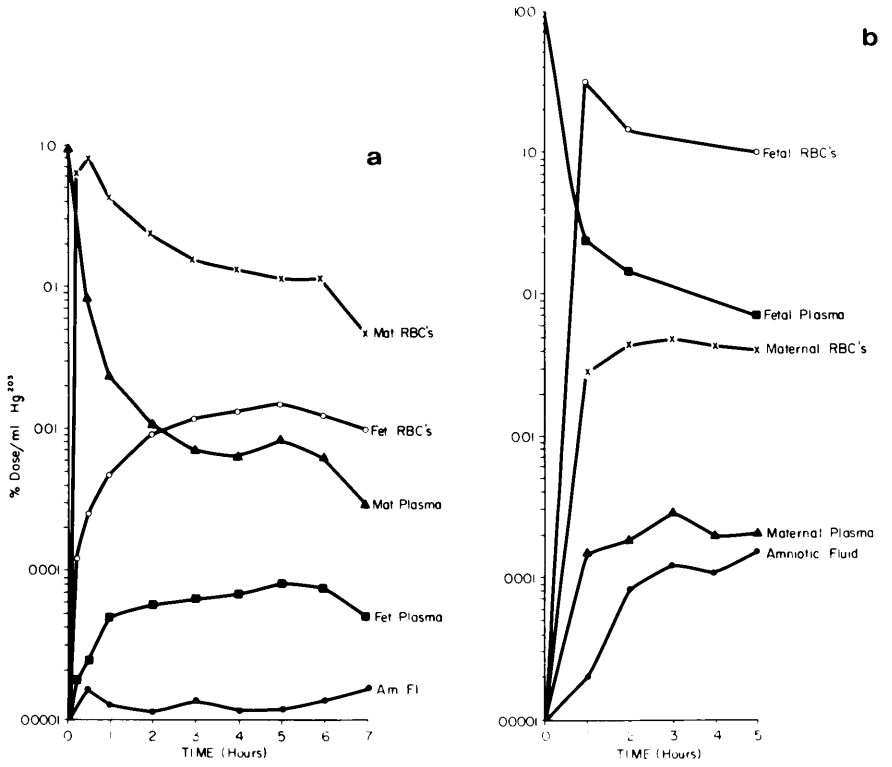

FIG. 1a. Levels of ^{203}Hg in maternal and fetal circulations following maternal intravenous administration of methylmercury chloride (averages of five experiments). Note logarithmic ordinate. Fetal levels did not approach maternal levels during the experimental period. b. Maternal and fetal levels of ^{203}Hg after fetal intravenous administration of methylmercury chloride. Note logarithmic ordinate. The gradient between fetal and maternal levels of radioactivity was greater in this experiment than in those with maternal administration.

In the experiment in which methylmercury was administered directly into the fetal circulation, movement of radioactivity into the maternal circulation had occurred by 1 hr. (Fig. 1b). The fetal–maternal ratio of radioactivity was never lower than 25:1 for red blood cells and 36:1 for plasma. Thus, the fetal–maternal ratio was greater following fetal than was the maternal–fetal ratio after maternal administration of methyl-203-mercury chloride, suggesting that transfer of mercury from mother to fetus occurred more readily than movement in the opposite direction. To test this finding further, 14 μCi of methyl-203-mercury chloride was administered orally at six intervals over 12 wk to another pregnant rhesus monkey. At delivery fetal blood levels of ^{203}Hg were 2.25 times greater than those found in maternal blood. Thus, on a chronic basis as well, transfer of mercury into the fetus occurs more readily than loss of mercury from the fetal into the maternal circulation.

The somewhat larger amount of radioactivity reaching the amniotic fluid following fetal, compared with maternal, methylmercury administration likely reflects the greater importance of fetal mechanisms in amniotic fluid formation. Fetal urine, however, is probably not the major fetal source since relatively little mercury is excreted by the kidney, in comparison to the gastrointestinal tract.

Both maternal and fetal red blood cells contained 10–20 times more labeled mercury than did plasma. In all experiments except one, the affinity of red blood cells for mercury was initially greater in the mother than in the fetus but after several hours the ratios were quite similar in mother and fetus. The mercury content of red blood cells in human

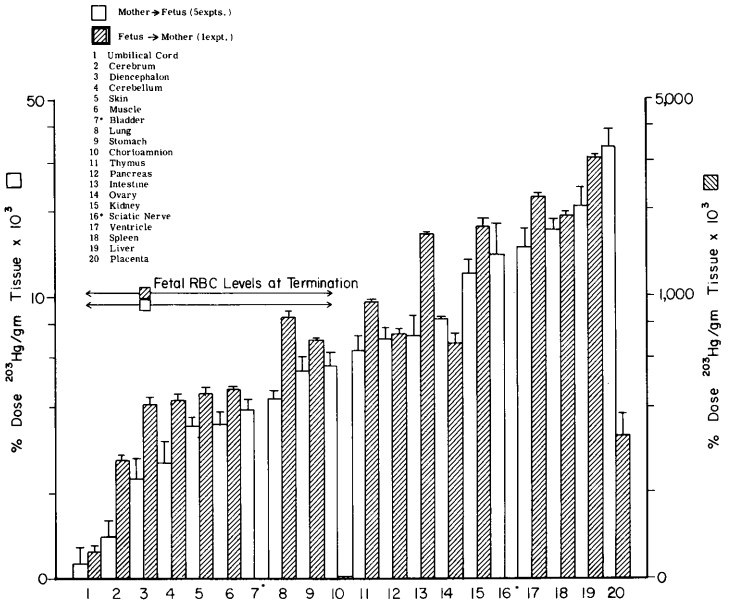

FIG. 2. Tissue levels of ^{203}Hg at termination of the six experiments. Note logarithmic ordinate. With the exception of placenta and chorioamnion, levels following fetal or maternal administration follow the same general pattern. Horizontal bars denote mean radioactivity (on a percentage dose basis) found per ml of packed red cells derived from cord blood at the end of the experiments. Vertical bars represent SEM. Asterisk (*) denotes tissues obtained only in those experiments involving maternal administration.

newborns has been reported to be about a third higher than in mothers (1). However, the present data represent acute levels following a single bolus of radioactive mercury; fetal red cell accumulation and retention of mercury over many weeks may well be reflected in higher red cell values in the fetus than in the mother.

In general, the patterns of fetal tissue levels of radioactivity were similar whether radioactive methylmercury was administered to mother or fetus (Fig. 2). Of course, actual tissue levels were considerably higher in the fetus receiving the compound directly rather than transplacentally. The two notable exceptions were placenta and chorioamnion whose high levels of ^{203}Hg following maternal administration probably reflect accumulation of mercury in these tissues, effectively retarding its movement into the fetal circulation and amniotic fluid, respectively. Brain levels of radioactivity were far below those found in kidney, liver, and gastrointestinal tract (Fig. 2). The low levels of labeled mercury found in the fetal brain after 5–7 hr of exposure suggest the presence of a blood-brain barrier. Similarly, others (12, 13) have shown a slow rate of accumulation of mercury by the adult rodent brain, suggesting that the blood-brain barrier affords some initial protection against this toxic substance. In adult squirrel monkeys chronically exposed to methylmercury and exhibiting neurologic symptoms of mercury poisoning, just the reverse is true, with brain levels exceeding those of the liver and kidney (14). Regional brain differences in the accumulation of mercury have been reported for the adult monkey (14), dog (15), and piglet (16). In the present study, levels of ^{203}Hg were significantly higher in the fetal cerebellum than in the fetal cerebrum following maternal ($P < 0.05$) or fetal ($P < 0.02$) administration. The apparent regional difference may be based on differences in gray and white matter content of these areas since the most extensive localization of organic mercury appears in association with gray matter (17).

The blood-brain barrier and the placenta are often likened because of their functional similarities. In the present study, the re-

tarded transfer of radioactive mercury into the fetal brain and across the placenta may be related to extensive binding of mercury by red blood cells which would impede the movement of mercury across cell membranes.

Other tissue levels of ^{203}Hg, such as skin, muscle, lung, thymus, pancreas, and ovary probably exhibit, in large part, the vascularity of the particular organ since their levels did not exceed those of fetal red blood cells (Fig. 2). An intriguing exception is spleen whose high content of radioactivity could be the result of extensive binding by the numerous formed blood elements contained in this organ.

The present study indicates that, while the placenta may afford the primate fetus some protection from acute maternal mercury poisoning, the fact that organic mercury moves more readily into the fetal circulation than out of it probably accounts for the fetal hazard following chronic exposure. Once in the fetal circulation, the blood-brain barrier seems to impede movement of methylmercury into the brain. However, this may be true only late in fetal life when the blood-brain barrier is mature. Moreover, it is entirely possible that delayed clearance may also occur in the brain, to account for the well-known propensity to brain damage with methylmercury poisoning.

Summary. Radioactive methylmercury given to rhesus monkeys in late pregnancy crossed the placenta slowly from mother to fetus. The maternal–fetal ratio in both plasma and erythrocytes was as low as 10:1 several hours after maternal administration. Transfer from fetus to mother was even slower with the concentration gradient remaining above 25:1. Organic mercury was generally distributed throughout fetal tissues in a similar manner regardless of the routine of administration. The placenta and blood-brain barrier each appear to represent partial impediments to acute transfer of organic mercury, probably because of extensive erythrocyte binding.

While the hemochorial placenta, by virtue of its limited permeability to organic mercury, appears to afford the fetus some degree of protection from acute mercury poisoning, the fact that mercury moves out of the fetal circulation even more slowly than into it probably accounts for the fetal hazard with chronic exposure.

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