Features of Efferent and Afferent Components of Neural Vascular Control System in the Spontaneously Hypertensive Rat

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Possible participation of the sympathetic nervous system in the pathogenesis, or at least, in the maintenance of hypertension has long been suggested. Unequivocal agreement, however, has not been reached as to whether the sympathetic nervous activities are increased in hypertensive state. This is partly because we have not had a convincing evidence for the increased sympathetic activities, and/or, better to say, partly because a reliable technique has not been established to evaluate the sympathetic "tone" directly. On the other hand, we know from considerable numbers of reports that vascular reactivity is increased in hypertensive subjects. This has been reviewed briefly but comprehensively by Somlyo and Somlyo. If the blood vessels of hypertensive subjects react more to catecholamine released from sympathetic nerve terminals, hypertension necessarily has a greater dependence on neural tone even though the latter is normal. From this the idea has come that sympathetic outflow down from the brain stem may not necessarily be increased in hypertension of which maintenance is generally agreed to be dependent on sympathetic nerve system.

We designed and carried out the following experiment so that we could know more precisely how much a neural participation was in the hypertension of the spontaneously hypertensive rat (SHR). Another purpose was to evaluate the role of vascular reactivity for the formation of this neural component. We used a neurologically intact hind limb perfused artificially by means of a metal finger type motor pump with the animal's own blood.

Animals, 3 to 4 months of age, were anesthetized with intravenous chloralose. An iliocal artery and contralateral femoral artery were connected to a perfusion system. A sigma pump placed in the perfusion system isolated the hind limb from systemic circulation and delivered the animal's own blood at a constant flow rate from the iliocal artery to the femoral artery of the perfused hind limb. Perfusion pressure, monitored through a pressure transducer, gave a proportional index of the peripheral resistance of the hind limb because the flow rate was kept constant.

Initial perfusion pressure was found to be very high in SHR (152 ± 5 mmHg in SHR; 102 ± 2 mmHg in controls), indicating that the peripheral vascular resistance was increased in SHR. Cardiac output was reported to show no significant difference between SHR and controls. Therefore, total peripheral resistance is expected to be increased in SHR; otherwise, their high blood pressure could not be explained. Indeed, our result yielded an evidence that vascular resistance of the hind limb was increased in SHR.

In order to evaluate the neural component in this increased peripheral resistance in SHR, we removed the sympathetic innervation to the hind limb. This was achieved by mechanical decentralization of the spinal nerves at the lumbarplexus on the base of the fact that sympathetic postganglionic fibers run within the spinal nerves to the extremities. After denervation the perfusion pressure dropped rapidly with a greater fall in SHR (51 ± 4 mmHg in SHR; 22 ±

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1 mmHg in controls) (Fig.1). It was now evident that a great part of the increased peripheral resistance in SHR was dependent on neural tone. The increased neural component of hypertension was also reported by Smirk in his genetically hypertensive rats of New Zealand strain. He used "neurally maintained component" in stead of neural component because he was afraid that the latter might lead to an assumption that sympathetic activities were necessarily increased.

As mentioned before, the neural dependence of the increased peripheral vascular resistance may be a result either of increased sympathetic activities or of increased vascular reactivity to catecholamine from nerve terminals or of both. The solution of this problem was challenged by the following procedure. When the perfusion pressure was stabilized at a lowered level after denervation, various amounts of norepinephrine (NE) were given directly into the perfusion system. The resultant responses of the perfused artery were compared between SHR and controls. At the same time, the peak of each response was compared with the initial perfusion pressure level, i.e., the level before denervation. The purpose of the latter was to guess the sympathetic tone to the hind limb blood vessels from the amount of NE, a physiological equivalent of sympathetic discharges, which was required to restore the effect of denervation.

SHR showed a much greater responsiveness to every amount of NE than controls (Fig.1). However, the amount of NE which compensated the denervation effect and restored the perfusion pressure to the initial level was greater in SHR than in controls (Fig.1). These results indicate that the increased vascular reactivity alone does not explain the much more increased neural component in SHR. Necessarily, the increase in the latter component is due to an increase in NE release to the vascular receptor sites. There may be two possibilities for this increased NE liberation: the increased sympathetic activities and the increased NE release in response to a unit quantity of sympathetic discharge. The former possibility seems to be more probable from our previous studies.

Recently Folkow proposed a concept to explain the maintenance of hypertension. According to him, resistance vessels undergo an adaptive structural change, medial hypertrophy, in a considerably short duration of high blood pressure. It is evident that such structurally narrowed arteries show an increased vascular reactivity even in absence of the increased reactivity of each effector cell. Indeed, we observed that the basal perfusion pressure after denervation was higher in SHR than in controls (100 ± 4 mmHg in SHR; 72 ± 3 mmHg in controls). It is likely that this higher basal level reflects such a structural adaptation on the base of which vascular hyperreactivity of SHR is effectuated.

A disputable problem involved in our above study was adequacy of exogenous NE for mimicking the sympathetic discharges. However, endogenous NE induced by tyramine or sympathetic nerve stimulation will give a reliable result only when the catecholamine turnover is definitely equal between two groups of animals.

The foregoing experiment showed that sympathetic efferent outflow may be increased in SHR. Then, we have to know the functions of
the afferent feed back component, i.e., of baroceptors so that we could understand the nature of the change of the efferent functions.

Baroceptor functions are well known to be reset in chronic renal hypertension. In SHR we also reported such a resetting in aortic baroceptors. The experiment that Nosaka and Wang carried out yielded more detailed characteristics of SHR baroceptors. Unlike the previous study on hypertensive baroceptors they investigated steady state functions and transient state functions separately. The reason was that baroceptors respond to a rate of change in pressure (transient response) but adapt rapidly to a new steady state (steady state function).

Carotid sinuses were isolated and perfused artificially and the perfusion pressure was kept constant for a long time at various levels (steady state) or was changed stepwise (transient state; step input). The resultant baroceptor responses, as revealed by reflex blood pressure responses or electrophysiological recordings of carotid sinus nerve activities, were compared between SHR and controls. On the base of the results obtained the steady state and transient state sensitivities were summarized in a schematic fashion in Fig.2 and 3, respectively.

In steady state relationship between carotid sinus perfusion pressure (CSPP) and baroceptor response, the whole curve showed a shift in SHR to higher CSPP altogether with shifts of threshold pressure and of a pressure to elicit a maximum response (Fig.2).

Transient state sensitivity of baroceptors was found to be dependent on basal CSPP. For example, in controls a step change of 20 mmHg elicited a remarkable baroceptor response when the basal CSPP was 100 mmHg, but the response to the same increment was negligible when the basal CSPP was 60 mmHg (Fig.3). Also, a greater increment was required to bring about a maximum response at the basal CSPP of 60 mmHg than at 100 mmHg. In other words, baroceptor sensitivity was high at 100 mmHg but low at 60 mmHg in controls. In SHR, however, baroceptors were not sensitive at 100 mmHg but the sensitivity was definitely increased at 160 mmHg. Therefore, it is clear that the transient state function of baroceptors in SHR was also shifted to high CSPP.

These results suggest that the effective operation range of SHR baroceptors is definitely shifted to the vicinity of their high blood pressure level. This resetting, both in static and dynamic functions, stabilizes and maintains the hypertension.

The relation of the changes in the afferent component to those of the efferent activities is not clear. We cannot exclude the possibility that the former elicit the latter. However, either heart rate or cardiac output is not significantly increased in SHR. If the baroceptor changes precede hypertension, these hemodynamic features should appear dominantly. Therefore, it may be reasonable to assume that baroceptor changes are secondary to hypertension. Then, we may conclude that the increased sympathetic activities are intrinsic in its origin in the sense that they are not due to baroceptor dysfunction but may be due to an intrinsic change of central sympathetic nervous functions because baroceptors of SHR are operating at their elevated blood pressure with the same effectiveness as the control baroceptors at their normal blood pressure.

REFERENCES
2. ALBRECHT, I.: In Spontaneous Hypertension; Its Pathogenesis and Complications, edited by Oka
3. SMIRK, F. H.: In AHA Monograph No.32, Hyper
8. OKAMOTO, K., HAZAMA, F., TAKEDA, T.,
Tabei, R., NOSAKA, S., FUKUSHIMA, M.,
YAMORI, Y., MATSUMOTO, M., HAEBARA, H.,
ICHIJIMA, K., & SUZUKI, Y.: Jap. Circul. J. 30:
987, 1966.

CONCLUDING REMARKS:
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The author concluded that the increase in the sympathetic nervous tone played a major role in sustaining factors of hypertension in SHR.

This result was correlated with the thesis reported by the same research group as the author in which the decrease in catecholamine content in the brain due to the genetic change of a compound enzyme was the primary cause of hypertension in SHR.

The sustaining factor of hypertension, generally speaking, should be analysed separately from

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the causing factor of it although these two factors have the correlation. The specificity of a neural factor as sustaining of high blood pressure in SHR should be demonstrated by comparing the results obtained from SHR with those from the other type of experimental hypertensive animals. It also should be investigated at various period after development of hypertension. Furthermore, it should be analysed whether a neural factor causes the hypertension as a primary factor or it was induced secondarily by high blood pressure itself.

The following procedures were pointed as for the analysis of neural factor in experimental hypertension.
1. The biochemical or electrophysiological evidences in the brain stem or hypothalamus which correlate with the increase in sympathetic vasoconstrictor tone.
2. The increase in frequency of action potential in peripheral sympathetic nerves.
3. The increase in release of catecholamine in peripheral arterial walls (resistant vessels) as a whole or per unit discharge of sympathetic nerve.
4. Hypersensitivity of peripheral arteries (resistant vessels) for endogenous or exogenous catecholamines.
5. Resetting of baroreceptors for higher level.
6. Depressive effects following blocking the sympathetic nerve activity either by denervation of sympathetic nervous system, administration of sympathicolytic drugs or immunosympathectomy.

The author presented that the neural component was much greater in SHR than in control by comparing the depressor effect after the denervation of sympathetic nerves. The others discussed that the depressor effect by giving sympatholytic drugs was much greater in SHR than in goldblatt type experimental hypertensive animals. No available evidence has been reported by immunosympathectomized method in SHR.

The author represented vascular hyper-responsiveness to norepinephrine in SHR after sympathetic denervation. The explanation of the results, however, may be rather careful because the increase in vascular reactivity to norepinephrine is observed even in denervated animals as well as hypertensive ones and it may become variable at various stages after denervation as well as the development of hypertension.

Most discussors agreed with that the resetting of baroreceptors in hypertensive animals was induced in SHR as well as in the other type of hypertensive animals. They assumed that the resetting of baroreceptors were due to secondary adaptation mechanism for high blood pressure and not a primary and characteristic change in SHR. Moreover, there is no proof that the resetting of baroreceptors to higher level induces the increase in the efferent discharge of the sympathetic nerves to the resistance vessels.