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STEROIDS AND HYPERTENSION

FRANCO MANTERO,[1]* DECIO ARMANINI,[2] MARCO BOSCARO,[2] GUIDO CARPENÈ,[2] FRANCESCO FALLO,[2] GIUSEPPE OPOCHER,[2] STEFANO ROCCO,[2] CARLA SCARONI[2] and NICOLETTA SONINO[2]

[1]Chair of Endocrinology, Institute of Clinica Medica I, University of Catania and
[2]Institute of Semeiotica Medica, University of Padua, via Ospedale 105, 35123 Padova, Italy

Summary—Primary aldosteronism is the principal disorder of zona glomerulosa and a number of subsets have been identified: unilateral adenoma; bilateral micro- or macro-nodular hyperplasia (idiopathic aldosteronism); primary hyperplasia and aldosterone-producing carcinoma either adrenal or ectopic. The diagnostic criteria for a correct differential diagnosis of these subsets are now quite reliable and our experience is presented in detail. Unfortunately the pathogenesis of most of these forms is still poorly recognized and requires further investigation. An extreme sensitivity to angiotensin II is present in patients with idiopathic aldosteronism, and a role for adrenal renin is now being advocated. A peculiar form of hyperaldosteronism is the glucocorticoid-remediable subtype. An unusual sensitivity of aldosterone to ACTH is present in this form. A qualitative biochemical abnormality in this disorder consists of marked over-production of products of the cortisol C18-oxidation pathway, 18-hydroxycortisol and 18-oxocortisol, which are more abundant than aldosterone and 18-hydroxycorticosterone. A family with three affected sibs has been studied by our group. In other clinical situations, classical zona fasciculata mineralocorticoids [deoxycorticosterone (DOC), corticosterone and their 18-hydroxy compounds] are secreted in excess. The hypertensive diseases of this zone are rare DOC-secreting tumors and two forms of congenital adrenal hyperplasia (CAH), the 11β-hydroxylase (11-OHDS) and the 17α-hydroxylase deficiency syndromes (17-OHDS), which are identified by the presence of hypokalemia and suppressed renin activity. DOC is the only mineralocorticoid hormone (MCH) oversecreted in the 11-OHDS, while all ACTH-dependent MCH are very high in the 17-OHDS. The molecular basis of gene abnormalities of this disorder are currently under investigation, and preliminary data obtained in some of our patients are presented. Finally a syndrome of apparent mineralocorticoid excess, which is not a primary disorder of the adrenal cortex, describes the association of an unexplained hypermineralocorticoid state with a decreased rate of peripheral 11β-hydroxy dehydrogenation of cortisol to cortisone. Studies on this syndrome have led to the hypothesis that peripheral cortisol inactivation is the normal mechanism permitting specific mineralocorticoid recognition. The syndrome exists in two forms both characterized by a decreased turnover of a normal level of plasma cortisol, but in the type I variant an elevated cortisol/cortisone metabolite ratio is found, whereas in the type II variant this ratio is normal. Three patients of the latter form have recently been described by us and are shortly illustrated. A possible role of this impaired metabolism of cortisol in the pathogenesis of other forms of hypertension such as liquorice and carbenoxolone-induced hypertension has recently been suggested.

INTRODUCTION

Mineralocorticoid hormones (MCH) are secreted by both the zona glomerulosa (ZG) and the zona fasciculata (ZF) of the adrenal cortex: the ZG produces aldosterone (Aldo) and 18-hydroxy corticosterone (18OHB) under the major control of angiotensin II, the ZF produces mainly deoxycorticosterone (DOC), 18 hydroxy-deoxycorticosterone (18OH-DOC) and corticosterone (B) under ACTH regulation. In the presence of excess substrate, 18OHB can also be secreted by the ZF. The mechanism by which MCH raise blood pressure is multifactorial, and is, at least initially, sodium and volume dependent [1]. After an initial increase of plasma volume and exchangeable Na^+ due to a positive sodium balance, the "escape phenomenon" occurs, due to the intervention of natriuretic factors, including atrial natriuretic peptide, but hypertension and potassium loss persist [2].

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*To whom correspondence should be addressed at: c/o Institute of Semeiotic Medica.

The cardiac output tends to return to normal, whereas peripheral resistance increases. Additional mechanisms of the aldosterone-hypertensive properties include a direct effect on vascular membrane permeability to sodium and on the central nervous system [3].

Cortisol (F), the classic glucocorticoid (GC) steroid produced by the ZF, may also have MC activity when secreted in excess or when present at high concentrations at the tissue level [4]. It is also likely that F may induce hypertension through specific GC mechanisms, as will be discussed later.

Hypertension due to MC excess may be caused by elevated Aldo and DOC or B levels, or by a combination of both. Steroid excess may arise from neoplastic adrenocortical tissue (or ovarian tissue), from inborn errors of steroid biosynthesis or metabolism or due to iatrogenic causes, such as the use of 9α-fluorinated steroids and the ingestion of liquorice products.

The characteristic features of MC hypertension are elevated blood pressure, hypokalemia and suppression of the renin–angiotensin system (RAS). The incidence of MC hypertension is difficult to assess but it is probably near to 1% of all hypertensive patients [5]. Most patients have primary aldosteronism, which is by far, the most commonly encountered form of MC excess.

PRIMARY ALDOSTERONISM

Primary aldosteronism is the principal disorder of the ZG, and a number of subsets have been identified: unilateral adenoma (including the recently described renin-responsive adenoma), bilateral micro- or macro-nodular hyperplasia, (idiopathic aldosteronism), glucocorticoid-remediable hyperaldosteronism, primary hyperplasia and aldosterone-producing carcinoma, either adrenal or ectopic (e.g. ovarian) [6].

The diagnostic criteria for a correct differential diagnosis of these subgroups have continuously improved during the last few years and today the distinction between surgically-remediable subtypes can be accurately made in most cases [7].

The subdivision of patients in our series of 113 cases with primary aldosteronism is presented in Table 1. Approximately 60% of the cases have a unilateral adenoma; the hypertension in most patients is either cured or improved. Most of the remaining have a bilateral hyperplasia; their hypertension is seldom cured by subtotal or total adrenalectomy. Unfortunately, the pathogenesis of this latter form is poorly understood and requires further investigation.

Table 1. Primary aldosteronism, $n = 113$

	n	%
Aldosterone producing adenoma (APA)	57	50.5
Idiopathic hyperaldosteronism (IHA)	50	44.2
Primary adrenal hyperplasia	1	0.8
Dexamethasone-suppressible hyperaldosteronism	3	2.65
Aldosterone producing carcinoma	2	1.66
adrenal	1	
ectopic	1	

An extreme sensitivity to angiotensin II is present in patients with idiopathic aldosteronism, and a role for adrenal renin is now being advocated. Unusual secretagogues for aldosterone such as POMC-derivated peptides (especially from the 16K fragment), catecholamines and serotonin may also be involved.

Progress in the differential diagnosis between aldosterone producing adenoma (APA) and idiopathic hyperaldosteronism (IHA)

Baseline data from our patients show that there is no difference in the blood pressure levels of the 2 main types of primary aldosteronism, whereas hypokalemia is more severe in the APA group. Approximately 30% of patients with IHA had normal serum potassium, whereas only 5 patients with adenoma (about 10%) had normokalemia. This is probably due to a more severe degree of hyperaldosteronism in APA; however, in our patients even the level of upright plasma renin activity (PRA) and urinary aldosterone were not significantly different in the 2 groups. Only supine plasma Aldo levels were higher in APA than in IHA. A likely explanation of these findings is that the conventional PRA assay doesn't allow a distinction between low and very low levels of renin activity, and that differences between plasma and urinary Aldo may be due to the distinct circadian patterns of Aldo secretion, including the different response to upright posture in the 2 forms.

The classic manoeuvres which are employed in the differential diagnosis between APA and IHA are the postural test and the response of plasma Aldo to exogenous angiotensin II infusion. After the upright posture, in most of the patients with APA, plasma Aldo did not increase or even decrease, whereas it rose quite frequently in IHA patients. In our experience,

employing a 70% increase over the basal level as a discriminatory value, 70% of IHA showed a positive response to posture and only 25% of APA showed a similar response. This corresponds to a sensitivity of 75% and a specificity of 70% with an accuracy of 71%. The value is only slightly improved if F changes are also taken into account in order to minimize the effect of stressful events, by subtracting the % increase of F from the % increase of Aldo. In our series, only 1 case had a different Aldo response when data were elaborated in such a way.

The different sensitivity to angiotensin II of the 2 subsets is considered to be responsible for this pattern of Aldo response to the upright posture. In fact, when exogenous angiotensin II is infused, almost all patients with IHA but rarely those with APA show a clear-cut and dose-dependent Aldo increase [8].

By combining these two tests, however, a new small subset of so called aldosterone-producing renin-responsive adenoma (APRA) has been identified in patients with a clearly demonstrable unilateral tumour who were responsive to these manoeuvres [9, 10]. In our experience, restricted to a limited number of cases, only 2 out of 23 patients with APA showed both a significant increase of Aldo after a 1 h infusion of 2 ng/kg/min of angiotensin II and a significant response of Aldo to the upright posture.

Captopril test. This test was proposed by our group for recognizing primary aldosteronism, because of the small changes observed in plasma Aldo after acute Captopril administration as compared to other forms of hypertension [11].

Within these minor changes, we also observed that there was a greater tendency towards a decrease in the values of plasma Aldo in IHA patients than in those with APA. In the same patients, PRA levels were also slightly increased by Captopril. Furthermore, an acute hypotensive effect was seen with inhibition of angiotensin-converting enzyme (ACE) whereas this was not the case in the APA group. The relatively greater effect of Captopril on plasma Aldo in the IHA could suggest a role for angiotensin II (in spite of its low circulatory levels) in maintaining the Aldo hypersecretion in this subset of primary aldosteronism. A possible contribution of local adrenal renin to this effect has to be considered, since it has been shown that an *in vitro* ACE-inhibitor can reduce Aldo secretion in human adrenal slices when added directly to the perfusion medium [12].

The sensitivity of the Captopril test is inadequate for a differential diagnosis, but it may be useful when associated with the postural test, since, in our experience, only patients with IHA presented concomitantly with an increase of Aldo after posture and a decrease after Captopril [13].

Other steroids. Precursors in the Aldo biosynthetic pathway (DOC, 18OHB) and 19norDOC are often elevated in patients with APA [6–13]. In our experience, only the values of 18OHB were significantly higher in the adenoma group. Furthermore, the naturally occurring steroids, 18OH-cortisol (18OHF) and 18oxocortisol are often found increased in patients with autonomous lesions, as well as in patients with the glucocorticoid-remediable subtype [9–15].

It is interesting to note that in the new subset of APRA mentioned previously, the Aldo precursors show lower levels, comparable to those found in IHA [10].

Atrial natriuretic factor (ANF). ANF is characteristically increased in primary aldosteronism probably as a consequence of a volume expanded status [16]. In APA patients, we found values which were 2 or 3 times higher than in normal subjects. Values obtained in a subgroup of patients with IHA were somewhat in between, similar to those found in hypertensive patients. The data are quite consistent and could even be considered as an additional tool for the diagnostic distinction between the 2 forms, since the sensitivity of the test is comparable to that of the postural test. In both groups, volume manipulation, such as a postural change and acute saline infusion, was still able to induce the expected physiological changes. The higher levels generally found in APA patients are consistent with the presence of different haemodynamic patterns in the 2 forms, since the ECF volume and exchangeable sodium are increased only in the adenoma group [17].

Taken together, these findings (the response of Aldo to posture, angiotensin II and Captopril, the levels of MC and ANF) are in agreement with the idea that idiopathic aldosteronism is a clinical entity different from the classical Conn's syndrome and probably more related to essential hypertension.

Morphological studies. It is quite obvious that the functional tests so far discussed maintain a certain degree of imprecision and, even when they are in agreement with the presence of an adenoma, they do not tell where the tumour is located.

Adrenal computerized tomography (CT) has become the method of choice, since the new generation-high resolution CT can detect adenomas as small as 0.5 cm dia. In several series, including our own, the overall results obtained with CT scans of progressively increasing sensitivity attained a success rate for correct diagnosis of 85%.

Isotopic scanning techniques using iodo- or selenio-cholesterol tracers under dexamethasone suppression correctly identified the adenoma in 86% of the patients with a tumour demonstrated at surgery. We combined these 2 procedures to obtain a greater amount of information. However, the radiocholesterol scan is in general less routinely available and could be indicated only for those cases not clarified by the CT scan alone.

As an alternative, or even in addition to adrenal scintigraphy, when both tests have failed to give the final answer, bilateral adrenal vein catheterization should be performed. In our experience, the predictive value of this procedure in a group of 43 patients was 96% [13].

Primary adrenal hyperplasia (PAH)

This rare form of hyperaldosteronism has been described by Biglieri *et al.* [10] and is characterized by the same biochemical picture seen in adenoma patients (lack of response of Aldo to posture, angiotensin II, high levels of 18OHB, DOC and 18OHF). However, the pathology shows only unilateral or sometimes bilateral hyperplastic glands, but no adenoma. In our series of 113 patients, only 1 case of PAH has been clearly identified. In this case, adrenal scintiscan showed a complete lateralization of the uptake of labelled cholesterol and adrenal vein catheterization confirmed oversecretion of the Aldo from the right adrenal. The CT scan was negative and at surgery (right adrenalectomy) no adenoma was found, but blood pressure, serum potassium and Aldo secretion were normalized.

GLUCOCORTICOID REMEDIABLE HYPERALDOSTERONISM

Another unusual form of hyperaldosteronism with bilateral involvement is the so-called dexamethasone or glucocorticoid-remediable hyperaldosteronism.

This is an autosomal dominant disorder, which can be differentiated biochemically from IHA since, like APA, there is no response of Aldo to the upright position, to angiotensin II infusion and to Captopril [18].

However, the glands are bilaterally overactive and especially sensitive to both acute and prolonged ACTH stimulation. The degree of hyperaldosteronism is generally mild to moderate in this disorder and the possibility of other MC involved in the genesis of hypertension has been suggested both by the experiment of New *et al.* [19] who was unable to reproduce the hypertensive effect obtained with ACTH by infusing only Aldo, and by the data on plasma MCH receptor binding material of these patients, which resulted in higher levels than expected by the sum of measured levels of Aldo, DOC and F [20].

A qualitative biochemical abnormality in this disorder consists of the marked oversecretion in the products of the F C18 oxidation pathway, 18-OHF and 18-oxocortisol, which bind to the MCH receptor sites and are even more abundant than Aldo and 18OHB. These observations are consistent with a defect in the ZF, reflecting activation of the latent *P*450 corticosterone-methyl-oxidase, possibly involving 11β-hydroxylase [15].

The data obtained in a family with 3 affected siblings has been presented elsewhere [21]. The final diagnosis of dexamethasone-suppressible hyperaldosteronism rests upon the prompt reversal of the features of MC excess by glucocorticoid therapy. During treatment, the responsivity of plasma Aldo to angiotensin II tends to return. With prolonged treatment, the initial, beneficial response to blood pressure becomes less effective and hypertension recurs requiring additional antihypertensive drugs.

ZF HYPERTENSIVE DISORDERS

In other clinical situations, classical ZF mineralocorticoids (DOC, B and their 18-hydroxy compounds) are secreted in excess.

DOC-secreting tumours, either benign or malignant, are very rare; more often adrenal carcinoma may secrete a mixture of steroids including DOC [22]. In these patients DOC levels cannot be suppressed by dexamethasone.

According to Biglieri *et al.* [23], this model of tumoural hyperMC hypertension can also offer useful information on the existence of a control for the 17-deoxy pathway separate from the ACTH–F axis. In fact, studies performed after tumour removal showed a dissociation between the delayed recovery of DOC and the prompt

recovery of the F response to ACTH. Functional studies performed in patients with AIDS and chronic pituitary insufficiency also confirm this hypothesis [24, 25].

Secondary hyperDOCism can be identified in those forms of congenital adrenal hyperplasia (CAH) where hypertension is usually observed, such as 11β-hydroxylase (11-OHDS) and 17α-hydroxylase deficiency syndrome (17-OHDS) which are also characterized by the presence of hypokalemia and suppressed renin activity. They differ, from one another, however, in that the classic clinical symptoms of CAH (virilization in female, pseudoprecocious puberty in male patients) are present only in 11-OHDS, while in 17-OHDS signs of hypoovarism in female and pseudohermaphroditism in the male patients are found [26]. This unusual combination of MCH hypertension and sexual characteristics is due to the fact that 17-hydroxylation is necessary for both adrenal and gonadal steroids. Deficiency of this enzyme results in an impairment of the production of both glucocorticoid and sex hormones. The lack of F is reflected by a rise in ACTH, which, in turn, stimulates the MCH pathway, where 17-hydroxylation is not required [27].

Thus DOC, 18OH-DOC and B increase, whereas Aldo is reduced, probably due to the DOC-induced sodium retention, the expansion of circulating volume and suppression of plasma renin, or from some other intradrenal event which leads to a functional block of 18-hydroxylase [28]. During treatment with glucocorticoids, PRA and Aldo return to normal levels, although it may take years to obtain a complete normalization of the functional response of the renin–angiotensin–aldosterone axis [29].

17-OHDS is inherited in an autosomal recessive manner; the gene (CYP 17) is localized on chromosome 10 and its molecular analysis, performed on a few patients with the deficiency, has revealed different mutations (in general small changes such as a single or a few base substitutions) [30]. However, in the 3 siblings studied by our group, in collaboration with Dr E. Simpson, a large deletion (518 bp) combined with an insertion of 468 bp, leading to the synthesis of a fragment 51 bp shorter than the normal gene, was identified [31].

Patients with 11-OHDS have hypertension and hypokalemia of a lesser degree, and sometimes these signs are even absent. In this syndrome, the enzymatic system is missing in the MC and in the glucocorticoid pathways of the ZF leading to impaired production of F and B. As a consequence, patients with 11-OHDS have high ACTH levels and high concentrations of all steroids proximal to the defect, i.e. progesterone (PRO), 17-OH-progesterone (17OHP), androgens, DOC and deoxycortisol. Steroids distal to the enzyme defect i.e. F, B and Aldo are variably low. PRA is suppressed by the DOC-dependent extracellular sodium and volume expansion. A very interesting hormonal aspect in this syndrome is the finding of low levels of 18OH-DOC and 18OHB. This finding further supports the idea that the 11- and 18-hydroxylating enzymes of mithocondrial origin may be either the same enzyme or fractions that are part of the enzyme protein [32].

Whether there is a similar defect in 11-hydroxylation in the ZG is still controversial. In fact, in the untreated state corticotropin stimulation is further able to increase DOC and S, whereas B, Aldo, 18OH-DOC, 18OHB and F remain unchanged; moreover, Aldo may not respond to dietary sodium restriction, while it may be stimulated, to some extent, by a graded infusion of angiotensin II. Other studies, demonstrating an increase of Aldo during glucocorticoid therapy when renin is stimulated by low salt diet, support the hypothesis that the renin stimulable ZG is not defective in 11β-hydroxylation [33]. Moreover, the normal rise in 18OHB together with Aldo after renin stimulation indicated that the 18-hydroxylase as well as the 11β-hydroxylase, were not defective in the glomerulosa. The most likely explanation for the possible Aldo production in 11-OHDS relies on the hypothesis that two separate pathways of MCH exist, one in the ZF, which is ACTH-dependent and does not synthesize Aldo, and one in the ZG, angiotensin II-dependent, synthesizing 18OHB and Aldo. The latter is turned off when renin is suppressed by excessive DOC production by the fasciculata, but it shows, at least, a partial ability to produce Aldo when adequately stimulated by angiotensin II.

Recently, the gene (CYP 11B1) encoding for 11β-hydroxylase co-localized with another gene (CYP 11B2) with a 95% omology on chromosome 8, has been found to present a point mutation (Arg 448) in Jewish patients with 11-OHDS [34].

HYPERTENSION IN CUSHING'S SYNDROME

The prevalence of hypertension in Cushing's syndrome is about 70% and varies with the

Table 2. Hypertension in hypercortisolism

	Total No.	Hypertension	% of Hypertension
Cushing's disease	82	52	64
Cushing's syndrome			
Adrenal adenoma	38	27	70
Adrenal carcinoma	6	6	100
Ectopic ACTH	4	4	100

cause of hypercortisolism [35]. 130 Patients with Cushing's syndrome of different etiologies were studied (Table 2) in our institution. Hypertension was present in 64% of the 82 patients with pituitary-dependent Cushing's syndrome and in 70% of those with adrenal adenoma and with bilateral nodular hyperplasia. All patients with an adrenal carcinoma and ectopic ACTH source were hypertensive. The prevalence of hypertension does not appear to be related to the duration of the disease nor to the sex of the patients. Hypertensive patients were significantly ($P < 0.05$) older than normotensive. In a minority of cases with Cushing's disease a slight hypokalemia was observed, while significant differences between hypertensive and normotensive patients were not observed (Table 3).

However, 32% of hypertensive patients presenting with an adrenal adenoma and all of those with adrenal carcinoma or ectopic ACTH production had low serum potassium levels. Few normotensive patients with an adrenal adenoma were hypokalemic. Signs of cardiovascular damage were observed in a high proportion of hypertensive patients but also in several normotensive patients. This suggests that other factors are involved in the pathogenesis of vascular complications.

Adrenal factors: glucocorticoids

F shows a marked MC activity at high concentrations due to its binding to type 1 receptors [35]. However, hypokalemia occurs in a minority of patients with Cushing's syndrome and at a lower frequency than hypertension. In a number of patients, especially those with an adrenal adenoma, F is the only steroid elevated, thus suggesting that this hormone, by itself, may have a pathogenetic role in hypertension. In experimental models, the hypertension induced by glucocorticoids is not sodium-dependent, and cannot be blocked by spironolactone, but only by the GC-antagonist RU-486 [36]. However, no significant differences in urinary F levels were found between hypertensive and normotensive patients and no significant correlation between blood pressure and urinary F levels was observed. It cannot be excluded that 18-oxo-compounds of F can play a contributive role in the hypertension of Cushing's syndrome, as well as a functional failure of 11β-hydroxysteroid dehydrogenase, the enzyme which converts F to the biologically inactive cortisone, which results in an increased intrarenal free F that is able to bind type 1 MC receptors [37].

Adrenal factors: MCs

In agreement with previous reports, Aldo levels have been found normal or low and elevated only occasionally. No correlations among Aldo, PRA, serum potassium and blood pressure have been found. The findings of normal or subnormal Aldo levels in adrenal disorders due to ACTH excess is not surprising. It is well known that in experimental conditions chronic ACTH administration may induce a reduction of basal Aldo levels [38]. A functional suppression of adrenal ZG has been proposed as a possible mechanism of this phenomenon [38]. Previous studies have shown that in patients with hypothalamic–pituitary forms of Cushing's syndrome DOC and B were frequently normal and in ectopic ACTH syndrome were always increased [39]. It has been suggested that these weak MCs might be responsible for the electrolyte abnormalities and hypertension. An increase of DOC and B plasma levels has been found in a small number of our patients with

Table 3. Clinical and laboratory features

	Hypertensive	Normotensive
No. of patients	89	41
Sex (F/M)	76/13	34/7
Age (yr)	43 ± 2.9^a	31 ± 3.2
Duration of the disease (yr)	3 ± 1.5	2.5 ± 1.0
Funduscopy (0–I/II–III, K–W scale)	76/10	10/0
Left ventricular hypertrophy	53	11
Serum potassium (mequiv/l)	3.8 ± 0.2	4.1 ± 0.3

$^aP < 0.05$

Cushing's syndrome of different etiologies. In these cases, no relationship between MCs and blood pressure was observed. Plasma 18OH-DOC was also slightly elevated in some cases, while 18OH-B was high in a case of adrenal carcinoma. However, the finding of high levels, even in some cases of normotensive patients with Cushing's syndrome is against a primary contribution of these hormones to the pathogenesis of hypertension. Similar to that of ACTH and F, we have found the circadian rhythm of these hormones to be altered. While B and Aldo levels are constantly in the low–normal range [40], DOC was occasionally above the normal range, but never high enough to support the hypothesis of a DOC-dependent hypertension. It has been reported that the excretion of urinary free DOC is elevated in a number of patients with Cushing's syndrome, especially in cases of adrenal carcinoma, and tends to correlate with free F. F excess could occupy more protein-binding sites, thus leaving more free DOC to affect the MC receptors.

Other factors

The levels of plasma catecholamines are reported to be normal in Cushing's syndrome. However, enhanced glucocorticoid-induced vascular smooth muscle responsiveness to circulating catecholamines or to other vasopressor substances has been postulated as a mechanism for hypertension in Cushing's syndrome. Infusion of catecholamines in patients with Cushing's syndrome and in healthy subjects given pharmacological doses of glucocorticoids was followed by an increase in vascular reactivity [41].

In patients with Cushing's syndrome excessive production of F is known to increase the formation of renin substrate, i.e. angiotensinogen [42]. Glucocorticoids could increase plasma renin in man, as shown in rats given methylprednisolone [43]. However, PRA tends to be normal or low and responds normally to various stimuli. Also in our patients, PRA was normal or low and only in a few cases higher than normal [44]. No significant differences were observed between normotensive and hypertensive patients. However, Captopril, an ACE inhibitor which reduces blood pressure in experimental glucocorticoid hypertension [45], had an hypotensive effect in some patients [46]. Furthermore, increased pressor response to angiotensin II in patients with Cushing's syndrome and in animals given dexamethasone has been demonstrated [41].

Reduced activity of the depressor systems, such as the prostaglandins (PGs) and kallikrein-kinin, might contribute to hypertension in Cushing's syndrome. Glucocorticoids induce the synthesis of an intracellular protein, macrocortin. This acts to inhibit phospholipase A2 and thereby preventing the release of arachidonic acid [47]. The expected effect of hypercortisolism therefore would be the suppression of both PGs and leukotriens and the modification of intrarenal regulatory mechanisms with a possible influence on blood pressure [48].

APPARENT MINERALOCORTICOID EXCESS (AME) SYNDROME

This syndrome, first described by Ulick *et al.* in 1979 [49], is characterized by the association of an unexplained hyper-mineralocorticoid clinical state and a defective peripheral metabolism of F.

Low renin hypertension and hypokalemic alkalosis along with excessive transepithelial sodium flux occur in the face of subnormal levels of Aldo and other known MCs. Plasma F levels are normal but further administration of F or ACTH exacerbate hypertension and hypokalemia. A genetic defect of the 11β-hydroxysteroid dehydrogenase enzyme system results in an inadequate conversion of F to cortisone. Due to the alterated enzyme kinetics, F half-life is prolonged. Normal free and bound F levels are maintained by normal CBG levels together with low F secretion rates. Diagnosis of the disease is based on the high ratio of the sum of THF + Allo THF/THE, in the face of a low F secretion rate [50].

The proposed mechanism of hypertension is based on the recent acquisitions in the specificity of corticosteroid receptor interactions.

A receptor structurally identical to the renal type 1 MC receptor obtained from nonrenal sites, such as rat hippocampus, aorta, human monocytes or by cloning, demonstrated equally high binding affinity for glucocorticoids and MCs [51]. This evidence of the MC potential of F raised the question of how MC target tissues might be able to respond specifically to Aldo in the presence of much larger amounts of circulating F. It was to this question that studies of the inborn error in the AME-syndrome provided the most plausible explanation. Edwards *et al.* [52] suggested that impaired peripheral metabolism in the disorder exposes the kidney to unoxydized F, unmasking its MC potential.

This hypothesis implied that the normal mechanism permitting recognition of the renin-angiotensin-dependent Aldo signals involves oxidation of F at or near MC target tissue sites. Several patients with this disorder have been described during the last few years [53, 54].

We have recently described [55] a new variant of this Syndrome (type 2) in 3 patients, in whom all the features of the syndrome were present except for the F/cortisone metabolite ratio, which was normal (1.4, 1.42 and 1.25, respectively; normal value 1–1.5), in spite of a markedly reduced F turnover quotient (29, 24 and 21, respectively; normal values 250 ± 50).

A possible explanation of this finding could be that a concomitant defect of the reduction (11-keto-reduction of cortisone to F) might mask a defect of the 11β-OHS dehydrogenase, leading to a normal ratio [55], as suggested by Stewart *et al.* [56] in the case of carbenoxolone (see below). An alternative and more likely mechanism could involve an impairment of A ring reduction in addition to 11-hydroxy-oxidation decrease. In both cases, it is likely that a delayed removal of the GC from strategic receptor sites unmasks its potential agonism. Evidence for this is also provided by the correction of AME by a low dose of dexamethasone in all the patients detected.

The same mechanism which causes the MC hypertension in AME is likely to be involved in individuals who ingest excessive amounts of liquorice or carbenoxolone. Glycyrrhizic and glycerretinic acid or their derivatives, besides their intrinsic MC activity, inhibit the same enzyme, namely the 11β-hydroxydehydrogenase, and probably other enzymes involved in metabolism. It produces the same features of hypertension, hypovolemia, suppressed renin activity and Aldo [57]. The biochemical abnormalities are the same in liquorice-induced hypertension, whereas carbenoxolone fails to induce any change in the THF/THE ratio, in spite of an overall decrease of the F metabolite which mimics the findings of type II AME-syndrome [58].

Another form of exogenous MC excess is due to the use of excessive amounts of fluoro-hydrocortisone for the treatment of orthostatic hypotension [50] or, more frequently, at least in some countries including Italy, due to the abuse of topical products (nasal spray, dermatological cream, etc.) containing 9α-fluoro-prednisolone [59].

The use of these drugs as anti-inflammatory compounds, which have a MC receptor affinity and a biological activity similar to Aldo, has been for years the cause of several cases of very severe hypokalemia and hypertension. After withdrawal, the suppressed PRA, Aldo and serum K-values are normalized within 2 weeks, whereas blood pressure takes much longer to return to normal. Only recently after the recognition of their potential hazard, the incidence of such cases has progressively decreased.

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