REVIEW OF LEAD-RENIN-ANGIOTENSIN RELATIONSHIPS

Michael Tuck, M.D.

Human Studies

Most studies of lead intoxication in man have shown reduced plasma renin activity (PRA) in response to various stimuli such as sodium restriction (Sandstead, 1970)[1], furosemide (Gonzolez, 1979)[2] and infusion of beta adrenergic agonist (Bertel, 1978).[3] In the study by Sandstead et al., PRA did not increase to the normal range in 8 of 9 men lead-intoxicated by ingestion of illicitly distilled whiskey after both acute stimulation with furosemide and chronic stimulation with low sodium diet. Mild hypertension was present in one man, thus there was no link in this study between PRA levels and hypertension in lead intoxication. Gonzalez et al examined 33 patients with a history of "moonshine ingestion" divided into 3 groups (group I lead-intoxicated with hyperkalemia; group II lead-intoxicated without hyperkalemia; group III not lead-intoxicated). There was a marked blunting of PRA basal and post-furosemide in group I but not group II that had a comparable level of lead toxicity. Hypertension was found in 6/9 in group I and 6/16 in group II and none in group III. This would suggest that hypertension in lead toxicity occurs independently of the level of PRA. The blunted aldosterone response in group I may explain the hyperkalemia, but this group was also older and had significant renal impairment secondary to presumed lead nephropathy. As these subjects were older, the authors suggested that duration of lead toxicity may be important in the effect on PRA. The report by Bertel et al. of a patient with lead toxicity, hypertension and low PRA examines beta-adrenergic control finding a high plasma norepinephrine and blunted cardiovascular and PRA responses to infusion of the B-agonist, isoprenaline. Their conclusions, quoted on page 11 of the EPA Addendum are highly speculative[4]. There is insufficient evidence that lead enhances norepinephrine relase thereby causing alpha-mediated vasoconstriction based on this one study (page 11, para 1, line 7). Likewise, the statement that it interferes with beta receptor-adenylate cyclase activity and blunts vasodilatory reponses is pure speculation (page 11, para 1, line 9). The most recent report by Campbell of workers exposed to lead with a wide range of blood lead

levels (0.4 - 3 u mole/l) showed a positive correlation of lead levels to PRA levels.[5] The group had a higher mean PRA (8.3 ± 5ng/ml/h) but no normal range was given. All subjects were normotensive but it was postulated that these changes "may be a precedent to development of hypertension" (page 11, para 1, line 14). This is entirely speculative without the appropriate longitudinal study. One can conclude from these studies that in man there is an association between lead intoxication and elevation of blood pressure and a similar link between lead intoxication and changes in PRA with the majority of studies showing reduced PRA. There is no direct evidence that PRA is etiologically linked to lead-toxicity associated changes in blood pressure. In some of the human studies, no control values for PRA were reported; therefore definitions of renin status were arbitrary and might be misleading in light of the wide range of PRA under normal physiologic conditions.

Acute in vitro lead exposure

There is an undeniably acute effect of lead in animals to increase PRA levels probably secondary to decreased tubular reabsorption of sodium with enhanced excretion and subsequent volume depletion being the stimulus for PRA release (Mouw, 1978)[6]. However, this same investigative group (Goldman, 1981)[7] showed that the increase in PRA following lead administration was due to a reduced total hepatic removal of PRA with renin secretion being increased in only 3/9 dogs. Based on these 2 rather straight forward acute effects of lead on PRA levels, the Addendum makes several debatable and unwarranted conclusions (page 12, para 2, line 11-20). The definition of angiotension II (A II) being proportionally lower than PRA and suggesting impaired conversion of A I to A II is not warranted. There is no evidence that angiotensin-converting enzyme (ACE) is rate limiting or that lead impairs ACE activity. The conclusion (lines 17-20) on "elevated PRA with simultaneous impaired ACE activity in lead exposure contributing to hypertension" is not based on results from the acute lead administration studies and makes no sense physiologically. If anything, inhibition of ACE should lower blood pressure.

Chronic lead exposure

The addendum is correct in stating (page 13, para 1) that studies on lead toxicity in chronic experiments in animals is conflicting and inconsistent regarding changes in the renin-angiotensin system and blood

pressure. Hypertension was most commonly observed when relatively low doses of lead were given over a long period of time. If anything these studies would appear to show an inverse relationship between blood pressure and PRA. Victery et al (1982a)[8] reported the effect of 100 and 500 ppm lead in drinking water of rats showing that lower but not high doses of lead increased blood pressure in male but not female rats. The lower dose of lead decreased PRA and A II but increased blood pressure. This would suggest that nonrenin mechanisms increase blood pressure in lead toxicity produced by low dose lead in drinking water of rats. In the Addendum draft, it is postulated (page 13, para 3) that the animals had low renin hypertension and volume expansion could be a factor as suggested by slight increments in weight and decrements in hematocrit. No direct measurements of volume were made and, if anything, through its effect on decreasing renal sodium reabsorption, lead should decrease body volume. At very small doses of level 2 or 25 ppm lead did not increase blood pressure but the 25 ppm dose decreased PRA. The authors of the Addendum thus conclude from these studies that these experiments are similar to toxicity in humans where there is decreased conversion of A I to A II (page 14, para 3, line 4-9) and again postulate some defect in conversion of A I to A II, a conclusion that has no experimental basis. In fact, in the sudy of Victery (1982b)[9] there was no effect of these low doses of lead on blood pressure. The conclusion from the studies of chronic lead ingestion in animals is that it has a variable effect on PRA levels but that there does not appear to be any consistent relationship in the directional changes in PRA and in blood pressure.

The variable effect of lead on renal renin release is further supported by examination of in vitro renin release from kidney slices. Keiser et al (1983a)[10] found reduced renin release at low doses and increased release at higher doses of lead. The Addendum draft suggests lead could act in the intracellular mechanisms for Ca^{++}-mediated renin release (page 15, para 3, line 10) but no data are provided to prove this. In one other study of kidney slices lead enhanced renin secretion (Meredith, 1985)[11] and calcium channel blockers attenuated this response. The conclusion that lead affects Ca^{++}-mediated renin release is only conjectured with no proof from the above study. If lead does promote Ca efflux and increased renin secretion then if the same is occurring in

vascular cells this would tend to reduce vascular reactivity and blood pressure.

Vascular reactivity and lead

Most studies of vascular reactivity show enhanced responsiveness to alpha adrenergic agents in isolated arteries from lead-exposed animals. Thus, lead exposure does appear to enhance vascular reactivity in animals; however, no studies of vascular reactivity in lead-exposed man have been done. As hypertension and structural changes in the vascular bed also enhance vascular reactivity to alpha-adrenergic agonists it becomes difficult to separate this effect from a direct action of lead. In general, autonomic blockade could reduce vascular reactivity. Iannaccone (1981)[12] showed enhanced vascular reactivity in lead exposed rats to both norepinephrine and angiotensin II. This suggests that lead-induced vascular reactivity increments are not related to specific effects on agonist-related regulation of receptor activity. It does not mean, however, as included in the Addendum (page 16, para 4, line 7), a decrease in conversion of A I to A II or any other effect on ACE activity. Based mainly on the requirements for calcium in the medium for in vitro contractability and exaggeration of agonist-enhanced vascular responses in arteries from lead toxic animals, it seems possible that lead inhibits calcium extrusion or alters cellular calcium binding. However, the Addendum report makes it appear as if there was a well-documented effect whereby lead increased vascular reactivity to norepinephrine and angiotensin II through changes in calcium transport in vascular smooth muscle cells. This postulate remains to be proven. Thus, it is equally feasible that lead alters agonist-receptor interactions that can regulate vascular responses to the pressor hormones, norepinephrine and angiotensin II.

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