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Evidence for Effects of Chronic Lead Exposure on Blood Pressure in Experimental Animals: An Overview

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Information obtained in a number of experimental studies conducted over the last 40 years on the effects of lead on blood pressure is reviewed. Differences in animal species, age at beginning of exposure, level of lead exposure, indices of lead burden, and blood pressure effects of each study are reported. In several of the high-dose experiments, hypertension was observed, but nephrotoxicity of lead may have contributed to its development. Moreover, in other high-dose experiments, no hypertension was observed, and in at least one experiment, the evidence suggested that lead could reduce an elevated blood pressure. In contrast, the lower dose experiments consistently demonstrated a hypertensive effect. Overall, the data suggest a biphasic dose response. Establishment of an appropriate animal model to study blood pressure effects of lead will require careful assessment of dietary interactions with lead, unstressed blood pressure monitoring with standardized techniques, and documentation of biologically effective lead burden. Future research should examine lead exposure at more environmentally appropriate levels in order to determine the validity of associating this pollutant with blood pressure effects in the human population.

Introduction

The literature reporting effects of lead exposure on blood pressure in experimental animals is scattered among international journals and proceedings over at least a 40-year period; in many cases, the authors' knowledge of similar or divergent experimental findings was not noted. It is not surprising that the results sometimes appear inconsistent. The purpose of this paper is to review these studies, examining the lead dose, route of exposure, age at initiation of exposure, when the effects were first observed, how long the animals were followed, and any indication of the internal lead burden. These findings will orient the reader to the papers in this issue, which discuss several possible targets of lead's cardiovascular toxicity.

An underlying question for most researchers is whether the lead dose administered should be of sufficient magnitude to induce nephrotoxicity prior to the onset of hypertension or if hypertension may develop prior to renal damage. Over the years, the experimental lead dose range for rats has varied between 70 mg per day (*1,2*) and 3.0 μg per day in animals consuming approximately 30 mL of 0.1 ppm lead in drinking water (*3*). Clearly, in the former case it is likely that renal pathology can be observed, while in the latter, only subtle renal changes are observed.

The route of administration varies somewhat among studies, but it is usually oral (by gavage, in drinking water, or mixed in the food). The amount absorbed varies widely and depends on other nutritional factors and the age of the animal. The length of time for which exposure continues has been between 2 months and 2 years. The length of exposure before initiating monitoring and for continuation of monitoring varies greatly; in fact, some investigators have not followed a large enough group of control and experimental animals to detect statistical significance between the groups. Blood pressure monitoring is usually performed indirectly (by tail cuff plethysmography), either on the anesthetized or unanesthetized animal, or directly by insertion of an arterial catheter and detection by a pressure transducer. For repeated measurements in the same animal, the plethysmography is preferable but has the disadvantage that the animals are prewarmed, which is enough of a stress that some lead-exposed rats did not survive this procedure (*4*). If the animals are unanesthetized, they must be conditioned to the restrainer so that unstressed values are obtained. Anesthetics also affect the blood pressure, so that this stress must also be evaluated. At the termination of the exposure period, it

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is quite helpful to have a direct blood pressure measurement to correlate with the indirect measurements previously obtained.

Species studied include rats, dogs, and pigeons. Sex of the animal may have a role in determining susceptibility to cardiovascular toxicity of lead, although this has not been clearly established. Animal housing and handling conditions are especially important if the animals are to be monitored in the unanesthetized, unstressed state. Indicators of the body burden of lead (such as blood or kidney lead concentrations) have frequently not been performed; if so, the extent of a dose-response relationship between the amount of lead administered, blood lead, and blood pressure changes could be quantified.

Table 1. Summary of studies relating chronic, high-level lead exposure to blood pressure effects in rats.

Reference	Species	*n*	Lead exposure	[PbB], μg/dL[a]	Age exposure begun	Duration of exposure	Effects on blood pressure	Renal effects
(*1*)	Rats	15	70 mg/day gavage, 6 times/week	—	Adults (150–200 g)	30–80 days	All that survived 40 days were hypertensive	Not studied
(*2*)	Rats	11/30 (survived 60 days)	70 mg/day, gavage, 6 times/week	—	Young	50 days	10/11 were hypertensive at 45 and 60 days (mean 146 ± 7.6 and 182.2 ± 6.6, respectively)	Some gross pathologic changes; intranuclear inclusion bodies in renal tubular epithelium; no histologic changes in arterioles, arteries of kidneys and other organs
(*5*)	Rats	30	35 mg/100 g 3 times/week for 9 weeks; 140 mg/100 g 3 times/week for 10 weeks by stomach tube	—	Adults (250 g)	224 days total	No effect under ether anesthesia; however, both controls and exposed were elevated	Increased kidney weight, at 135–152 days, histologic changes in tubules; no effect on GFR; 21% increase in T_m PAH for 100 days, then fell to pretreatment value
(*7*)	Rats	5–10 animals /dose	10,[b] 20, 40 mg lead phosphate/ week, SC	—	Adult	23 weeks; 60 weeks	20 mg: > 130 mm Hg under ether anesthesia; 40 mg "too toxic"	Hypertrophy of arterioles in kidneys, other organs
(*6*)	Rats, male	10 exposed 9 control	40 mg/day for 30 days gavage, 80 mg/day gavage also 1.5% lead acetate in drinking water	Control: 18 Exposed: 76	Not stated	173 days	Higher in controls over entire period	No change in BUN, proteinuria, concentrating ability, intranuclear inclusion bodies in proximal tubular epithelium
(*9*)	Rats	9 exposed 5 controls	10,000 ppm in drinking water	17.0 23.5	Weaning	6 weeks	19 weeks after exposure ended, systolic increased 13 mm Hg	Decreased GFR, both whole kidney and single nephron; also decreased renal blood flow, decrease in function of both superficial and deep nephrons

[a][PbB], blood lead concentration.
[b]Rats exposed to 10 mg lead served as controls.

Experimental Findings

Table 1 presents a brief summary of the literature citations in which rats were administered relatively high lead doses. The experiments of Griffiths and Lindauer (*1*) and Diaz-Rivera and Horn (*2*) used similar protocols, administering 70 mg of lead per day by gavage to rats; this dose produced hypertension in animals that survived the dosing period. Nephrotoxic effects were clearly observed in the animals that were examined. Pardoe (*5*) and Padilla et al. (*6*) also used similar protocols (30 to 40 mg for the initial dose, with even higher doses in the subsequent exposure period). The lead exposure did not elevate blood pressure with respect to controls; there were marked changes in renal histology, although there were no decrements in several measured parameters of renal function. Pardoe reported that the tubular transport maximum for *p*-aminohippuric acid (PAH) was elevated by 20% at 3 months, indicating an increase in tubular excretory function that paralleled the increase in kidney weight. This effect appeared to be reversible in the later period of the experiment. Of the earlier experiments, Padilla et al. (*6*) are the only authors to report blood lead concentrations; however, the validity of the blood lead analysis appears questionable considering both the high control values and the relatively low values in the exposed group. The paper with the most relevance for comparison to more recent studies is that of Cottier et al. (*7*). Lead phosphate in a dose of 20 mg per week administered SC elevated systolic pressure above 130 mm Hg. Lead phosphate contains 76% lead, which would be equivalent to 15 mg lead per week. Twice this dose (40 mg/week) was "too toxic." In the report (to be described later) by Victery et al. (*8*), a rat consuming 100 ppm lead in drinking water might average 30 mL/day × 7 days/week, or 21 mg/week. Extrapolation between these two papers should be performed with caution to the different routes of administration (SC vs. oral). There are no reported blood lead values in the Cottier paper.

The last paper in this group (*9*) used a very different treatment protocol: 1% lead was administered for 6 weeks and the blood pressure and renal function tests were performed 19 weeks later. Mean blood lead concentration exceeded 150 μg/dL at the end of exposure and fell to 24 μg/dL at the time of the procedure. Blood pressure was elevated by 13 mm Hg and there were decreases in whole kidney glomerular filtration rate (GFR) and single nephron GFR, as well as decreases in renal plasma flow.

Table 2 presents the more recent experimental reports of blood pressure effects when lower levels of lead exposure was used beginning as early as *in utero*. A similar presentation of this information is incorporated in the comprehensive review paper of Sharp et al. (*10*). Perry and Erlanger (*3*) report initial results from a large series of studies. The most striking findings from among the published reports from this group are that significant increases in systolic blood pressure are

Table 2. Summary of blood pressure studies with low-level, chronic exposure.

Reference	Species	*n*	Lead exposure, ppm	[PbB], μg/dL[a]	Age exposure begun	Duration of exposure	Effects on systolic blood pressure	Renal effects
(*3*)	Rats, female	45	0	—	Weaning	18 months	At 5 ppm, 12–14 mm Hg greater than controls, lightly anesthetized with pentobarbital	Not studied
		15	0.1					
		15	1.0	—				
		15	5.0					
(*11*)	Rats, male	15	0	13.6	Adult	160–180 day	Increase of 54 mm Hg systolic from controls under pentobarbital anesthesia	Not studied
			50.0	38.4				
(*8*)	Rats, male	19	0	2.2	*In utero*	6 months	Unanesthetized at 3.5 months, 100-ppm animals increase of 17 mm Hg; no change in 500 ppm	Increased kidney weight with both intranuclear inclusion bodies with 500 ppm; no evidence of renal disease
		19	100	40.4	*In utero*			
		13	500	70.8	*In utero*			
(*17*)	Rats, male	20	0	—	*In utero*	5 months	No difference	Not studied
		20	5	5.6				
		13	25	18.2				
(*12*)	Rats, male	10	0	—	Weaning	180 days	Pentobarbital anesthesia, 48 mm Hg increase	Not studied
		10	50	—				

[a][PbB], blood lead concentration.

found in rats exposed to as little as 0.1 ppm lead in the treatment drinking water, with a dose-dependent relationship holding for the higher exposure regimens (up to 5 ppm). All animals were fed a rye-based diet with low levels of trace minerals; mineral supplements were present in the drinking water. However, no blood lead values were obtained.

In the early 1980s, a number of similar studies were performed by a group of Italian scientists and by Vander and colleagues at the University of Michigan. Rats were exposed to doses of lead between 5 and 500 ppm in the drinking water. The studies reported by Iannaccone et al. (*11*) and Carmignani et al. (*12*) used 50 ppm beginning at weaning to 6 months of age. Under pentobarbital anesthesia, these animals had an approximate 50-mm Hg increase in blood pressure compared to controls and were studied for a number of other cardiovascular parameters, some of which are discussed in the papers published in this volume (*13–16*). Blood pressure was not followed over time, so it is not known when the pressure change occurred or whether there was evidence of a dose-response relationship. Blood lead values for the 50-ppm lead-exposed group were approximately 40 μg/dL, compared to 14 μg/dL for controls, as reported by Iannaccone (*10*).

In the Michigan studies reported by Victery et al. (*8,17*), 0, 5, and 25 ppm lead in drinking water was administered to rats beginning *in utero* and continuing to 5 to 6 months of age in one study, and 100 and 500 ppm doses were used in the other. Blood pressure was monitored approximately every 2 weeks in conscious, restrained rats by tail cuff plethysmography. Although no changes in blood pressure were detected in the lower dose experiments, there were significant changes in the renin-angiotensin system of 25-ppm animals (*15*). Blood lead concentrations averaged 5.6 and 18.2 μg/dL for the 5- and 25-ppm animals, respectively. Exposure to 100 ppm (but not 500 ppm) produced a significant 17-mm Hg elevation in blood pressure beginning at 3 1/2 months of age and continuing until 6 months of age. Renal function was not evaluated. Kidney weights were significantly elevated at 100 ppm, and some morphologic changes were observed at 500 ppm. Blood lead levels averaged 40 μg/dL for 100 ppm and 70 μg/dL for 500 ppm.

Table 3 presents the results of two recent studies evaluating the effects of lead on the cardiovascular system of rats of the spontaneously hypertensive strain (SHR). The paper by Wiecek et al. (*18*) reports a lead dose-dependent decrease in blood pressure in the SHR rats and control (WKR) rats, and the authors conclude that their findings are contradictory to the findings of Victery et al. (*8,17*). However, the findings are not contradictory because it appears that these authors have made a mistake in calculation of the lead dose used by Victery et al. and actually treated their animals with 2.5 to 50 times higher doses than our hypertensive dose. This is verified by their statement that blood lead values in their rats were "much higher" than those reported by Victery et al. (*8,17*).

In another study, Evis et al. (*4*) administered lead (at 250 and 1000 ppm) to SHR and control rats. The authors evaluated a number of cardiovascular parameters including conscious and anesthetized blood pressure. The higher dose of lead significantly increased blood pressure in both groups of rats, which had reported blood lead concentrations of 40 μg/dL. Interestingly, lead accelerated the development of hypertension in the SHR animals and also increased their sensitivity to the warming required for dilation of the tail artery used for measuring conscious blood pressure (seven of eight animals died).

Results obtained in other species (pigeons and dogs) are summarized in Table 4. In pigeons (*19*), a low dose of lead (in combination with a number of other dietary parameters) produced a significant elevation in

Table 3. Summary of effects of lead exposure on blood pressure in spontaneously hypertensive rats.

Reference	Species	*n*	Lead exposure, ppm	[PbB], μg/dL[a]	Age exposure begun	Duration of exposure	Effects on blood pressure	Renal effects
(*18*)	Rat WKR	7 11 11	0 250 1250				Significant dose-dependent decrease under light ether anesthetized or conscious instrumented rat	Not studied
	SHR	11 11	2500 5000	"Very high"	3 months	10 weeks		
(*4*)	Rat	10–15/dose	0 250 1000	 19.9 43.7	 Weaning	 3 months	Beginning at 5 weeks of exposure, significantly elevated in SHR and Sprague-Dawley rats. At 12 weeks, 1000 ppm anesthetized Sprague-Dawley rats had 15 mm Hg increase in systolic prior to cardiac studies	Not studied
	Normotensive Sprague-Dawley, male	10–15/dose	0 250 1000	 17.0 38.1	From conception	3 months post weaning		

[a][PbB], blood lead concentration.

Table 4. Summary of effects of chronic lead exposure on blood pressure in other species.

Reference	Species	*n*	Lead exposure	[PbB],[a] µg/dL	Age exposure begun	Duration of exposure	Effects on blood pressure	Renal effects
(*19*)	Pigeon male,	—	0.8 ppm	—	6 months	3 months	20 mm Hg increase in systolic	Not studied
(*20*)	Dog, female	2	32.5 g for 160 weeks; 1.9 g died during short exposure	—	160 weeks	1 year	None	Not studied
(*21*)	Dog, female	3 3	0 1 mg/kg daily	9.2 35.8	5 months	3 months	12 mm Hg increase in mean arterial pressure	No difference in extracellular fluid, plasma volume, GFR, serum creatinine, or renal plasma flow

[a]PbB], blood lead concentration.

blood pressure, which could be alleviated by increasing the calcium concentration in the drinking water. The exposure of two dogs to very high levels of lead did not invoke an increase in blood pressure but did produce acute episodes of lead poisoning (*20*). In a paper by Fine et al. (*21*), three young dogs received a low dose of lead (1 mg/kg daily, blood lead concentration of 36 µg/dL) and were found to develop a persistent (from 10 days to 20 weeks) 12-mm Hg increase in mean arterial pressure when compared to their paired control dogs. Additional determinations of the renin profile show that renin is initially elevated (at 28 days exposure) but then returns to normal levels while blood pressure remains elevated.

Conclusions and Directions for Future Research

This short overview illustrates the complexity of interpreting data from experimental models that have been used to evaluate the relationship of lead exposure at different levels to changes in blood pressure. Based on the collective results of the studies reviewed, it appears that lead administered at relatively nontoxic levels produces an elevation in blood pressure that is sustained over a considerable portion of the animal's life span. In contrast, high doses are not consistently associated with hypertension and may actually lower blood pressure. Could this be related to certain protective or adaptive mechanisms reducing lead's effects or to an effect on the general health of the animals? In any case, these high doses may not be relevant to the human situation. For the experimental literature to be specifically relevant to human environmental exposures, findings of alterations in cardiovascular parameters in the blood lead range of 5 to 40 µg/dL would be most suitable.

A number of blood pressure regulatory control systems have been shown to be altered by various lead exposure protocols. These include several hormone and neurobehavioral regulatory systems, changes in vascular smooth muscle reactivity, cardiac muscle contractility, changes in cell membrane cation transport systems, and possible effects on vascular endothelial cells. Changes in at least one of these systems have been reported at all of the lower lead dose ranges, with some exceptions at higher doses. Which systems are most important contributors to a significant, persistent elevation in blood pressure have not been established definitively. There may be a number of sequential changes that occur and are no longer observable depending on the time of examination. However, it appears that there are sufficient experimental data available to confirm that chronic lead exposure at low levels can affect blood pressure levels in a consistent fashion.

Inevitably, the dose range and shape of the dose-response curve become issues for debate because they are relevant to the question of whether or not the lead exposure range is comparable to that of the general human population or only to those individuals occupationally exposed to lead. It appears from some experimental studies that the blood pressures measured at higher doses are lower than would be expected, suggesting a biphasic dose-response curve.

The exact dose-response range for this finding has not been well established, primarily because of different methodology used by each group of investigators. A standardized protocol for preparing and administering the lead dose, dietary components, rat strain, and age-at-initiation of exposure should be developed. Methodology for measuring blood pressure on a continuing basis in the conscious animal has improved so that tail cuff measurements can be performed without warming, and recordings can be obtained on several animals at once. These techniques should be applied in a carefully controlled setting along with validation of the biological markers of lead exposure.

Once these conditions have been well established,

other important questions should be addressed. These include: Can the effect on adult blood pressure be established by an early exposure period at environmentally appropriate levels? Can the effect on blood pressure be reversed by removal of the lead source and reducing the lead burden? Answers to these questions would be valuable because they would help to evaluate the need to continue reductions in environmental lead exposure to the human population.

REFERENCES

1. Griffith, J. Q., Jr., and Lindauer, M. A. The effect of chronic lead poisoning on arterial blood pressure in rats. Am. Heart J. 28: 295–297 (1944).
2. Diaz-Rivera, R. S., and Horn, R. C., Jr. Postmortem studies on hypertensive rats chronically intoxicated with lead acetate. Proc. Soc. Exp. Biol. Med. 59: 161–163 (1945).
3. Perry, H. M., Jr., and Erlanger, M. W. Pressor effects of chronically feeding cadmium and lead together. In: Trace Substances in Environmental Health—XII: Proceedings of University of Missouri's 12th Annual Conference on Trace Substances in Environmental Health, Columbia, MO (D. D. Hemphill, Ed.), University of Missouri, Columbia, MO, 1978, pp. 268–275.
4. Evis, M. J., Dhaliwal, K., Kane, K. A., Moore, M. R., and Parratt, J. R. The effects of chronic lead treatment and hypertension on the severity of cardiac arrhythmias induced by coronary artery occlusion or by noradrenaline in anaesthetised rats. Arch. Toxicol. 59: 336–340 (1987).
5. Pardoe, A. U. Renal function in lead poisoning. Br. J. Pharmacol. 7: 349–357 (1952).
6. Padilla, F., Shapiro, A. P., and Jensen, W. N. Effect of chronic lead intoxication on blood pressure in the rat. Am. J. Med. Sci. 258: 359–365 (1969).
7. Cottier, P., Kunz, H. A., and Zollinger, H. U. Experimenteller Beitrag Zur Frage der Bleihypertonie. Helv. Med. Acta 20: 443–449 (1953).
8. Victery, W., Vander, A. J., Shulak, J. M., Schoeps, P., and Julius, S. Lead, hypertension, and the renin-angiotensin system in rats. J. Lab. Clin. Med. 99: 354–362 (1982).
9. Aviv, A., John, E., Bernstein, J., Goldsmith, D. I., and Spitzer, A. Lead intoxication during development: Its late effects on kidney function and blood pressure. Kidney Int. 17: 430–437 (1980).
10. Sharp, D. S., Becker, C. E., and Smith, A. H. Chronic low-level lead exposure: Its role in the pathogenesis of hypertension. Med. Toxicol. 2: 210–232 (1987).
11. Iannaccone, A., Carmignani, M., and Boscolo, P. Neurogenic and humoral mechanisms in arterial hypertension of chronically lead-exposed rats. Med. Lav. 72: 13–21 (1981).
12. Carmignani, M., Boscolo, P., Ripanti, G., and Finelli, V. N. Effects of chronic exposure to cadmium and/or lead on some neurohumoral mechanisms regulating cardiovascular function in the rat. In: Heavy Metals in the Environment: Proceedings of an International Conference, Heidelberg, West Germany. CEP Consultants Ltd., Edinburgh, 1983, pp. 557–560.
13. Boscolo, P., and Carmignani, M. Neurohumoral blood pressure regulation in lead exposure. Environ. Health Perspect. 78: 101–106 (1988).
14. Chai, S., and Webb, R. C. Effects of lead on vascular reactivity. Environ. Health Perspect. 78: 85–89 (1988).
15. Vander, A. J. Chronic effects of lead on the renin-angiotensin system. Environ. Health Perspect. 78: 77–83 (1988).
16. Kopp, S. J., Barron, J. T., and Tow, J. P. Cardiovascular actions of lead and relationship to hypertension: A review. Environ. Health Perspect. 78: 91–99 (1988).
17. Victery, W., Vander, A. J., Markel, H., Katzman, L., Shulak, J. M., and Germain, C. Lead exposure, begun *in utero*, decreases renin and angiotensin II in adult rats. Proc. Soc. Exp. Biol. Med. 170: 63–67 (1982).
18. Wiecek, A., Mann, J. F. E., Nowack, R., and Ritz, E. Effects of lead intoxication on blood pressure and vascular reactivity in spontaneously hypertensive rats. J. Hypertension 4 (suppl. 6): S45–S47 (1986).
19. Revis, N. W., Zinsmeister, A. R., and Bull, R. Atherosclerosis and hypertension induction by lead and cadmium ions: An effect prevented by calcium ion. Proc. Natl. Acad. Sci. (U.S.) 78: 6494–6498 (1981).
20. Fouts, P. J., and Page, I. H. The effect of chronic lead poisoning on arterial blood pressure in dogs. Am. Heart J. 24: 329–331 (1942).
21. Fine, B. P., Vetrano, T., Skurnick, J., and Ty, A. Blood pressure elevation in puppies during low level lead poisoning. Toxicol. Appl. Pharmacol., in press.