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Cardiovascular Effects of Chronic Barium Ingestion

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ABSTRACT

Because high barium levels (1-10 ppm) in human drinking water have been reported to be associated with high cardiovascular mortality, we sought cardiovascular effects following chronic exposure of rats to 1, 10 and 100 ppm Ba in drinking water. Barium produced no change in growth rate or evidence of toxicity, but systolic pressure of unanesthetized rats increased after exposure to 100 ppm Ba for one month or 10 ppm Ba for 8 months. Rats sacrificed at 1 month had increased aortic potassium for both 100 ppm and 10 ppm Ba groups, and both K and Mg were suggestively increased in serum of 100 ppm Ba rats. There were no other differences in metal content or in organ weights nor were there any changes in serum catechol levels. Rats exposed to 100 ppm Ba for 16 mo had depressed rates of cardiac contraction and depressed electrical excitability. For them, the Ba-induced hypertension of unanesthetized rats was evident under ketamine and xylazine anesthesia but absent with pentobarbital. In "16 month-100 ppm" rats, cardiac ATP, phosphocreatine and phosphorylation potential were decreased and ADP was suggestively increased as measured by ^{31}P-NMR spectroscopy. Although the induced increase in blood pressure of rats was modest, comparable mild Ht in man would have major health implications.

INTRODUCTION

The purpose of this paper is to report the cardiovascular effects which we have observed in rats chronically fed Ba. Our study was undertaken in response to a report that human mortality rates were increased in areas of Illinois with high levels of Ba in drinking water. A population of about 25,000 which was exposed to high Ba levels (2-10 mg/l, i.e. ppm) in drinking water was compared with a demographically similar population of 50,000 with low Ba exposures (<0.2 ppm). In the "high barium" areas, total deaths, after correction for the age and sex composition of the population, were greater by 10% and heart disease deaths by 15%. Both of these differences were statistically significant, with $p<0.05$ (2). In a subsequent study, the blood pressures of people living in high and low Ba areas were compared. No differences were found in the incidence of hypertension (Ht) or in the

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average level of diastolic pressure; however, the populations examined in this second report were less than 2,500 in total numbers (1).

MATERIALS AND METHODS

Rats were exposed to 3 widely differing doses of barium in drinking water. During the 16-mo experiment, individual weights were measured and systolic pressures were indirectly determined without anesthesia after 6 different intervals of Ba exposure (after 1,2,4,8,12 and 16 mo). Animals were sacrificed after 3 different exposure intervals (after 1,4 and 16 mo); weights of heart, liver, kidney and aorta were measured in these animals; barium, calcium, magnesium, potassium and sodium contents of these organs were measured. In addition, more extensive studies were done on hearts of rats with the highest and longest Ba exposure. This experimental plan is indicated in Table I.

TABLE I. PLAN OF EXPERIMENT

Barium exposure for	1	2	4	8	12	16	Months
Individual weight	✓	✓	✓	✓	✓	✓	At least 12 rats in 1,10 & 100 ppm Ba groups & > 20 controls
Systolic Pressure	✓	✓	✓	✓	✓	✓	
Organ weight	✓		✓			✓	At least 12 rats sacrificed per Ba group and > 20 controls
Metal concentrations	✓		✓			✓	
Conductivity and contractility studies						✓	Hearts of 11 rats with 16 mo exposure to 100 ppm Ba, 16 controls
^{31}P-NMR analysis of phosphate metabolites						✓	

Legend: Three populations of 65 rats each were used: 26 were controls (only 21 tested - see footnote in Materials and Methods) and groups of 13 each were exposed to 1,10 and 100 ppm Ba. Population 1 was sacrificed at one month immediately after systolic pressure was measured. Population 2 was sacrificed at 4 mo, having had their pressures measured at 2 and 4 mo. Population 3 was sacrificed at 16 mo, having had their pressures measured at 8,12 and 16 mo.

A total of 195 female weanling Long-Evans rats were used; they were divided into 3 similar populations of 65 rats each; these populations were designated "1 month", "4 month" and "16 month" populations. In each population, there were 3 Ba exposure groups, each initially containing 13 animals, and a control group of 26 animals*. The Ba exposure groups received 1,10 and 100 ppm Ba (as the chloride) in their drinking water, which was fortified with 5 essential metals: (1 ppm Mo, 1 ppm Co, 5 ppm Cu, 10 ppm Mn and 50 ppm Zn). All animals received our standard rye-based diet with low trace metal content (6,11). Each group of 12-13

*At time of sacrifice, at least 12 rats were in each Ba group. Systolic pressure, organ weight and tissue metal were measured in only 21 control rats; the remainder were used solely to keep numbers comparable in all cages.

animals was housed in a large stainless steel cage which was kept in our standard, very low contamination environment with a 12-hr light cycle and a constant temperature of 21°C (6). The 26 control animals received the same fortified water without the Ba and were housed in 2 cages under conditions identical to the Ba-exposed animals. Except for testing and routine cage cleaning animals were not removed from their cages or disturbed.

Individual weights and systolic pressures were measured only at 1 mo for the "1 month" population, at 2 and 4 mo for the "4 month" population and at 8,12 and 16 mo for the "16 month" population. Systolic pressure was measured by the indirect tail cuff procedure in trained unanesthetized animals which had been previously warmed to 39°C for 10 minutes (11). After the final weight and blood pressure measurements, each population was sacrificed; organs were collected, weighed and assayed for metal concentration. Calcium, Mg, K and Na were measured by atomic absorption spectrography; Ba was measured by inductively coupled plasma atomic emission spectrography. Food and water intakes were approximated for the first week of each month throughout the experiment.

Exploratory physiologic and biochemical studies were performed on the hearts of rats exposed to 100 ppm Ba for 16 mo and on the hearts of matching control rats. Electrical conductivity was examined by electrocardiograms and Hiss Bundle electrograms; cardiac contractility was measured by the rate of pressure increase in the left ventricle and by contractile element shortening; phosphatic metabolite pattern was determined by ^{31}P-NMR spectrography as described previously (4,5).

The blood pressure measurements were submittad to a 2-way (time X Ba level) analysis of variance procedure. All computations were performed with the SAS GLM procedure and type III sum of squares used. Least square mean comparisons were used to compare average blood pressures across treatments within time periods (1-tail tests).

RESULTS

A significant pressor effect averaging 12 mm Hg was observed in the 100 ppm Ba group after only 1 mo of exposure ($p=0.0002$). The increase in average pressure for 100 ppm Ba rats was consistently present at all subsequent measurements and it gradually increased to 16 mm Hg after 16 mo of exposure. Ten ppm of Ba also induced a pressor effect but the effect was less marked, being statistically significant ($p<0.05$) only at 8,12 and 16 mo. The data tabulated in Table II are increases in average blood pressure of 12 or more Ba-exposed rats when compared to the average blood pressure of 20 or more control animals.

TABLE II. BARIUM-INDUCED HYPERTENSION IN RATS

ppm Ba	1 mo	2 mo	4 mo	8 mo	12 mo	16 mo
1	1	-1	1	2	1	1
10	3	1	5	6*	7*	9*
100	12**	6*	12**	15**	16**	16**

Significantly different from control: *$p<0.01$; **$p<0.001$.

Legend: Average increase in systolic pressure (13 rats) in mm Hg measured against control average (26 rats) for each period. See test for description of populations.

Average water and food intake and average heart and body weight are indicated for control animals (Table III). None of the 3 levels of Ba exposure had a significant effect on water or food intake. No group of Ba-exposed rats had a diminished growth rate, nor were there other obvious toxic manifestations associated with Ba exposure.

TABLE III. AVERAGE DATA FOR CONTROL RATS

Months	Daily Intake Per Rat (ml H_2O)	(g Food)	Average Weight (g) Heart	Body
1	12	15	0.69	170
2	15	20		228
4	19	22	0.75	301
8	21	20		348
12	23	21		405
16	22	19	1.10	435

Legend: Approximate food and water intake and average cardiac and body weight for control rats. Barium-exposed groups had approximately the same daily intake of water and food as control; there were no appreciable differences in average cardiac or body weight between control and Ba-exposed groups.

The average cardiac concentrations of Ba, Ca, Mg, K and Na (in μg metal/g of wet weight) after 4 mo of exposure are cited in Table IV. The only statistically significant difference between the control and Ba-exposed animals is seen in the Ba concentration in the heart of animals with the highest exposure. These data are generally representative of the data in the heart at 1 and 16 mo.

TABLE IV. ALKALINE EARTHS AND ALKALI METALS IN "4 MONTH HEART"
(Average Total Concentration in μg/g Wet Weight)

	Ca x1	Mg x10	K $x10^2$	Na $x10^2$	Ba $x10^{-2}$
0 ppm Ba	27	24	33	14	0.010
1 ppm Ba	22	23	33	14	0.014
10 ppm Ba	23	23	31	14	0.014
100 ppm Ba	27	23	32	15	0.058*

*$p<0.001$.

The remaining results are from additional but preliminary studies on the hearts of rats exposed to 100 ppm Ba for 16 mo. Figure 1 presents a potentially very important observation. As indicated above, without anesthesia Ba-exposed rats had a higher average systolic pressure than control rats. With pentobarbital anesthesia, which we had previously used routinely, the peak left intraventricular pressure of the Ba-exposed rats fell below that of control rats. With ketamine plus xylazine anesthesia, however, the Ba-exposed animals again had the average systolic pressure. The inhibition of the pressor effect of Ba by the frequently used pentobarbital anesthesia could mask Ba-induced Ht.

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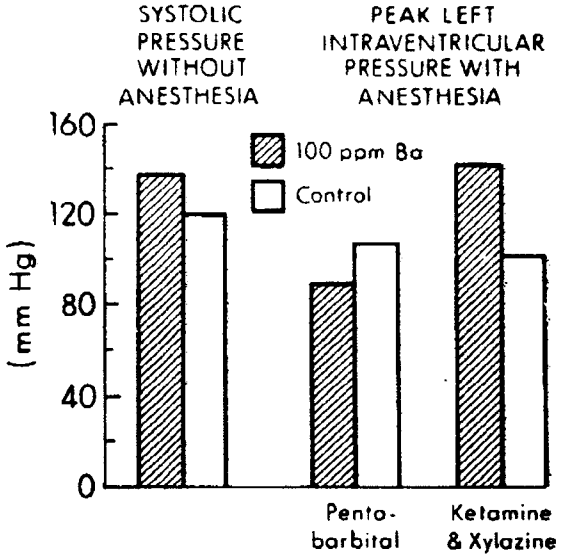

FIGURE 1-EFFECT OF ANESTHESIA IN RATS EXPOSED TO 100 PPM Ba FOR 16 MO. With no anesthesia, Ba rats had significantly higher systolic pressures than controls. With ketamine and xylazine anesthesia, Ba rats had significantly higher left intraventricular pressures than controls; however, with pentobarbital anesthesia controls had somewhat, but not significantly, higher left intraventricular pressures.

Two measures of *in vivo* contractility were examined. With ketamine plus xylazine anesthesia, rate of increase in left ventricular pressure (dP/dT) increased more rapidly in Ba-exposed animals than in control animals; however, the shortening velocity of contractile elements was diminshed in Ba-exposed animals relative to control animals. The rate of electrical conduction was examined by electrocardiogram and by Hiss Bundle electrogram. Ventricular activation time (P-R interval) and the atrioventricular nodal conductivity (A-H interval) were significantly prolonged in the Ba-exposed rats but there was no change in the P-A or H-V intervals.

Perchloric acid extracts of myocardium were assayed by ^{31}P-NMR spectrography for 20 phosphatic metabolites. Barium reduced ATP and phosphocreatinine (Fig. 2) and therefore the high energy phosphate available to muscle contraction. This was reflected in a reduced phosphorylation potential (ATP/(ADP x Pi)) of myocardium (µm/g ATP vs. µm/g ADP x µm/g inorganic phosphate).

DISCUSSION

Barium has long been recognized as causing contraction of smooth muscle, including that in blood vessels. Therefore it is not surprising to find that chronic Ba exposure can induce Ht. Prior attempts to show that

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Ba feeding induces a prolonged pressor effect in intact animals have failed, although vasoconstrictive effects have been demonstrated in isolated aortic strips (13).

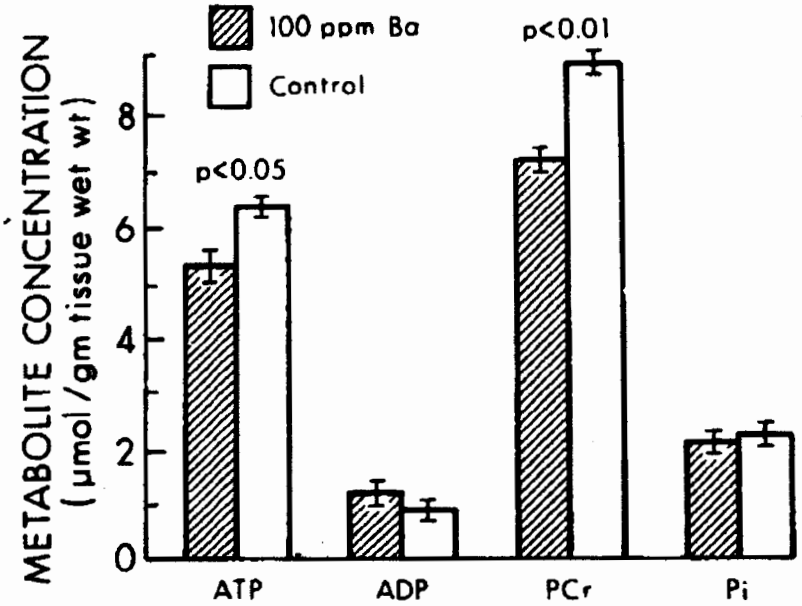

FIGURE 2-BARIUM-INDUCED CHANGES IN ATP, ADP, PHOSPHOCREATININE (PCr) AND INORGANIC PHOSPHATE (Pi). Preliminary data on perchloric acid extracts of myocardium from rats exposed to 100 ppm Ba for 16 mo. Rats were sacrificed after being anesthetized with ketamine plus xylazine.

Long-term ingestion of 3 different heavy metals, Ba, Cd and Pb - all widely distributed in nature - can cause similar elevations in the systolic pressure of rats (Fig. 3) (9,11). These elevations in pressure are not associated with any recognized toxic manifestations or with any decrease in the growth rates of young rats; toxic exposure levels are generally considered to be much higher than the pressor levels. It is noteworthy that these pressure elevations in animals have been induced by exposures somewhat above, perhaps, but comparable to the environmental exposures of large numbers of Americans.

Although the basis of their pressor effects has not been defined, all 3 metals produced somewhat similar changes in the pattern of energy-related, phosphate-containing compounds in the heart. Various mechanisms by which metals might induce Ht have been suggested. The most likely 4 would seem to be a) sodium retention (10), b) direct vasoconstriction (8,13), c) stimulation of the renin-angiotensin system (7,14) and d) increase in cardiac output (12). A direct vasoconstrictor effect seems likely in the case of Ba. Sodium retention seems very probably the mechanism in the case of Cd, although there may well be some direct vasoconstriction. The data are less clear in the case of Pb.

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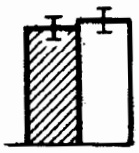

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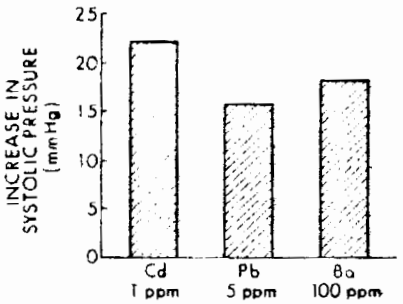

FIGURE 3-AVERAGE INCREASES IN SYSTOLIC PRESSURE IN GROUPS OF FEMALE LONG-EVANS RATS EXPOSED UNDER STANDARD CONDITIONS TO INDICATE CONCENTRATIONS OF METALS IN DRINKING WATER FOR 16-18 MO FROM TIME OF WEANING. Note: Cadmium and Pb can have similar effects over considerable concentration ranges.

Thus, based on life-long but low-level feeding experiments in animals, 3 heavy metals seem to be possible contributors to human Ht and hence to human cardiovascular disease. All 3 metals can certainly elevate blood pressure in animals, and do so in low concentrations to which many Americans are continuously exposed. The question is whether any of these metals actually raise blood pressure in human beings and if so, is the increase, which averaged only 15 mm Hg, of potential clinical significance?

We cannot answer the first question. In answer to the second, however, it is worth emphasizing that an average blood pressure increase of 15 mm Hg would clearly be clinically significant in man. As shown in Table V, during a 6-yr period, this relatively small increase in pressure would be associated with an increase of from 0.1% to more than 1.0% in the clinical appearance of coronary heart disease (3). Since there are about 10 million men with mild Ht in the U.S., a pressor effect of this magnitude could lead to thousands of new cases of CHD annually.

TABLE V. PROBABILITY OF CORONARY HEART DISEASE (CHD) IN MEN DURING 6 YEARS AS SYSTOLIC PRESSURE INCREASES FROM 120 TO 135 mm Hg
(Without Cigarettes, LVE or Glucose Intolerance)

	35 Yr	45 Yr	55 Yr
Increase in CHD	0.3%	0.6%	1.2%

1% incidence = 100,000 men/10 million hypertensive

Legend: Pressure-related increase in coronary heart disease (CHD): Increase in new CHD for men in 3 age groups during 6 years of followup as a function of an increase in systolic pressure from 120 to 135 mm Hg. Data are from Framingham Study (3) and hence are limited to whites. They assume moderate total cholesterol (260 mg%) and no cigarettes, left ventricular enlargement by EKG or glucose intolerance. Absolute increases in CHD rates would be larger if any of these additional risk factors were present.

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CONCLUSIONS

Hypertension was periodically sought in weanling female Long-Evans rats exposed to 1,10 and 100 ppm barium in drinking water for up to 16 months. After only one mo of exposure to 100 ppm Ba a statistically significant increase in systolic pressure occurred. The Ht persisted with a slow but steady increase during the remainder of the 16-mo exposure period. These animals showed no evidence of Ba toxicity, although after 4 mo they did have demonstrable increases in tissue Ba. Additional preliminary studies were performed on the hearts of rats with the longest and highest Ba exposures. There were Ba-induced decreases in PR and AH interval conduction rates and in the velocity of contractile element shortening. There were also Ba-induced increases in ATP and phosphocreatin of myocardium.

The animals exposed to 10 ppm Ba, a dose to which human beings in high Ba areas may be exposed, also developed elevated systolic pressures; however, these were only half as large as with the higher dose and did not appear until the eighth month of exposure. No changes were sought in contractility, conduction or phosphatic metabolites.

Because rats respond to doses of Ba which Americans regularly receive without occupational or other specific exposure, it seems appropriate to consider in detail how to test whether human beings with high Ba exposure (10 ppm Ba in drinking water) exhibit any significant cardiovascular changes.

ACKNOWLEDGMENTS

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DISCUSSION

Inquirer: John D. Bogden, New Jersey Medical School, Newark, NJ

Q. Have you analyzed the food of your experimental animals for Cd, Pb or Ba?

A. Yes, the cadmium, lead and barium concentrations in food were 0.01, 0.26 and 1.5. Our standard rye-based diet, which was used in this experiment, has been analyzed for all essential metals, many non-essential metals and various other dietary components. (Perry, H.M., Jr. and M.W. Erlanger. Effect of diet on increases in systolic pressure induced in rats by chronic cadmium feeding. *J. Nutr.* 112:1983, 1982.)

Inquirer: Carl Marienfeld, Environmental Health Surveillance Center, University of Missouri, Columbia, MO

Q. Does pentobarbital similarly prevent Cd and Pb hypertension - liver enzymes?

A. Pentobarbital anesthesia does not interfere with Cd- or Pb-induced hypertension. The effect on barium hypertensive enzymes is a very recent observation and we have not investigated liver.

Inquirer: H. Zumkley, Medzinische Poliklinik der Westfalischen Wilhems-Universität, Munster, Federal Republic of Germany

Q. Have you measured sodium excretions in urine of the rats with Ba induced hypertension?

A. No.

Inquirer: Edward V. Ohanian, U.S.E.P.A., Washington, DC

Q. 1) Do you expect to find similar cardiotoxic effects with 10 ppm Ba?
2) Do you expect to find similar Ba-induced cardiovascular effects in other strains of rats?

A. Unfortunately we have no information about "other" cardiovascular effects (in addition to hypertension) with 10 ppm barium and none about the "strain specificity" of Ba-induced Ht. The preliminary physiologic and biochemical studies reported here were not part of the experimental plan. They were done only after Ht was observed with a Ba exposure comparable to the human environmental exposure in some areas. Although no funding for such studies was available, we felt it was important to determine whether other cardiovascular changes could be demonstrated, and Dr. Kopp's laboratory, which had been working with us on cadmium- and lead-induced Ht, was able to study a few animals. We chose to study those with the longest and heaviest exposure to Ba. As for strain specificity, that is the next item on our priority list, but it has not yet been examined. The initial experiments were simply to determine whether chronic Ba ingestion could induce Ht using the test system we used for studying Cd- and Pb-induced Ht.

Inquirer: C.D. Klaassen, University of Kansas Medical Center, Kansas City, KS

Q: How reproducible is your technique for quantitating blood pressure in rats?

A: We think it is very reproducible. The pressure value we use for each rat at each visit is the median of three consecutive measurements taken within a period of two minutes. For an individual rat, these median pressures change relatively little during the first eight months after weaning. For a typical group of 28 control animals, the standard deviation of five median pressures for individual rats (for the 1,2,3,4, and 8 month visits) ranged from 2-9 mm Hg, with an average standard deviation of 5 mm Hg. This is more reproducible than induced human diastolic pressure measurements for which the standard deviation is usually 7 or 8 mm Hg.

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