Clinical Aspects of Hyper- and Hypo-Mineralocorticoidism*

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Mineralocorticoid (MC) plays an important role in regulating sodium and potassium balance in vivo. This term originates from the neologism which H. Selye termed as one of the main adrenocortical hormones in addition to glucocorticoid (GC) and testoid. Most of MC activity is exhibited by aldosterone (aldo) in human beings. Deoxycorticosterone (DOC) is an intermediate steroid in the biosynthetic pathway of aldosterone and its MC activity is around 1/5 of that of aldo. Recently, the possibility is being clarified that DOC is produced in situ from precursor steroids not only in adrenal glands but also in other tissues such as kidneys and aorta, and might participate in exhibiting MC action locally. Also, it is shown that 18-OH-DOC, 19-nor-DOC as DOC by-products, and, theoretically, 18, 19 di-OH-DOC¹⁾ can be produced, and some pathological significance has become a subject to be studied concerning MC activity of 19-nor-DOC.

As for MC, disorders of hyper- and hypo-mineralocorticoidism are known, like in many other endocrine diseases. As to also primary and secondary aldosteronism are well-established states of adrenoglomerular dysfunction, and 17 α -hydroxylase deficiency (Biglieri's syndrome) and 11 β -hydroxylase deficiency as to DOC. Insufficiency of aldo secretion is described here as syndrome of hypo-aldosteronism (aldosterone deficiency). Independent disease which develops abnormal production of DOC-by-products has not been known hitherto.

According to the above-mentioned idea of MC, the author will present the clinical and biochemical features of major diseases of hyper- and hypo-mineralocorticoidism and report the experimental results of our study on effects of drugs on the

biosynthesis and metabolism of aldosterone.

I. Hypermineralocorticoidism

1. Syndrome of primary aldosteronism

Over a quarter of a century since primary aldosteronoma was discovered through the keen insight of J. W. Conn, clinicopathological entity of aldosteronism due to adrenocortical hyperplasia is still now complex, and it is classified into three or four subtypes at least. Therefore, it is better to call "syndrome of primary aldosteronism" (Biglieri, EG 1983)²⁾, including classic primary aldosteronism (aldosteronoma), together with aldosteronism due to either glomerulosa hyperplasia or adrenocortical carcinoma.

1) **Epidemiology:** The syndrome is important for having the highest frequency in occurrence among endocrine hypertension, and idiopathic aldosteronism for being able to show a clinical profile which mimics essential hypertension. By our recent survey (1982–1984)³⁾, 395 cases of the syndrome, among which there were 330 cases of aldosteronoma (83.5%), 43 cases which were diagnosed as idiopathic aldosteronism (10.9%), 6 cases of GC remidiable aldosteronism (1.5%) and other six cases (4.1%). This figure is converted into 132 cases in the average annual incidence, which is approximately identical with the results of previous author⁴⁾ so far (125 cases/year), and accounts for 0.30% of the hypertensive population under medical treatment in Japan.

2) **Screening and biochemical diagnosis:** Concerning 47 cases of aldosteronoma among 50 cases of our series, they showed hypertension of $184.9 \pm 23.1/106.5 \pm 15.5$ mmHg and U wave on ECG was noticed 87%, serum K was 2.8 ± 0.7 Eq/l, urinary K excretion 40.2 ± 12.8 mEq/day, PRA

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0.26 ± 0.19 ng/ml/h, plasma (p) aldo 35.4 ± 22.1 ng/dl, urinary aldo 23.2 ± 13.1 μ g/day.

The simple screening method for MC excess, which measures rectal potential difference (RPD) is useful in being conducted at the patient's bedside, as far as measuring conditions are adequate. RPD correlates well to p-aldo at the time of measurement, and both show a parallel circadian rhythm. A significant negative correlation is observed between RPD and p-aldo; $r = 0.868$, $p < 0.001$ ($n = 85$). Although this method is useful for the screening of MC excess, there is a limitation in diagnosing syndrome of primary aldosteronism only by this method.

Differential diagnoses of classic primary aldosteronoma, idiopathic aldosteronism (due to adrenocortical hyperplasia) and low renin essential hypertension (LREH): Various methods have been proposed for differential diagnoses of subtypes of primary aldosteronism. One (a) is based on differentiating the biochemical properties of aldo secretion from aldosteronoma and hyperplastic glomerulosa cells. The second (b) is an adrenal image diagnosis, and the third (c) is a functional diagnosis which combines (a) and (b) adrenal scintigraphy and measurement of steroid in adrenal venous blood, before and after administering dexamethasone (DXM).

a) Biochemical diagnosis

It is said that aldo secretion from aldosteronoma is ACTH dependent and A II independent, while that of hyperplasia is rather A II dependent. In our study the circadian rhythm of plasma aldo was, in general, synchronous to cortisol in aldosteronoma, and in most cases plasma aldo showed an exaggerated response to exogenous ACTH load, but failed to response to A II (or A III) load. The same response pattern to ACTH and A II, were observed when p-18-OH-B, a precursor steroid of aldo, was used as parameter.

Recently, a corticotropin-releasing factor (CRF) has been to increase p-aldo. In our study⁵⁾, CRF injection (100 μ g iv) evoked a significant increase up to the peak value 37.4 ng/dl in 45 minutes and maintained high values until 90 minutes after the injection in patient with aldosteronoma. Concerning cases which were tested again after surgical resection of aldosteronoma, p-

aldo responses to CRF closed to those of the control group were shown. On the other hand, such exaggerated response of p-aldo to CRF injection was not observed as to 1 case of idiopathic aldosteronism. The same hyperresponse pattern as of p-aldo was observed in p-18-OH-B.

Biglieri²⁾ described the diagnostic usefulness of p-18-OH-B measurement as a steroid other than p-aldo, postulating that the cases could be considered aldosteronoma with few exceptions when p-18-OH-B values (8:00 AM) exceeded 100 ng/dl, while such p-18-OH-B rises were not observed for idiopathic aldosteronism. The results of our measurement showed a positive correlation of p-18-OH-B with p-aldo, and also showed the significantly elevated values for the patients with aldosteronoma compared with those for the normotensive control and the essential hypertension groups, but did not grant absolute parameter because there were value overlaps among each group.

Idiopathic aldosteronism is generally considered to show an increase in p-aldo to upright posture or to the exogenous angiotensin infusion test. However, the results of "idiopathic aldosteronism" in our research group of disorders of adrenal hormones did not necessarily provide such property of aldo secretory dynamics. Moreover, there was a fact that some cases of LREH had an indistinguishably exaggerated response of p-aldo from idiopathic aldosteronism to exogenous A II infusion⁶⁾.

DXM suppressive tests is important in diagnosing glucocorticoid remidiable hyperaldosteronism. Generally, p-aldo is only reduced transiently by DXM administration in aldosteronoma and idiopathic aldosteronism, while in glucocorticoid remidiable hyperaldosteronism relatively low administration of DXM 1–2 mg/day brings about continuous falls in p-aldo, as shown in our case (69 years old, ♀).

b) Adrenal image diagnosis: Adrenal CT, adrenal venography, ultrasonic diagnosis and scintigraphy with ¹³¹I adosterol are now widespread. The results of our morphological study of adrenal glands by CT scanning showed that, in 132 cases of essential hypertension, somewhat enlarged adrenal glands were observed in about

10% cases, but they had not evidences for idiopathic aldosteronism by other tests. As for 3 cases which showed obviously enlarged adrenal, but only one of the cases had biochemical properties of aldo secretion as idiopathic aldosteronism. The diagnostic accuracy of localization of an adenoma was 92% for adrenal venography, 60% for ^{131}I adosterol scintigraphy in our series.

c) The measurement of aldo in adrenal vein blood also gave high diagnostic accuracy of 90.1%. So nearly 100% diagnosis was possible as to aldosteronoma when these various tests were combined, the problem lies in diagnosis of idiopathic aldosteronism which was no more than 53% even in combined diagnosis of various observations.

In addition, the problem to be discussed is adrenal tumors which are discovered "incidentally" in abdominal CT scanning (incidentaloma). Again, (asymptomatic) adrenal venous steroid measurement provides useful information whether such incidentally discovered adrenal mass is functional or not.

Secondary aldosteronism: In this state renin-angiotensin system is activated by the extraadrenal cause with secondarily increased secretion of aldo. However, hyperaldosteronism is not necessarily a constant observation in maintaining edema or ascitic fluid. For instance, decompensated liver cirrhosis showed elevated p-aldo during ascitic retention and on diuretic administration with a concomitant decrease in Na excretion, while it showed normal or rather low p-aldo in the equilibrium state without increased fluid retention; renal tubular hypersensitivity to p-aldo might be involved in such state⁷⁾. As for congestive heart failure, antagonism between atrial natriuretic peptide (ANP) and renin-angiotensin system is assumed⁸⁾ but in our study there was no correlation between p-aldo and p-hANP.

17 α -Hydroxylase deficiency (Biglieri's syndrome)⁹⁾

Three cases in our clinic were respectively 32 years of age (chromosome analysis 46 XY), 20 years of age (46 XX) and 24 years of age (46 XY), among which two cases were male pseudohermaphroditism. They showed elevated p-ACTH, DOC, B and 18-OH-B values and on the other hand, lowered p-cortisol and p-DHEA, estrogen and testosterone values, and low or normal values in p-

aldo. Also, all cases showed hypertension and, by DXM treatment, improvements in hypokalemia and suppressed PRA were observed with normalization of hypertension. As for 21 cases which were reported recently in Japan, there were 6 cases of consanguineous marriage, the ages of the patients were 14–50 (average age: 25), those whose genetic sex was obvious were 17 cases (6 cases of 46 XX and 11 cases of 46 XY), and male pseudohermaphroditism was observed in 8 cases among 46 XX cases. Hypertensive cases above 160/95 mmHg were 17/20 cases, hypokalemia below 3.5 mEq/l were 15/18 cases, decreases in urinary 17-OHCS and 17-KS were 17/20, 18/20 cases respectively. Among 19 cases examined lowered p-aldo was observed in 8 cases, normal p-aldo in 4 cases and elevated p-aldo in 7 cases, thus showing no definite trend. It was considered that cross reactions with other steroids in the radioimmunoassay or difference in the degree of hypervolemia was involved in the reasons for normal or elevated p-aldo. As for adrenal lesion, among 5 cases on which surgery or autopsy was administered, hyperplasia was observed in 2 cases and nodular hyperplasia in 3 cases. Among 3 cases of our clinic 1 case (20 years old female) showed enormously enlarged adrenal mass bilaterally in adrenal CT, and this CT observation has not changed despite of the continuous treatment by prednisolone for more than 2.5 years.

II. Syndrome of hypoaldosteronism (Aldosterone deficiency, renal tubular acidosis, type 4)

Aldo deficiency is recently classified as renal tubular acidosis, type 4 and also classified into two large groups; the group which is accompanied by GC deficiency (Addison's disease, 21-hydroxylase deficiency, adrenalectomized state, adrenal hemorrhage etc.) and the group where p-aldo or p-aldo lowers selectively. With the widespread of PRA measurement, classification based on pathogenesis became possible and the latter group is now subclassified into hyperreninemic hypoaldosteronism (selective hypoaldosteronism, type 1, SHA I) and the latter, into hyporeninemic hypoaldosteronism (SHA II). Thirdly, hypoaldosteronism, due to the defective aldo receptor in the target, is typed, apart from the above two, into pseudohypoaldosteronism.

1. Selective hypoaldosteronism (SHA I, II)

SHA is often found as asymptomatic hyperkalemia. When candidates of SHA were screened as asymptomatic hyperkalemia which is difficult to explain from renal dysfunction, the frequency of hyperkalemia ($5.0 \text{ mEq/l} <$) was 1.3% (78 cases/all cases) but hypoaldosteronism which fulfilled our diagnostic criteria were only 2 cases of SHA I and 5 cases of SHA II. Though diabetes is known to be an underlying disease of SHA II, there are not many cases which show hyperkalemia. We¹⁰⁾ first reported a case of SHA I associated with diabetes which seemed to have defect in the conversion step from 18-OH-B to aldo, and recently the possibility of similar cases in some of severely ill patients in emergency has been reported. In our series hyperreninemic hypoaldosteronism (PRA $> 3.0 \text{ ng/ml/h}$ and p-aldo/PRA < 0.85 , Zipser RD, et al)¹¹⁾ was found in 6 cases among 32 cases of severely ill patients in emergency.

The underlying diseases of SHA II (9 cases) included diabetes (4 cases), IgA nephropathy, cerebrovascular disorder and cardiovalvular disease. They showed the average value of serum K $6.1 \pm 1.0 \text{ mEq/l}$, Cl $109.3 \pm 4.0 \text{ mEq/l}$, PRA $0.31 \pm 0.15 \text{ ng/ml/h}$ and p-aldo $2.0 \pm 1.1 \text{ ng/dl}$, lacked p-aldo response upon A II (or A III), and

showed low or no response to ACTH load. In addition, it was interesting to see in a case¹²⁾ (64 years old female) in which flufenamic acid treatment caused a reversible elevation of hyperkalemia.

III. Drugs which affect secretion and metabolism of mineralocorticoid

1. Inhibitors of aldosterone-biosynthesis

We run the in vitro experiments of inhibitory effects of several compounds on p-450-catalyzed reactions in steroidogenesis using the reconstituted steroid monooxygenase system¹³⁾.

The results are shown on Table 1. The figures on the table are K_i values and show that inhibitory effects become larger as K_i values become smaller.

2. Effects of antibiotics on peripheral metabolism of aldosterone (metabolism by intestinal flora)

Aldo is mainly metabolized in liver and kidney for the glucuronic acid conjugation at C-3 in liver and 18-oxo conjugation in kidneys.

On the other hand, aldo and its reduced metabolites which are excreted into intestine through liver, are metabolized by enzymes which are produced by intestinal bacteria, and then excreted into urine via intestinal-hepatic circulation. We analyzed steroids produced by incubation of aldo with intestinal bacteria (*Clostridium paratrificum* and 10^3 diluted fecal suspension)

Table 1. The effect of imidazole-derivatives and some other inhibitors of steroidogenesis on P-450-catalyzed reactions.

		Ketoc.	Etom.	0, p-DDD.	Aminogl.	Trilo.	Metyra	α -hANP
		$K_i = (\text{UM})$						
Mitochondria	P-450 sec (Chol $\rightarrow$ Δ_5 -P)	0.98	0.21	(-)	(-)	(-)	160	(-)
	P-450 _{11β} (DOC $\rightarrow$ B)	0.56	0.74	(-)	4.83	(-)	0.10	(-)
	Electron Transfer system	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Microsome	P-450 _{c₂₁} (P $\rightarrow$ DOC)	1.26	(-)	(-)	(-)	(-)	(-)	(-)
	P-450 _{scc_{II}} (P $\rightarrow$ [7 α -P] (17 α -P $\rightarrow$ Δ_4 A))	2.60	16.0	(-) (-)	(-) (-)	(-) (-)		
	Electron Transfer system	(-)	(-)	(-)	(-)	(-)	(-)	(-)

Ketoconazole, Etomidate, Aminogluthethimide, Trilostane, Metyrapone, Δ_3 P: pregnenolone, Δ_4 A: Androstenedione

and showed that clostr. paraputrificum converted Aldo into tetrahydroaldosterone in the coexistence with *E. coli*, and, when Aldo was incubated with fecal suspension, 21-deoxytetrahydroaldosterone was detected. 21-deoxygenation is considered to be a unique metabolism peculiar to intestine.¹⁴⁾

From the results of the above *in vitro* experiment, we investigated the effect of Kanamycin on the urinary 21-deoxymetabolites of Aldo. When Kanamycin (1.0 g/day) was administered to healthy normal men for six days and changes in urinary Aldo, 21-deoxyAldo (21-DO-Aldo) and 21-deoxytetrahydro-Aldo (21-DOTH-Aldo) were measured before and after the administration, 21-DO-Aldo decreased from $8.2 \pm 2.2 \mu\text{g/d}$ to $3.7 \pm 0.7 \mu\text{g/d}$, and 21-TH-Aldo decreased from $1.2 \pm 0.3 \mu\text{g/d}$ to $0.8 \pm 0.2 \mu\text{g/d}$. The same results were obtained in patients with liver cirrhosis ($n = 11$).

CONCLUSION

With special reference to the diagnostic problems in hyper- and hypo-mineralocorticoidism, the author reported the results of our recent study and some results of the national research group focused on cases in 1982–1984, and introduced the results of studies on drugs which affect aldosterone biosynthesis and its intestinal metabolism.

Since the clinical features as well as pathophysiology of idiopathic aldosteronism among syndrome of primary aldosteronism are still unknown, it should be postulated to need further investigation for elucidating the regulatory mechanism of Aldo secretion, other than ACTH and angiotensin.

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