Effects of Angiotensin on Catecholamine Metabolism in Rat

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ENGELMZN *et al.* found using the double isotope method that total catecholamines (CA) are higher in cases of essential hypertensive patients than in normal adults.

It was also reported that the sensitivity to blood noradrenaline (NA) is enhanced in essential hypertensive cases.

These findings, however, have not given sufficient grounds to establish the pathogenesis of the disease.

On the other hand, the CA metabolism has been investigated on SHR, which is believed to resemble essential hypertensive cases, in an attempt to elucidate the mechanism for the development of the latter.

Yamori *et al.* reported the lower NA level and also the lower dopa-decarboxylase activity in the hypothalamus which they suspected as the pathogenesis of hypertension.

In view of the well known facts that NA is present in the hypothalamus at high concentration and that destruction of the hypothalamus causes hypertension, the changes in CA in the adrenal medulla, myocardium and hypothalamus and their relation to electrolytes were explored on acute angiotensin-induced hypertension so as to throw light from a different angle on the

pathogenesis of essential hypertension by comparatively studying the findings on SHR.

First adrenal perfusion was attempted to study the angiotensin action on the adrenal medulla. While the perfusion fluid was continuously introduced from the distal end of the lumboadrenal artery, the lumboadrenal vein was ligated centripetally to the adrenal as occasion demanded and blood was obtained. (Fig. 1.)

As a result, it was found that the change in the Ca^{++} concentration in the perfusion fluid little affected the NA release from the adrenal. Although the administration on angiotensin increased NA, an increase in the Ca^{++} concentration brought about a decrease rather than an

Fig.1. Experimental method of adrenal perfusion.

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Fig. 2. Relationship between NA changes before and after angiotensin II administration and Ca^{++} concentration.

—: after angiotensin II administration
 ---: before angiotensin II administration

Fig. 3. Relationship between NA changes before and after angiotensin II administration and Mg^{++} concentration.

—: after angiotensin II administration
 ---: before angiotensin II administration

Fig. 4. Relationship between NA changes before and after angiotensin II administration and K^{+} concentration.

—: after angiotensin II administration
 ---: before angiotensin II administration

Fig. 5. The effect of angiotensin on noradrenaline content in adrenal gland.

increase of NA except for the case at the level of 17.5 mM, as compared with the control. (Fig. 2.)

Similarly the effect of the Ca^{++} concentration on adrenaline (A) was studied. The results obtained were similar to those with NA, i.e., the A level was lower than in the control in spite of the higher Ca^{++} concentration.

As it was impossible by this way of perfusion

Fig. 6. The effect of angiotensin on noradrenaline in hypothalamus and striatum.

Fig. 7. Effects of angiotensin on noradrenaline in hypothalamus with high Ca^{++} intraventricular perfusion.

Fig. 8. Effects of angiotensin on noradrenaline and dopamine in hypothalamus and striatum with Ca^{++} free intraventricular perfusion.

to bring down the Ca^{++} concentration to zero, the Ca^{++} action as a coupler could not be confirmed. But the finding may be attributed to the drop of the Ca^{++} influx.

When the Mg^{++} concentration in the perfusion fluid was increased, the NA release tended

to be slightly decreased.

The increase in the NA release following the angiotensin administration was also absent. (Fig. 3.)

A similar study of the Mg^{++} action on A yielded a similar result.

As for the K^{+} action, it was revealed that excess K^{+} caused an increase in the NA release. This occurred irrespective of the angiotensin administration, or in other words, K^{+} seemed to stimulate the adrenal just as Ang does. (Fig. 4)

A similar study on A brought about the same result as with NA.

In the next place, the tissue CA concentration was determined after the angiotensin administration. In the adrenal, the NA level was rather rapidly reduced. (Fig. 5)

Similar finding with A was studied.

As for the NA change in the hypothalamus, it was noted that NA was significantly decreased in the hypothalamus, as seen on Fig. 6 illustrating the NA levels three minutes after the angiotensin administration.

Ventricular perfusion was carried out to study the angiotensin effect by changing electrolyte concentrations in the hypothalamus. That is, a needle was inserted into the lateral and third ventricles respectively and the perfusion fluid was induced into the lateral ventricle at a rate of 0.1 ml/min. and drained from the third ventricle. After 15 minutes of perfusion, angiotensin was administered into the caudal vein. Three minutes later the animal was frozen and the hypothalamus and striatum were excised to be studied.

As first the Ca^{++} concentration in the perfusion fluid was made varied. After a perfusion with high Ca^{++} fluid, hypothalamic NA showed no significant difference from the normal level. A simultaneous administration of angiotensin caused no significant decrease. (Fig. 7)

Next, a perfusion with Ca^{++} -free fluid and the angiotensin administration also failed to cause the NA decrease. (Fig. 8)

It was made clear that after high Ca^{++} fluid was induced by intraventricular injection or ventricular perfusion, the hypothalamic Ca^{++} concentration was decreased. This may be due to the decrease of the Ca^{++} influx in spite of the higher Ca^{++} concentration in the perfusion fluid, resulting in the lack of the NA decreased by the angiotensin administration. It was speculated that there exists an optimum Ca^{++} concentration in perfusion for its coupler action.

A similar tendency was also noted with the

Fig.9. Effects of angiotensin on noradrenaline in hypothalamus with intraventricular perfusion of free and high K^+ .

Fig.10. Effects of angiotensin on blood pressure with K^+ free, high K^+ and Ca^{++} free intraventricular perfusion.

Fig.11. The effect of angiotensin on MAO activity in hypothalamus and striatum.

adrenal.

In order to study the role of K^+ , fluids containing K^+ in various concentrations were perfused.

It was found that angiotensin had its action

Fig.12. The effect of angiotensin on COMT activity in hypothalamus and striatum.

without K^+ as it caused the NA decrease after K^+ -free perfusion.

The NA decrease occurred either by high K^+ perfusion alone or by the high K^+ perfusion and the angiotensin administration. (Fig.9)

To examine the effect of such perfusion on the hypertensive action of angiotensin, blood pressure curves were obtained for the formal electrolyte concentration, high K^+ , K^+ -free and Ca^{++} -free perfusions with the concurrent angiotensin administration. (Fig.10)

The blood pressure rose immediately as high K^+ fluid was perfused. The angiotensin administration in the course of this hypertensive change did not affect the blood pressure, but as switched to the normal fluid perfusion, the blood pressure was restored to the normal level.

By the K^+ -free perfusion and the angiotensin administration, the blood pressure rose irrespective of K^+ .

The Ca^{++} -free perfusion and the angiotensin administration did not cause sufficient hypertensive reaction.

Then the MAO activity was determined on the hypothalamus and striatum before and after the angiotensin administration.

The hypothalamic MAO activity was decreased after administration. (Fig.11)

As for the COMT activity, it was increased in the hypothalamus after the angiotensin administration. (Fig.12)

Using the SHR, Yamori et al. found a decrease of NA in the brain stem. From the fact that this NA change was not affected by the removal of

the adrenal, they attributed to this the pathogenesis of hypertension in the SHR. The hypertensive condition produced by angiotensin administration in the present study was an acute change, with an abnormally high blood angiotensin level and with no persistency of hypertension, which is fairly different from essential hypertension. These facts should be kept in mind in discussing the results of the present study. As already stated, it was revealed that, in the adrenal, angiotensin releases endogenous NA, that the Ca^{++} concentration in the perfusion fluid does not affect the NA release, and that K^+ , like angiotensin, stimulates the adrenal.

These findings on the adrenal hold true with the hypothalamus. That is, hypothalamic NA decreases three minutes after the angiotensin administration.

Although this may be due to such causes as a decrease of the NA synthesis rate, accelerated metabolism, increased NA release, and reduced NA re-uptake, the possibility of the increased NA release is strongly suggested in view of the rapid decrease of NA and the demonstration of its release from the adrenal.

As the enzyme activities were studied in relation to the CA metabolism, it was found that the MAO activity was reduced but the COMT activity enhanced. Such changes in the enzyme activity may have resulted in some changes in the NA metabolism, but no definite explanation for these phenomena is as yet possible.

As to the relation between the electrolytes in the perfusion fluid and the hypertensive reaction, the significant participation of the central nervous system and the important role played by the electrolytes in this system in the mechanism for antihypertension are indicated, even if the effect of the ventricular perfusion is taken into account, from the facts that the high K^+ perfusion induces hypertension by itself, that the hypertensive action of angiotensin is preserved in the absence of K^+ , and that angiotensin hypertension is not sufficiently achieved in the Ca^{++} -free condition.

The NA decrease in the hypothalamus is a common finding with the SHR, so taking the changes in the SHR into consideration, it may be inferred that there is a significant relation between hypertension and the hypothalamic NA decrease.

Discussion:

Chairman: Dr. K. ARAKAWA

In reply to the questions asked by Drs. Y. Kaneko, T. Kokubu and K. Fukiyama, as to the methodology, Dr. I. Tsunoda answered as follows:

Angiotensin was administered intravenously from rat tail. It is believed to pass through blood brain barrier and reaches to the brain stem. A decrease of catecholamines in hypothalamus was thought to have been caused by this angiotensin reached. Whether the decreased catecholamine in hypothalamus thus produced is connected to the mechanism of the blood pressure elevation is not known, but it seems to be common in any other types of hypertension too, such as reported in SHR.

As to the action of angiotensin and its pathogenesis in hypertension, Dr. Y. Yamori commented as follows:

Since the first report by Professor Ueda, the action of angiotensin to the central nervous system has been studied both in this as well as other countries. Dr. Yamori himself also reported it at this conference last year. According to his data, angiotensin seemed to act through post-synaptic nerve because pretreatment by α -agonist (clonidine) extraordinarily enhanced the pressor action of angiotensin. Thereby, angiotensin II might be antagonizing to depressor action of α -agonist. An attitude of central nervous system, however, differs by the kind of hypertension, and depressor action of α -agonist (L-DOPA) is very strong in SHR, and DOCA hypertension, whereas weak in renal hypertension. Suppression of decarboxylase activity as seen in SHR does not appear true in renal hypertension. A rapid decrease of noradrenalin in the brain stem as the authors have observed may be resulted from an activation of noradrenergic mechanism which mediates a reflectoric depressor action of central nervous system, because it is already well known that baroreceptor reflex is mediated by central noradrenergic mechanism. Relation of central noradrenalin to blood pressure regulation is determined by the amount of noradrenalin supplied to central α -receptor. It is not the content, but a rate of active turn-over which should be studied. Therefore, whether the decrease of noradrenalin in hypothalamus by the administration of angiotensin was due to an inhibition of biosynthesis or enhanced release, should be determined by estimating the noradrenalin in the perfusate after a pretreatment with labeled noradrenalin. (Moderator: Kikuo Arakawa)