ADRENOCORTICAL FUNCTION OF THE PATIENTS WITH HYPERTENSION AND WITH CORONARY HEART DISEASES*

MOTOTAKA MURAKAMI, KYUICHI KURAKANE, RYOYU TAKEDA, MASAKAGE KIMURA, HIROSHI AZUMA, SUSUMU MIYABO, SHINPEI MORIMOTO AND AKIRA SAKAI

Second Department of Internal Medicine, Faculty of Medicine, Kanazawa University, Kanazawa

In spite of the cumulative evidence that the adrenal cortex plays an important role in the pathogenesis of hypertensive diseases directly or indirectly, the nature of the role of corticosteroids in causing the diseases still remains obscure. Most of earlier studies speculating the hypercorticism to be causative of the development of the diseases, failed to find the elevated or the altered pattern of corticosteroid secretion (Selye, 1947; Tobian and Joseph, 1949; Corcoran et al., 1950; Hetzel and Hine, 1952), although the poor reliability of the method used in the past might be responsible for these inconclusive results according to the authors' opinion.

With the more recent progress in the knowledge about the sodium retaining hormone, it has now become a favorite subject of many clinicians to explore the participation of aldosterone in hypertensive diseases. However, in view of the Selye's concept of "stress" (1954), the importance of glucocorticoid should also be kept in mind.

On the other hand, it is noteworthy that the overdosage of glucocorticoid can promote the blood coagulability and inhibit the endogenous clearing activity (Murakami et al., 1958; Murakami, 1959). Moreover, as ascertained in the authors' laboratory, the lipomobilizing factor produced by the administration of glucocorticoid enhances significantly the development of atherosclerosis in animals (Murakami, 1959), which suggest that similar mechanism is likely to predispose men to myocardial infarction or angina pectoris. On the basis of these observations the authors were inclined to adopt a working hypothesis that the adrenal cortex of patients with these cardiovascular diseases might exhibit higher activity than normal.

In the study reported here an attempt was made to investigate the adrenocortical function of the hypertensive patient and patients with myocardial infarction and angina pectoris.

METHODS

Experimental subjects The test subjects of this study were selected from the in-patients in the

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Method for the determination of plasma cortisol and urinary corticosteroids The heparinized blood samples for the determination of plasma cortisol were drawn from the individual before breakfast. Plasma cortisol was estimated according to Sweat's method modified by Takeda (1956) and the urinary total 17-hydroxycorticosteroids were estimated principally by Glenn-Nelson's method (1953), with chromatography omitted. The 17-ketosteroids were determined fractionally by the method reported previously from the authors' laboratory (Azuma, 1957). For the estimation of dehydroisoandrosterone the buffer hydrolytic procedure proposed by Bitman and Cohen (1951) was employed to avoid the artificial alteration of this compound.

ACTH tests To evaluate the adrenocortical functional capacity, the response of adrenal cortex to a dose of 25 U of intravenously injected ACTH represented by the fluctuation of the plasma cortisol level was used. In some patients 40 U of ACTH-Z was administered intramuscularly and the urinary total 17-hydroxycorticosteroids were estimated for 4 consecutive days.

Disappearance of exogenous cortisol The removal of cortisol from plasma was estimated at 1/2, 1, 2, 3, 4 and 5 hrs. after the intravenous injection of cortisol-free alcohol using 1 mg per kg body weight dissolved in 200 ml of Ringer's solution.

RESULTS

As shown in Figure 1, the plasma cortisol was found to be generally elevated in hypertensive patients. The elevation was more marked in the younger patients than the older and 44% of those over 50 yrs. of age showed normal distribution. As depicted in Figure 2, the degree of elevation in both systolic and diastolic blood pressure seemed to be roughly proportional to the plasma cortisol level and it was observed that the increased cortisol level fell with the fall of blood pressure in the
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Fig. 2. The levels of plasma cortisol and urinary total 17-hydroxycorticosteroids plotted against systolic and diastolic blood pressure

9 patients in whom repeated determination was performed. The excretion of 17-hydroxycorticosteroids also suggested a positive correlation with the degree of hypertension, although not always as clearly as in the case of the plasma cortisol level.

Electrocardiographically there was no significant difference on the plasma cortisol or urinary 17-hydroxycorticosteroids level between the patients having abnormal signs of RS-T segment and T wave and those having no signs.

In the 14 cases of myocardial infarction, the plasma cortisol level averaged 13.9μg, exceeding the normal range in one-half of the case, and the urinary 17-hydroxycorticosteroids averaged 3.9 mg daily, one-third of them showing levels above normal (Fig. 3).
Fig. 3. The levels of plasma cortisol and urinary total 17-hydroxycorticosteroids in the patients with myocardial infarction (MI) and with angina pectoris (AP).

Fig. 4. The urinary 11-oxygenated 17-ketosteroid levels in the younger adults (YA), the elderly person (EL) and the patients with hypertension (HT) and with coronary diseases (CD).
In the cases of angina pectoris, on the other hand, the mean level of plasma cortisol was 13 µg%, including one case which gave an exceptionally high value 25.9 µg% and that of urinary 17-hydroxycorticosteroids was 3.2 mg daily (Fig. 3).

As shown in Figure 4, urinary 11-oxygenated 17-ketosteroids were found to be low in all the patients, comprising 2 hypertensive and 13 coronary diseases. But such lowering of 17-ketosteroids excretion was also found in the elderly subjects having no diseases. In the fractionating determination of 17-ketosteroids, it was noticed that the level of dehydroisoandrosterone tended to decline in most cases and in a few cases androsterone and etiocholanolone also showed considerable decreases, similar to the prepuberty pattern (Fig. 5).

Figure 6 shows the average cortisol response of 2 hypertensive and 2 cases of myocardial infarction, measured 6 hrs. after the intravenous infusion of a dose of 25 U of ACTH. The slope of the mean value in this group was somewhat greater than in the normal human, but the significance of the difference is uncertain. In the normal adults the excretion of 17-hydroxycorticosteroids increased to 2 to 4 times to their initial levels following the infusion of ACTH-Z.
and returned gradually toward the initial levels. On the other hand, in the patients with hypertension and coronary diseases, the response to ACTH-Z was high, especially in 3 out of 6 hypertensives, 1 out of 5 cases of myocardial infarction, and 1 out of 2 were afflicted simultaneously with both diseases. Among them a patient of hypertension responded with an extremely higher level, as much as 17 times of the initial level (Fig. 7).

In the case which showed high level of cortisol, disappearance of cortisol from
plasma was slower than normal, as depicted in Figure 8. The biological half-life of cortisol was calculated to be 102 mins. in the group of patients, in contrast to 90 mins. obtained from normal adults.

DISCUSSION

It is very interesting that the causative correlation between blood pressure and plasma cortisol level suggested in the present study shows good agreements with the observation that in rats with adrenal regeneration hypertension, the plasma level of corticosterone, a predominant glucocorticoid in this species, attains supernormal values with development of hypertension and thereafter declines to the subnormal level (Kurakane et al., 1959). Moreover, the plasma cortisol response to ACTH stimulation was somewhat greater than normal and the increase in urinary 17-hydroxy-corticosteroids following the ACTH-Z injection was often quite pronounced beyond the normal range in these patients.

The data from the patients with myocardial infarction, on the other hand, were not so much in favor of the authors' hypothesis as alluded to before; they showed a moderate elevation of plasma cortisol in only half of the instances and two-thirds of them did not show increased excretion of total 17-hydroxycorticosteroids. In angina pectoris no significant elevation of corticoids was found in urine.

Consequently, the data are as yet insufficient to ascertain whether the hypercortisolemia of hypertension and myocardial infarction reflect an absolute hypersecre-
tion or not, that is, as may be inferred from the measurement of the disappearance rate of exogenous cortisol from plasma, it is possible that the hypercortisolemia is in part associated with the delay of metabolism involving reduction and oxidation of cortisol. In that case, it might be expected that the urinary 17-keiosteroids and 17-hydroxycorticosteroids decrease in the patients with coronary diseases, as above mentioned. It was already demonstrated that the excretion of cortol and cortolone, the ultimate reduced form of cortisol, decreased significantly in these patients, as reported elsewhere (Azuma, 1959).

Perkoff et al. (1954) also described the striking elevation of plasma 17-hydroxycorticosteroid amounting to 47 µg to 74 µg% in four patients with myocardial infarction, and in those cases it should be noted that all of their samples were obtained at the preterminal state, which made the cortisol metabolism extremely lagged as pointed out by Tyler et al. (1953). There still remains a possibility that the discrepancy between the plasma cortisol and urinary 17-hydroxycorticosteroids in coronary diseases is caused by the impaired excretion of free and conjugated 17-hydroxycorticosteroids. To elucidate this point, therefore, the renal clearance of free and conjugated 17-hydroxycorticosteroids must be taken into consideration. In this regard, a recent work reported by Kornel (1959) gives an instructive hint. He observed in hypertensive patients that in basal condition, the renal clearance of the conjugated 17-hydroxycorticosteroids was grossly impaired and this in turn resulted in the accumulation of cortisol in blood, whereas on ACTH administration the renal clearance was slightly increased. However, as far as hypertensive patients was concerned in the present study, the excretion of total 17-hydroxycorticosteroids in basal condition was not impaired. Under usual circumstances the elevation of cortisol, simultaneously with the augmented excretion of 17-hydroxycorticosteroids may be good enough to prove hypercorticism.

The authors failed to obtain the result to support positively the adrenocortical hyperfunction in the patients with angina pectoris. The reason, however, may be due to the fact that samples were taken at the resting phase of the disease in most cases. In fact, inasmuch as the authors observed the striking increase of plasma cortisol in a patient with angina pectoris, which was attributed to the anginal attack, they think that in such a case there has to be adrenocortical hyperactivity induced by some mechanism.

The authors have experienced a patient who was attacked with anteroseptal infarction during cortisol treatment. It is difficult at present time to tell what caused this infarction. Since there was a significant shortening of prothrombin time in this case, the condition appears to have been due more to the blood hypercoagulability rather than to the cardiotoxic effect of cortisol, as has been postulated by Selye (1958), or hyperlipemia and decrease of endogenous clearing activity induced by the increased cortisol.

SUMMARY

The adrenocortical function in patients with hypertension, myocardial infarction, and angina pectoris was investigated.
1) These patients had higher plasma levels of cortisol than normal subjects, and after ACTH infusion, the plasma levels of cortisol rose higher than normal.

2) The increase of urinary 17-hydroxycorticosteroids was not always so marked as that of the plasma levels of cortisol, but after ACTH-Z injection, the excretion of 17-hydroxycorticosteroids increased much more than normal, indicating adrenocortical hyperactivity.

3) The excretion of 17-ketosteroids was found to be decreased in these patients.

4) The disappearance of exogenous cortisol from plasma lagged in these patients.

5) From these results, it was suggested that the elevation of plasma levels of cortisol in these patients is due in part to modified metabolism of cortisol.

6) Certain clinical evidences relevant to these data were discussed.

REFERENCES

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