The Role of Neural Factors in Experimental Renal Hypertension

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The peripheral vascular reactivity, function of baroceptors and sympathetic activity were studied in experimental renal hypertensive dogs and the isolated smooth muscle strips of renal hypertensive rats. Increased sensitivity of peripheral vessels to noradrenaline was demonstrated in vivo and in vitro experiments in hypertensive dogs. The baroceptors were resetted to the higher blood pressure level, and their sensitivity itself remained unchanged in renal hypertension. The sympathetic overactivity was not recognized in hypertension. Thus, only increased sensitivity of peripheral vessels to noradrenaline contributes to a part of the pressor mechanism in renal hypertension, while the baroceptors and sympathetic activities are passively adjusted to the higher blood pressure levels in hypertension.

SINCE Goldblatt succeeded in the production of experimental renal hypertension in rabbits in 1934,1) many studies on the humoral mechanism of hypertension, especially on the pressor substances, have been reported.2,3) Thus, many findings were accumulated in this field. On the other hand, symptoms and signs of essential hypertension suggest that neural disorders are involved in the production and the maintenance of hypertension, and the important role of the nervous system in essential hypertension is also pointed out by the fact that most of the current, effective antihypertensive drugs interfere with sympathetic vasoconstrictor outflow. From these points, attentions have been given to the neural factors in hypertension.4) The mechanism of the production of renal hypertension may be studied from the points of the pressor substances and the reactivity of the blood vessels in the hypertensive subjects. An attempt was therefore made to study from the latter point. The followings are considered to influence the reactivity or responsiveness of the blood vessels; (1) increased sensitivity to normal amounts of pressor substances...
substances or changes in the reactivity of the smooth muscles, (2) changes in baroceptor functions, and (3) sympathetic activities.

Generally, experimental renal hypertension goes through an early acute phase before the prolonged chronic phase becomes established. A change in the basic mechanism of the 2 phases seems to be established. The humoral mechanism may mainly play an important role in the acute phase, while the neural mechanism is important in the chronic phase. However, here still remain some questions. Is there any change in the reactivity of blood vessels in hypertension? Why do baroceptors fail to react to the elevated blood pressure? Does sympathetic overactivity participate in the renal hypertension?

The present study is concerned with testing the possibility of vascular hyperresponsiveness, the changes in baroceptor functions and sympathetic overactivities in renal hypertension. Thus, (1) The effect of anesthetics on the blood pressure was tested in renal hypertension to see the general role of the nervous system, and the pressor responses to noradrenaline, angiotensin and Pitressin were tested before and after the production of renal hypertension in the same dogs. On the other hand, the responsiveness to these agents of the isolated smooth muscle strips of intestine or uterus of normotensive and hypertensive rats was tested to find the real hyperresponsiveness: (2) The activity of carotid sinuses was tested by the isolated perfusion of carotid arteries at the different intrasinusal pressure in normal and renal hypertensive dogs; And (3) the effect of ganglioplegics on blood pressure and the influence of extensive sympathectomy on blood pressure were compared in normotensive and hypertensive dogs. At the same time, the urinary excretion of adrenaline and noradrenaline was measured in the course of the production of experimental renal hypertension in dogs.

**Methods**

*Production of renal hypertension in dogs and rats:*

Renal hypertension was produced in 34 dogs by partial constriction of renal artery on one side by a silver clip and contralateral nephrectomy, or by unilateral perinephritis induced by cellophane (Du Pont)-wrapping by Page's method and contralateral nephrectomy.8),9)

Renal hypertension was also produced in 14 adult female albino rats by partial constriction of one renal artery by Byrom and Wilson's method,10) cellophane-wrapping by Page's method,9) or by 8 figure ligation by Grollman's method.11)

*Blood pressure measurement and recording:*

Arterial blood pressure was measured by direct puncture of one femoral artery once a week in the course of the production of renal hypertension in
unanesthetized dogs. Except checking the blood pressure, dogs were anesthetized by pentobarbital (30 mg./Kg. of body weight) and the level of the anesthesia was maintained by intramuscular injection of small doses of pentobarbital in all experiments in dogs. The blood pressure was recorded on the smoked drum by a mercury manometer connected to a cannulated femoral artery. The arterial blood pressure was measured in unanesthetized rats by modified Gallagher and Grimwood's microphonic method described by Ito and Amano.\textsuperscript{12)

**Depressor responses to anesthetics:**
Under local anesthesia by procaine, a canula was inserted into the femoral artery of dogs. Sodium pentobarbital (30 mg./Kg.) was injected intravenously in one and a half minutes and the blood pressure was recorded continuously for 20 minutes after the injection.

**Pressor responses to vasoactive agents and depressor responses to ganglioplegics:**
The rise of blood pressure by the intravenous injection of a single dose of noradrenaline ($5 \times 10^{-6}$ gamma), angiotensin ($0.5 \times 1.0$ gamma) and Pitressin ($0.1 \times 0.2$ units) was recorded before and after the production of chronic renal hypertension in the same dogs. The depressor responses to pentolinium (25 mg.), hexamethonium (5 mg., 12.5 mg.), tetraethylammonium bromide (50 mg.) and KK-25-S (N-dimethylaminopropyl-4, 7-endoethylene-3, 4, 7, 8-tetrahydro-isoindoline 1.75 mg.) were also measured in the course of the production of renal hypertension in 5 dogs.

**Responses of isolated smooth muscle strips:**
The contractions or relaxations of the smooth muscle strips of about 2 cm. in length isolated from uterus, small intestine or rectum of rats were recorded on the smoked drum. After exsanguination these organs were rapidly dissected free, and placed in Ringer-Bülbring solution of 32°C. The muscle strips were transferred to a muscle bath containing 20 ml. of the solution. The muscle strips were exposed to the various concentrations of noradrenaline, adrenaline, angiotensin, serotonin and acetylcholine, contained in 0.1 ml. of solution, successively at 3 to 5 minutes intervals. For each experiment, the strip was stretched just enough to produce a tension of 0.5 Gm. and 30 minutes elapsed before any drugs were added to keep a stable tone. The threshold, the minimal effective concentration, for noradrenaline, adrenaline, angiotensin, serotonin, and acetylcholine of the isolated smooth muscle strips of small intestine, rectum, or uterus from 8 hypertensive, 6 operated normotensive, and 11 control rats was determined and the magnitude of the contractions or relaxations of the muscle strips to these agents was also measured.

**Isolated perfusion of the carotid sinus areas:**
The carotid sinus was completely isolated from the systemic circulation and intrasinusal pressure was maintained by a pump as Kezdi\textsuperscript{13) had described. A common carotid artery was tied and the sinus end was cannulated. As many of the distal branches as possible were ligated without damaging the nerve, and the carotid sinus area of the other side was resected. The system was filled with isotonic saline at the body temperature and was connected to a pump producing pulsatile pressure. Vago-depressor trunks were dissected and direct femoral artery pressure and pressure in the carotid sinus region were recorded on a drum. Tetraethylammonium bromide (TEAB 5 mg./Kg.) response was
then tested at different intrasinusal pressure levels.

*Sympathetic innervation on carotid sinus activity:*

When supersensitivity of the denervated effectors was produced 2 weeks after cervical sympathectomy of one side, a small amount of noradrenaline was injected into the adventitia of the denervated carotid sinus area and the resulting blood pressure fall and the depression of the carotid occlusion reflexes were compared with those following the injection of the same dose of noradrenaline into the adventitia of the innervated side. The details of this method was described in the previous paper. To investigate the influence of the sympathetic innervation on carotid sinus activity in renal hypertensive dogs, the same experiment was performed in chronic hypertensive dogs. Ten gamma of noradrenaline was injected subadventitiously into the carotid sinus areas, and the blood pressure fall and the depression of the carotid sinus occlusion reflexes were compared by the same method.

*Extensive sympathectomy:*

Both superior, middle and inferior cervical ganglia, stellate ganglia, splanchnic nerves and lumbar sympathetic trunks were resected extensively in normotensive and renal hypertensive dogs.

*Urinary excretion of adrenaline and noradrenaline:*

Daily urinary excretion of adrenaline and noradrenaline was measured by Lund's method after the purification by von Euler and Orwen's method.

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**Results**

1. Pressor and depressor responses to various agents in hypertensive dogs

   (1) Effect of anesthetics on blood pressure

   The changes in the mean arterial blood pressure by the injection of pentobarbital (30 mg./Kg.) in normotensive, acute renal hypertensive, and neurogenic hypertensive dogs are shown in Fig. 1. In normotensive and acute renal hypertensive (within 2 weeks after the second operation) dogs, the blood pressure returned to the previous level following the transient blood pressure fall within 10 minutes, while in chronic renal hypertensive dogs, the transient blood pressure fall was more marked and the recovery of the blood pressure was slower, thus the blood pressure did not return to the previous level within 20 minutes. And in neurogenic hypertensive dogs induced by the section of both carotid sinus nerves and aortic depressor nerves, the transient blood pressure fall was remarkable, but the blood pressure returned to the previous level without any delay.

   (2) Responses to pressor substances

   The pressor responses to noradrenaline, angiotensin and Pitressin before and after the production of chronic renal hypertension of 3 to 15 weeks' duration in the same dogs are shown in Fig. 2. The augmentation of
Fig. 1. The influence of anesthetics on blood pressure in normotensive and hypertensive dogs.

the responses to noradrenaline was demonstrated after 3 weeks following the second operation, but those to angiotensin and to Pitressin were not so remarkably augmented. The relationship between the blood pressure levels and the pressor responses is shown in Fig. 3. After the produc-
tion of renal hypertension, the pressor responses to noradrenaline were markedly augmented, but those to angiotensin were not significantly augmented and there was few augmentation of the responses to Pitressin.

(3) Responses to ganglionic blockades

The depressor responses to ganglionic blockades, as pentolinium, hexamethonium, TEAB and KK-25-S, in the course of the production of renal hypertension in 5 dogs are shown in Fig. 4. The depressor responses to these relatively high doses of ganglioplegics were not always augmented after the production of renal hypertension. It has been known that the responses to pressor substances were augmented by the administration of ganglioplegics in normal animals. So, it is interesting to

Fig. 3. (a) Pressor responses to noradrenaline in normotensive and hypertensive dogs. (b) Pressor responses to angiotensin in normotensive and hypertensive dogs.
Fig. 3. (c) Pressor responses to Pitressin in normotensive and hypertensive dogs.

Fig. 4. Depressor responses to ganglion blocking agents in experimental renal hypertensive dogs.

compare the augmentation by the ganglioplegics before and after the production of chronic renal hypertension in the same dogs. But, the grade of the augmentation of the responses to noradrenaline, angiotensin and Pitressin by these ganglioplegics was affected by neither the presence nor the absence of hypertension,
2. Role of baroceptors in hypertensive dogs

(1) Sensitivity of carotid sinuses

When the intrasinusal pressure was lowered by a pump, femoral artery pressure became elevated. The relationship between the carotid arterial pressure and the corresponding systemic pressure was parallel in normotensive and hypertensive dogs as shown in Fig. 5. Thus, the degree of change in the systemic blood pressure corresponding to a change in the carotid arterial pressure was constant both in normotensive and renal hypertensive dogs. In other words, the sensitivity itself of the baroceptors was unchanged in normotensive and hypertensive groups.

The responses to the sufficient amounts of TEA at different intrasinusal pressures following bypass of the carotid sinus were studied in normotensive and renal hypertensive dogs to find the amounts of the reflex sympathetic outflow. When the intrasinusal pressure was lowered and the femoral arterial pressure elevated, the responses to TEA were also enhanced, indicating increased sympathetic outflow at the low intrasinusal pressure levels. The blood pressure levels after the intravenous administration of TEA at the different intrasinusal pressures were also parallel in normotensive and hypertensive dogs, as shown in Fig. 6. At the point where the systemic and the intrasinusal pressures were equal, in other words, at the own blood pressure levels of the dogs, the responses to TEA were equal in normotensive and renal hypertensive dogs. A similar response pattern was also demonstrated in renal hypertension except the upward shift.
of the blood pressure level.

(2) Influence of the sympathetic innervation on carotid sinus activity

The fall of the blood pressure and the depression of the carotid occlusion reflexes by a local injection of 10 gamma of noradrenaline into carotid sinus areas were more marked on the denervated side than those on the innervated side in chronic renal hypertensive dogs as shown in Fig. 7. These results were similar to those in normotensive dogs reported previously. The influence of the sympathetic innervation on the carotid sinus activity, therefore, was the same in the chronic renal hypertensive animals as in the normotensive animals.

3. Responses of isolated smooth muscle strips

The thresholds for adrenaline, noradrenaline, acetylcholine, angiotensin and serotonin of the smooth muscle strips of uterus, small intestine and rectum in normotensive and renal hypertensive (over 160 mm. Hg) rats are shown in Table I. Although the differences in these 2 groups were not so remarkable, the thresholds for acetylcholine, angiotensin and serotonin were often elevated in hypertensive group, while those for adrenaline and noradrenaline were slightly diminished in hypertensive rats.
Table I. Threshold for Various Drugs of the Smooth Muscle Strips in Normotensive and Renal Hypertensive Rats

<table>
<thead>
<tr>
<th></th>
<th>Adrenaline</th>
<th>Noradrenaline</th>
<th>Acetylcholine</th>
<th>Angiotensin</th>
<th>Serotonin</th>
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<tr>
<td><strong>Uterus</strong></td>
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<td></td>
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<td>$5 \times 10^{-6}$ $\sim 1 \times 10^{-8}$</td>
<td>$8 \times 10^{-8}$</td>
<td>$5 \times 10^{-12}$ $\sim 5 \times 10^{-15}$</td>
<td>$5 \times 10^{-12}$ $\sim 5 \times 10^{-13}$</td>
<td>$5 \times 10^{-11}$ $\sim 3 \times 10^{-14}$</td>
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<tr>
<td>Hypertensive</td>
<td>$5 \times 10^{-7}$ $\sim 1 \times 10^{-8}$</td>
<td>$5 \times 10^{-7}$</td>
<td>$5 \times 10^{-10}$</td>
<td>$5 \times 10^{-8}$</td>
<td>—</td>
</tr>
<tr>
<td>Normotensive Operated</td>
<td>$5 \times 10^{-9}$</td>
<td>$5 \times 10^{-9}$ $\sim 5 \times 10^{-9}$</td>
<td>$1 \times 10^{-9}$</td>
<td>—</td>
<td>$1 \times 10^{-6}$ $\sim 5 \times 10^{-9}$</td>
</tr>
<tr>
<td><strong>Small Intestine</strong></td>
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<tr>
<td>Control</td>
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<td>$1 \times 10^{-9}$ $\sim 1 \times 10^{-9}$</td>
<td>$5 \times 10^{-9}$ $\sim 5 \times 10^{-16}$</td>
<td>$5 \times 10^{-9}$ $\sim 5 \times 10^{-13}$</td>
<td>$5 \times 10^{-16}$</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>$5 \times 10^{-8}$ $\sim 1 \times 10^{-11}$</td>
<td>$5 \times 10^{-8}$ $\sim 1 \times 10^{-11}$</td>
<td>$5 \times 10^{-10}$ $\sim 1 \times 10^{-14}$</td>
<td>$5 \times 10^{-8}$</td>
<td>$1 \times 10^{-6}$ $\sim 1 \times 10^{-10}$</td>
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<tr>
<td>Normotensive Operated</td>
<td>$5 \times 10^{-9}$ $\sim 1 \times 10^{-10}$</td>
<td>$5 \times 10^{-8}$</td>
<td>$1 \times 10^{-9}$ $\sim 5 \times 10^{-10}$</td>
<td>$5 \times 10^{-8}$</td>
<td>$5 \times 10^{-6}$ $\sim 1 \times 10^{-8}$</td>
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<tr>
<td><strong>Rectum</strong></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>$5 \times 10^{-9}$</td>
<td>$5 \times 10^{-9}$ $\sim 5 \times 10^{-10}$</td>
<td>$5 \times 10^{-12}$</td>
<td>$5 \times 10^{-14}$</td>
<td>$5 \times 10^{-9}$</td>
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<tr>
<td>Hypertensive</td>
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<td>$5 \times 10^{-8}$</td>
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<td>$5 \times 10^{-6}$</td>
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<tr>
<td>Normotensive Operated</td>
<td>$5 \times 10^{-7}$</td>
<td>$5 \times 10^{-7}$</td>
<td>$5 \times 10^{-12}$ $\sim 1 \times 10^{-14}$</td>
<td>$5 \times 10^{-8}$</td>
<td>$5 \times 10^{-8}$ $\sim 1 \times 10^{-9}$</td>
</tr>
</tbody>
</table>
No. 18 (9/13/60): Dog (No. 16, ♂, 11.0Kg.) (8/30/60 Right Cervical Sympathectomy) 6 weeks post-op.

Before the Section of R. C. S.  
NOR. 10γ (L. C. S.)  
NOR. 10γ (R. C. S.)

After the Section of R. C. S.  
NOR. 10γ (R. C. S.)

Fig. 7. The influence of the sympathetic innervation on carotid sinus activity in hypertensive dogs.

Thus, the responses to acetylcholine, angiotensin and serotonin were depressed in hypertensives, while the responsiveness to adrenaline were slightly sensitized in hypertensive rats. Normally, the muscle strips which did not react to acetylcholine, angiotensin or serotonin, also did not react to adrenaline or noradrenaline. But interestingly, in hypertensives, the muscle strips which did not react to the formers did react slightly to the low concentration of adrenaline or noradrenaline. Usually, the magnitude of the responses was smaller in hypertensive group than in normotensives. Even though the responses to adrenaline or noradrenaline were recognized in hypertensives at the lower concentrations than in normotensives, the magnitude of the responses was smaller. In other words, in hypertensive group, the thresholds for angiotensin, serotonin or acetylcholine were elevated and at the same time the magnitude of the contraction was smaller, but the thresholds for adrenaline or noradrenaline were lowered, while the magnitude of the relaxation was smaller (Fig. 8).

4. Role of sympathetic nervous system
   (1) Effects of sympathectomy
   The magnitude of the blood pressure fall as a direct influence by the extensive sympathectomy was not significantly different in normotensive and in hypertensive dogs as shown in Fig. 9. The blood pressure level after sympathectomy in renal hypertensive dogs was higher than the control value before the production of hypertension.
(2) Urinary excretion of adrenaline and noradrenaline

Urinary excretion of adrenaline and noradrenaline was measured in the course of the production of renal hypertension in dogs. As shown in Fig. 10, in the period of the blood pressure rise, the daily urinary excretion of noradrenaline showed a slightly increasing tendency, but in the period of continuing high blood pressure level, no deviation was found in the urinary excretion of adrenaline or noradrenaline.

![Graphs showing control, hypertensive, and normotensive responses to adrenaline.](image)

**Fig. 8.** Responses to adrenaline of small intestine in normotensive and hypertensive rats.

**Fig. 9.** (a) The influence of sympathectomy on blood pressure in a normal dog.

![Graph showing blood pressure changes after sympathectomy.](image)
DISCUSSION

It has been supposed that there might be some effective augmenting mechanism of the effect of the known pressor system in chronic renal hypertension so that the muscle fibers of the arterioles and arteries of hypertensive subjects would respond to normal amounts of circulating...
vasopressor material and normal amounts of noradrenaline released at sympathetic nerve endings with a greater than normal amount of shortening.\textsuperscript{18),19)\textsuperscript{\dagger}} To investigate the general role of the nervous system in chronic renal hypertension, the effects of anesthetics were discussed.\textsuperscript{5),20)\textsuperscript{\dagger}} Ogden postulated that the role of nervous system in hypertension was increased with the progress of renal hypertension, while the role of kidney was decreased, since the blood pressure fall by the removal of the constricted kidney was inversely related to the period after the operation for the production of renal hypertension and the blood pressure fall by pentobarbital was more marked in chronic renal hypertension. Results of the present study showed that the fall of the blood pressure by pentobarbital was more marked and continued longer in chronic renal hypertensive dogs, suggesting the possibility that the nervous system played a role in the maintenance of chronic renal hypertension. However, a question still remains undetermined as to which parts of the nervous system play the most important role. Many studies have been carried out to make sure whether the increase in the responsiveness of blood vessels was really present in hypertensive patients and renal hypertensive animals.\textsuperscript{18),19),21)-23)}\textsuperscript{\dagger} It was reported that the increase in the peripheral resistance to adrenaline or noradrenaline was more marked in hypertensive patients than in normotensives.\textsuperscript{19),24)}\textsuperscript{\dagger} Haas and Goldblatt\textsuperscript{18)}\textsuperscript{\dagger} showed that the responses to renin, angiotensin, noradrenaline and methylisothiourea were augmented in renal hypertensive dogs, especially the augmentation to the latter 2 being remarkable. The responses to Pitressin, directly acting on the vascular smooth muscles as methylisothiourea, were also augmented in renal hypertensive rabbits according to the experiments by Ogden.\textsuperscript{23)} While, Doyle and Black\textsuperscript{19)} reported that the responses to angiotensin, noradrenaline and methylisothiourea were only slightly augmented in hypertensives but after the administration of hexamethonium these responses were markedly augmented in hypertensives. These results seemed to be variable according to the kinds of the pressor substances and of animals used in the study, also depending upon the state of anesthesia. As the responses to pressor substances are generally different individually, the responses must be tested in the course of the production of renal hypertension in the same animals. In our experiments the responses to noradrenaline were remarkably augmented in chronic renal hypertensive dogs but the augmentation to angiotensin and Pitressin was not so marked. There are 2 distinct factors which will cause an apparent hyperresponsiveness of hypertensive subjects to pressor agents. First, stenotic process of the lumens by the organic changes of the vascular walls can produce apparent hyperresponsiveness without actual hyperresponsiveness. Second, there could be some changes of the spontaneous tone or the responsive-
ness of the vascular smooth muscles. Some investigators\textsuperscript{23),26),27) have postulated that this hyperresponsiveness was not due to the augmented arteriolar contraction, but due to the decreased diameter of the arteriolar lumens induced by the thickness of the wall by edema, cellular hypertrophy or arteriolar sclerosis, and that the contraction of the vessels in normal way resulted in the abnormal increase in the peripheral resistance. From our results it seems to be reasonable to consider that there may be some changes in the peripheral vascular sensitivity in chronic renal hypertension, since only the responses to noradrenaline were markedly augmented while those to the other vasoactive agents were not significantly augmented. Redleaf and Tobian\textsuperscript{23}) reported that hyperresponsiveness to noradrenaline of spirally cut strips of aorta was not shown in hypertensive rats and only the spontaneous tone was increased. Mallov\textsuperscript{28}) also reported the depression of the responsiveness to adrenaline or noradrenaline of aortic muscle spirals. On the other hand, Griesman,\textsuperscript{29}) who studied the reactivity of the capillary bed of the nailfold to circulating noradrenaline in patients with normal blood pressure and others with essential hypertension, showed a lower threshold for ischemia of the nailfold in the latter group. In our experiment the thresholds of isolated smooth muscle strips of hypertensive rats were lowered only for adrenaline or noradrenaline, while the magnitude of the responses was smaller. But, as the reaction in the body takes place at a very low concentration of endogenous adrenaline or noradrenaline, the lowering of the thresholds seems to have more important significance. The direct evidence obtained in these in vitro experiments on isolated smooth muscle strips cannot be transferred immediately to the behavior of arterioles in human hypertension. However, it is interesting that the hyperresponsiveness to noradrenaline was demonstrated in isolated smooth muscle strips from renal hypertensive rats as well as in pressor responses in renal hypertensive dogs.

Since the studies on baroceptors by Heymans,\textsuperscript{30}) the role of baroceptors in hypertension has been discussed. Heymans suggested that one of the important factors to produce hypertension was the change of the function of baroceptors. McCubbin\textsuperscript{31}) recorded the impulses from the carotid sinus nerves of normotensive and renal hypertensive dogs by electroneurogram at the different intrasinusal pressure levels and showed the resetting of carotid sinuses to higher blood pressure levels in chronic renal hypertensive dogs. From our results, the function of the baroceptors was essentially unchanged in normotensive and renal hypertensive animals and the equilibrium among intrasinusal pressure, carotid sinus discharge and the sympathetic outflow was obtained in higher levels in chronic hypertensive animals. Heymans has postulated that the direct stimulation to the carotid sinus was not the change in intrasinusal pressure itself but
the distension of the sinusal wall, thus he explained the resetting by the decrease in the tension of the arterial wall in hypertension. But the real mechanism by which resetting of baroceptors in chronic renal hypertension is produced remains obscure. Several factors may be involved. The structural changes in the arterial walls of carotid sinus and aorta or some biochemical changes may be concerned. The influence of sympathetic innervation on carotid sinus activity in chronic renal hypertension was as same as in normals.

In relation to the problem of the sympathetic overactivity in hypertension, the responses to the ganglionic blockades were investigated. The responses to the sufficient amounts of ganglioplegics were not always augmented in hypertension. On the other hand, augmentation of the responses to pressor substances by ganglioplegics was not affected by the presence of hypertension. Here, the role of sympathetic system was not significantly different between the normotensive and hypertensive subjects. Although sympathectomy has been performed as one of the treatments of essential hypertension, it has been shown that no significant fall of the blood pressure occurred after the extensive sympathectomy in hypertensive dogs.32) Our results also suggest that in renal hypertensive dogs the sympathetic nervous system is not the chief factor in the genesis or maintenance of hypertension. The urinary excretion of adrenaline or noradrenaline was reported to be normal in hypertensive patients.33),34) The result in our study also showed that except the stadium when the blood

Fig. 11. The role of nervous factors in renal hypertension.
pressure was rising, the urinary excretion of adrenaline or noradrenaline was not significantly changed. Here again sympathetic overactivity was not demonstrated in chronic renal hypertension.

It may be concluded, as schematically shown in Fig. 11, that only the increased sensitivity of peripheral vessels to noradrenaline contributes to a part of the pressor mechanism in renal hypertension. And baroceptors are resetted to the higher blood pressure levels without the changes in the sensitivity. There is no increase in the sympathetic vascular tone in the chronic phase of experimental renal hypertension. Thus, baroceptors and sympathetic system are only passively adjusted to the higher blood pressure levels. The problem of the role of vasomotor centers or higher central nervous system in the genesis and maintenance of renal hypertension remains to be studied in future.

Summary

The role of neural factors in experimental renal hypertension was studied from the points of peripheral vascular reactivity, function of baroceptors and sympathetic activity in renal hypertensive dogs and the isolated smooth muscle strips of hypertensive rats.

1. The hypotensive responses to pentobarbital was more marked and continued longer in chronic renal hypertensive dogs than the controls.

2. The pressor responses to noradrenaline was remarkably augmented in renal hypertensive dogs, while the changes in those to angiotensin and Pitressin were not so marked.

3. The threshold for adrenaline or noradrenaline of isolated smooth muscle strips of intestine, rectum and uterus of rats was lower in hypertensive rats than in the operated normotensive and control groups. But the threshold for angiotensin and acetylcholine was rather higher in the hypertensive group.

4. The sensitivity of baroceptors examined by using the isolated perfusion method was unchanged and the baroceptors were resetted to the higher blood pressure level in chronic renal hypertension.

5. The influence of sympathetic innervation on carotid sinus activity was not different between the normotensive and renal hypertensive dogs.

6. The depressor responses to the sufficient amounts of ganglioplegics were not significantly changed in hypertensive dogs compared with the normotensives.

7. After the extensive sympathectomy the direct blood pressure fall was not significantly different between the normotensive and renal hypertensive dogs and the final blood pressure level was higher in renal hypertension than the control level.
(8) The urinary excretion of adrenaline and noradrenaline was not significantly changed in chronic renal hypertensive dogs except the slight increase in the stage of blood pressure rising.

Thus, increased sensitivity of peripheral blood vessels to noradrenaline was demonstrated in vivo and in vitro experiments in hypertensive animals. The baroceptors were resetted to the higher blood pressure level, and their sensitivity itself remained unchanged in renal hypertension. The sympathetic overactivity was not recognized in hypertension. Therefore, only the increased sensitivity of peripheral vessels to noradrenaline contributes to a part of the pressor mechanism in renal hypertension, while the baroceptors and sympathetic activities are passively adjusted to the higher blood pressure levels in hypertension.

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The outline of this study was reported in symposium on renal hypertension at the 3rd annual meeting of Japanese Society of Nephrology in 1960.

References