Effect of Lead Acetate on the Susceptibility of Rats to Bacterial Endotoxins

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Received for publication 24 September 1965

ABSTRACT

SELYE, H. (Université de Montréal, Montreal, Canada), B. TUCHWEBER, AND L. BERTÓK. Effect of lead acetate on susceptibility of rats to bacterial endotoxins. *J. Bacteriol.* **91**:884-890. 1966.—A single, normally well-tolerated, intravenous injection of lead acetate increases the sensitivity of the rat to the endotoxins of various gram-negative bacteria about 100,000 times above normal. Under the conditions of these experiments, the mortality and organ changes normally produced by the intravenous injection of 100 μ g of *Escherichia coli* endotoxin were essentially the same as those obtained by use of 1 nanogram in lead-sensitized rats. The sensitizing effect of lead acetate for *E. coli* endotoxin is greatest when the two agents are given simultaneously. However, considerable sensitization is still detectable when endotoxin is injected up to 1 hr before or 7 hr after sensitization with lead. No sensitization was noted when the endotoxin was administered 24 hr before or after lead acetate. Under our experimental conditions, the minimal dose of lead acetate which could still induce significant sensitization to *E. coli* endotoxin was 1 mg per 100 g of body weight. Although lead acetate induces a high degree of susceptibility to various endotoxins, other reticuloendothelial blocking agents did not acquire unusual toxicity after pretreatment with lead. Finally, none of the other metals or reticuloendothelial blocking agents tested could duplicate the pronounced decrease in endotoxin resistance induced by lead acetate.

In the course of our investigations on certain pharmacological actions of heavy metals, it was observed incidentally that lead greatly increases the susceptibility of the rat to bacterial endotoxins to which this species is otherwise notoriously resistant. For example, a single intravenous injection of lead acetate, at a dose which normally produces no detectable disturbance, regularly makes the rat about 100,000 times more susceptible to the concurrent intravenous administration of *Escherichia coli* endotoxin.

It is the purpose of this communication to describe the circumstances under which this increased susceptibility can best be obtained. Special attention will be given to the possible participation of the reticuloendothelial system, which is known to play an important part in the defense against bacterial endotoxins.

MATERIALS AND METHODS

Female Sprague-Dawley rats of the Holtzman farms, with a mean body weight of 100 g (90 to 110 g), were subdivided into equal groups of 10 animals each and treated as indicated in Tables 1 to 6. The follow-

ing compounds were used: agar, USP (Brickman Co., Montreal, Quebec, Canada); bismuth trichloride ($\text{BiCl}_3 \cdot \text{H}_2\text{O}$; Fisher Scientific Co., Fair Lawn, N.J.); carboxymethylcellulose (Nordic Biochemicals Ltd., Montreal, Quebec, Canada); cerium trichloride ($\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$; Fisher Scientific Co.); chromium chloride ($\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$; Fisher Scientific Co.); Col-largol (colloidal silver 70%; Siegfried S. A., Zofingue, Switzerland); egg yolk (50% suspension of hen's egg yolk in distilled water, filtered through three layers of Kleenex tissue paper); endotoxin of *E. coli* O26:B6, B (Difco); endotoxin of *E. coli* O26:B6, W (Difco); endotoxin of *E. coli* O8 (A. Wander, AG Forschungsinstitut, Freiburg, Germany); endotoxin of *Salmonella abortusovae* (Difco); endotoxin of *S. abortusovae* 3390 S₃ (O. Westphal, Max-Planck Institute, Freiburg, Germany); endotoxin of *S. abortusovae* 3390 S₃ (Dr. Lüderitz, Max-Planck Institute); endotoxin of *S. enteritidis* (Difco); endotoxin of *Shigella flexneri* (Difco); endotoxin of *Serratia marcescens* (Difco); endotoxin of *Salmonella typhosa* 0901 (Difco); ferric chloride ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$; Fisher Scientific Co.); gallium sulfate [$\text{Ga}_2(\text{SO}_4)_3$; K & K Laboratories Inc., Plainville, N.Y.]; Imferon (ferric dextran, "Fe-Dex"; Bengel Laboratories, Ltd., England, distributed by Fisons Ltd., Toronto, Ontario, Canada); India ink (Higgins, Brooklyn, N.Y.); lanthanum trichloride

($\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$; Fisher Scientific Co.); lead acetate [$\text{Pb}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 3\text{H}_2\text{O}$; Fisher Scientific Co.]; Liquoid (polyanetholesulfonic acid sodium salt; Hoffmann-La Roche Co., Montreal, Quebec, Canada); mixed fecal flora (fresh), obtained by treating one part fresh rat feces and four parts distilled water in a glass homogenizer and filtering the resulting suspension through three layers of Kleenex tissue paper (this stock solution was diluted as indicated in the text); mixed fecal flora (boiled), obtained by boiling the preceding preparation for 20 min and then filtering it through three layers of Kleenex tissue paper; mercury chloride (HgCl_2 ; Fisher Scientific Co.); neodymium trichloride (NdCl_3 ; K & K Laboratories Inc.); Proferrin (ferric oxide saccharate, "Fe-OS"; Merck Sharp & Dohme, West Point, Pa.); scandium trichloride (ScCl_3 ; K & K Laboratories Inc.); thorium nitrate [$\text{Th}(\text{NO}_3)_4 \cdot 4\text{H}_2\text{O}$; Fisher Scientific Co.]; thorium tetrachloride (ThCl_4 ; Fisher Scientific Co.); Thorotrast (thorium dextrin, "Th-Din"; Testagar, Detroit, Mich.); trypan blue (Chroma-Gesellschaft, Stuttgart-Untertürkheim, Germany); zinc chloride (ZnCl_2 ; Fisher Scientific Co.); zirconium oxychloride ($\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$; Fisher Scientific Co.). Each of these materials (in 1 ml of water) was injected intravenously into rats under light ether anesthesia. However, since total doses and the spacing of injections differed, for the sake of convenience, these and other variables will be discussed in connection with the description of each experiment in the next section.

All experiments were terminated 24 hr after the injections by killing the survivors with chloroform. At autopsy, the lesions were judged by inspection with a binocular loupe in terms of an arbitrary scale (12), in which 0 = no lesion, 1 = just detectable, 2 = moderate, and 3 = most severe lesions. Specimens of the affected organs were fixed in Susa solution saturated with picric acid for subsequent embedding in paraffin and staining with the periodic acid-Schiff technique for polysaccharides. A polychrome stain

(phosphotungstic acid, aldehyde fuchsin, and alcian blue), particularly useful in the detection of thrombohemorrhagic lesions (13), was also used.

RESULTS

Sensitization by lead acetate to various bacterial endotoxin preparations. Our first problem was to establish under rigidly controlled conditions that lead acetate can significantly increase the susceptibility of the rat to otherwise well-tolerated amounts of various bacterial endotoxins. For this purpose, nine groups of rats were given 5 mg of lead acetate; group 1 received no other treatment, but groups 2 to 9 were injected with various endotoxin preparations immediately after the lead acetate in the usual manner.

The results are summarized in Table 1, which also lists the individual dosages of the endotoxin preparations, the percentage of mortality, and the mean intensity of the organ lesions (graded as outlined under Materials and Methods). Control experiments performed under otherwise similar conditions in rats not sensitized with lead acetate showed that none of the endotoxin preparations used here produced any mortality or organ lesions at the same dose level. Indeed, the purified endotoxins given to groups 2 to 5 elicited little if any mortality, even when administered in doses of 100 μg , whereas the mixed fecal flora preparations (whether fresh or boiled) were well tolerated in concentrations as high as 5 to 10%.

It is evident from Table 1 that a dose of lead acetate which, in itself, produces no mortality or detectable organ lesion causes the rat to become highly sensitive to minute amounts of various endotoxins which are normally well tolerated.

TABLE 1. *Sensitization by lead acetate to various bacterial endotoxin preparations*

Group	Treatment*	Mortality	Organ lesions†
		%	
1	None	0	0.1
2	<i>Salmonella abortusovae</i> 3390 S ₃ endotoxin (Westphal), 1 μg	80	0.5
3	<i>S. abortusovae</i> 3390 S ₃ endotoxin (Lüderitz), 1 μg	90	0.8
4	<i>Escherichia coli</i> O26:B6, B endotoxin (Boivin), 1 μg	90	0.8
5	<i>E. coli</i> O26:B6, W endotoxin (Westphal), 1 μg	90	0.7
6	<i>S. abortusovae</i> (Difco), 1 μg	100	0.9
7	<i>S. enteritidis</i> , 1 μg	90	1.0
8	<i>Shigella flexneri</i> , 1 μg	100	1.0
9	<i>Serratia marcescens</i> , 1 μg	100	1.0
10	<i>Salmonella typhosa</i> 0901, 1 μg	100	0.8
11	Mixed fecal flora (fresh), 0.1%	60	0.6
12	Mixed fecal flora (boiled), 0.1%	10	0.4
13	Mixed fecal flora (fresh), 1%	80	0.9
14	Mixed fecal flora (boiled), 1%	60	0.6

* In addition to the treatments listed in this column, all animals were sensitized with 5 mg of lead acetate given intravenously as described in the text.

† For scale, see Materials and Methods.

Organ lesions elicited by the endotoxins in the lead acetate-sensitized animal were essentially the same, irrespective of the type of endotoxin used. The spleen almost invariably exhibited numerous hemorrhages accompanied by thromboses of its veins. In the kidney, we found fibrin thromboses in the glomerular capillaries, often associated with hemorrhagic necrosis of the medium-sized and small arterioles, as well as occasional thrombus formation in the afferent glomerular vessels. At the same time, there was renal cortical necrosis with intense venous engorgement of the medulla. Thus, the renal changes were virtually identical with those characteristic of the general Sanarelli-Shwartzman phenomenon. Massive hemorrhages were also found around the branches of the portal vein in the hepatic hilum and less frequently in the heart and thymus (Fig. 1 to 3).

"Critical period." Our next problem was to determine the length of the "critical period" during which lead acetate can increase susceptibility to a preceding or subsequent endotoxin injection. For this purpose, seven groups of rats were sensitized with 5 mg of lead acetate; in

addition, all of them received 1 μ g of *E. coli* O8 endotoxin at various times before, simultaneously with, or after the lead acetate. In Table 2, the time of lead acetate injection is taken as "0 hr," and the preceding and following hours are designated as "-" and "+," respectively.

The highest mortality and the most pronounced organ changes occurred in the case of simultaneous treatment with lead and endotoxin (Table 2). However, severe lesions and a comparatively high mortality were also noted when the endotoxin was administered 1 hr before or up to 7 hr after the lead.

Minimal effective dose of endotoxin. In the preceding experiments, we arbitrarily used 1 μ g of the various purified endotoxin preparations, since this dose is perfectly tolerated by normal rats, but highly pathogenic to animals pretreated with lead acetate. To establish the minimal amount that exhibits toxicity after sensitization, rats were treated with descending doses of *E. coli* O8 endotoxin (Table 3) always given intravenously in 1 ml of distilled water. The first two groups were not sensitized and acted as controls; groups 3 to 13 received intravenous injections of

FIG. 1-3. Characteristic organ lesions in rats given 1 μ g of *Escherichia coli* O8 endotoxin after sensitization with lead acetate. (1) Two glomeruli with partial thrombosis of the capillaries (arrows) surrounded by necrotic tubules [periodic acid-Schiff (PAS), $\times$ 350]. (2) High magnification of one of the glomeruli shown in Fig. 1. Most of the capillaries are thrombosed and some of the thrombi (arrows) are strongly PAS-positive (PAS, $\times$ 1,000). (3) Around the portal vein (arrow), there is a massive hemorrhage which surrounds a bile duct (left) and two branches (middle and top) of the hepatic artery (PAS, $\times$ 80).

5 mg of lead acetate in 1 ml of distilled water just before the endotoxin injection.

As shown in Table 3, most of the normal rats tolerated up to 100 μ g of endotoxin (groups 1 and 2), a fact which is consonant with the findings of many earlier investigators emphasizing the extraordinary endotoxin resistance of this species. On the other hand, after sensitization with lead acetate, all animals given 10, 7, 5, or 3 μ g (groups 3 to 6) died. Mortality was still very high at the 1- and 0.1- μ g levels (groups 7 and 8) and even 10- and 1-nanogram amounts of endotoxin (groups 9 and 10) were no better tolerated by lead acetate-sensitized rats than were 100- μ g amounts by normal controls (group 1). The intensity of the organ lesions ran approximately parallel to the mortality rate, except in the lead acetate-sensitized rats receiving the highest doses of endotoxin, most of which died too early to develop detectable morphological changes.

Minimal effective dose of lead. Having thus established the minimal dose of endotoxin that can kill a rat sensitized with a standard dose of lead acetate, we wanted to know how much lead acetate would suffice to make the rat sensitive to a standard amount of endotoxin. For this purpose, four groups of rats were given intravenous injections of 1 μ g of *E. coli* O8 endotoxin in 1 ml of distilled water immediately after varying amounts of lead acetate were administered in the same manner. The minimal dose of lead acetate capable of appreciably sensitizing the rat to the toxic action of 1 μ g of endotoxin was in the vicinity of 1 mg (Table 4).

Specificity of lead action. At this point, it became of interest to determine whether the sensitizing effect of lead acetate is specific. Hence,

TABLE 2. "Critical period" for interaction between lead acetate and *Escherichia coli* O8 endotoxin

Group	Time of endotoxin injection*	Mortality	Organ lesions†
	hr	%	
1	-24	0	0
2	-7	0	0.1
3	-1	70	1.2
4	0	90	1.1
5	+1	50	0.6
6	+7	40	0.5
7	+24	0	0.1

* In addition to the treatments listed in this column, all animals were sensitized with 5 mg of lead acetate given intravenously as described in the text. The time of lead acetate injection is taken as 0 hr, and the preceding and following hours are designated as - and +, respectively.

† For scale, see Materials and Methods.

TABLE 3. Minimal effective dose of endotoxin

Group	Dose of endotoxin*	Mortality	Organ lesions†
	μ g	%	
1	100	10	0
2	10	0	0.2
3	10	100	0.5
4	7	100	0.6
5	5	100	0.3
6	3	100	0.5
7	1	90	0.7
8	0.1	80	0.8
9	0.01	30	0.6
10	0.001	30	0.3
11	0.0001	0	0.1
12	0.00001	0	0.1
13	0.000001	0	0

* In addition to the dose of endotoxin listed in this column, the rats of groups 3 to 13 were sensitized in the usual manner with 5 mg of lead acetate given intravenously just before the endotoxin.

† For scale used, see Materials and Methods.

TABLE 4. Minimal effective dose of lead

Group	Dose of lead acetate	Mortality	Organ lesions†
	mg	%	
1	5.0	90	1.2
2	2.5	50	0.6
3	1.0	30	0.4
4	0.1	0	0

* Immediately after the intravenous injection of lead acetate at the doses listed in this column, all animals received 1 μ g of *Escherichia coli* O8 endotoxin intravenously.

† For scale, see Materials and Methods.

under otherwise identical conditions, a number of additional predominantly metallic compounds were tested, many of which are known to share certain pharmacological actions of lead in that they affect blood clotting, calcification, or the reticuloendothelial system. Intravenous injections of 1 μ g of *E. coli* O8 endotoxin in 1 ml of distilled water were given to 19 groups of rats immediately after the administration of compounds whose potential sensitizing action was to be determined. Pb-acetate, ScCl₃, CeCl₃, LaCl₃, NdCl₃, FeCl₃, BiCl₃, ThCl₄, Th(NO₃)₄, ZrOCl₂, and CrCl₃ were each administered intravenously in a dose of 5 mg in 1 ml of distilled water. However, since FeCl₃ is poorly tolerated, it was given in two portions of 2.5 mg each at 30 min before and immediately preceding the endotoxin. Agar (2 mg), ZnCl₂ (2.5 mg), Ga₂(SO₄)₃ (10 mg), HgCl₂ (50 μ g), and polyanetholesulfonic acid

sodium salt (500 μ g) were also given in 1 ml of water. India ink (30%) and ferric oxysaccharate or "Fe-OS" (in an amount corresponding to 10 mg of metallic iron) were both given in 0.5 ml. Thorium dextrin was injected in 0.2 ml corresponding to 5 mg of thorium dioxide. Control experiments performed simultaneously on another 19 groups of rats showed that, when administered by themselves, these doses of most of the potentially sensitizing compounds are tolerated, but that they are close to fatal, several of these agents causing mortality, even without additional endotoxin treatment.

Among all the compounds listed, only ScCl_3 and $\text{Th}(\text{NO}_3)_4$ approximated the sensitizing potency of lead acetate when given at a dose causing no mortality without endotoxin (Table 5). The other compounds had little or no effect, and, even though mortality occurred in some groups, the associated organ lesions were qualitatively unlike those produced by heavy overdosage with endotoxin in the normal rat or by small doses of endotoxin after sensitization with lead acetate. It would be beyond the scope of this communication to give a detailed description

of all the pathological changes observed, but, since the characteristic splenic thromboses and renal lesions were almost invariably absent here, it may be concluded that none of these compounds equals—and only ScCl_3 and $\text{Th}(\text{NO}_3)_4$ approximate—the effect of lead acetate as a sensitizer for endotoxin.

Specificity of endotoxin action. Since endotoxins are known to interfere with the function of the reticuloendothelial system, we had to establish whether nonmicrobial reticuloendothelial blocking agents would also become highly toxic after pretreatment with lead acetate. For this purpose, 10 groups of rats were pretreated with intravenous injections of 5 mg of lead acetate in 1 ml of distilled water. Immediately afterwards they received, again intravenously, aqueous preparations (solutions or suspensions) of: Fe-OS (100%, 0.3 ml), thorium dextrin (100%, 0.2 ml), India ink (30%, 0.5 ml), agar (2 mg, 0.2 ml), polyanetholesulfonic acid sodium salt (500 μ g, 0.2 ml), carboxymethylcellulose (5%, 1 ml), egg yolk (50%, 1 ml), trypan blue (100 μ g, 1 ml), ferric dextran (1 mg of elementary iron, 1 ml), and colloidal silver 70% (1 mg in 1 ml of 5% glucose). Control experiments (not reported here in detail) had shown that in every case the amounts of the reticuloendothelial blocking agents employed here were close to the maximal dose that can be administered safely. The same lead acetate treatment increased the toxicity of *E. coli* endotoxin about 100,000-fold; hence, if lead had acted merely by raising sensitivity to reticuloendothelial blocking agents in general, combined treatment with lead acetate and the blocking agents should have been fatal to virtually all the rats of this experiment.

Only a few of the blocking agents listed in Table 6 caused considerable mortality after pretreatment with lead acetate; these produced only mild organ changes, usually unlike those induced by lead plus endotoxin. Thus, in the present series, the pronounced splenic and periportal hemorrhages, as well as the renal glomerular thromboses (characteristic of endotoxin intoxication after sensitization with lead), were evident only in group 6, which received agar after pretreatment with lead. Even here, the most severe changes were the hemorrhagic necroses of the duodenum and jejunum which are characteristic of agar, not of endotoxin, intoxication. Occasional periportal hemorrhage was also noted in the rats given ferric oxide saccharate or India ink in combination with lead acetate (groups 1 and 5); since this change does not occur after treatment with any of reticuloendothelial blocking agents or endotoxins alone, it is presumably

TABLE 5. *Specificity of lead action*

Group	Treatment*	Mortality (%)		Organ lesion†	
		Not treated with endotoxin	Treated with endotoxin	Not treated with endotoxin	Treated with endotoxin
1	Pb-ac	0	90	0	0.8
2	ScCl_3	0	60	0	0.9
3	$\text{Th}(\text{NO}_3)_4$	0	60	0	0.2
4	Agar	0	20	0	0.1
5	ThCl_4	0	45	0	0.2
6	NdCl_3	0	20	0	0.1
7	Fe-OS‡	0	30	0	0.2
8	CeCl_3	0	10	0	0.2
9	LaCl_3	0	10	0	0.3
10	Thorotrast‡	0	10	0	0.7
11	ZnCl_2	40	50	0.1	0.3
12	ZrOCl_2	20	30	0.1	0.1
13	FeCl_3	0	0	0	0
14	CrCl_3	0	0	0	0
15	BiCl_3	0	0	0	0
16	$\text{Ga}_2(\text{SO}_4)_3$	0	0	0	0
17	HgCl_2	0	0	0	0
18	Liquoid‡	0	0	0	0
19	India ink	0	0	0	0.1

* Immediately after administration of the compounds listed in this column, all the rats received 1 μ g of *Escherichia coli* 08 endotoxin intravenously.

† For scale, see Materials and Methods.

‡ Trade names; generic names given in Materials and Methods.

referable to additional treatment with lead. In any event, it is clear that, although pretreatment with lead may increase the toxicity of some reticuloendothelial blocking agents, it is not nearly as potent a sensitizer for any of these as it is for endotoxins. The possibility that some of our reticuloendothelial blocking preparations might have been contaminated with endotoxins has not been excluded; it is conceivable, therefore, that even the moderate increase in the sensitivity to some of these agents induced by lead acetate is due to sensitization for endotoxin effects.

DISCUSSION

It has long been known that various reticuloendothelial blocking agents (including thorium dextrin, ferric oxide saccharate, and trypan blue) can increase sensitivity to bacterial endotoxins (2, 4, 8, 14); hence, it would be tempting to assume that, in the present series of experiments, lead acetate acted through the same mechanism. However, our comparative studies show that, among the numerous reticuloendothelial blocking agents tested, none equals the extraordinary sensitizing effect of lead acetate. Nevertheless, lead might increase endotoxin sensitivity by inactivating the reticuloendothelial system, but, if so, we must assume that its blocking effect is greater than that of any other agent tested. It is difficult to see why this should be the case. Possibly, when injected into the circulation, lead forms a precipitate which, because of some physical or chemical characteristic (e.g., particle size or direct toxic action on the phagocytes by

which it is ingested), is singularly adapted to produce a blockade of the reticuloendothelial system.

It must be kept in mind, however, that the extraordinary innate endotoxin resistance of the rat can be overcome by other means as well. For example, corticoid deficiency after adrenalectomy greatly decreases resistance against various bacterial products (1, 3, 5, 6, 7, 9, 10, 11, 15). It may be profitable, therefore, to explore the possibility that lead may act by interference with the defensive function of the adrenals or with some other metabolic phenomenon, but, at present, we have no evidence to support this view.

In any event, it is clear that a single intravenous injection of lead acetate is extraordinarily effective in making the rat susceptible to a variety of bacterial endotoxins to which this species is otherwise unusually resistant. Thus, the rat pretreated with lead may be used as a convenient test object for minute amounts of endotoxins.

ACKNOWLEDGMENTS

This investigation was supported by the John A. Hartford Foundation and the Medical Research Council of Canada.

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TABLE 6. *Specificity of endotoxin action*

Group	Treatment*	Mortality	Organ lesions†
		%	
1	Fe-OS‡	50	0.3
2	Thorotrast‡	0	0
3	Fe-Dex‡	0	0
4	Collargol‡	0	0.1
5	India ink	50	0.4
6	Agar	80	0.8
7	Liquoid‡	10	0.1
8	Carboxymethylcellulose	70	0
9	Yolk	0	0
10	Trypan blue	0	0

* In addition to the treatments listed in this column, all animals were sensitized with 5 mg of lead acetate given intravenously as described in the text.

† For scale, see Materials and Methods.

‡ Trade names; generic names given in Materials and Methods.

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