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COMMENTARY

THE ROLE OF STEROIDS IN HUMAN ESSENTIAL HYPERTENSION

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The adrenal cortex has long been suspected of playing a role in the pathogenesis of essential hypertension in some patients [1]. To date, hypertension has been associated with three types of adrenal disorders. Primary aldosteronism, first described by Conn [2], is produced by the excessive secretion of aldosterone, a mineralocorticoid, from the zona glomerulosa of the adrenal. The salient features of this disorder are hypertension accompanied by hypokalemia. Cushing's Syndrome is characterized by the excessive secretion of cortisol, a glucocorticoid, and sometimes mineralocorticoids such as deoxycorticosterone. The exact mechanism of the hypertension present in about 80–90% of patients with Cushing's Syndrome is unknown [3–5]. In 11β- and 17α-hydroxylase deficiency of the adrenal gland, there is an excessive secretion of ACTH-dependent mineralocorticoids [6]. However, these three disorders combined are involved in only a minority, probably no more than 0.5%, of cases of hypertension. In the much larger group of hypertensive patients remaining, a search for an adrenal etiology has produced unimpressive results so far.

The finding that primary aldosteronism is associated with a deficient plasma renin activity (PRA) response to various stimuli led to the postulate that 20% of patients with essential hypertension who have low PRA (low renin hypertension or LRH) had primary aldosteronism [7]. Most of the patients actually have normal or low aldosterone excretions and, therefore, do not have primary aldosteronism [8, 9]. The possibility that these patients secrete another mineralocorticoid which acts in much the same way as aldosterone does was postulated upon finding that these patients share several clinical features with primary aldosteronism. These were: low plasma renin activity that is unresponsive to sodium depletion [10]; low salivary sodium/potassium ratio [11]; normalization of blood pressure after the administration of aminogluethimide, an inhibitor of steroidogenesis [12, 13], or spironolactone, a mineralocorticoid antagonist [14]; increased blood volume [15]; increased total exchangeable sodium [12]; and increased extracellular fluid volume [16]. Unfortunately, when these variables were carefully re-studied, some of the earlier findings were not confirmed. These include the changes in total blood volume, plasma volume [17], extracellular fluid volume [17, 18], and total exchangeable sodium [19]. The response to spironolactone, a mineralocorticoid antagonist, which early studies showed to be greater in patients with LRH than in those with normal renin hypertension [14] has more recently been shown not to be significantly different in these two groups [20].

Aldosterone secretion can be normal, high or low in patients with LRH. By definition a high aldosterone secretion rate indicates the presence of primary aldosteronism. Since the administration of small doses of exogenous deoxycorticosterone acetate (DOCA) to normal subjects is associated with low PRA and aldosterone concentrations [21], by analogy the group in which the presence of an unknown steroid with mineralocorticoid activity is most likely to be found is the one with low PRA and low aldosterone secretion rates. This combination is present in 8% of patients with essential hypertension [22]. However, these findings can also be produced by any cause of essential hypertension which is volume dependent, such as in the type of hypertension associated with a solitary kidney [23].

Aldosterone and other mineralocorticoids act through a receptor in the kidney tubule to induce sodium retention. These receptors show very high affinity for aldosterone, while having a lower affinity for the other mineralocorticoids, which is proportional to their potency. Occupancy by the steroid of the mineralocorticoid receptor is a function of the concentration of the free steroid outside the cell and its affinity for the receptor. Using this principle, Baxter *et al.* [24] designed a radioreceptor assay using adrenalectomized rat kidney slices which are incubated with tritiated aldosterone in the presence of plasma from normal and hypertensive individuals. Patients with primary aldosteronism, having greater plasma concentrations of aldosterone, displaced the tritiated aldosterone from the cytosol receptor to a greater extent than normal individuals. If plasma from patients with LRH contained elevated concentration of unknown steroid, one would expect greater displacement of tritiated aldosterone from the receptor. However, the displacement ability of the plasma from patients with LRH was similar to that of normal individuals, suggesting that the plasma of these patients did not contain unknown mineralocorticoids acting through Type I mineralocorticoid receptors. If the incidence of the hypothetical patient with LRH

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plus increased secretion of unknown steroids is small, patients with excess unknown mineralocorticoids could have been missed because of the few individuals studied. Alternatively, the steroid produced in excess could be acting through a separate receptor system (i.e. Type III corticosteroid receptor [25]). This latter possibility is tenable in view of the finding that corticosterone binds to a receptor in the kidney which is different than the mineralocorticoid (Type I) and glucocorticoid (Type II) receptors. By autoradiography, these receptors have been localized in the distal tubule of the kidney and seem to undergo nuclear translocation. As these experiments were done in the presence of a great excess of cold aldosterone and dexamethasone, one is reassured that this is a receptor truly separate from that of aldosterone. Corticosterone could actually represent a suboptimal inducer and the unknown mineralocorticoid could be the optimal inducer of a "Type III" receptor. The tubular localization by autoradiography of corticosterone in the kidney is very similar to that of aldosterone and is in an area where sodium is reabsorbed [26, 27].

All the above arguments seem to deny a role for an unknown steroid with Type I mineralocorticoid properties in the pathogenesis of LRH, a view that is shared by many groups [19, 23] even though there are possible explanations which will be dealt with presently to circumvent the arguments.

To further explore the possibility that steroids could actually be etiologic in some cases of human essential hypertension, we will review the various types of steroids and mechanisms by which steroids can cause elevation of the blood pressure in experimental animals. There are at least four mechanisms by which steroids induce hypertension.

First, the mineralocorticoids act primarily in the kidney to promote sodium and fluid retention and potassium excretion. Guyton postulates that, along with this sodium and fluid retention that results in volume expansion and an increase in blood pressure, there is an increase in the "set point" of the renal function curve. Thus, a few days after the onset of mineralocorticoid infusion the blood pressure will rise to the new set point at which time sodium excretion will again match intake and pressure will remain stable, though at a higher level. In the steady state one would expect a normal sodium balance and an elevated extracellular fluid volume and exchangeable sodium [28]. The studies of Onoyama *et al.* [29] have shown that, in mineralocorticoid hypertension in the dog, it is the restoration of sodium stores rather than volume expansion that plays a role in the initiation of the hypertension. The effect on vascular smooth muscle of the interaction of sodium with electrolyte active steroids results in increased vascular resistance and, hence, elevated arterial blood pressure. The total exchangeable sodium was not measured in this study but the extracellular fluid volume was not different between the mineralocorticoid hypertensive and the control normotensive dogs. If this mechanism were responsible for LRH, it would explain the normal extracellular fluid volume but one would expect an increased exchangeable sodium.

Second, the effect of glucocorticoids on blood pressure varies depending on the species. The administration of glucocorticoids to the rat is associated with an elevation of the blood pressure which is independent of sodium intake [30, 31]. In the dog, pure glucocorticoids produce a decrease in blood pressure associated with marked natriuresis and a negative sodium balance [32]. The incidence of hypertension in patients chronically treated with exogenous glucocorticoids is low [33]. These types of steroids are very unlikely to play a role in natural human hypertension. However, a steroid with dual activity could be involved. Several of the patients with hypokalemic, hypoaldosteronemic, hyporeninemic, spironolactone-responsive hypertension also had low production rates of cortisol and ACTH, suggesting that a compound having both gluco and mineralocorticoid activity [34, 35] might be involved.

Third, hypertensinogenic steroids. This concept emanates from the studies of the Howard Florey Research Institute investigations of ACTH-induced hypertension in sheep. The parenteral administration of ACTH to sheep is associated with a rather rapid elevation of the blood pressure which becomes significant within 24 hr and continues to increase throughout the first 5 days of the administration of ACTH [36]. The administration of a steroid mixture of aldosterone, cortisol, corticosterone, deoxycorticosterone and 11-deoxycortisol, designed to reproduce the plasma concentrations attained after the administration of ACTH, was associated with electrolytic changes similar to those produced when ACTH is administered, but it produced only minimal elevation of the blood pressure [37]. These studies suggested that an additional adrenal secretory product was required to elevate the blood pressure. Two steroids, 17α-20α-dihydroxy-4-pregnen-3-one and 17α-hydroxyprogesterone, were isolated from ACTH-stimulated adrenal venous effluent; their co-administration with the steroid mixture elevated the blood pressure with the same temporal pattern as that when ACTH is administered [38]. The doses chosen were said to be similar to the secretory rates of these steroids but the data have never been published. The mechanism of action of these two steroids is yet unknown. They hardly interact with Type I and II corticoid receptors in the sheep kidney *in vitro* and in view of their plasma concentration would not be expected to occupy either receptor *in vivo*. A study of synthetic steroids that can reproduce the temporal pattern of ACTH-hypertension was undertaken, and it was found that 9α-fluorocortisol administration produced hypertension very similar in temporal and electrolytic pattern to that after ACTH administration [39]. Administration of dexamethasone and aldosterone at a dose designed to reproduce the gluco- and mineralocorticoid activity of 9α-fluorocortisol was ineffective in producing hypertension [39, 40]. The administration of 17α-20α-dihydroxy-4-pregnen-3-one with a steroid mixture, and 9α-fluorocortisol by itself, can reproduce the temporal pattern of the hypertension induced by ACTH and they have been classified as "hypertensinogenic steroids". The mechanisms by which they work are yet unknown but retain the potential to explain low renin essential hypertension. In the dog, ACTH does not induce hypertension by

itself; however, when administered along with an infusion of angiotensin II, it produces an increment in blood pressure greater than in controls. The administration of cortisol or aldosterone under similar conditions does not increase the blood pressure, further suggesting that an additional factor from the adrenal is required for this pressor effect of ACTH [41] in dogs.

Fourth, mineralocorticoid amplificators. This concept was initially proposed by Melby and Dale [42] to explain the possible role of 16α-18-dihydroxydeoxycorticosterone in patients with LRH. This steroid was initially reported to be inactive by itself in an adrenalectomized-rat bioassay, but it could potentiate the action of sub-threshold doses of aldosterone [42]. Unfortunately, these findings could not be reproduced in another laboratory [43]. Another steroid, 4,5α-dihydrocortisol, was found in increased quantities in a young patient with low renin hypertension [44] and was reported to be a weak mineralocorticoid [45] and to potentiate the action of aldosterone [46]. Unfortunately, the excretion of 4,5α-dihydrocortisol in this patient returned to control levels spontaneously without affecting the course of the hypertension [6], and when it was administered to rats in combination with deoxycorticosterone it did not potentiate the effects of the latter steroid on the blood pressure [47]. These studies suggest that 4,5α-dihydrocortisol is an unlikely candidate as a factor in the etiology of LRH. Two steroids, 19-hydroxyandrostenedione [48] and 19-nor-androstenedione [49], were found to potentiate the effects of sub-threshold doses of aldosterone. When administered to rats, these steroids can induce hypertension with features similar to those of mineralocorticoid hypertension [50], even though in the bioassay they do not have inherent mineralocorticoid activity [48, 49]. It is unclear whether 19-hydroxy- and 19-nor-androstenedione are acting as potentiating steroids. An alternative explanation is that these steroids could act by a mechanism similar to that of testosterone-induced hypertension where there is inhibition of the 11β-hydroxylase enzyme in the adrenal resulting in increased plasma concentrations of deoxycorticosterone [51]. The latter explanation would seem, at this point, more likely. The exact significance of steroids that potentiate the effects of normal circulating levels of mineralocorticoids is unknown. These findings could be artifacts due to the intraperitoneal route of administration of the steroid. The sensitivity of the bioassay is decreased when aldosterone is given intraperitoneally instead of subcutaneously [52], probably due to partial inactivation when it is absorbed and carried directly by the portal circulation to the liver. Perhaps the coadministration of a large dose of other steroids that are degraded by the same hepatic enzymes could allow a greater proportion of aldosterone to survive this first passage. The only steroid reported to potentiate the effect of aldosterone, which also has been found to be elevated in LRH, is 19-hydroxyandrostenedione. However, these increases were very small [53], making it very unlikely that any of the so-far-reported steroids are of any significance in LRH; nevertheless, this mechanism remains an important, if yet poorly supported, theoretical possibility.

In spite of all the negative features presented above, there remains support for the possibility that excess action of a mineralocorticoid(s) causes some cases of low renin hypertension. This increased mineralocorticoid activity could be caused by any of four possibilities. Support for the first of these, the presence of unknown mineralocorticoids, comes from three sets of reports. One of these in the *in vivo* human bioassays reported by Skrakal [54] who measured the "subtracted" electrical potential across the human rectum, e.g. the electrical potential across the rectal mucosa, a mineralo-glucocorticoid responsive epithelium, minus the electrical potential across the oral mucosa, a mineralo-glucocorticoid unresponsive tissue, was measured in normal individuals, in patients with primary and secondary aldosteronism, and in patients with essential hypertension. He found that the "subtracted" electrical potential across the rectal mucosa in patients with primary or secondary aldosteronism was clearly elevated in comparison to those of normal controls. Four of eighty-one patients with hypertension (4.9%) had a difference in electrical potential that was above the 95% confidence limit of the normal individuals. Two of these patients (2.5%) had the same level as patients with primary aldosteronism and one of these (1.2%) was hypokalemic, had low plasma aldosterone concentrations, and responded well to spironolactone. This type of measurement is probably the only direct way of classifying patients. If the series reported truly represents an unselected hypertensive population as claimed, it suggests that the incidence of patients with essential hypertension involving an unknown mineralocorticoid is very small.

The second set of evidence supporting an excess of an as yet undetermined mineralocorticoid is comprised of multiple case reports of juvenile and adult patients who presented with hypertension, hypokalemia, low renin and low aldosterone hypertension and responded well to spironolactone [6, 55, 56] or to ACTH suppression [57, 58]. By inference, as these patients responded to maneuvers designed to lower mineralocorticoid levels yet had no measured mineralocorticoid excess, an unidentified steroid was invoked.

The last set of evidence for an as yet undiscovered mineralocorticoid agent comes from two different case reports of glucocorticoid-remediable hyperaldosteronism. In the first patient studied by New and Levine [59], the hyperaldosteronism was readily corrected by low doses of dexamethasone, which also corrected the hypertension. The administration of 1 mg of aldosterone while the patient was suppressed with dexamethasone did not increase the blood pressure; however, administration of ACTH under similar circumstances was associated with a prompt increase in blood pressure. Other known mineralocorticoids were tried and were also ineffective, leaving the suggestion that ACTH was stimulating a factor, other than those mineralocorticoids tried, which was responsible for the blood pressure elevation.

The second case was reported by Lan *et al.* [60] who used the radioreceptor assay previously discussed in combination with the measurement of known mineralocorticoids to study a case of

glucocorticoid-remediable aldosterism. It was found that there was a large portion of the total radioreceptor assayable activity that could not be explained by the simultaneously measured aldosterone, cortisol and deoxycorticosterone. These two clinical cases also suggest that the presence of normal concentrations of aldosterone does not rule out the simultaneous existence of an unknown mineralocorticoid.

The second possibility for the excess involvement of mineralocorticoid action in some forms of hypertension has been conceived of as a hypersensitivity to mineralocorticoids by Lan *et al.* [60]. These authors have reported that the mineralocorticoid radioreceptor assay of the plasma of the patients reported by New *et al.* [55] and Winter and McKenzie [56] showed a decreased total radioreceptor activity of their plasma which could be explained by the simultaneously measured mineralocorticoids. These patients responded well to spironolactone and the suggestion was made that there was a hypersensitivity to the action of normal or even low concentrations of mineralocorticoids. It is also possible that a situation exists similar to the one reported by Zava *et al.* [61] who showed that a human breast cancer cell line, MCF-7, which does not require estrogen for growth can be inhibited with antiestrogens. Perhaps sodium retention and hypertension in these individuals are stimulated by the mineralocorticoid receptor by itself in spite of the absence of the hormone, and thus the binding of the antimineralocorticoids to the receptor antagonizes this stimulation resulting in normalization of blood pressure. This possibility remains highly speculative.

The third possibility is that the "normal" concentrations of plasma aldosterone are actually "inappropriate" and play a role in the pathogenesis of the hypertension. This concept was initially suggested by Grim *et al.* [62]. Normal plasma aldosterone in patients with low renin hypertension is probably due to hypersensitivity to the actions of angiotensin II [63]. Support for the concept for the role of the "inappropriate" levels of aldosterone was nicely presented by Taylor *et al.* [13] who found that normalization of blood pressure after the administration of aminogluethimide to patients with LRH was associated with marked depression of the plasma aldosterone which initially had been normal. All other steroids measured were unchanged. In addition, in a large segment of patients with hypertension, aldosterone production is not suppressed by the administration of high salt loads [64, 65] which suggests that, in a society consuming a high salt diet, the aldosterone levels considered normal are actually inappropriately high and play a direct role in the pathogenesis of the hypertension.

The fourth possibility could be the role that 19-nor-deoxycorticosterone (19-nor-DOC) may play in LRH. 19-Nor-deoxycorticosterone is a powerful mineralocorticoid initially isolated in the urine of rats with regenerating adrenals [66] and shown to also be present in human urine [67]. Its excretion is responsive to ACTH administration and has been shown to be elevated in some patients with LRH [68]. This steroid is not produced in the adrenal but is a product of peripheral conversion of an adrenal precursor 19-oic-deoxycorticosterone (19-oic-DOC) [69]. The site of conversion is as yet unknown. The possibility that 19-nor-DOC plays a role in LRH is based, at this time, more on the lack of negative findings than on the strength of positive reports. The conversion of 19-oic-DOC to 19-nor-DOC may occur at the target organ and thus the amount of 19-nor-DOC that could interact with the receptor would be augmented by either an increase in the production of its precursor or in the conversion of the precursor in the target organ. If either were the case, the measurement of peripheral values might not reflect what is actually happening. If an increase in precursor occurs the measurement of 19-oic-DOC would reflect the action of 19-nor-DOC at the target organ best. The second case, increased conversion, would be more difficult to study but the response to spironolactone, a receptor antagonist, would support, but not prove, the idea. These ideas are highly speculative at this time.

The existence of unknown steroids with mineralocorticoid activity is the easiest to support at this stage, but in some patients with essential hypertension the presence of steroids that could be classified as "hypertensinogenic" remains an attractive possibility for further research. Excessive secretion of 17α-20α-dihydroxy-4-pregnen-3-one has never been studied in the human and remains an important factor that could explain the pathogenesis of hypertension in Cushing's Syndrome. The existence of "hypertensinogenic" steroids that can act by themselves independently of known gluco or mineralocorticoids is unknown. 9α-Fluorocortisol, which at low doses can induce hypertension acutely without electrolyte changes in sheep [39] could serve as a probe in the search for this type of steroid.

In conclusion, most evidence suggests that known and unknown steroids produced by the adrenal gland play a role in the pathogenesis of the hypertension in only a small percentage of cases. New ideas borrowed from experimental hypertension models present the opportunity to explore the possibility that steroids which can neither be classified as glucocorticoid nor mineralocorticoid are implicated in the pathogenesis of some cases with essential hypertension.

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