In vivo and in vitro effects of lead on vascular reactivity in rats

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WEBB, R. CLINTON, RAYMOND J. WINQUIST, WINONA VICTERY, AND ARTHUR J. VANDER. *In vivo and in vitro effects of lead on vascular reactivity in rats.* Am. J. Physiol. 241 (Heart Circ. Physiol. 10): H211–H216, 1981.—The effects of lead on vascular responsiveness were examined in rats. Adult rats, which had received levels of lead acetate in their drinking water to produce blood levels similar to those seen in some urban human populations, consistently had higher systolic blood pressures compared to age-matched controls. Helical strips of tail arteries from the lead-treated rats displayed a greater force-generating ability in response to the cumulative addition of methoxamine to the muscle bath. There were no differences in ED_{50} between the two groups. Similar results were obtained when norepinephrine was used. The calcium-entry blocker, D 600, was less effective in reducing contractions induced by methoxamine in lead-treated rats than in controls. There were no differences between the two groups in responses to KCl or electrical stimulation of nerve endings. Contractile responses to norepinephrine, methoxamine, KCl, and nerve stimulation in arteries from untreated rats were unaltered by addition of lead acetate to the muscle bath. These results demonstrate that hypertension induced by moderate levels of lead intake is associated with an increased vascular responsiveness to α-adrenergic agonists.

norepinephrine; D 600; methoxamine; vascular smooth muscle; tail artery

A CONSIDERABLE CONTROVERSY exists concerning the possible role of lead in the etiology of human hypertension (see Ref. 1 for example). In an extensive study (15) of rats exposed chronically (beginning in utero) to a relatively modest amount of lead, we observed that rats drinking 100 ppm lead (which produced blood lead concentrations of ~40 μg/dl) developed a chronic significant 15- 20-mmHg elevation in systolic blood pressure. This study was designed to investigate one possible mechanism for this hypertension: increased vascular responsiveness to pressor agents. The experiments were performed on isolated tail arteries from lead-treated and control rats.

METHODS

Experiments were performed on adult male Wistar rats that were given drinking water containing 100 ppm lead (as lead acetate) or sodium acetate (supplying an identical amount of acetate) for 7 mo. The rats had been weaned from nursing mothers that had received a similar treatment in their drinking water beginning 1 wk after conception. During the 7-mo treatment period, body weights were monitored, and systolic blood pressures were measured in the unanesthetized state by the tail-cuff technique. An additional group of untreated adult male Wistar rats (7–9 mo old) were used to study the effects of lead added in vitro on vascular reactivity. These rats received tap water for drinking. All rats were maintained on a diet of Teklad laboratory chow.

The rats were killed by either a blow to the head or by decapitation. Tail arteries (0.8–1.0 mm OD) were excised, dissected free of loose connective tissue, and cut helically into strips (0.8 x 10 mm) under a dissecting microscope. The helical strips were mounted vertically on either a glass or plastic holder in a tissue bath containing physiologic salt solution (PSS; described below). The upper end of each strip was connected to a force transducer (Grass FT .03). Before the start of experiments, the strips were allowed to equilibriate for 60–90 min in PSS, maintained at 37°C, and aerated with a mixture of 95% O_2-5% CO_2. At the end of the equilibration period, the resting tension of each strip was adjusted so that it produced a maximum active tension in response to a standard dose of methoxamine. PSS composition was as follows (in mM): NaCl 130, KCl 4.7, KH_2PO_4 1.18, $MgSO_4 \cdot 7H_2O$ 1.17, $CaCl_2 \cdot 2H_2O$ 1.6, $NaHCO_3$ 14.9, dextrose 5.5, $Ca\text{-}Na_2\text{-}EDTA$ 0.03 (pH 7.4). Higher concentrations of potassium (10–130 mM) in the bathing medium were achieved by equimolar substitution of NaCl with KCl.

Strips of tail artery were electrically stimulated by the use of two platinum wire electrodes placed parallel to the preparations. Electrical impulses consisted of square waves (12 V, 0.3 ms) provided by a Grass stimulator (SM6).

In experiments designed to investigate the in vitro effects of lead on vascular responsiveness, the arterial strips were allowed to equilibriate in PSS containing either lead acetate (10^{-9} to 10^{-3} M) or sodium acetate (10^{-9} to 10^{-3} M) for 15 min before the addition of vasoactive agents or transmural nerve stimulation.

Drugs used were: norepinephrine bitartrate (Winthrop Laboratories), methoxamine hydrochloride (Burroughs Wellcome), D 600 (methoxy derivative of verapamil, Knoll AG), and phenotlamine mesylate (CIBA Pharmaceutical). All drug concentrations were expressed in terms of the base.

The results of these experiments were analyzed by

several statistical procedures. Concentration-response curves were calculated as geometrical means (data for each arterial strip were normalized to its maximal response to pressor agent to allow interpretation of results in terms of vascular reactivity and sensitivity). Paired and unpaired t tests, analysis of variance, chi-square analysis, and curve-fitting procedures (logit transformation) were performed. $P < 0.05$ was considered statistically significant.

RESULTS

The systolic blood pressures of rats treated with 100 ppm lead acetate were significantly higher than those treated with 100 ppm sodium acetate (at time of death, lead-treated rats weighed 147 ± 4 mmHg and control rats weighed 133 ± 4 mmHg; $P < 0.05$). Chronic exposure to lead treatment had no effect on body weight (lead-treated rats 527 ± 7 g, control rats 496 ± 12 g). The blood levels of lead were higher in rats treated with lead acetate compared to the controls (lead-treated rats 40.4 ± 1.4 μg/dl, control rats 2.2 ± 0.3 μg/dl; $P < 0.05$).

Concentration-response to methoxamine and norepinephrine. Cumulative addition of methoxamine (2.2×10^{-8} to 10^{-4} M; Fig. 1 and Table 1) or norepinephrine (10^{-9} to 10^{-5} M; Table 1) to the muscle bath produced contractile responses in tail-artery strips from rats treated with lead acetate or with sodium acetate. The maximal contractile response to either agonist was significantly greater in arterial strips from lead-treated rats ($P < 0.05$). There was no difference in the 50% effective doses (ED_{50}) for norepinephrine or methoxamine between the two groups of rats when the dose-response curves were normalized to their respective maximal responses.

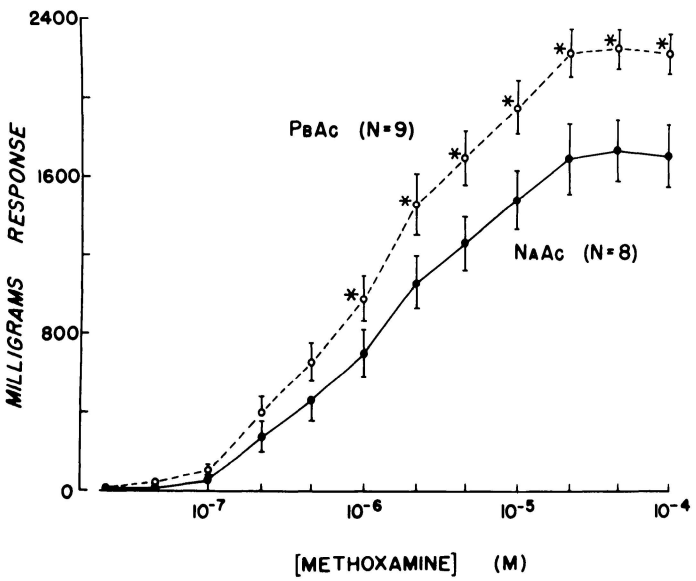

FIG. 1. Concentration-response curve to methoxamine. Helical strips of tail artery from rats treated with sodium acetate (NaAc) or lead acetate (PbAc) were made to contract in response to cumulative addition of methoxamine to muscle bath. Arterial strips from PbAc-treated rats developed more force in response to all concentrations of methoxamine than did those from control rats. Values are means ± SE; n, no. of rats. *Statistically significant difference between groups at $P < 0.05$ (unpaired t test).

TABLE 1. *ED_{50} for dose-response curves*

Agonist	ED_{50} (M) or EF_{50} (Hz)	Maximum Response (mg)
	Sodium acetate-treated rats	
Methoxamine ($n = 8$)	2.1×10^{-6} M	1,736 ± 179
Norepinephrine ($n = 8$)	6.0×10^{-8} M	2,190 ± 181
Potassium ($n = 6$)	3.6×10^{-2} M	799 ± 87
Nerve stimulation ($n = 6$)	5.2 Hz	1,249 ± 196
	Lead acetate-treated rats	
Methoxamine ($n = 9$)	1.6×10^{-6} M	2,243 ± 111*
Norepinephrine ($n = 9$)	5.2×10^{-8} M	2,612 ± 121*
Potassium ($n = 7$)	3.9×10^{-2} M	664 ± 96
Nerve stimulation ($n = 6$)	5.6 Hz	1,450 ± 126*

Values are means ± SE; n, no. of rats. Concentration-response and frequency-response curves were calculated as geometrical means. The concentration of an agonist that produced a half-maximal contraction (ED_{50}) was determined by logit transformation. The frequency that produced a half-maximal contraction (EF_{50}) was estimated from graphic representations of individual curves. * Statistically significant differences between rats treated with lead acetate and those treated with sodium acetate ($P < 0.05$; unpaired t test).

Effect of D 600 and methoxamine. Treatment of arterial strips for 10 min with 10^{-6} M D 600 (before addition of methoxamine) decreased the magnitude of contractile responses induced by 2.2×10^{-5} M methoxamine (Fig. 2). The absolute change in tension was similar for both groups of rats (785 ± 83 mg for lead acetate-treated rats and 647 ± 60 mg for sodium acetate-treated rats; Fig. 2*A*). When the methoxamine contraction in the presence of D 600 was normalized to its respective control response, the contractions of arterial strips from rats treated with lead acetate were less affected by the drug than were those treated with sodium acetate (Fig. 2*B*).

Nerve stimulation. Cumulative frequency-response curves in tail-artery strips were performed subsequent to obtaining reproducible contractions with a 4-Hz test stimulus. Stimulation began at 1 Hz with the frequency increasing stepwise to 2, 4, 8, 16, and 32 Hz when the contractile response to the previous stimulation frequency had reached a maximum (Fig. 3). Contractile responses were abolished by 1.3×10^{-6} M phentolamine. Maximal contractile responses to electrical stimulation in the tail-artery strips from lead-treated rats were significantly greater than sodium-treated rats (Table 1). However, when responses were normalized to the maximum response to exogenous norepinephrine to eliminate differences in force-generating ability, there were no significant differences (Fig. 3).

Relaxation after methoxamine and electrical stimulation. Strips of tail artery from rats treated with lead or sodium were contracted with either 2.2×10^{-5} M methoxamine or 32-Hz electrical stimulation. After the contractile response had reached a maximum level, the strips were immediately rinsed twice and then rinsed at 2-min intervals until the level of tension returned to base line.

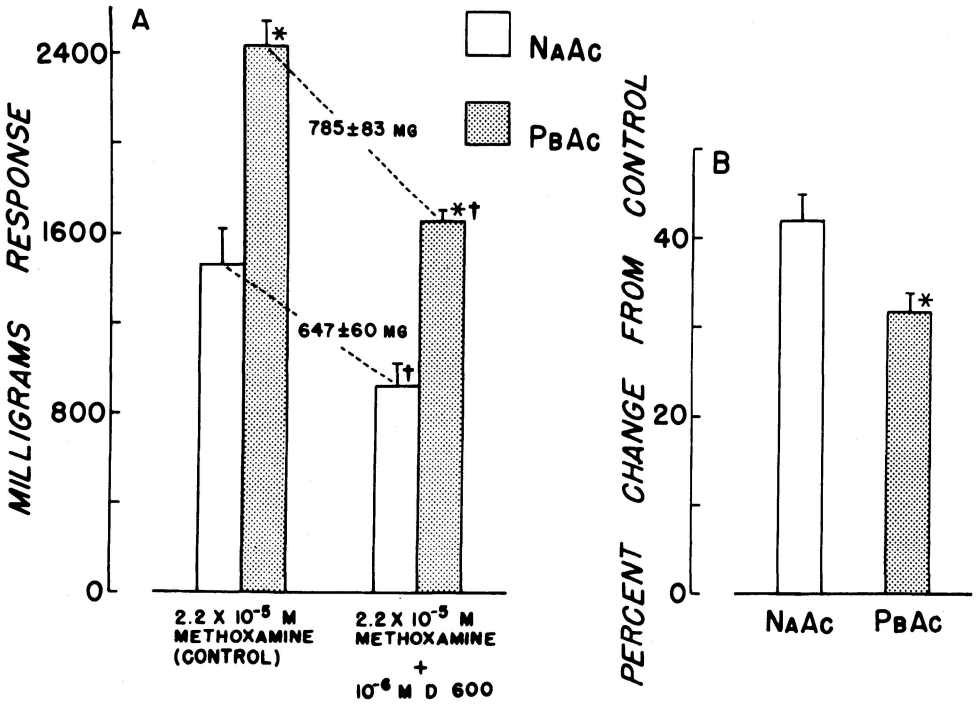

FIG. 2. D 600 and contraction induced by methoxamine. Helical strips of tail artery from rats treated with sodium acetate (NaAc) and lead acetate (PbAc) were made to contract in response to 2.2 $\times$ 10^{-5} M methoxamine in presence and absence of 10^{-6} M D 600. In absence of D 600, arterial strips from PbAc-treated rats developed more force than those from control rats. In presence of D 600, contractile responses in both groups of rats were depressed; but absolute magnitude of depression was similar for both groups (*A*). Normalization of contractile responses in presence of D 600 to their respective control responses indicated that arterial strips from PbAc-treated rats had a smaller component of total contraction that was sensitive to calcium-entry blocker (*B*). Values are means ± SE for 5 rats in each group. *Statistically significant difference between rats treated with NaAc and PbAc at $P < 0.05$ (unpaired *t* test). †Statistically significant difference between untreated condition (control without D 600) and treatment with 10^{-6} M D 600 within each group of rats at $P < 0.05$ (paired *t* test).

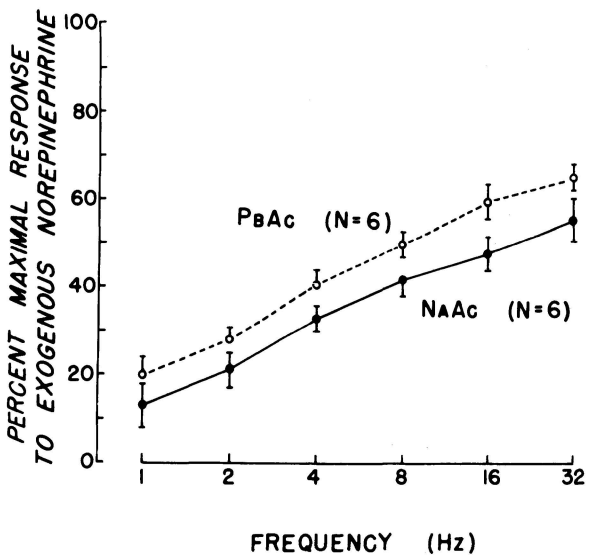

FIG. 3. Frequency-response relationship. Helical strips of tail artery from rats treated with sodium acetate (NaAc) and lead acetate (PbAc) were made to contract in response to electrical-field stimulation of adrenergic nerve endings. Arterial strips from both groups of rats responded similarly at all frequencies of stimulation when contractile responses of each arterial strip were normalized to its maximal response to exogenous norepinephrine. Values are means ± SE; *n*, no. of rats.

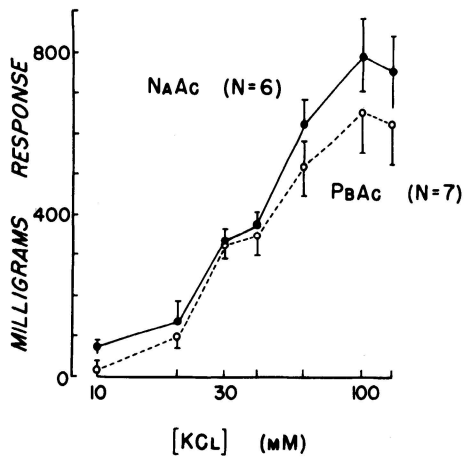

FIG. 4. Concentration-response curve to KCl. Helical strips of tail artery from rats treated with sodium acetate (NaAc) and lead acetate (PbAc) were made to contract in response to KCl. Desired concentration of KCl was achieved by equimolar substitution of NaCl and KCl. Arterial strips from both groups of rats responded similarly to all concentrations of KCl. Values are means ± SE; *n*, no. of rats.

The period of time required to reach half-maximal relaxation ($t_{1/2}$) was significantly greater in strips from lead-treated rats [after methoxamine (n = 16) $t_{1/2}$ = 5.6 ± 0.2 min, after 32-Hz electrical stimulation (n = 6) $t_{1/2}$ = 20 ± 2 s] compared to those from control rats [after methoxamine (n = 14) $t_{1/2}$ = 4.7 ± 0.2 min, after 32-Hz electrical stimulation (n = 5) $t_{1/2}$ = 15 ± 1 s].

Concentration-response to elevated potassium. Tail-artery strips from lead-treated and sodium-treated rats were made to contract in response to the cumulative addition of potassium to the muscle bath in the presence of 1.3 $\times$ 10^{-6} M phentolamine. There was no difference in the contractile responses of tail artery strips from lead-treated rats to potassium and those from sodium-treated rats (Fig. 4 and Table 1).

Spontaneous activity. Some arterial strips used in these experiments exhibited spontaneous activity (Fig. 5). Phasic contractions were observed in tail-artery strips from both groups, the incidences being similar. These contractions were characteristically small in amplitude (10–100 mg), and their frequency ranged from 2 to 6 contractions/min. These spontaneous phasic contractions never continued throughout an entire experiment (4–6 h) and, when present, were always observed during the 60- to 90-min equilibration period. Nine out of 28 arteries from lead-treated rats exhibited phasic contrac-

tions superimposed on a tonic contraction during the equilibration period. These tonic contractions were large in magnitude (200–500 mg), disappeared by the end of the equilibration period, and were also inhibited by 1.3 $\times 10^{-6}$ M phentolamine. Tonic contractions were never observed in tail arteries from sodium-treated rats. The total incidence of spontaneous activity (phasic or a combination of tonic and phasic) was significicantly greater in lead-treated rats. The incidence of phasic contractions alone was similar in both groups of rats, and the incidence of phasic contractions superimposed on tonic contractions was greater in lead-treated animals (Fig. 5).

In vitro effects of lead. The direct effects of lead were tested in tail arteries from rats that received tap water for drinking. Control studies were performed using an equilmolar concentration of sodium acetate. The strips were allowed to equilibriate in a solution of either lead acetate (10^{-9} to 10^{-3} M) or sodium acetate (10^{-9} to 10^{-3} M) for 15 min before addition of norepinephrine or transmural nerve stimulation. The addition of lead acetate had no effect on contractile responses to either exogenous norepinephrine or electrical stimulation (Table 2).

Cumulative addition of lead acetate (10^{-9} to 10^{-3} M) to the muscle bath did not alter tension in unstimulated preparations. Contractions induced by 2.2 $\times 10^{-5}$ M methoxamine, 100 mM KCl, or 2.0-Hz electrical stimulation were not altered by the cumulative addition of lead acetate (10^{-9} to 10^{-3} M) to the muscle bath during the plateau phase of the response.

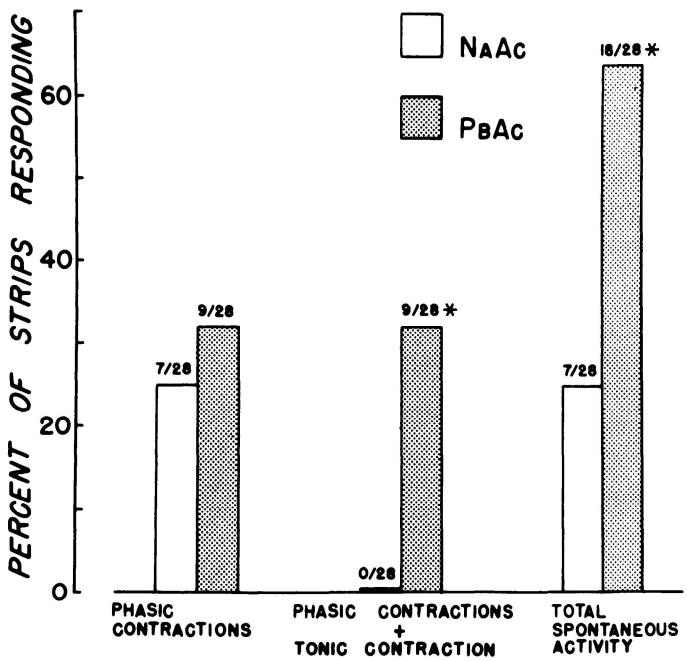

FIG. 5. Incidence of spontaneous activity in tail arteries. Some tail-artery strips used in these experiments developed spontaneous activity. Phasic contractions were observed in strips from both sodium acetate-treated (NaAc) and lead acetate-treated (PbAc) rats. Phasic activity superimposed on a tonic contraction was observed in arterial strips from PbAc-treated rats only. Addition of 1.3 $\times 10^{-6}$ M phentolamine to muscle bath inhibited phasic and tonic contractions. *Statistically significant difference between groups at $P < 0.05$ (chi-square analysis). *Numbers above each column*, no. of strips showing spontaneous activity/total no. of strips.

TABLE 2. *In vitro effects of lead acetate*

Concn	Agonist	ED_{50} (M) or EF_{50} (Hz)	Maximum Response (mg)
Control	Norepinephrine (n = 14)	6.5×10^{-8} M	1,857 ± 161
	Nerve stimulation (n = 6)	5.2 Hz	913 ± 190
10^{-9} M lead acetate	Norepinephrine (n = 4)	7.3×10^{-8} M	1,985 ± 330
10^{-7} M lead acetate	Norepinephrine (n = 10)	6.3×10^{-8} M	1,938 ± 241
	Nerve stimulation (n = 6)	5.2 Hz	917 ± 153
10^{-5} M lead acetate	Norepinephrine (n = 4)	7.1×10^{-8} M	1,763 ± 153
10^{-3} M lead acetate	Norepinephrine (n = 4)	9.5×10^{-8} M	1,708 ± 133

Values are means ± SE; n, no. of rats. Concentration-response and frequency-response curves were calculated as geometrical means. The concentration of an agonist that produced a half-maximal contraction (ED_{50}) was determined by logit transformation. The frequency that produced a half-maximal contraction (EF_{50}) was estimated from graphic representations of individual curves. Statistical comparisons were made by analysis of variance between groups.

DISCUSSION

The major goal of this investigation was to compare the reactivity of vascular smooth muscle obtained from normotensive rats and rats with lead-induced hypertension. The increased force-generating ability in response to α-adrenergic agonists (norepinephrine and methoxamine) of arterial strips from lead-treated rats was a striking and consistent observation. This result contrasts with an earlier study (19) in which bolus injections of norepinephrine in lead-treated rats produced increases in mean arterial pressure similar to those seen in untreated controls. However, there are many differences between our study and that of Williams et al. (19). The rats used by Williams et al. (19) received lead via maternal milk for only 21 days, whereas our rats were treated for a much longer period of time. The lead concentration in the drinking water in our study was 100 ppm, whereas Williams et al. (19) used a concentration of 2,000 ppm. Additionally, the rats used by Williams et al. (19) were not hypertensive. It should also be pointed out that, because these investigators only measured systemic blood pressure responses to norepinephrine, they could not determine whether the blood pressure response was due to a change in vascular reactivity or to a change in cardiac output (or both). In our studies, we measured changes in vascular reactivity (or responsiveness) in isolated tail-artery segments. This preparation has been shown to be a useful model for studies of vascular reactivity in other forms of hypertension. For instance, the vascular changes observed in isolated resistance arteries (150 μm ID) from spontaneously hypertensive rats (9, 18) are very similar to those reported for tail arteries from the same rats (6, 17).

It is doubtful that the difference in response to α-adrenergic agonists is caused by a difference in the amount of preload (i.e., existence of hypertension) or passive tension placed on the arterial strips from the two groups of rats. The optimum passive force for maximum response to methoxamine was similar for arterial strips

from lead-treated and control rats (~600 mg). Furthermore, there was no difference between the two groups in the maximum force-generating ability in response to high potassium concentrations. A difference in the length-tension relationship would be predicted to result in a generalized change in contractility. Thus, the experimental observations suggest that a specific change in force-generating ability in response to activation of α-adrenergic receptors occurs in blood vessels of lead-treated rats.

One possible explanation of the increased responsiveness of arterial strips from lead-treated rats is a decreased β-adrenergic component. The total tension development of a vascular preparation to norepinephrine is the sum of two receptor-mediated events: *1*) α-adrenergic receptor-mediated contraction, and *2*) β-adrenergic receptor-mediated relaxation. A decrease in the number or affinity of β-adrenergic receptors could result in an increased contractile response if the number and affinity of α-adrenergic receptors remained constant. However, this is an unlikely explanation for our results, because a change in receptor number or affinity usually produces a change in agonist sensitivity manifested by a shift in the normalized concentration-response curve. It should also be noted that the increased responsiveness of arterial strips from lead-treated rats was evident when methoxamine was used as the α-adrenergic agonist; this drug has insignificant β-adrenergic receptor activity (2). Finally, we observed no qualitative or quantitative differences in relaxation produced by isoproterenol in arterial strips from lead-treated rats and control animals (3 expt on KCl-contracted strips in presence of phentolamine; data not shown).

Another possible cause of the difference in α-adrenergic responsiveness (for norepinephrine) is a decrease in the neuronal uptake mechanism of nerve endings present in the arterial walls of lead-treated rats. Neuronal uptake of norepinephrine plays an important role in transmitter disposition in vascular smooth muscle (14), and a decrease in its activity could lead to an enhanced receptor activation and an increased contractile response. Our results do not support this hypothesis for the following reasons: *1*) methoxamine is not taken up by the nerve endings (2), *2*) changes in neuronal uptake activity are not usually accompanied by changes in the maximum force-generating ability of the vascular preparation (16), *3*) changes in the function of adrenergic nerves are usually associated with changes in catecholamine sensitivity (14, 16, 17), and *4*) the experiments with transmural nerve stimulation also argue against any significant change in adrenergic nerve endings in lead-treated rats.

The experiments on the effects of in vitro lead treatment on vascular reactivity suggest that the change in maximum force-generating ability is not an acute alteration but requires chronic exposure to the trace element; however, it is also possible that exposure of the vessels to lead for only 15 min was not long enough to permit lead uptake and alteration of tissue function. In rabbit saphenous artery (4), administration of lead to the perfusate inhibited nerve-mediated increases in perfusion pressure, whereas responses to exogenous norepinephrine were not altered. In our experiments, we observed no acute lead-induced changes in contractile responses to either exogenous norepinephrine or to endogenously released norepinephrine. The reasons for the differences between this study and that by Cooper and Steinberg (4) in terms of nerve-mediated responses are not evident.

The increased maximum force-generating ability of tail-artery strips from lead-treated rats appears to be related to an alteration in the intracellular pool of activator calcium. The basis for this conclusion is that norepinephrine and potassium chloride depend on two different mechanisms to produce contraction. Increased potassium concentration causes membrane depolarization, and the contractile response is the result of an influx of extracellular calcium into the cell (see Ref. 3 for review). In contrast, norepinephrine-induced contractions are caused by an initial release of intracellularly bound calcium followed by an increased cellular membrane permeability to the cation. Contractile responses to elevated potassium concentrations were similar in the two groups of rats, whereas contractions induced by norepinephrine and methoxamine were greater in the lead-treated animals, suggesting an increased intracellular pool of activator calcium in lead-treated animals. Further support for this hypothesis is the observation that treatment with D 600, a calcium-entry blocker, inhibited contractile responses to methoxamine in lead-treated rats to a lesser extent (percent basis) than those in control rats. An enlarged intracellular calcium pool may also be partly responsible for the decreased relaxation (indicated by increased $t_{1/2}$) after contraction induced by methoxamine and transmural nerve stimulation in tail arteries from lead-treated rats.

Further evidence suggesting a change in the intracellular pool of activator calcium is obtained from the work of Piccinini et al. (10). These investigators observed that in vitro treatment with lead increased the tissue content of radioactive calcium in rat-tail artery. The half-life of the slow component of the radioactive calcium washout (which probably represents the discharge of calcium from the cytosolic compartment) was retarded in the presence of lead, suggesting that intracellular calcium binding sites are involved in the action of this element in vascular smooth muscle. Although we did not observe contraction of tail-artery segments in response to in vitro treatment with lead, it must be remembered that a change in radioactive calcium uptake or efflux does not necessarily reflect contraction, because calcium may not be made available to the contractile proteins.

In the present study, arterial strips from lead-treated rats exhibited a greater incidence of spontaneous activity than did those from control rats. These spontaneous contractions were only apparent during the equilibration period of the experiment and were probably due to the spontaneous leakage of norepinephrine from nerve endings in the vessel wall (14, 16). Other investigators have also noted phasic activity in rat-tail artery to be inhibited by phentolamine (16), but the development of a tonic contraction appears to be unique to arterial strips from lead-treated rats. The reasons for this phenomenon in lead-treated animals are not apparent but suggest that lead may have an action on the spontaneous leakage of the neurotransmitter. Alternatively, the amount of spontaneous leakage is similar in lead-treated and control

rats, but the difference in force-generating ability accounts for the spontaneous contractions.

The results of these experiments suggest a mechanism whereby chronic exposure to moderate levels of lead could cause hypertension. A portion of the increased blood pressure may be due to the increased reactivity of the vasculature to α-adrenergic-receptor activation. The mechanism of this increased reactivity appears to be related to a larger pool of intracellular calcium available for activation of contraction. Finally, it should be emphasized that increased vascular responsiveness to pressor agents may be only one of several factors contributing to the development of hypertension. Abnormalities in cardiac function have been noted in patients with clinical existence of lead intoxication (13) and in rats (7). Rats treated with lead during the first 5 wk of life show an increased susceptibility to the arrhythmogenic action of norepinephrine (18). Chronic lead exposure has also been shown to elicit an increase in the urinary excretion of catecholamine metabolites (11) and to enhance adrenergic function in the central nervous system (12). Alterations in the renin-angiotensin system have also been noted after both acute and chronic exposures to lead (5, 8).

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