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Lead-Induced Hypertension: Interplay of Nitric Oxide and Reactive Oxygen Species

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Abstract

An elevation of mean blood pressure was found in rats treated with low lead (0.01% lead acetate) for 3 months, as contrasted to paired Sprague-Dawley control rats. In these rats, measurement of plasma and urine endothelins-1 and -3 revealed that plasma concentration and urinary excretion of endothelin-3 increased significantly after 3 months (plasma: lead group, 31.8 +/- 2.2, versus controls, 23.0 +/- 1.7 pg/mL, P < .001; urinary excretion: lead group, 46.6 + 11.7, versus controls, 35.6 + 6.7 pg/24 h, P < .05), whereas endothelin-1 was unaffected. Plasma and urinary nitric oxide (NO) and cyclic GMP concentrations were not significantly changed. However, assay of plasma and kidney cortex malondialdehyde by high-pressure liquid chromatography, as a measure of reactive oxygen species, was elevated in lead-treated rats compared with that in control rats (plasma: lead group, 4.74 + 1.27, versus controls, 2.14 + .49 micro mol/L, P < .001; kidney cortex: lead group, 28.75 + 3.46, versus controls, 16.38 + 2.37 nmol/g wet weight, P < .001). There was increased NO synthase activity in lead-treated rat brain cortex and cerebellum. In lead-treated rat kidney cortex, the endothelial constitutive NO synthase protein mass was unaffected, whereas the inducible NO synthase protein mass was increased. These data suggest a balance between increased NO synthesis and degradation (by reactive oxygen species) in lead-treated rats, which results in normal levels of NO. Thus, the hypertension may be related to an increase in the pressure substances, endothelin-3 and reactive oxygen species, rather than to an absolute decrease in nitric NO. (Hypertension. 1997;30:1487-1492.)

Key Words nitric oxide; endothelins; reactive oxygen species; lead

Selected Abbreviations and Acronyms

ecNOS = endothelial constitutive nitric oxide synthase

EDRF = endothelium-derived relaxing factor

ET = endothelin

iNOS = inducible nitric oxide synthase

MDA-TBA = malondialdehyde-thiobarbituric acid adduct

NO = nitric oxide

NOS = nitric oxide synthase

ROS = reactive oxygen species

Continuous exposure to low but not high levels of lead has been shown to result in increased blood pressure in both humans and animals. [1-6] Our laboratory verified that rats treated continuously with low lead (0.01% lead acetate) had significantly increased blood pressure compared with age-matched controls. Elevation in blood pressure was observed after 3 months of lead exposure and continued for 1 year of persistent lead exposure. The elevation in blood pressure also persisted for 6

months after lead exposure was discontinued. [5,6] We suggested that elevation in blood pressure was related to an increase in an endothelial-derived vasoconstrictor, endothelin-3, an increase in the Na-K-ATPase inhibitor-containing hypertension-associated protein, and a decrease in cyclic guanosine monophosphate as a second messenger for the vasodilator compound, EDRF, which has been identified as NO. [7-9] Previous investigators demonstrated both increased and decreased plasma renin activities in lead-exposed rats, [10,11] with decreased activity shown in rats that were most comparable to the present study (100 ppm lead for 6 months). [10]

The purposes of the present study were (1) to investigate the effects of lead exposure on plasma concentration and urinary excretion of NO, plasma concentrations of ET-1 and ET-3, and urinary excretion of these hormones; (2) to investigate the effects of lead on plasma and kidney MDA-TBA, a reflection of lipid peroxide formation (and thus, ROS); and (3) to determine whether lead exposure affects NO production by inducing changes in NOS activity or protein mass.

Methods

Animals

From the age of 2 months, male Sprague-Dawley rats (purchased from Charles River, Inc, Wilmington, Mass) weighing 200 g were fed a standard rodent Purina laboratory chow (containing 1% calcium) and were also given 0.01% lead acetate (100 ppm) in their drinking water for 3 months. The experimental animals had age-matched controls. Six animals each were included in experimental and control groups. Rats were weighed before entering into he study and also at the time of death.

Measurement of Blood Pressure

Conscious rats were placed in a restrainer and allowed to rest inside the cage for 15 minutes before blood pressure measurements. Rat tails were placed inside a tail cuff, and the cuff was inflated and released a few times to allow the animal to be conditioned to the procedure. Mean blood pressure values (four consecutive readings) were taken by a rat tail blood pressure monitor attached to a student oscillograph (Harvard Apparatus Limited) and averaged for presentation. This apparatus is capable of recording both mean blood pressure and systolic blood pressure.

Collection of Blood and Urine

One day before killing, rats were individually placed in metabolic cages during the day, and 24-hour urine samples were collected in plastic tubes placed on ice. Urine samples were centrifuged and frozen at -80 [degree sign] Celsius for determination of cGMP, NO, creatinine, and ET-1 and ET-3 concentrations. On the day of killing, rats were anesthetized with methoxyflurane nd their blood was removed through the heart with an ice-cold syringe. An aliquot (1 mL) of whole blood was stored at 4 [degree sign] Celsius for determination of blood lead. Plasma was separated from the red blood cells by centrifuging the blood at 3000 rpm for 15 minutes at 4 [degree sign] Celsius. Plasma aliquots (1 mL) were stored at -80 [degree sign] Celsius for determination of cGMP, NO, creatinine, MDA-TBA, and ET-1 and ET-3 levels.

Collection of Tissues

After removal of blood, kidneys and brains were excised quickly and placed on ice. Kidney cortex, brain cortex, and cerebellum were separated and placed into liquid nitrogen. All tissues were stored at -80 [degree sign] Celsius.

Determination of Lead in Blood

Lead content of whole blood was measured using an atomic absorption spectrophotometer (Varian, model 400Z with graphite furnace). Whole-blood lead values were expressed as micrograms per deciliter.

Measurements of Urine and Plasma Nitrite and Nitrate (NO $_{(x)}^{-/NO_3^-}$)

The concentration of total NO_2^{-/NO_3^-} (NO $_{(x)}$) in the test samples was determined by the modification of the procedure described by Braman and Hendrix [12] using the purge system of a Sievers Instruments model 270B Nitric Oxide Analyzer (NOA, Sievers Instruments Inc). Briefly, the urine samples were diluted 10 times in distilled water before analysis. A saturated solution of VCl_3 in 1 mol/L HCl was prepared and filtered before use. A total of 5 mL of the reagent was added to the purge vessel and purged with nitrogen gas for 5 to 10 minutes before use. The purge vessel was equipped with a cold-water condenser and a water jacket to permit heating of the reagent to 95 [degree sign] Celsius, using a circulating water bath. The hydrochloric acid vapors were removed by a gas bubbler containing [nearly =] 15 mL of 1 mol/L NaOH. The gas flow rate into the chemoluminescence detector was controlled using a needle valve adjusted to yield a cell pressure of [nearly =] 7 mm Hg. The flow rate of nitrogen into the purge vessel was adjusted to prevent vacuum distillation of the reagent.

Samples were injected into the purge vessel to react with the VCl3/HCl reagent, which converted nitrite, nitrate, and S-nitroso compounds to NO. The NO product was stripped from the reaction chamber (by purging with nitrogen and vacuum) and detected by ozone-induced chemiluminescence in the chemiluminescence detector. The signal generated (NO peak and peak area) was recorded and processed by a Hewlett-Packard model 3390 integrator. In a typical assay, 5 micro Liter of the test sample was injected to the purge vessel, and all samples were run in triplicate. Plasma samples were deproteinized with cold ethanol and injected as the urine samples above.

A standard curve was constructed using various concentrations of NO_3^- (5 to 100 micro mol/L) relating the luminescence produced to the given NO_3^- concentrations of the standard solutions. The amount of NO_x in the test sample was determined by interpolation of the result into the standard curve.

Determination of cGMP, ET-1, and ET-3

ET-1 and ET-3 in extracted plasma and urine were measured by radioimmunoassay kits purchased from Peninsula Laboratories. cGMP in plasma and urine was also measured with an radioimmunoassay kit supplied by New England Nuclear.

Determination of Lipoperoxides in Plasma and Kidney Cortex

Lipoperoxides in plasma were determined by high-performance liquid chromatography measurement of MDA-TBA according the method of Wong. [13-14] The whole procedure, briefly, is as follows: A volume of 50 micro Liter plasma was mixed with .75 mL 0.44 M H_3PO_4, 0.25 mL aqueous 42 mmol/L TBA, and 0.45 ml H_2O. The mixture was heated in a boiling water bath for 60 minutes. After cooling on ice, an equal volume of alkaline methanol (50 mL methanol + 4.5 mL 1 N NaOH) was added. A volume of 50 micro Liter of the neutralized reaction mixture was then injected into a 4.6 x 250-mm chromatographic column packed with micro Bondapak C18 (5-micro meter particle diameter). A guard column, 3.9 x 23 mm, packed with Bondapak Corasil C18 (37- to 50-micro meter particle diameter) was used. Mobile phase was a mixture of 50 mmol/L phosphate buffer (pH 6.8; 600 mL) and methanol (400 mL). The flow was 1 mL/min, and detection was done at 532 nm. The concentration of plasma lipoperoxides was determined from the calibration curve prepared with a tetramethoxypropane standard solution (.61 to 4.86 micro mol/L), processed exactly as the plasma samples.

Lipoperoxides in kidney cortex were measured by high-performance liquid chromatography measurement of the MDA-TBA according to the method of Draper et al. [15] The tissue samples were minced, and duplicate 0.5-g samples were placed in 15 x 100-mm pyrex tubes. A total of 5 mL of 10% trichloracetic acid plus 0.25 mL of 500 ppm BHT in methanol were added. After heating in a boiling water bath for 30 minutes, the sample was collected and centrifuged at 2500 rpm for 10 minutes. A total of 0.25 mL of supernate was combined with 0.25 mL of saturated aqueous TBA solution and heated in a boiling water bath for 30 minutes. After cooling, the reaction mixture was extracted with 1 mL of n-butanol using a vortex mixer. A 0.5-mL aliquot of the mixture was mixed with 0.25 mL methanol and 0.25 mL mobile phase. A total of 20 micro Liter of the mixture was diluted to 1 mL with mobile phase, and 50 micro Liter of this solution was injected into the column as above. A mobile phase of 15% acetonitrile and 0.6% tetrahydrofuran in 5 mmol/L phosphate buffer, pH 7, was used. The flow rate was 1 mL/min, and detection was done at 532 nm. The concentration of MDA-TBA in the supernate was determined from the calibration curve prepared with a tetramethoxy-propane standard solution.

Detection of Kidney Cortex NOS Protein Mass by Western Blotting

Kidney cortex ecNOS protein mass was measured by Western blotting. [16-18] Briefly, 0.2 g kidney cortex was homogenized in 0.8 mL of lysis buffer (320 mmol/L sucrose, 0.1 mmol/L EDTA, 10 mmol/L HEPES pH 7.4, 1 mmol/L DTT, 10 micro gram/mL leupeptin, 20 micro gram/mL aprotinin). The tissue lysates were centrifuged at 12 000 rpm at 4 [degree sign] Celsius for 20 minutes. The supernates were removed to fresh ice-cold microfuge tubes, and protein content was determined using the Bio-Rad Protein Assay. The samples (100 micro gram protein) were diluted in electrophoresis sample buffer, boiled for 2 minutes, and resolved by electrophoresis through 4% to 12% Tris-Glycine gels (Novex). Proteins were electrophoretically transferred to Hybond-ECL membrane (Amersham Life Science Inc). The membranes were quenched in blocking solution (6.5% nonfat dried milk in washing solution [10 mmol/L Tris, pH 7.5, 100 mmol/L NaCl, 0.1% Tween 20]) for 30 minutes in a 37 [degree sign] Celsius water bath with gentle shaking. The blocking solution was decanted, and membranes were incubated for 30 minutes at 37 [degree sign] Celsius with a monoclonal anti-ecNOS antibody (purchased from Transduction Laboratories) raised in mouse (1:2500 diluted in blocking solution). Membranes were washed for 30 minutes with several changes of washing solution at room temperature. The membrane was then incubated in the blocking solution plus diluted anti-mouse IgG-horseradish peroxidase. The washes were repeated before the membrane was developed with a light-emitting nonradioactive method using ECL reagent (Amersham Inc). The membrane was then subjected to autoradiography for 15 seconds. The autoradiographs were scanned with a laser densitometer (model PD 1211, Molecular Dynamics) to determine the relative optical densities of the bands. Kidney cortex iNOS protein mass was measured by a similar procedure, except that 200 micro gram protein was used with mouse monoclonal anti-iNOS antibody purchased from Transduction Laboratories.

Determination of NOS Activity in Brain Cortex and Cerebellum

NOS activity in the cytoplasmic fraction of brain cortex and cerebellum was determined by the method of Matsumoto et al, [19] in which the conversion of ^{3}H-arginine to ^{3}H-citrulline is determined. Control for nonspecific counts was an incubation tube containing the NOS inhibitor nitroarginine. An attempt to measure NOS activity in kidney cortex was unsuccessful because of the competition between NOS and arginase for the metabolism of L-arginine in the kidney. [20]

Statistical Treatment of Data

Statistical analysis of the data was performed using unpaired t test and ANOVA where appropriate. Results were expressed as mean + SD. Statistical significance for the t test was assessed using a two-tailed level of $P < .05$.

Results

Blood Pressure, Weight, and Blood Lead Concentration

There was a sustained increase in mean blood pressure of rats treated with 0.01% lead acetate in their drinking water. Mean blood pressure elevation was observed after 1 month of lead exposure (Figure 1). At the end of 3 months of lead exposure, blood lead concentration in lead-treated rats was significantly higher than that of control rats (12.4 +/- 1.8 versus < 1 micro gram/dL; $P < .001$). Body weights were not significantly different between the two groups.

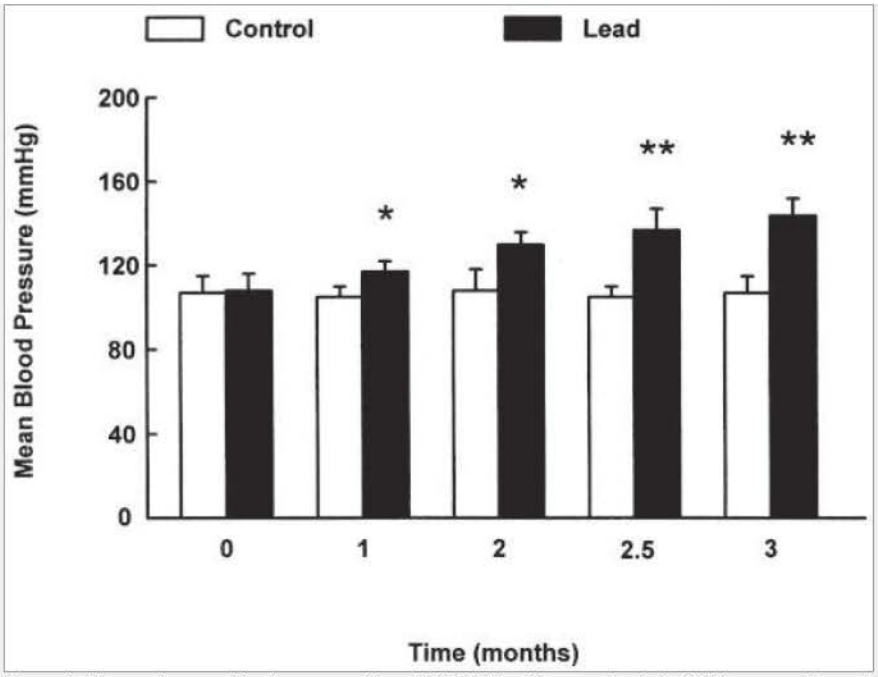

Figure 1. Changes in mean blood pressure of rats fed 0.01% lead acetate in their drinking water for various time periods. In this Figure andthe subsequent figures, values are expressed as mean +/- SD. *P <.01; **P < .001 compared with control.

Plasma Concentration and Urinary Excretion of NO_x and cGMP

There were no significant differences in plasma NO_x levels when lead-treated rats were compared with control rats. NO_x urinary excretion was also not significantly different between the two groups. Plasma cGMP concentration and cGMP urinary excretion were similarly unaffected by lead treatment (Table 1).

	NO_x		cGMP	
Animal Groupings	Plasma, μmol/L	Urine, μmol/g Cr	Plasma, nmol/L	Urine, nmol/mg Cr
Control	14.3±4.1	283±130	11.6±4.4	1.6±0.5
Lead	11.8±3.8	401±99	15.2±2.2	1.7±0.2

NO_x indicates nitrite and nitrate; Cr, creatinine.

Table 1. NO_x and cGMP Plasma Concentrations and Urinary Excretion in Lead-Treated Rats

Plasma Concentrations and Urinary Excretion of ET-1 and ET-3

In lead-treated rats, the plasma concentration of ET-3 was increased significantly above that of the control rats (Table 2), but there was no change in plasma concentration of ET-1. Urinary excretion of ET-3 in lead-treated rats was also significantly higher than that of control rats, but there was no change in urinary excretion of ET-1 (Table 2).

	ET-1		ET-3	
Animal Groupings	Plasma, pg/mL	Urine, pg/24 h	Plasma, pg/mL	Urine, pg/24 h
Control	7.8±2.8	40.3±9.2	23.0±1.7	35.6±6.7
Lead	8.0±0.7	48.8±11.0	31.8±2.2*	46.6±11.7†

*P<.001 compared with control; †P<.05 compared with control.

Table 2. ET-1 and ET-3 Plasma Concentrations and Urinary Excretion in Lead-Treated Rats

Lipoperoxides in Plasma and Kidney Cortex

Lipoperoxides in plasma, represented by the MDA-TBA level, were significantly higher in lead-treated rats than that in control rats after lead exposure. MDA-TBA content of kidney cortex also was higher in lead-treated rats (Figure 2).

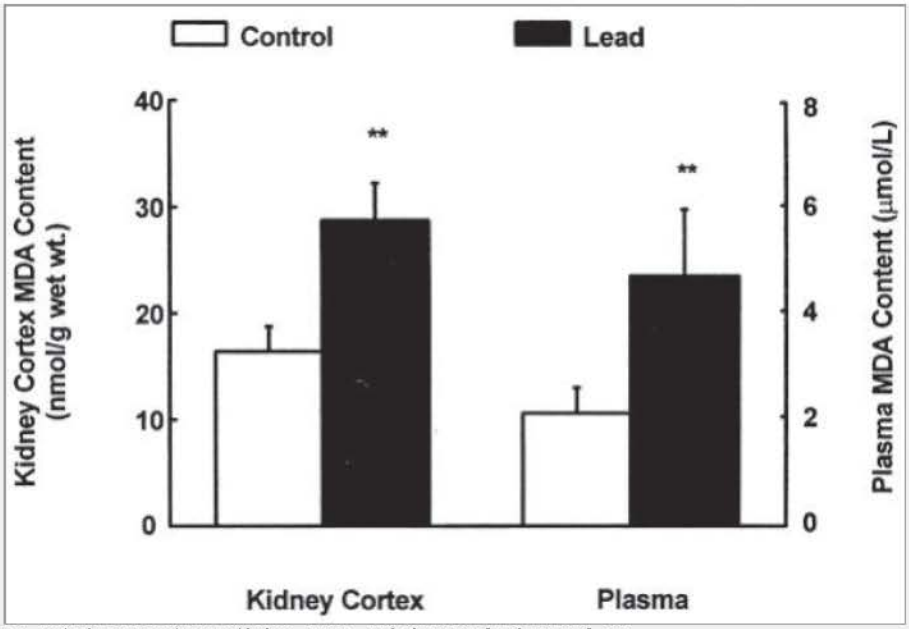

Figure 2. Contents of MDA of kidney cortex and plasma in lead-treated rats.

Kidney Cortex NOS Protein Mass

There were no significant differences in kidney cortex ecNOS protein mass when lead-treated rats were compared with control rats, whereas iNOS protein mass was significantly elevated (Figure 3).

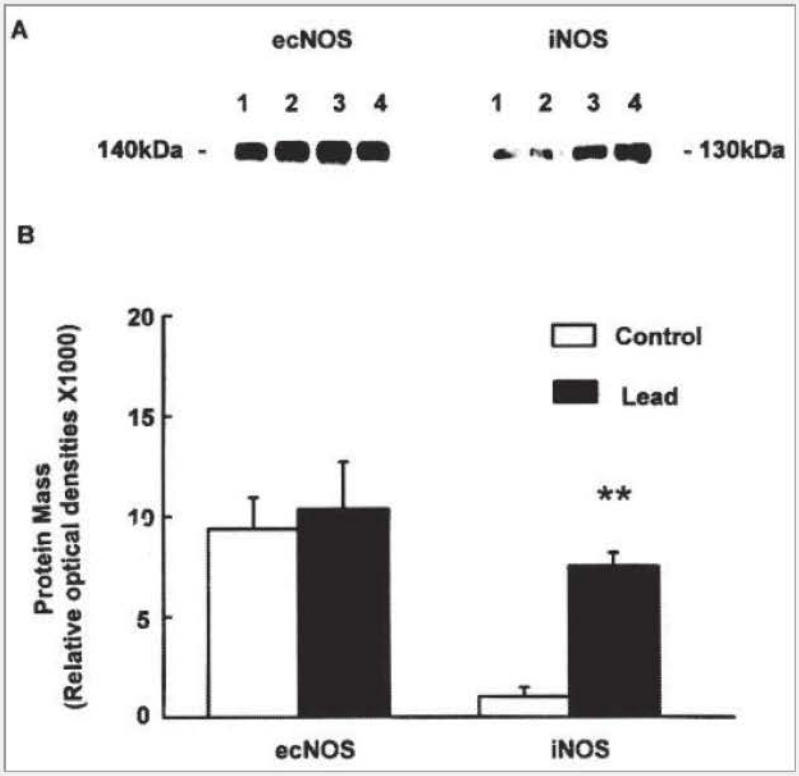

Figure 3*. A, Immunoblot analysis for ecNOS and iNOS protein under denaturing conditions. Lanes 1 and 2 show lysates of control rat kidney cortex. Lanes 3 and 4 show lysates of lead-treated rat kidney cortex. For ecNOS, 100 micro gram of lysate protein was used; for iNOS, 200 micro gram was used. B, Relative optical densities of the blots in the study groups.

NOS Activity in Brain Cortex

NOS activity in both brain cortex and cerebellum was elevated in lead-treated rats compared with controls (Figure 4). NOS activity in cortex was 1169 +/- 111 in lead-treated rats versus 810 +/- 97 counts per milligram protein in controls ($P < .001$); similarly, NOS activity in cerebellum was 967 +/- 126 in lead-treated rats versus 737 +/- 103 counts per milligram protein in controls ($P < .01$).

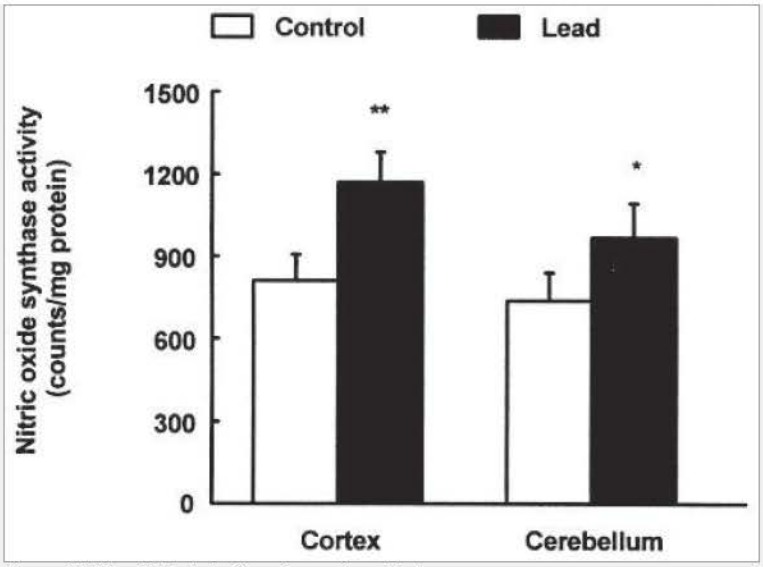

Figure 4. NOS activity in brain cortex and cerebellum.

Discussion

Exposure to low but not high levels of lead has been reported to cause hypertension in humans and animals. [1-6] An increase in blood pressure of rats occurs at low lead exposure levels of approximately 0.1 to 100 ppm, which is similar to the exposure levels seen in the environment. However, rats exposed to concentrations greater than 500 ppm of lead (equivalent to industrial level exposure) do not develop hypertension. Our previous studies suggested that the elevation in blood pressure was related to an increase in an endothelial-derived vasoconstrictor (ET-3) associated with decreased cyclic GMP as a second messenger for the vasodilator compound, EDRF, and that another vasoconstrictor, the Na, K, ATPase inhibitor-containing hypertension-associated protein, was also increased with low lead feeding. (A recent report [21] showed that inhibition of Na, K, ATPase by ouabain causes impairment of acetylcholine-induced relaxation in human resistance arteries, consistent with an effect on EDRF synthesis or release and therefore affording a possible link between these two effects.) We showed also that low lead feeding increased rather than decreased glomerular filtration rate and that no morphological or renal functional abnormalities were associated. [22]

In the study presented here, blood lead concentrations at 3 months in lead-treated rats (0.01% lead acetate in drinking water) were much higher than those in control rats but lower than those in low lead-treated rats studied previously (12.4 +/- 1.8 versus 29.4 +/- 4.1 micro gram/dL). The apparent reason for the difference was that a standard chow was used in place of the synthetic diet used previously. The latter is known to increase susceptibility to lead toxicity, possibly through a lower calcium content (48% of laboratory chow). [23] Despite the lower blood lead levels, an elevation of blood pressure produced by exposure to lead was confirmed by the present investigation.

There was a significant increase in plasma concentration and in urinary excretion of ET-3 but no change in plasma concentration or urinary excretion of ET-1. The plasma results were compatible with the results of the prior study, [5] although the absolute values for plasma concentrations of ET-3 and ET-1 were lower because of the use of extracted rather than unextracted plasma. It was noteworthy that urinary levels of ET-3 were also elevated, inasmuch as several studies have shown that urinary endothelin is a better reflection of intrarenal events. [24-26] As lead deposition is localized primarily to the proximal tubule of the kidney [27] and as ET-3 is produced within this segment of the nephron, [28] this suggests that the effect of lead on endothelin production may occur via increased renal tubular rather than vascular endothelin synthesis. Although ET-3 is a less potent vasoconstrictor than ET-1, [29-31] it appears to be a contributory factor to the hypertension induced by lead.

EDRF was also thought to play a critical role in lead-induced hypertension in our earlier study, as both plasma and urinary levels of cGMP, the second messenger for EDRF, were reduced by lead administration. [5] In the present experiment, by contrast, EDRF, as measured by plasma and urine cGMP and more directly by NO, was unaffected by lead. However, NO levels reflect the balance between NO synthesis via NOS and NO degradation, a process affected by exposure to ROS. [32,33] Levels of circulatory NO may be increased, normal, or decreased when iNOS activity and ROS are simultaneously increased, as exemplified by studies of experimental colitis in rats, [34] in which tissue NO and iNOS levels were enhanced by cytokines despite a concomitant decrease in superoxide dismutase (and thus an increase in the ROS superoxide anion).

Measurement of NOS activity in brain was found to be increased after lead exposure, whereas in kidney cortex iNOS, but not ecNOS, protein mass was increased, indicating that NO synthesis was upregulated. Of interest is the in vitro observation that lead inhibits rather than stimulates brain constitutive NOS activity [35,36] while having no effect on cytokine-inducible brain NOS activity, [36] therefore implying that in the present study the increased NOS activity is a compensatory response to NO degradation by ROS or secondary to another biochemical change induced by lead exposure. An increased production of ROS in response to lead, previously suggested by Hermes-Lima et al, [37] was confirmed by the elevated levels of MDA-TBA in plasma and kidney cortex of lead-treated rats.

A further implication of the results is that under the circumstances of the present study, increased ROS, rather than decreased EDRF, may be one of the principal reasons for lead-induced hypertension. First, we have shown that the ROS scavengers 2,3-dimercaptosuccinic acid (a lead chelator and scavenger of ROS) and lazaroid (a pure scavenger of ROS) return blood pressure and ROS toward normal. [38,39] In addition, Nakazono et al [40] found that infusion of a fusion protein-bound form of superoxide dismutase, the enzyme that degrades superoxide anion, lowered the blood pressure of spontaneously hypertensive rats. Katusic and Vanhoutte [41] further demonstrated that superoxide anion, generated by xanthine and xanthine oxidase in the presence of catalase, caused contraction of canine basilar arteries in vitro. There is also preliminary evidence that another ROS, the hydroxyl radical, may be more potent than superoxide anion in eliciting vascular contractions. Auch-Schwelk et

al [42] demonstrated that aortic rings from spontaneously hypertensive rats had concentration-dependent contractions on exposure to xanthine plus xanthine-oxidase-derived ROS. Although superoxide dismutase and catalase (the enzyme that degrades hydrogen peroxide) showed modest effects in reducing the contractile tension, deferoxamine, the iron chelator that prevents the generation of hydroxyl radical from hydrogen peroxide, totally abolished the contractions. Dreher and Jurod [43] also demonstrated that hypoxanthine-xanthine oxidase exposure led to an increase in intracellular calcium in human umbilical vein endothelial cells, and this increase was inhibited by o-phenanthroline, a compound that blocks the iron-catalyzed formation of hydroxyl radical.

In summary, low lead administration increases blood pressure via an increase in the vasoconstricting compounds ET-3 and ROS. EDRF levels were unaffected in the present study as increased synthesis and degradation were balanced.

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IMAGE GALLERY

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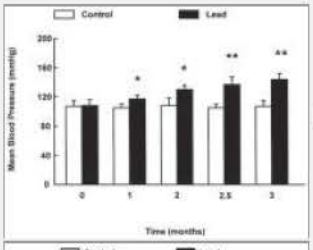


Figure 1

Animal Groupings	NO_x Plasma, μmol/L	NO_x Urine, μmol/g Cr	cGMP Plasma, nmol/L	cGMP Urine, nmol/mg Cr
Control	14.3±4.1	283±130	11.6±4.4	1.6±0.5
Lead	11.8±3.8	401±99	15.2±2.2	1.7±0.2

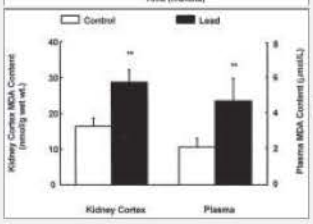
NO_x indicates nitrite and nitrate; Cr, creatinine.

Table 1

Animal Groupings	ET-1 Plasma, pg/mL	ET-1 Urine, pg/24 h	ET-3 Plasma, pg/mL	ET-3 Urine, pg/24 h
Control	7.8±2.8	40.3±8.2	23.0±1.7	35.8±6.7
Lead	8.0±0.7	48.8±11.8	31.8±2.2*	46.6±11.7†

*P<.001 compared with control. †P<.05 compared with control.

Table 2



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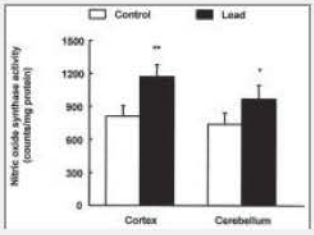

Figure 4

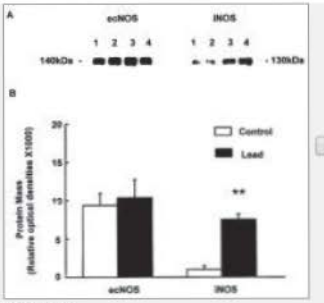

Figure 3°. A, Immuno...

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