On the Role of Aldosterone to Hypertension ; Especially an Extent of Its Participation*

TATSUO ODA

MANY researchers¹⁻⁷ have studied since 1950 that aldosterone might have some roles on the etiology of hypertension, while it has a homeostatic effect on the maintaining of human's life which protect sodium losing from human's body.

Since it had been found by *Davis et al.*⁸ (1961), *Laragh et al.*⁹ (1962) that a main stimulating factor for aldosterone secretion was renin from the Juxta-glomerular apparatus of kidneys, a concept of Renin-Angiotensin-Aldosterone system became to establish to some extent on the etiology of hypertension and regulating mechanism of blood pressure.

Among many diseases with hypertension, especially fairly advanced or accelerated hypertension and malignant hypertension have more or less a renal vascular damage, reduced renal blood flow and increased renin secretion, and secondarily promote a secretion of aldosterone from an adrenal cortex. Generally it has been thought that both of renin and aldosterone have a large role to the etiology of such kinds of hypertension. The etiology of renovascular hypertension has been also realized on the same mechanism due to renal artery constriction. However the patients of hypertension with primary aldosteronism have the suppression of renin response and hyperaldosteronism.

On the other hand, one has realized that in

Key Words : Aldosterone
Renin Response
Hypertension
Primary Aldosteronism
Adrenal Cortex
Adenomatous Hyperplasia

Fig. 1. Vascular reactivity to synthetic angiotensin II.

the edematous state, especially in the initial stage of edema formation, renin is primarily and then aldosterone is secondarily promoted to secrete, but in such so-called secondary aldosteronism hypertension is not occurred. Fig. 1 shows that the vascular reactivity to synthetic Angiotensin II infusion is apparently reduced in edematous state (cardiac, hepatic, and renal) comparing with normal persons¹⁰. Fig. 2 shows the results of urinary aldosterone excretion in

Department of Medicine, School of Medicine, Nihon University, Itabashi, Tokyo.

* Presented at the symposium on 'the Pathogenesis of Hypertension' of the 34th Annual Meeting of the Japanese Circulation Society, March 1970, Kobe.

Fig. 2. Urinary aldosterone excretion and eyeground in hypertensive patients and normotensive persons.

normal persons and patients with essential hypertension. The method which was used in this study was due to a combination of thin layer chromatography and blue tetrazolium coloration.

According to these results, the levels of urinary aldosterone excretion in normal persons were 5–20 $\mu\text{g}/\text{day}$ and within the normal variants in patients with essential hypertension (KW I and KW II except one case) and 22–40 $\mu\text{g}/\text{day}$ in most of severe and malignant hypertension (KW III and IV cases). All three cases with renovascular hypertension showed high levels of urinary aldosterone.

We have measured the renin levels in the kidney tissues with unilateral renal artery constriction and the intact kidney on the other side of Goldblatt's hypertensive rats separately^{12, 13}.

The renin content of the kidneys with the constricted renal artery reached to maximum in 1 or 2 weeks and after 3 weeks they fell a little but gradually and maintained the same level up to 5 weeks. On the contrary, the one in the contralateral intact kidney was almost within normal in 1–2 weeks, but thereafter

Fig. 3. Following up of B. P., renin contents of both kidneys and urinary aldosterone excretion of Goldblatt's rats.

decreased to some extent.

And so we would like to suggest that the urinary aldosterone excretion highly depends on the sum of the renin levels of both kidneys, because the sum of renin levels was quite parallel with the urinary aldosterone excretion. Moreover, the renin contents of intact kidneys, the urinary aldosterone excretion and blood pressure returned promptly to normal level, when the kidneys with constricted renal arteries were removed (Fig. 3).

Next, we examined the renin responses on sodium restriction and upright position in normotensive persons and patients with various types of hypertension.

All cases with primary aldosteronism showed the inhibition of plasma renin response and we found that the cases which had the suppression of renin response were included in a part of patients with essential hypertension^{13–19}. Moreover it was very interesting that many of the aged patients more than 60 years old showed the lower responses than younger groups (Fig. 4).

I am going to report our cases with normokalemic primary aldosteronism^{20–30} which were difficult to differentiate from cases with essenti-

Fig. 4. Variation of plasma renin response.

Fig. 5. Primary aldosteronism. (K.K. 33 yrs, F) the whole course of six years' duration before operation.

al hypertension, because they did not show a hypokalemia at some time or consistently.

Especially it is assessed that many cases have normokalemic stages in an initial stadium of this disease.

The first case is 33 years old woman. This case was confirmed by a normokalemic stage before six years, when she had already very high blood pressure (200/120), then persisted the same levels during six years. And her first

visit to our clinic serum potassium was 2.3 mEq/L on an average. We found an adenoma (1.7×1.8 cm) in right adrenal. Since then all signs and symptoms were improved promptly (Fig. 5).

The second case is 27 years old woman. She began to raise the blood pressure soon after the second delivery. Her serum potassium level is low normal (3.5 mEq/L) at her first visit to our hospital. After six months she showed a

definite low level of serum potassium (2.7 mEq/L).

The third case is 41 years old woman. She showed a constant normal potassium level for a long time. She was operated and found a tiny adenoma with 3 mm diameter (already reported³⁰).

The author is going to refer the so-called secondary primary aldosteronism^{32~36} which was adapted with Conn's criteria (Hyperaldosteronism, PRA suppression etc) but could not be found any adenomas by operation. The cause of these cases is still obscure, but generally one suggest a factor except ACTH or Renin-Angiotensin.

The first case (51 yr. women) shows a definite hypokalemia and high blood pressure (200/120). She was satisfied by Conn's criteria and operated but as we found no adenoma, performed by subtotal adrenalectomy. Microscopic finding of adrenals showed a diffuse, partly wedge-shaped hyperplasia of zona glomerulosa and moderate connective tissue reaction in clear cell zone, partly with nodular formation (already reported³⁰).

The second case is 13 years old girl. We

Fig. 6. (T. K. 33 yrs, F) A microscopic hyperplasia of zona glomerulosa a homogeneous thickening of the zone and wedge-typed invasion into zona fasciculata in some places.

Fig. 7. (T. H. 27 yrs, F) A larger tumor: well capsulated, mature adenoma; a smaller one: completely uncapsulated adenomatous hyperplasia. left & under: a proper adrenal cortex.

could not find any adenomas in adrenal cortex. Adrenals showed a remarkably developed zona glomerulosa with homogenous widening of the width and composed of $2/5-1/3$ width of the total adrenal cortex (already reported³⁰).

The third case is 33 years old female. Because she showed a remarkable suppression of P.R.A. response and an increase of urinary aldosterone and hypertension with typical hypokalemia, she was operated.

However any adenomas were not found and microscopically well developed zona glomerulosa with partly wedge-shaped invasion into zona fasciculata was found. Zona glomerulosa occupied about $1/3$ width of total adrenal cortex. Zona fasciculata was very thin and not recognized partly (Fig. 6). Such cases were reported by *Laragh, Davis, Ross, Katz, Vecsei* and others. Especially *Laragh* reported six of sixteen cases in 1967.

Next, I am going to show you 27 years old female with primary aldosteronism which showed an interesting histological findings of adrenal cortex. She had a hypertension (220/110), hypokalemia, hyperaldosteronism (24 $\mu\text{g}/\text{day}$ in urine) and negative P.R.A. response.

Histologically one adenoma ($1.5 \times 1.8 \text{ cm}$) and one small nodule ($0.5 \times 0.3 \text{ cm}$) were found in left adrenal. The larger one an all-around proper capsule but the smaller one had no capsule and shifted to a proper adrenal cortex which occupied $3/5$ width of total adrenal cortex and zona glomerulosa became gradually thinner as far as distant from the nodule (Fig. 7).

The adrenal glands surgically removed from 19 cases in total of primary aldosteronism were histopathologically examined in our laboratory, as well as others. The adrenocortical lesions showed a wide variety of histological patterns, and they were tentatively classified into three main types, a) subnormal (1/19), b) hyperplasia (10/19), c) adenoma (8/19). The hyperplasia type was subdivided into 1) diffuse hyperplasia (3/10), 2) micro-nodular hyperplasia (4/10) and 3) adenomatous hyperplasia (3/10).

When more than one types were combined, the diagnosis was made upon the latter one in the order of the classification. The diffuse

hyperplasia were always composed of those of the glomerulosa cell.

On the contrary, the fasciculate cells were predominant in the micronodular or adenomatous hyperplasia and the glomerulosa cells were rather poorly participated. The adenomas were also composed mainly of the clear cells with or without pleomorphism and the glomerulosa cells were inconstantly encountered.

Frequent occurrence of the combined types in the same adrenal cortex strongly suggested the possible development of the adenoma from the diffuse hyperplasia, via micro-nodular or adenomatous hyperplasia.

SUMMARY

1) A role of aldosterone in the etiology of essential hypertension is yet obscure; except severe and malignant hypertension which have an increased renal damage. However in the latter two diseases aldosterone has some significance in the maintenance of hypertension.

2) We have found the cases with primary aldosteronism showed a normokalemic stage especially in their initial stadium.

3) In our experienced cases of primary aldosteronism there were some cases of so-called secondary primary aldosteronism with bilateral adrenocortical hyperplasia (zona glomerulosa).

4) In diagnoses of primary aldosteronism only the suppression of P.R.A. response is not satisfied and the existence of hyperaldosteronism must be recognized, because not a little percentage out of essential hypertension show often a low P.R.A. and P.R.A. response to sodium restriction and upright position. More sensitive and accurate method of determining plasma renin is necessary to resolve the problem which include a true incidence of primary aldosteronism in essential hypertension.

5) From our cases histologically the following possibility was considered that first zona glomerulosa caused hyperplasia and thereafter gradually transit to adenomatous hyperplasia and matured adenoma.

REFERENCES

1. GENEST, J., KOIW, F., NOWACZNSKI, W.: *Proc. Soc. Exp. Biol. Med.* **97**: 676, 1958.
2. VENNING, E.H., DYRENFURTH, I., DOSSETOR, J.B.: *Circulation* **23**: 168 1961.
3. GARST, J.B., SHUMWAY N.P., SCHWARTZ, H.: *J. Clin. Endocri.* **20**: 1351, 1960.
4. LARAGH, J.H., SEALEY J.E., SOMMERS, S.C.: *Cir. Res.* **18** (Suppl 1): 158, 1966.
5. STREETEN, D.H.P., SCHLETTER, F.E., CLIFT, G.V.: *Amer. J. Med.* **46**: 844, 1969.
6. WEINBERGER, M.H., DOWDY, A.S., NOKES, G.W.: *J. Clin. Endocr.* **28**: 359, 1968.
7. MURAI, R.: *Nichidai I.Z.* **19**: 513, 1960.
8. DAVIS, J.O. et al.: *J. Clin. Invest.* **40**: 684, 1961.
9. LARAGH, J.H.: *Circulation* **25**: Part II, 203, 1962.
10. IIDA, K.: *Jap. J. Nephrology* **11**: 529, 1969.
11. KUGA, T.: *Jap. Circul. J.* **29**: 1349, 1965.
12. ODA, T., OSHIMA, K.: *Jap. Circul. J.* **30**: 171, 1965.
13. CHANICK, B.J., V. ADLIN, A.D. MARKS: *Arch. Int. Med.* **123**: 131, 1969.
14. JOSE, A.J., N.M. KAPLAN: *Arch. Int. Med.* **123**: 141, 1969.
15. WOODS, J.W., G.W. LIDDLE, E.G. STANT, A.M. MICHELAKIS, A.B. BRILL: *Arch. Int. Med.* **123**: 366, 1969.
16. KAPLAN, N.M.: *Arch. Int. Med.* **123**: 152, 1969.
17. LEDINGHAM, J. M., M. B. BULL, J. H. LARAGH: Hypertension Vol. 15 (RENIN MECHANISMS AND HYPERTENSION) *Am. Heart. Assoc.* **II**-177, 1967.
18. GREDITOR, M.C., U.K. LOSCHKY: *Amer. J. Med.* **43**: 371, 1967.
19. JOSE, A., J.R. CROUT, N.M. KAPLAN: *Ann. Int. Med.* **72**, 9, 1970.
20. CONN, J.W., ROVNER, D.R., COHEN, E.L.: *Ann. Int. Med.* **63**: 266, 1965.
21. CONN, J.W., ROVNER, D.R., COHEN, E.L., NESBIT, R.M.: *J.A.M.A.* **195**: 111, 1966.
22. CONN, J.W., COHEN, E.L., ROVNER, D.R., NESBIT, R.M.: *J.A.M.A.* **193**: 200, 1965.
23. SIEGENTHALER, W., J. MÖHRING, P. WEIDMANN: *Dtsch. Med. Wschr.* **92**: 1570, 1967.
24. GUNNELLS, J.C., N.M. BATH, J. SODE, R.R. ROBINSON: *Arch. Int. Med.* **120**: 568, 1967.
25. RHAMY, R.K., R.M. MC COY, H.W. SCOTT, L.M. FISHMAN, A.M. MICHELAKIS G.W. LIDDLE: *Ann. Surg.* **167**: 718, 1968.
26. WOLFF, H.P., CH, BARTH, G. BIRO, A. BOHLE, G. DHOM, A. DISTLER, A. HELBER, H. LIEBAU, I. PURJESZ, S. ROSCHER, J. SCHURHOLZ, P. VECSEI, K.F. WEINGES: *Klin. Wschr.* **46**: 357, 1968.
27. SIEGENTHALER, W., K. BAUMANN, K. KIEPENHEUER, M. SCHÖNBECK, F. RHOMBERG, E. GYSLING, P. WEIDMANN, C. WERNING: *Schw. Med. Wschr.* **99**: 825, 1969.
28. H.P. WOLFF, CH. BARTH, A. DISTLER, G. DUSTERDIECK, F. KRÜCK, S. ROSCHER, P. VECSEI, K.F. WEINGES: *Deut. Med. Wschr.* **15**: 760, 1969.
29. KUBOTA, K.: *Jap. Circul. J.* **33**: 323, 1969.
30. ODA, T.: *Jap. Circul. J.* **33**: 1621, 1969.
31. CONN, J.W. et al.: *Arch. Int. Med.* **123**: 113, 1969.
32. DAVIS, W.W., H.H. NEWSOME, JR., L.D. WRIGHT, W.G. HAMMOND, J. EASTON, F.C. BARTTER: *Amer. J. Med.* **42**: 642, 1967.
33. ROSS, E.J.: *Amer. J. Med.* **39**: 994, 1965.
34. KATZ, F.H.: *Ann. Int. Med.* **67**: 1035, 1967.
35. BIGLIERI, E.G., P.E. SLATON, S.J. KRONFIELD, M. SCHAMBELAN: *J.A.M.A.* **201**: 510, 1967.
36. LAGAGH, J.H. et al.: *Trans. Ass. Amer. Physicians* **80**: 168, 1967.
37. KWAOI, A.: *Acta Path. Jap.* **19**: 115, 1969.
38. SAKAI, M.: *Nichidai I.Z.* **28**: 775, 1969.
39. SCHAMMA, A.H., GODDARD, J.W., SOMMERS, S.C.: *J. Chron. Dis.* **8**: 588, 1958.
40. DÉVÉNYI, I.: *J. Clin. Path.* **20**: 49, 1967.
41. RUSSI, S., BLUMENTHAL, H.T., GRAY, S.H.: *Arch. int. Med.* **76**: 284, 1945.
42. TSUCHIYAMA, H.: *Acta Path. Jap.* **17**: 155, 1967.