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Intestinal Accumulation of Lead Salts and Milk Lead by Suckling Rats (42645)

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Abstract. Absorption of lead is known to be enhanced during infancy. In this study, the sites of intestinal accumulation of Pb by suckling rats have been determined under various conditions using ^{203}Pb as a tracer. When ^{203}Pb was administered intragastrically (IG) as a soluble salt, accumulation occurred primarily in the duodenum, regardless of dose and vehicle. In contrast, when rat pups suckled from a dam which had received ^{203}Pb, the only region of the small intestine showing accumulation of radioactivity was the ileum. To confirm that these differences were not related to the route of administration, rat milk was labeled with ^{203}Pb and was then used for IG administration. Once again, accumulation (4 hr post-administration) was confined to the ileum. When the dose was increased 10-fold, milk Pb displayed some accumulation in duodenal tissue, but very much less than that of soluble Pb at the same time and dosage. At 20 hr postadministration, there was negligible ^{203}Pb in any region of the small intestine following administration as a soluble salt, but substantial retention in ileal tissue following administration in milk. The strikingly different patterns of intestinal accumulation obtained with Pb salts as compared with milk Pb suggest different modes of absorption of Pb ingested in these two forms.

Avid absorption of Pb has been found in the young of humans (1–3), monkeys (4, 5), rats (6, 7), and mice (8). To date, absorption studies in experimental animals have all utilized soluble salts of Pb (4–8). However, for the suckling offspring the principal source of Pb would be mother's milk. Investigations in rodents have shown substantial transfer of Pb from mother to offspring via milk (9, 10). The importance of this source for human infants is illustrated by the recent report indicating that of the environmental predictors examined, milk Pb is the strongest correlate of 6-month blood Pb (11).

Using the rat model we have found that Pb in milk is predominantly associated with the casein micelles (12). Since there is minimal digestion of proteins in the gastrointestinal tract of the suckling rat (13), it is likely that milk Pb remains protein bound as it traverses the stomach, duodenum, and jejunum. Ileal epithelium has a high capacity for nonspecific pinocytosis (14–17) which is the principal route of absorption of dietary proteins at this age (18). Thus, if Pb remains associated with casein, it should show a pattern of ileal uptake.

Previous studies with suckling rodents have identified two sites of accumulation of Pb after intragastric administration as a soluble salt, namely the duodenum and the ileum (19–21). In these studies, animals were allowed to nurse following dosing with Pb. Thus, the pattern observed may have been due in part to an association of Pb with milk components in the stomach. Moreover, it could be argued that the duodenal component (19, 20) was an artifact due to the rather high dose of Pb (5 μg/g body wt) used in these studies. Thus, the aims of the current investigation were (a) to study the intestinal accumulation of Pb salts using lower doses and to compare the results obtained when pups were allowed to nurse following administration of Pb to those obtained when pups were fasted, and (b) to compare the accumulation patterns obtained using soluble salts of Pb with those obtained using milk Pb.

Materials and Methods. *General Methods: Animals.* Timed-pregnant Sprague–Dawley rats (Charles River Crl:CD(SD)BR) were received from Charles River Breeding Laboratory (Wilmington, MA) on the 15th day of gestation. They were housed individually in opaque polystyrene cages and provided with food (Rodent Laboratory Chow 5001; Ralston Purina, St. Louis, MO) and water *ad libitum*. Animal quarters were air-conditioned (22 ± 1°C) and maintained on a 12-hr light-dark cycle. On the due date, cages were

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checked every 2 hr for births. The birth date was regarded as day 0. Approximately 24 hr postpartum, litters were culled to nine pups. Experiments were conducted when pups were 9–16 days of age.

Chemicals. $^{203}PbCl_2$ (trace labeled) in 0.5 *M* HCl was purchased from New England Nuclear (Boston, MA). Nonlabeled lead acetate and lead chloride were reagent grade from Matheson, Coleman and Bell (Cincinnati, OH) and Mallenckrodt (St. Louis, MO), respectively. Oxytocin (grade III synthetic) was from Sigma, St. Louis, MO).

Intragastric intubation. To prevent interference from food in the stomach, all pups were fasted overnight. Experiments were initiated by accurately administering 0.2–0.5 μCi of ^{203}Pb (in various forms, depending on the particular experiment) directly into the stomach via a length of PE-20 tubing attached to a syringe and introduced through the mouth. The pups were not anesthetized during intubation, as we have found that they remain in better condition if the procedure is done without anesthetic. It is very rapid (approximately 30 sec) and, apart from the temporary restraint, does not appear to distress the animal. Use of conscious animals overcame the problems of variable gastric emptying noted in our previous study with anesthetized animals (19) and thus obviated the need to express data as tissue:lumen ratios.

In all experiments, the intubation volume was 7 μl/g body wt. Preliminary experiments established this to be less than the largest volume (10 μl/g body wt) that fasted pups could receive intragastrically without forcing entry into the duodenum. After intubation, pups were either fasted or returned to the dam to suckle, depending on the experiment (see below).

Tissue removal. At intervals following administration of ^{203}Pb, pups were killed by decapitation. The entire small intestine was carefully removed, beginning at the pylorus, noting the distance from there to the ligament of Treitz (i.e., duodenal length) and continuing to the ileocecal junction. It was laid on a glass plate on ice and divided into 12 approximately equal segments, segment 1 beginning at the pyloric end. Only the odd-numbered segments were utilized. The measurements indicated that the ligament of Treitz was always located in segment 2. Thus, for the data presented in this paper, segment 1 represents the duodenum, segments 3 and 5 represent the jejunum, and segments 7, 9, and 11 represent the ileum. Each segment was slit open, washed, blotted, weighed, and then was placed in a polypropylene tube for gamma counting. The lungs from each animal were also subjected to gamma counting to determine whether the ^{203}Pb was correctly administered. When significant amounts (>1.5% of the administered dose) were found in the lungs, the animal was excluded from the study. For the data presented, this criterion resulted in the exclusion of only one animal (which had 9% of the dose in the lungs).

Solutions used for washing intestinal segments were either 0.9% NaCl or 150 m*M* Na acetate containing 5 m*M* EDTA (pH 6.3). Preliminary experiments established that the latter, more stringent wash was necessary in animals that were fasted after intubation with ^{203}Pb. In fed animals there was negligible difference in tissue values obtained following washing with either of these solutions. Thus, in the experiments described below, 0.9% NaCl was used for the first two experiments whereas the acetate/EDTA solution was used for the latter three.

Quantitation of data. The ^{203}Pb content of all tissue samples was determined by counting in a Packard gamma counter with the energy window set at 70–467 keV. The cpm values thus obtained were corrected for decay using a $T_{1/2}$ value for the ^{203}Pb of 52.1 hr, and using the time of administration of ^{203}Pb as the reference point for each experiment. The dosing solution from each experiment was also counted so that for each tissue segment, the ^{203}Pb content could be expressed as percentage dose/segment and percentage dose/milligram or gram tissue. In all cases these two modes of expressing the data resulted in the same general patterns. Thus, only one mode (per unit weight) is given in the figures. Values are plotted as means ± SE. Lack of error bars indicates that the SE was smaller than the symbol.

Experiment 1. Pb salt: Effect of dose. Eight littermates were intubated with $^{203}PbCl_2$ mixed with nonlabeled Pb acetate in 150

m*M* Na acetate, pH 6.5, such that the total dose was 5 μg Pb/g body wt for half of the pups and 0.01 μg Pb/g body wt for the other half. Following intubation all pups were returned to their dam and allowed to nurse for 4 hr prior to sacrifice. All other details were as under General Methods.

In this experiment trunk blood was collected in heparinized tubes for determination of its ^{203}Pb content. Values obtained were less than twice background, therefore were not considered reliable, and are not presented. On a weight/volume basis, blood values were in the range 4–8% those of (average) intestinal tissues from the same animals, emphasizing the extent to which Pb is retained in the intestinal mucosa. As blood values for ^{203}Pb had no direct bearing on the general questions addressed in this study, increasing the dose of isotope to obtain accurate blood values was deemed unwarranted. Blood was not collected in subsequent experiments.

Experiment 2. Milk Pb received by suckling. A dam was separated from her pups overnight. The following morning the dam received a trace dose of $^{203}PbCl_2$ (25 μCi, 3.4 μg Pb) by ip injection. She was then returned to her pups, who were allowed to nurse for 4 hr prior to sacrifice. All other details were as under General Methods.

Experiment 3. Milk Pb and salt Pb received by gavage. Rat milk was collected by manual expression following ether anesthetization and injection with oxytocin (1 unit). The milk was labeled with ^{203}Pb such that both the amount of radioactivity and the amount of Pb was similar to that obtained by *in vivo* labeling (Experiment 2). For this purpose 0.1 ml of 150 m*M* Na acetate, pH 6, containing $^{203}PbCl_2$ (1 μCi, 0.14 μg) was added to 0.9 ml of rat milk and incubated at 37°C for 2 hr. These conditions had previously been shown to result in the same extent of association of the ^{203}Pb with casein micelles as occurs following *in vivo* labeling (12). To create an equivalent dosing solution containing Pb as a soluble salt, the same amounts of ^{203}Pb and nonlabeled $PbCl_2$ were mixed with 0.9 ml of 150 m*M* Na acetate, pH 6.5.

Four pups were intubated with the ^{203}Pb-labeled milk and four littermates were intubated with the ^{203}Pb salt solution. In both cases the dose of Pb was 0.001 μg/g body wt. Following administration of ^{203}Pb, all pups remained in the fasted state for a further 2 hr until sacrifice. All other details were as under General Methods.

Experiment 4. Effect of time on Pb uptake. This experiment was the same as Experiment 3 except that 20 hr was allowed to elapse between intubation and sacrifice. To assure detectable levels of ^{203}Pb in tissues, the amount of label was kept constant at approximately 0.2 μCi/pup. However, because this experiment was performed several days after Experiment 3, keeping the amount of label constant necessitated using more of the stock $^{203}PbCl_2$ and resulted in the dose administered (both as salt and as milk) being 0.003 μg Pb/g body wt.

Experiment 5. Effect of dosing solution on Pb uptake. In this experiment, three dosing solutions were prepared: (A) $^{203}PbCl_2$ in 0.9% NaCl containing 0.1% bovine serum albumin (BSA); (B) $^{203}PbCl_2$ in 150 m*M* Na acetate, pH 6.5; and (C) ^{203}Pb-labeled milk. These dosing solutions were prepared as described in Experiment 3 except that the amount of nonlabeled $PbCl_2$ was increased so that the total dose in each case would be 0.01 μg Pb/g body wt. After fasting overnight, four pups received the ^{203}Pb in 0.9% NaCl with 0.1% BSA (dosing solution A); another four received dosing solution B; and a further four received dosing solution C. They remained in the fasted state for 4–5 hr until sacrifice. All other details were as under General Methods.

Results. Figure 1 shows results from Experiment 1, namely the intestinal accumulation of ^{203}Pb following its intragastric administration as a soluble salt at the high dosage (5 μg Pb/g body wt) used previously (19, 20) and at a lower dose (0.01 μg Pb/g body wt). It can be seen that at both doses there were two sites of tissue accumulation, the duodenum and the ileum. The former was accentuated at the lower dose. Thus, it is apparent that the duodenal uptake previously observed (19, 20) was not simply an artifact of the high dose used. In Experiment 1, animals were allowed to nurse following intubation, so there remains the question of whether the ileal component is due to association of ^{203}Pb

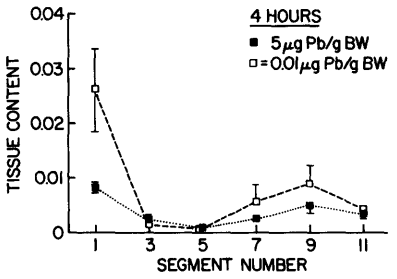

FIG. 1. Intestinal content of ^{203}Pb in rat pups 4 hr after intragastric administration as a soluble salt (Experiment 1). The doses were (■) 5 μg Pb/g body wt (n = 4); and (□) 0.01 μg Pb/g body wt (n = 3). Data are expressed as percentage dose per milligram tissue.

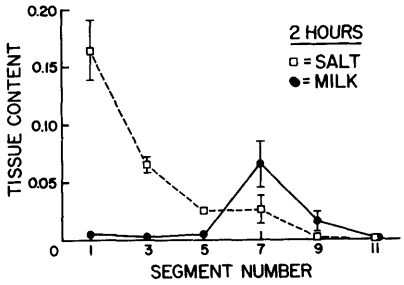

FIG. 3. Intestinal content of ^{203}Pb in rat pups 2 hr following intragastric administration as (□) soluble salt or (●) in milk (Experiment 3; n = 4 for both groups). Data are expressed as percentage dose per milligram tissue.

with milk in the stomach following intubation.

A very different pattern of Pb accumulation was observed when rat pups suckled from a dam which had received an injection of ^{203}Pb (Experiment 2). Under these circumstances (Fig. 2) there was essentially no accumulation of ^{203}Pb in the duodenum, but a marked degree of accumulation in all regions of the ileum. It should be noted that the absolute numbers are not directly comparable with Fig. 1 because in Experiment 2 the dose was administered to the dam rather than to the pups.

Before ascribing the different accumulation patterns in Figs. 1 and 2 to the chemical form of Pb, it was necessary to recognize that there was also a difference in the route of administration in these two experiments (intragastric intubation vs natural suckling). In order to directly compare the accumulation pattern of ^{203}Pb administered as a soluble salt or as milk, in Experiment 3 we prepared *in vitro*-labeled rat milk and used it for intragastric administration. The results (Fig. 3) indicate that even when the route of administration was identical, there was a marked difference in the patterns obtained with these two forms of Pb. Specifically, Pb salt accumulated primarily in the duodenum, somewhat in the jejunum, and minimally in the lower regions of the small intestine. In contrast, following administration in milk, ^{203}Pb was found only in the tissue of the upper ileum. When the tissue distribution of ^{203}Pb was examined 20 hr postintubation (Experiment 4), ileal content of milk Pb was enhanced, whereas there was essentially no tissue retention for ^{203}Pb administered as a salt (Fig. 4).

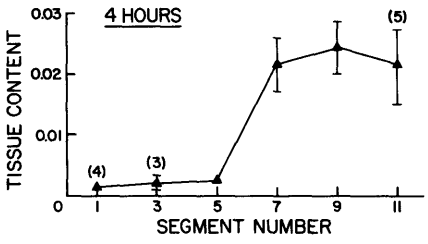

FIG. 2. Intestinal content of ^{203}Pb in rat pups following 4 hr suckling on a dam which had received an ip injection of ^{203}Pb (Experiment 2; n = 6 unless indicated in parentheses). Data are expressed as percentage dose (to the dam) per gram tissue.

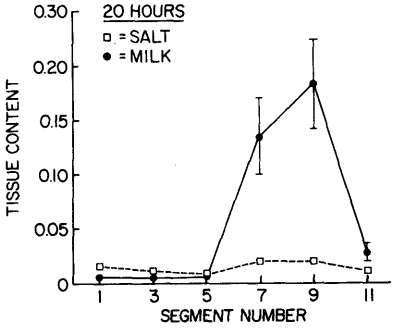

FIG. 4. Intestinal content of ^{203}Pb in rat pups 20 hr following intragastric administration as (□) soluble salt or (●) in milk (Experiment 4; n = 4 for both groups). Data are expressed as percentage dose per milligram tissue.

Two final questions were addressed in Experiment 5: (a) whether the salt pattern obtained in Figs. 1 and 3 is peculiar to $PbCl_2$ in Na acetate, and (b) whether milk Pb gives a different pattern of accumulation when administered at a higher dose. For this purpose ^{203}Pb was administered at a dose of 0.01 μg Pb/g body wt in 0.9% NaCl containing 0.1% BSA, in 150 m*M* Na acetate, or in milk. The results (Fig. 5) indicate once again that for milk Pb, accumulation occurred primarily in the ileum. However, at this dose there was also some accumulation in the duodenum, although less than that seen with Pb salts. Both salt solutions gave the same pattern seen in Fig. 3.

Discussion. These studies have shown that the pattern of intestinal accumulation of Pb is markedly influenced by the form in which it enters the stomach. When administered as a soluble salt, regardless of whether the dose was low (e.g., 0.001 μg/g body wt, Fig. 3), medium (e.g., 0.01 μg/g body wt, Figs. 1 and 5) or high (e.g., 5 μg/g body wt, Fig. 1), Pb accumulated primarily in the duodenum. The small ileal peak seen in Fig. 1 can be ascribed to association with milk, as pups were allowed to nurse following intubation in that experiment. In subsequent experiments, when pups were fasted following intubation (Figs. 3–5), there was no ileal peak for Pb salts. Likewise, the lower absolute values for duodenal Pb in Fig. 1 as compared with salt values in Figs. 3 and 5 probably represent a partial shift toward the "milk" pattern when animals suckle after dosing. The results of Experiment 5 showed that the general "salt" pattern of Pb content (i.e., high in duodenal tissue and declining distally) was independent of the salt solution in which the $^{203}PbCl_2$ was administered. The two solutions used were (a) 150 m*M* Na acetate (pH 6.5), thus making acetate the "reference" counterion as in studies of Pb absorption in adult rats (22); and (b) 0.9% NaCl containing 0.1% BSA, which has been used as a vehicle in studies of Ca absorption (23).

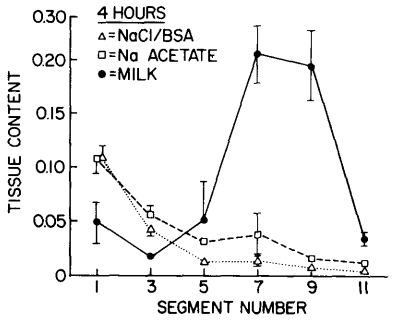

FIG. 5. Intestinal content of ^{203}Pb in rat pups 4 hr following intragastric administration in (△) 0.9% NaCl with 0.1% BSA, (□) 150 m*M* Na acetate, or (●) milk (Experiment 5; $n = 4$ for each group). Data are expressed as percentage dose per milligram tissue.

Although the duodenum was the principal site of accumulation of Pb salts at all doses, the data in Fig. 1 indicate that a much greater proportion of the lower dose accumulated in the tissue than did the higher dose. Such a pattern would be consistent with a saturable mode of tissue uptake. As suggested previously (20), one likely possibility is that ionic Pb competes for the Fe carrier in the duodenum.

In contrast to the pattern obtained with Pb salts, in all cases milk Pb accumulated primarily in the ileum. At low doses (0.001–0.003 μg/g body wt, Figs. 2–4) there was negligible Pb in duodenal tissue; however, at the higher dose (0.01 μg/g body wt, Fig. 5) the duodenum did accumulate modest amounts of Pb. This may reflect partial dissociation of Pb from the casein micelles in the stomach, thus giving rise to the "salt" pattern. It was not due to lack of binding during the *in vitro* labeling procedure, as other studies in our laboratory (12) have shown that the binding capacity of the casein micelles is at least 50-fold greater than that required for the 0.01 μg/g body wt dose used in Experiment 5.

The form of administration of Pb was important not only for tissue accumulation but also for the pattern of retention. When given in milk, ^{203}Pb was retained in the ileal mucosa for at least 20 hr (Fig. 4). In contrast, there was negligible retention in any region of the small intestine following administration of Pb as a soluble salt. These data suggest that the retention seen previously in studies with Pb salts (19) was the result of association between Pb and milk in the stomach during the nursing which followed intubation.

The distribution of ^{203}Pb along the length of the small intestine following administra-

tion in milk is very similar to that of marker macromolecules used to study nonspecific pinocytosis in infant rats (14–17). Thus, our data are consistent with the hypothesis that milk Pb remains associated with casein in the lumen of the gastrointestinal tract and is absorbed by pinocytosis in the ileum. Since pinocytosed materials are delivered to the giant phagolysosomal vacuole (24), ultrastructural studies should demonstrate Pb in this organelle. In addition, it will be important to determine whether the Pb is subsequently released to the bloodstream (and thus absorbed) or whether it is retained in the epithelial cells until their desquamation (and thus excreted).

An obvious question is whether these studies in infant rats have any bearing on intestinal uptake of milk Pb by human infants. In general, the digestive tract of the newborn human is considerably more mature than is that of the suckling rat (25). However, certain critical aspects of gastrointestinal function do display similarities in offspring from the two species. First, with respect to the stomach, the available human data indicate that production rates of both acid and pepsin (corrected for body weight) are quite low for at least 4 months and reach adult levels only at 2 years of age (26, 27). Although pancreatic protease production by the newborn human is generally considered to be adequate (25, 28), there is evidence which suggests that intact food proteins are absorbed more readily during infancy than later (25, 29). Thus, it appears that at least some dietary proteins may remain essentially intact as they pass through the stomach and upper small intestine of the human infant. Whether milk Pb would remain associated with portions of the casein molecule remains a matter of conjecture.

As indicated above, the identification of sites of accumulation of milk Pb as compared with Pb salts is an important first step in determining the mechanism of absorption of these two forms of Pb. The latter, in turn, may have a bearing on toxicological considerations. For example, if Pb salts are indeed absorbed in the duodenum via the Fe carrier, then Pb salts would be expected to be efficiently absorbed because of minimal dilution by intestinal fluid at the time of duodenal entry. Absorption would be further enhanced in the fasted or iron-deficient infant. On the other hand, if milk Pb is absorbed in the ileum, first the relative concentrations presented to the absorptive surface would be reduced as a result of dilution by intestinal fluid in the duodenum and jejunum. Second, since milk Pb is retained in the ileal tissue for at least 20 hr (Fig. 4), the rate of entry into the bloodstream would be expected to be considerably less than that from an equivalent dose of Pb salts. Thus, ingestion of soluble Pb by infants (e.g., in drinking water) may lead to greater toxicity than would ingestion of milk Pb.

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