LEAD, HYPERTENSION, AND THE RENIN-ANGIOTENSIN SYSTEM IN RATS

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Lead, hypertension, and the renin-angiotensin system in rats

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Rats were exposed continuously to Pb in utero and after birth by giving their mothers, during pregnancy and lactation, drinking water containing 0, 100, or 500 ppm Pb (as Pb acetate) and then continuing this regimen after weaning. Male rats receiving 100 ppm developed a significant elevation of systolic blood pressure (152 ± 3.7 mm Hg vs. 135 ± 5.6 for controls) at 3½ months and remained hypertensive until sacrifice at 6 months; 500 ppm rats remained normotenisve. Both 100 ppm and 500 ppm females remained normotensive. At 6 months, PRA was significantly reduced in the 100 ppm male group but was normal in the 500 ppm group. There were dose-dependent decreases in the AII/PRA ratio and in renal renin. Pulmonary converting enzyme activity was not changed by Pb exposure. Blood [Pb] was 40 and 71 μg/dl, respectively, and kidney [Pb] was 4.8 and 22.9 μg/gm. Renal histology was normal in the 100 ppm group. We conclude that doses of Pb which produce blood [Pb] seen in many people are capable of inducing modest hypertension in male rats; higher doses fail to do so. The hypertension is associated with a reduction in PRA and AII and therefore is unlikely to be due to hyperactivity of the RAS. (J LAB CLIN MED 99:354, 1982.)

Abbreviations: plasma renin activity (PRA), angiotensin I (AI), angiotensin II (AII), plasma renin increment (PRI), plasma renin substrate (PRS), renin-angiotensin system (RAS), ethylenediamine tetraacetic acid (EDTA)

The relation between long-term lead exposure and hypertension is highly controversial. Retrospective studies of lead workers have yielded inconsistent results, some reporting increasing incidence of hypertension (usually associated with renal disease)[1, 2] but others failing to find such an association.[3–5] The most extensive case-control epidemiologic study (performed in the west of Scotland, an area with elevated drinking-water lead) revealed a significant excess of male hypertensive cases with high levels of blood lead.[6]

Also inconsistent are the results of studies attempting to produce hypertension in experimental animals. Three groups of investigators have failed to produce hypertension with long-term administration of lead to dog[7] or rats.[8, 9] In two other earlier studies in rats,[10, 11] the authors reported that lead did produce hypertension; however, there were no

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control animals in these studies, and the designation of hypertension was determined by reference to an arbitrary upper limit of normal. All five of these animal studies employed very large doses of lead, and it is certainly possible that these doses would exert other toxic effects (for example, inhibition of Al-converting enzyme[12]) opposing the development of hypertension, as seems to be the case with cadmium-induced hypertension.[13] Consistent with this possibility is the report by Cottier et al.[14] that a weekly subcutaneous dose of 20 mg of lead phosphate produced hypertension in rats whereas twice this dose did not. Even more striking is the fact that Perry and his co-workers[13, 15] have produced a modest but significant elevation of blood pressure in rats given the very low Pb doses of 1 or 5 ppm in drinking water.

We chose to reinvestigate this question, using a dose of lead (100 ppm in drinking water) that produces blood lead concentrations of 30 to 50 μg/dl and no evidence of renal damage[16]; a dose five times this magnitude was also used to test the hypothesis that lead might exert a biphasic effect on blood pressure. The lead exposure was begun in utero in order to mimic the usual pattern of exposure of human beings. While our studies were in progress, Aviv et al.[17] reported that exposure of rats to lead during 3 to 9 weeks of age resulted in the development of hypertension in adulthood; however, these investigators used very large doses of lead (10,000 ppm in drinking water), which caused severe renal damage.

The second goal of this study was to investigate the effects of these regimens of lead exposure on the hormonal RAS. As with hypertension, the literature on lead and the RAS is inconsistent. Clinical studies have reported that heavy exposure to lead is associated with either a decrease in PRA[18, 19] or no change.[20] In contrast, short-term exposure of rats and dogs to intravenously administered lead[12, 21] and long-term exposure of rats to 500 ppm Pb[22] were associated with an increase in PRA. The present studies offered an opportunity not only to characterize the lead-induced hypertension in terms of the RAS but also to determine whether a lower long-term dose (100 ppm) and earlier time of onset of exposure might yield results in rats more like those reported for human beings.

Methods

Fifteen 7-day timed pregnant rats (Charles River Breeding Laboratories, Inc., Portage, Mich.) were obtained, housed individually, and placed on Teklad rat/mouse feed (4% fat content; Teklad Test Diets, Madison, Wisc.). Of the 15, five animals were placed on sodium acetate–containing drinking water prepared in deionized demineralized water, five on 100 ppm Pb (as acetate), and five on 500 ppm Pb (as acetate); all solutions contained acetate equimolar to the 500 ppm Pb solution. (The sodium drunk by the control animals (4 mM) increased total sodium intake by approximately 3%, an amount which we and others[23] have found to exert no effect on plasma renin.) After parturition all three groups of mothers were maintained on their respective drinking solutions throughout the period of nursing. All litters were weaned on the twenty-first day of age and separated by sex. Drinking water and diet were not changed but were continued throughout the remaining 6 months of the experiment. All data reported are for the offspring only.

At 1 month of age, all but 18 of the female offspring were sacrificed for hormone measurements to be reported elsewhere; the 18 females not sacrificed at 1 month were retained, their blood pressures being measured only at 4 and 5 months of age. All male offspring were included in the blood pressure study. There were 19 control male animals, 19 animals receiving 100 ppm, and 13 animals receiving 500 ppm. Blood pressure recordings were obtained approximately monthly after the animals had reached 2 months of age (approximately 200 gm weight). Indirect pressure readings by the tail-cuff method were obtained on each rat in the unanesthetized state, by using a Narco programmed electrosphygmomanometer (Model PE 300; Narco Bio-Systems, Inc., Houston, Texas). This instrument employs automatic constant inflation and deflation of a 3 cm width tail-cuff and a pneumatic pulse transducer recording on a Grass polygraph (Grass Instrument Co., Quincy, Mass.). The animals were

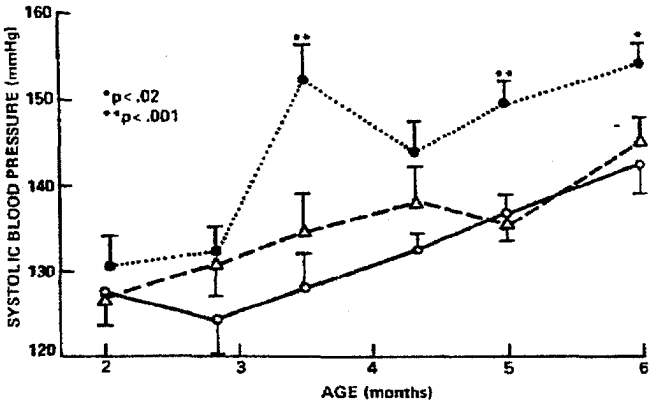

Fig. 1. Effects of Pb on systolic blood pressure in unanesthetized male rats. Statistical comparisons are between Pb-treated and control rats at each age. Δ, Control; •, 100 ppm; o, 500 ppm.

prewarmed for 10 to 15 min on a heating pad with a surface temperature of 40° C and were then transferred to a restrainer for blood pressure measurement. The base of the restrainer was heated to 42° C and the top was covered with a heating pad (surface temperature 42° C). The sensitivity of any given reading was 4 mm Hg. and in most cases, five consecutive recordings (approximately 30 sec apart) were performed "blind" and were averaged. Each week when blood pressure was not being measured, the animals were conditioned to the procedure by placing them in the restrainer for several minutes. Body weights were recorded at the time of pressure measurements or conditioning. At 6 months of age, each animal had its blood pressure measured by tail-cuff method while under light ether anesthesia; approximately 1 week later, the animals were sacrificed, most by decapitation. The rats had been conditioned on 3 separate days in advance by placing their necks in the guillotine. All decapitations were performed between 7:30 and 10 A.M. to avoid the afternoon rise in PRA seen normally in rats. Trunk blood was collected for 10 to 15 seconds into prechilled tubes containing 7.6 gm/dl ammonium EDTA as anticoagulant (approximately 10 μl/ml of blood); immediately after collection, a 1 ml aliquot was transferred to a tube containing the inhibitors required for AII analysis (50 μl of a solution of 7.6 gm/dl EDTA, 0.5% O-phenanthroline, and 0.2% neomycin sulfate), and a 100 μl aliquot of blood was placed into an equal volume of 5% Triton X-100 (Rohm & Haas Co., Philadelphia, Pa.) for blood lead determination. A microsample for hematocrit was then taken, and both the remaining blood and the sample for AII were centrifuged at 4° C, after which the plasma was separated and frozen. Both kidneys, a lung, the liver, and the adrenals were rapidly removed and either frozen or stored in formalin.

Decapitation was used for most of these animals in order to evaluate the RAS in a basal state, i.e., in the absence of the renin-releasing stimuli of anesthesia and surgery. However, some of the animals were subjected, instead, to pentobarbital anesthesia, laparotomy, and aortic puncture. This was done in order to permit (1) evaluation of the effect of lead on PRA during stimulated renin release and (2) evaluation of the relationship between PRA and AII over a wide range of concentrations of these hormones.

Analytical methods and statistics. Methods for measurement of PRA, PRS (angiotensinogen), PRI, plasma AII, renal renin concentration, plasma sodium and potassium concentrations, and plasma creatinine have all been described previously.[12, 21, 22] Pulmonary converting-enzyme activity was assayed as the rate of generation by lung homogenate of hippuric acid from hippuryl-L-histidyl-L-leucine.[24] The only modification from the cited procedure was that Tris HCl buffer (100 mM, pH 7.4) was used instead of 500 mM potassium phosphate (pH 8.3); this was done because of the concern that the concentrated phosphate buffer might remove lead from converting enzyme during the procedure. Plasma zinc was measured by standard atomic absorption (after protein precipitation with an equal volume of 20% trichloroacetic acid) and blood [Pb] by graphite furnace atomic absorp-

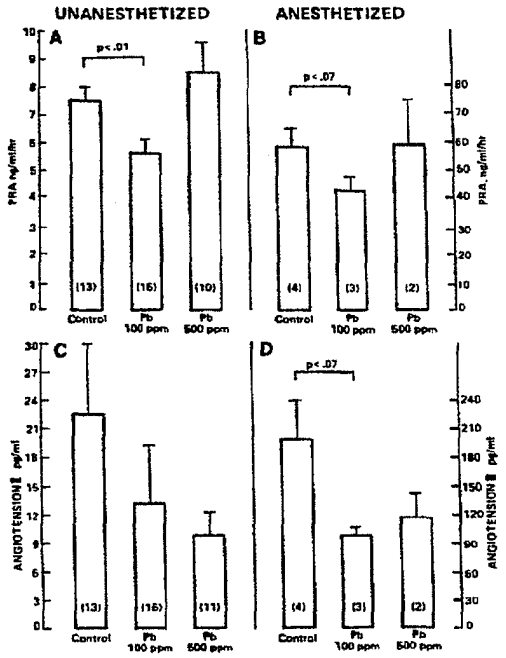

Fig. 2. Effects of lead on PRA and plasma AII concentrations in 6-month-old rats. The "anesthetized" values were for blood obtained by aortic puncture after laparotomy under pentobarbital anesthesia. Note the differences in magnitude of the left and right scales.

tion (Model 375: CRA90; Varian Associates, Inc., Palo Alto, Calif.) using methods of addition. Kidney [Pb] was measured in nitric acid–hydrogen peroxide digests by using standard atomic absorption.

All grouped data are presented as mean ± 1 S.E. Student's t test was used for computing the significance of the differences between Pb-exposed animals and controls.

Results

At 3½ months of age, the rats drinking 100 ppm Pb first manifested a statistically significant increase (relative to control rats at the same time) in blood pressure (152 ± 3.7 mm Hg vs. 135 ± 5.6) (Fig. 1). A difference persisted for the rest of the experiment and was also significant at 5 and 6 months. In contrast, the animals drinking 500 ppm Pb tended to have lower blood pressures than did controls throughout the experiment, but at no time was the difference statistically significant.

At 6 months of age, blood pressures were obtained by tail-cuff while the animals were under light ether anesthesia. The pressures in all three groups tended to be approximately 10 mm Hg lower than those obtained during the unanesthetized state (control, 135 ± 2.6 mm Hg; 100 ppm, 146 ± 3.4; 500 ppm, 133 ± 2.8), so that essentially the same significant difference of approximately 10 mm Hg between the control and 100 ppm groups persisted.

In contrast to the male animals, there were no significant differences in blood pressure between the female control and 100 ppm animals at 4 months (control, 129 ± 2.7 mm Hg; 100 ppm, 137 ± 4.3) and 5 months of age (130 ± 4.8 vs. 125 ± 4.3).

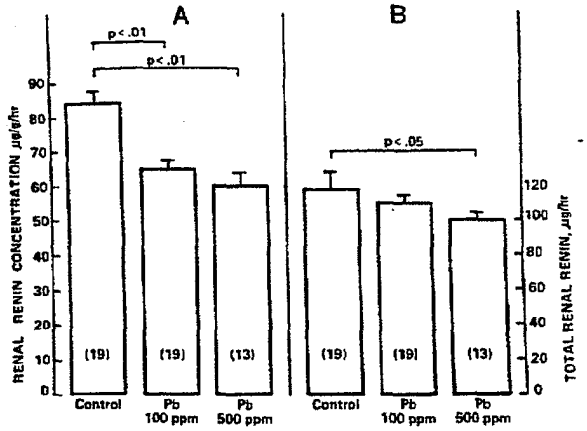

Fig. 3. Effects of Pb on renal renin content in 6-month-old rats. Values are expressed in (*A*) as renin concentration per gram wet weight and in (*B*) as the total mass of renin in the kidney (renal renin concentration × total kidney weight).

Fig. 2 summarizes the PRA and AII data for the 6-month-old animals. For both the unanesthetized and anesthetized animals, despite an approximately 10-fold difference in values between these two groups, the PRA patterns were similar in that PRA tended to be lower in the 100 ppm group but not in the 500 ppm group. This difference was significant for the unanesthetized animals but not for the anesthetized, which is not surprising given the very small sample size in the latter. AII (Fig. 2, *C* and *D*) tended to be lower in both Pb-treated groups, but the differences were not significant due to large variances. Pb exposure produced a dose-dependent decrease in the AII/PRA ratio for the unanesthetized animals: control, 2.6 ± 0.25; 100 ppm, 2.1 ± 0.40; 500 ppm, 1.1 ± 0.15. The difference between the control and 500 ppm groups was significant ($p < 0.01$). The same trend was apparent for the anesthetized groups (control, 3.4 ± 0.61; 100 ppm, 2.3 ± 0.21; 500 ppm, 2.0 ± 0.17), but the small numbers precluded the finding of statistical significance.

Fig. 3 summarizes renal renin concentrations and total renin contents in the three adult groups. Renin concentration decreased in the Pb-treated animals in a dose-dependent manner. Total renin content showed the same pattern but the differences were less striking.

PRS concentrations were not different among the three groups of adult animals: control, 1167 ± 51.2 ng/ml AI; 100 ppm, 1160 ± 72.8; 500 ppm, 1196 ± 45.4. Neither were the increments in AI generation produced by the in vitro addition of a small standard amount of hog renin (10^{-3} U/ml of plasma) (Calbiochem-Behring Corp., San Diego, Calif.): control, 81.1 ± 2.8 ng/ml AI per hour; 100 ppm, 82.2 ± 3.5; 500 ppm, 81.1 ± 2.8. The lack of difference in this measurement documents that observed differences in PRA represent differences in plasma renin concentration rather than altered activity of the renin molecule. There was no difference in pulmonary converting-enzyme activity (expressed as nanomoles of hippuric acid generated per minute per milligram of protein) among the three groups: control, 19.0 ± 2.05; 100 ppm, 20.5 ± 1.43; 500 ppm, 17.6 ± 1.09.

Table I summarizes the non-RAS data for the 6-month-old animals. The 500 ppm rats had a significantly lower body weight than the control group, but the 100 ppm rats actually

Table 1. Effects of Pb on variables other than the RAS in male rats sacrificed by decapitation at 6 months of age

	Control (n = 19)	*100 ppm Pb (n = 19)*	*500 ppm Pb (n = 13)*
Body weight (gm)	481 ± 9.3	513 ± 8.8†	440 ± 8.0†
Kidney weight (gm)	2.99 ± 0.076	3.33 ± 0.053†	3.43 ± 0.11†
$\frac{\text{Kidney wt}}{\text{Body weight}} \times 100$	0.62 ± 0.011	0.66 ± 0.016*	0.76 ± 0.018†
Adrenal weight (gm)	0.059 ± 0.0018	0.062 ± 0.0025	0.057 ± 0.005
$\frac{\text{Adrenal wt.}}{\text{Body weight}} \times 100$	0.011 ± 0.0008	0.012 ± 0.0008	0.013 ± 0.0012
$[\text{Creatinine}]_P$ (mg/dl)	0.56 ± 0.031	0.55 ± 0.036	0.47 ± 0.022*
$[Na]_P$ (mM)	143 ± 0.71	142 ± 1.0	139 ± 1.1†
$[K]_P$ (mM)	7.07 ± 0.17	7.12 ± 0.19	6.67 ± 0.18
$[Zn]_P$ (μg/dl)	101.4 ± 4.38	91.3 ± 2.26	90.1 ± 3.44
Hematocrit × 100	48.3 ± 0.40	47.1 ± 0.39*	46.2 ± 0.39†
$[Pb]_B$ (μg/dl)	2.2 ± 0.30	40.4 ± 1.44†	70.8 ± 1.80†
$[Pb]_K$ (μg/gm)	—	4.8 ± 0.45 (n = 5)	22.9 ± 1.6 (n = 8)
$[Pb]_L$ (μg/gm)	—	0.42 ± 0.06 (n = 5)	1.81 ± 0.15 (n = 5)

Subscripts P, B, K, and L refer to plasma, blood, kidney, and liver, respectively.
Because of the use of decapitation, the values for $[K]_P$ are artifactually elevated.
Note that $[Pb]_K$ and $[Pb]_L$ were measured in only a fraction of the animals from each Pb-exposed group.
p values vs. controls: *$p < 0.05$; †$p < 0.01$.

weighed significantly more. Kidney weights, both absolute and as percentages of body weight, were elevated in a dose-dependent manner. Adrenal weights were not different among the groups. Plasma sodium concentration was significantly reduced in the 500 ppm group, and there were no differences in potassium concentration. Plasma zinc concentrations tended to be lower in both Pb-treated groups, but in neither case was the difference significant. Hematocrit was reduced significantly by 1.2 and 2.1 percentage points in the 100 ppm and 500 ppm groups, respectively. Mean blood lead concentrations in the 100 ppm and 500 ppm groups were 40.4 and 70.8 μg/dl, respectively. Mean kidney lead concentrations in the two groups were 4.8 ± 0.45 and 22.9 ± 1.6 μg/gm, respectively. Mean liver lead concentrations were 0.42 ± 0.06 and 1.81 ± 0.15 μg/gm.

Examination of renal sections stained with hematoxylin and eosin revealed no abnormalities in the control or 100 ppm rats. The kidneys of rats treated with 500 ppm Pb showed varying degrees of hyperchromatic pleomorphic nuclei, with rare eosinophilic ~~catecholamines was investigated in these animals and has been reported in detail~~ inclusions.

Discussion

The most important finding of this study is that exposure of male rats to an appropriate dose of lead, beginning in utero, can produce a long-term significant elevation of blood pressure during adult life. This hypertension is not secondary to renal disease, as evidenced by the normal plasma creatinine and absence of renal histological changes in these animals and by other reports in the literature documenting the failure of lead to produce renal damage in experimental animals at a Pb dose of 100 ppm.[16, 25] The slight increase in renal weight produced by lead has been reported previously for rats exposed throughout their lifetime, beginning in utero, to doses of lead as low as 0.5 ppm.[26]

The failure of a higher dose of Pb, 500 ppm, to produce hypertension confirms our

hypothesis that, with increasing dose, additional effects of lead are brought into play which oppose the development of hypertension. The hypertension-producing 100 ppm dose used in these experiments is still extremely large compared to human exposures, but because of species differences in the metabolism of lead, this dose produces, in rats, blood lead concentrations (40 μg/dl) well within the range for urban human populations and equal to the values which the Occupational Safety and Health Administration has established, in its most recent standard, as the maximal concentration for protection of workers against health effects of lead. Indeed, were a similar biphasic dose response applicable to people, it would explain the failure to observe hypertension in heavily-exposed workers whose blood lead concentrations far exceed 40 μg/dl. Clearly, it will be essential to study the relationship between lead and hypertension in experimental animals at even lower doses and under a variety of conditions. Perry et al.[13] have already documented that, using rigorously controlled environmental conditions, as little as 1 ppm Pb in the drinking water can produce hypertension of the same magnitude reported here.

What clues does this study provide concerning the possible mechanism of lead-induced hypertension? At sacrifice, the hypertensive animals manifested a low-renin pattern (similar to that seen in approximately 30% of people with essential hypertension). This indicates that renin is not responsible for maintenance of the hypertension. A low-renin hypertension suggests the possibility that volume expansion might be an etiologic factor; consistent with this is the fact that the 100 ppm rats weighed more and had slightly lower hematocrits, but such findings are, of course, extremely indirect indications of body sodium and very likely represent processes having nothing to do with sodium balance (the hematocrit decrease, for example, is much more likely to represent an effect of lead on heme synthesis). Plasma sodium and potassium concentrations, also indirect indicators of electrolyte balance, were normal. Obviously, investigation of the volume-expansion hypothesis will require direct measurements of fluid compartments and exchangeable sodium. A second potential hypertensive mechanism—increased vascular responsiveness to catecholamines—was investigated in these animals and has been reported in detail elsewhere.[21] In brief, tail arteries obtained at sacrifice from the 100 ppm rats manifested, relative to controls, an increased maximal contractile force in response to alpha-adrenergic agonists.

The second aim of these experiments was to extend our information concerning the effects of lead on the RAS. Unlike our previous finding of an elevated basal PRA in rats treated for a long time with 500 ppm lead beginning later in life,[22] basal PRA was normal in the present rats exposed to 500 ppm Pb; moreover, the 100 ppm rats manifested a significant decrease in basal PRA, similar to that reported for Pb-exposed people.[18, 19] Renal renin was also measured in the experiments because, in chronic studies, this variable generally correlates with renin release. Again, in contrast to the finding (increased renal renin) for animals whose 500 ppm Pb exposure was begun later in life,[22] the present animals manifested a dose-dependent decrease in renal renin. This suggests that exposure to Pb during some critical, very early period of life produces an inhibitory effect on renin synthesis quite different from the effect seen when exposure is begun later in life. One factor present in the 100 ppm rats that would tend to reduce renin secretion is the hypertension itself, but this cannot account for the decreased renal renin of the 500 ppm rats, since the latter were normotensive; it is likely therefore that lead exerts at least one other direct or indirect inhibitory effect on renin synthesis and release. This is consistent with several reports of suppressed renin secretion in Pb-exposed humans.[18, 19]

The fact that PRA was normal in the 500 ppm rats despite decreased renal renin

strongly suggests that factors other than renin synthesis and release play a role in the Pb-induced changes in PRA at this dose. We have previously shown[12] that short-term exposure to Pb raises PRA mainly by inhibiting the hepatic clearance of renin; a similar phenomenon might be occurring in the present rats exposed for a long time to 500 ppm; that is, Pb-induced changes in renin secretion and renin clearance might balance each other, resulting in an unchanged PRA in these animals. It is clear that an understanding of the various changes in PRA produced by long-term exposure to lead must await direct measurements of the secretion and metabolic clearance rates of renin.

We have previously shown[12] that the short-term administration of large doses of lead greatly decreases the plasma AII/PRA ratio, suggesting either inhibition of converting enzyme or activation of angiotensinases. The present data strongly suggest that long-term exposure produces the same effect in a dose-dependent manner. This adds further support to the view that the renin-angiotensin system is not important in maintaining the hypertension seen in the 100 ppm rats and that a marked reduction in AII might actually constitute an antihypertensive effect of high doses of lead.

The constancy of pulmonary converting enzyme suggests that the decreased AII/PRA ratio reflects altered angiotensinases rather than inhibition of conversion of AI to AII. However, it is possible that the in vitro assay for pulmonary converting enzyme is not a valid indication of in vivo activity of this enzyme in Pb-exposed animals, since the conditions of the assay might possibly remove lead bound to the enzyme (we used Tris rather than a phosphate buffer to try to minimize this potential problem); therefore these data do not conclusively rule out changes in converting enzyme as the cause of the reduced AII/PRA ratio. Whatever the mechanism, the reduced AII would constitute yet another influence (in this case, stimulatory) on renin secretion, since AII exerts a strong negative feedback inhibition of renin release.

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