The Role of the Peripheral Sympathetic Nerves and the Adrenal Medulla in Maintaining Blood Pressure of Essential Hypertension

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It has been suspected that the sympathetic nervous system took a part in the origin of essential hypertension. Many studies on the relationship between the sympathetic nervous system and the essential hypertension have been reported, but there have not yet been clearly defined. 6-OH-DA\(^1\)\(^\text{2}\) is a new drug which markedly depletes stores of noradrenaline in the peripheral tissues\(^3\) and selectively destroys sympathetic nerve terminals\(^4\) and it was proposed as a drug of "Chemical sympathectomy"\(^5\). The present paper describes the effects of 6-OH-DA on normotensive and hypertensive rats, and a role of the peripheral sympathetic nerves and the adrenal medulla for maintaining blood pressure of essential hypertension was also studied in these rats.

METHODS

1. Animals:
   Male rats aged 9–10 weeks and weighing 170–200 g were used in the present study. The spontaneously hypertensive rats that were developed by Okamoto and Aoki\(^6\) were used. Agematched albino rats of the wister strain were used as normotensive rats.

2. The measurement of the catecholamines:
   Noradrenaline in the heart and adrenaline in the adrenal glands in the rats were determined by our method which modified the THI method\(^7\).

3. The measurement of blood pressure in the anesthetized rats:
   The blood pressures of rats anesthetized with sodium pentobarbital were measured by cannulation of the left carotid artery through U-shaped mercury manometer before and 5, 10, 15, 20, 25, 30 minutes after the injection of 6-OH-DA (0.7 mg/kg) through a femoral vein.

4. The measurement of blood pressure in the unanesthetized rats:
   The blood pressures were measured before and from one hour to 7 days after intravenous injection of 6-OH-DA (50 mg/kg) by a tail plethysmographic method.

5. The measurement of blood pressure in the adrenalectomized rats:
   The bilateral adrenal glands were removed in those rats under ethylether anesthesia and the blood pressures were measured by the same method mentioned in 3) after leaving for two hours.

RESULTS AND DISCUSSION

1. The cardiac noradrenaline contents in normotensive and hypertensive rats rapidly decreased by the treatment of 6-OH-DA, and the long-lasting depletion was produced, but the adrenaline contents in the adrenal glands of both groups were not changed (Fig. 1).

   It seems that uptake of 6-OH-DA was observed in the peripheral sympathetic terminals and noradrenaline was rapidly released from these terminals which was destroyed by 6-OH-DA. It seems that the long-lasting cardiac

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**Key Words:**
- Spontaneously hypertensive rats
- Peripheral sympathetic nerves
- Adrenal glands 6-hydroxydopamine
- Catecholamines

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Fig. 1. The effect of 6-OH-DA on catecholamine in normotensive and spontaneously hypertensive rats heart and adrenal glands. (Each value is mean ± SE of 5-6 rats).

In comparison of the caridac noradrenaline contents between normotensive and hypertensive rats before and after treatment of 6-OH-DA, the noradrenaline contents in hypertensive rats were 12% lower than those in normotensive rats before the treatment. 24 hours after the treatment, the noradrenaline contents in both groups were reduced more than 95%. 7 days after the treatment, the noradrenaline level in normotensive rats was $0.039 \pm 0.007 \mu g/g$ (M ± S.E.) and that in hypertensive rats was $0.054 \pm 0.011 \mu g/g$ (M ± S.E.). It seems that the recovery of the destroyed sympathetic nerve terminals in hypertensive rats is comparatively faster than that in normotensive rats within the period of 7 days observed.

2. The short term effects of 6-OH-DA on blood pressure (Fig. 2).

The blood pressure after the treatment of 6-OH-DA rapidly elevated in both of normotensive and hypertensive rats. The elevation in blood pressure reached a peak in less than two minutes, and then the blood pressures of normotensive rats fell comparatively faster than that of hypertensive rats.

A rapidly marked elevation of blood pressure suggests that noradrenaline was rapidly released from the nerve ending by 6-OH-DA. The comparatively longer-lasting pressor effect observed in hypertensive rats during 30 minutes after the treatment of 6-OH-DA suggested that those rats have the hypersensitivity of $\alpha$-receptor.

noradrenaline depletion was produced by selective destruction of the peripheral sympathetic nerve terminals with 6-OH-DA.
Fig. 3. The effects of blood pressure during the first 30 minutes after one intravenous injection of 6-OH-DA in adrenalectomized rats.
A) Normotensive rats.
B) Spontaneously hypertensive rats.
(Values are means ± SE of 5 rats).

to noradrenaline as reported by Thant et al.8

Since 6-OH-DA releases catecholamines from the adrenal medulla,9 the catecholamines which were released from the adrenal medulla also seem to contribute to the sympathomimetic effect. Furthermore, the rate of synthesis of adrenal catecholamine in hypertensive rats shows to be higher than that in normotensive rats as reported10-12.

3. The comparatively long term effects of 6-OH-DA on blood pressure (Fig. 3): The blood pressure after the treatment of 6-OH-DA rapidly fell in both rats and the blood pressure in hypertensive rats after the treatment was greater than that in normotensive rats and further the return to the initial blood pressure level in normotensive rats was faster than that in hypertensive rats. In spite of the recovery of the sympathetic nerve terminals in hypertensive rats was comparatively faster than that in normotensive rats, the recovery of the blood pressure in normotensive rats after the treatment of 6-OH-DA was faster than that in hypertensive rats. From these findings, the peripheral sympathetic nerves seems to contrib-

ute in maintaining blood pressure. It suggests that the function of the peripheral sympathetic nerves in hypertensive rats is increased than that in normotensive rats.

4. The short term effects of 6-OH-DA on blood pressure in the adrenalectomized rats (Fig. 4).

The adrenalectomized normotensive and hypertensive rats were used for removing effects of the adrenal medulla. In both of adrenalectomized and unadrenalectomized rats, the blood pressures after the treatment rapidly increased and thereafter the fall of the blood pressures in adrenalectomized rats were faster than that in unadrenalectomized rats. The chemical sympathectomy after the removal of the adrenal glands caused a rapid fall of the blood pressure in both rats. The catecholamines were released from the adrenal medulla seem to contribute in maintaining blood pressure as a compensatory role after chemical sympathectomy.

From these results, it seemed that the peripheral sympathetic nerves and adrenal medulla have an important role for maintaining blood pressure, and suggested that an important factor which maintains high blood pressure is a functional abnormality with hyperactivities in the peripheral sympathetic nerves and adrenal medulla of hypertensive rats, and not only functional abnormalities in the peripheral sympathetic nerves and adrenal medulla but also functional abnormalities in the brain13-15 and the endocrine organs16 such as the hypophysis and thyroid might be considered.

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Discussion:

Chairman: OSAMU IIMURA, Sapporo Med. Coll.

The present paper describes the results of study on how the sympathetic nerve system involved in the maintenance of hypertension, which was made by means of administration of 6-OH-DA to SHR with or without adrenalectomy. And the following discussion and comments were made.

Dr. YOSHIRO KANEKO (Yokohama City Univ.): It is impossible to accurately measure blood pressure under anesthesia because of the effect of the anesthesia itself. In such a case, some criteria should be provided, and the experiments be made under such conditions which meet the criteria.

On the other hand, why was the present observation of SHR limited to that in essential hypertension? Because there is no evidence that the etiology of essential hypertension is identical with that of SHR, it is necessary to clearly separate them from each other.

Dr. HONDA: Blood pressure falls by 10–30, mmHg under anesthesia with ethylether and Nembutal. It is, however, impossible to additionally inject an anesthetic agent during experiment because of individual difference in the response of rat to the additional injection. For this reason, the present experiments were made under anesthesia by only the initial injection of the anesthetic agents.

Dr. KYUZO AOKI (Nagoya City Univ.): In my experiments, adrenalectxomy in SHR (Okamoto–Aoki) failed to lower in blood pressure. It cannot, therefore, be concluded that the adrenal medulla is indispensable to the maintenance of hypertension in SHR.

Dr. YUKIO YAMORI (Kyoto Univ.): In our experiments, SHR was adrenalectxomized at the stage when hypertension was established and also in the course to the onset of hypertension. However, no fall in blood pressure resulted, and it, therefore, appears that the adrenal medulla is not associated with the maintenance of hypertension. It should rather be interpreted as indicative of enhanced tonus of the sympathetic nerve system that hypertension was maintained in adrenalectxomized condition. Also because the function was maintained and hypertension continued even if the animals were depleted of peripheral catecholamine by administration of 6-OH-DA, it appears inadequate to interpret the results of experiments with 6-OH-DA simply as indicative of chemical sympathectomy.

In our experiments, change in blood pressure following intravenous injection of 6-OH-DA were investigated in SHR and Wister/NIH and in neurogenic hypertension by Krieger's method, and it was revealed that high blood pressure was maintained even in a condition where peripheral catecholamine was markedly decreased. In other words, it appeared that the peripheral catecholamine content itself was not influential only if the content itself was not influential only if the receptors remained intact. It appeared that the function was maintained only if that amount of active catecholamines which was equivalent to about 1/10 of normal amount was supplied to the receptor sites.

Dr. OSAMU IIMURA (Sapporo Med. Coll.): It is true that even if the catecholamine content
is markedly decreased following the administration of reserpine, the cardiac function is maintained normal. It should, however, be considered that there is only reduced resistance to overloading under such condition.

Dr. HIROFUMI SOKABE (Jichi Med. School): In order to prove that the adrenal medulla is associated with the maintenance of blood pressure in SHR, it is necessary to demonstrate the following two points: (a) adrenal medullectomy results in a fall in blood pressure of SHR, and (b) administration of catecholamine restores the so lowered blood pressure to the previous level.