Pathogenesis of Spontaneous Hypertension as a Model for Essential Hypertension

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Hypertension in spontaneously hypertensive rats (SHR) develops initially without any obvious organic lesions, and mainly with hemodynamic alteration due to increased peripheral vascular resistance. It is then followed later by various cardiovascular complications such as stroke. These facts indicate that this spontaneous hypertension is very similar to essential hypertension in man.

Studies on the pathogenic mechanisms of spontaneous hypertension up to the present have revealed the following points.

- (1) This hypertension is genetically transmitted to the offspring in an additive mode by a relatively small number of major genes;
- (2) Environmental factors such as stress and salt-loading accelerate the hypertension;
- (3) Parabiosis between SHR and normotensive rats offered no positive evidence indicating the involvement of any strong humoral factors;
- (4) Assays on adrenal and thyroid hormones have suggested that this hypertension is not a simple endocrine hypertension;
- (5) The destruction of the central nervous system or sympathectomy on blood pressure or peripheral vascular resistance, as well as the recording of spontaneous sympathetic discharge, etc. have indicated the positive involvement of the autonomic nervous system in the development of this hypertension;
- (6) Changes in the enzyme activities of the central nervous system and in the central responses to various candidates of central neurotransmitters suggested that "noradrenergic inhibitory mechanisms for blood pressure regulation in the brainstem" (Yamori, Lovenberg and Sjoerdsma, 1970) might be insufficient and result in the initial enhancement of peripheral vasomotor tone causing labile hypertension;
- (7) Noradrenalin turnover study of the heart and hindlimb perfusion experiments indicated that the neural factor was mainly involved in the development or the early stage of hypertension; this finding was further

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- supported by the increased noradrenalin level or dopamine- β -hydroxylase activity in the blood;
- (8) Histometrical studies indicated that the structural component of the peripheral vascular resistance stabilized the hypertension;
 - (9) The initial neurogenic factors and successive involvement of non-neurogenic factors are relayed by the acceleration of protein metabolism of the vascular wall ("adaptive metabolic change", Yamori, 1974). This acceleration is commonly detected by amino acid incorporation study in both spontaneous and other experimental hypertension;
 - (10) Increased lysine incorporation into the noncollagenous protein of the mesenteric arteries detected in the prehypertensive SHR was experimentally confirmed to be influenced by neural innervation. This confirmation indicated the importance of such a trophic effect of the nervous system on the structural alteration of blood vessels in the development of hypertension (neurovascular linkage, Yamori, 1975).

From these findings, it can be concluded that labile hypertension primarily caused by neurogenic mechanisms is stabilized or maintained by medial hypertrophy of the arterial walls as well as by hypertensive diffuse arteriosclerosis. This hypertrophy is induced by increased noncollagenous protein synthesis due to pressure load or to increased vasomotor tone.

Arteriosclerosis is induced secondarily by the increased collagenous protein metabolism due to hypertension. The accelerated vascular protein metabolism preceding structural alteration of the arterial walls is "the final common mechanism", important for the maintenance mechanism of various hypertensions. It obscures the primary cause of hypertension in spontaneous hypertension as well as probably in essential hypertension in man.

VARIOUS experimental models for hypertension have been used for the elucidation of the pathogenesis of essential hypertension. Among them spontaneously hypertensive rats (SHR, Okamoto and Aoki, 1963)^{1,2} have been regarded as the best animal model so far for essential hypertension.^{3,4} Pathogenic mechanisms of hypertension have been studied from various aspects in this model, and by our extensive studies we have proven the importance of both neurogenic and nonneurogenic factors for the initiation and maintenance mechanisms of hypertension, respectively.⁵⁻⁶

1. Spontaneous Hypertension as a Model for Essential Hypertension

SHR are now in the F₄₀ generation and maintained at the Department of Pathology, Kyoto University, genealogically classified into several substrains with different characteristics. From among these substrains, stroke-prone and resistant SHR were successfully separated by selective breeding in 1974.^{8,9} The former develop stroke (cerebral hemorrhage and infarction) spontaneously over 80% and the latter less than 10% in adult males. Therefore, SHR is not only a good model for high blood pressure but also for typical hypertensive diseases such as stroke,

nephrosclerosis and myocardial infarction.

Hypertension in SHR is mainly caused by the increased peripheral vascular resistance, and it is hemodynamically similar to essential hypertension in man.¹⁰ Both hypertensions are the primary hypertension which is induced by gene-environment interaction without obvious organic lesions. Both are neither typical endocrine nor Goldblatt-type hypertension. Studies on the mechanisms of hypertension have shown no decisive difference between the two hypertensions, although a final conclusion of the mechanism has not been obtained in regard to either hypertension.^{2,3}

Antihypertensive agents which are useful in essential hypertension are also effective in SHR, and control of hypertension effectively reduces cardiovascular complications in both hypertensions.^{11,13}

From these observations it is concluded that SHR is so far the best animal model for essential hypertension.

2. Genetic and Environmental Factors in the Pathogenesis

Cross analyses between SHR and 3 strains of normotensive rats revealed that blood pressure in the F₁ generation was intermediate between that

in the parent strains and that the distribution of blood pressure in the F_2 segregate generations was continuous with the mean between hypertensive and normotensive levels.¹⁴ The distribution in the two back cross generations between F_1 and SHR or normotensive strains was also continuous with the mean between the two parent values. These results indicated that this hypertension was determined mostly by heredity in an additive mode with a relatively small number of major genes; the minimum number of major genes was 3 or 4 and the degree of genetic determination was over 80%.¹⁴

On the other hand, various kinds of stress¹⁵ or dietary salt loading accelerated the development of hypertension and augmented the grade or aggravated the hypertensive complications, supporting the importance of gene-environment interaction in the pathogenesis of this hypertension.

3. Mechanisms of Spontaneous Hypertension

a) Humoral Factors: Although various humoral pressor factors have been investigated in SHR, their active participation has not been proven. In the parabiosis experiment between SHR and normotensive rats, no blood pressure increase in normotensive partner in the parabiotic connection with SHR was seen, thus indicating that there were no humoral transmissible pressor factors in SHR.¹⁷

Although some deviation of steroidogenesis was detected, adrenal corticosteroids showed no clear-cut abnormality closely related to hypertension.^{18,19} A two-fold increase in plasma TSH with lowering of T_3 and T_4 was recently confirmed, but it seemed to have no pathogenic relation to hypertension.²⁰ The Renin-angiotensin system did not appear to be actively involved in the pathogenesis.²¹ However, detected only in adult stroke-prone SHR with hypertensive vascular lesions, an elevation of plasma renin concentration indicated the possible secondary involvement of this system in hypertensive complications.²²

b) Neural Factors: The importance of neural factors in SHR was experimentally confirmed by the effectiveness of the α -blocker or ganglion blockade.²³ It was further proved by a greater reduction of blood pressure after the destruction of the central nervous system,²⁴ as well as by recording the significantly increased frequency of spontaneous discharge from the splanchnic nerve in SHR under strictly-controlled experimental conditions.²⁴ The latter was later con-

firmed by different methodological approaches²⁵ and also by a similar recording of the spontaneous discharge from the renal nerves.²⁶ The hindlimb perfusion experiment indicated that higher initial pressure in SHR greatly reduced after denervation, but remained at a somewhat higher level than that in normotensive controls. This experiment also showed that, in SHR, infused noradrenalin elicited a greater increase in perfusion pressure.²⁷ Moreover, the noradrenalin turnover rate of the heart was significantly increased at the age of 30 and 60 days, but this rate was no longer significant at the age of 100 days.²⁸ Such increased noradrenalin turnover at the initial stage of hypertension indicated the active participation of neurogenic factors mainly in the initial stage of hypertension. This finding was coincident with increased serum dopamine- β -hydroxylase activity²⁹ and noradrenalin level³⁰ in young SHR. These data substantiated the importance of neurogenic factors and the participation of nonneurogenic vascular factors in the pathogenesis of spontaneous hypertension.

c) Vascular Factors: Retreatment of neurogenic factors after the development of hypertension as indicated by the noradrenalin turnover study is thought to be due to the participation of non-neurogenic vascular factors. The importance of structural vascular changes indicated by Folkow et al.'s physiological approaches was also confirmed by histometrical studies.^{31,32} Functional reversible vasoconstriction,^{31,32} was noted in the arteries or arterioles at the initial stage of hypertension, and medial thickening with hypertrophy or hyperplasia of smooth muscle cells was histometrically noted in SHR over 4 months of age.³⁴ The biochemical process of these structural vascular changes was studied by amino acid incorporation into the collagenous and noncollagenous proteins of the aorta and mesenteric arteries.^{28,35,36} In 30-day-old SHR which as of yet showed no definite increase in blood pressure, no significant increase in proline incorporation was observed. However, in 70-day-old SHR, in the early stage of hypertension, their blood pressure was significantly high and the specific activities of hydroxyproline as well as of non-collagenous protein were significantly increased both in the aorta and mesenteric arteries. DOCA and renal hypertensive rats, operated on one month previously, showed similar high blood pressure levels to those in SHR at the age of 10 weeks. The increased proline incorporation into the collagenous and noncollagenous proteins of

the mesenteric arteries was the common finding among these hypertensive rats. Moreover, Ooshima et al.³⁷ proved that prolyl hydroxylase activity was clearly increased in SHR and DOCA hypertensive rats, and concluded that vascular collagen synthesis was increased in hypertensive states. These studies indicate that the enhancement of vascular metabolism observed by proline incorporation into these proteins -especially in the mesenteric arteries -is subsequently induced by the development of hypertension, whatever the primary cause may be ("adaptive metabolic change", Yamori, 1974)^{5-7,36}

In addition to the secondary increase in vascular protein synthesis, lysine incorporation into the noncollagenous protein of mesenteric arteries increased in young SHR before the development of hypertension.^{36,38} This increase was attenuated by denervation or by the antihypertensive treatment blocking sympathetic innervation, but it was not attenuated by the vasodilating antihypertensive agent. Hence, neural innervation was confirmed to be important for vascular non-collagenous protein synthesis.^{39,40} This finding indicated a close linkage between the enhancement of vasomotor tone and arterial thickening in the process of the development of hypertension (Neurovascular-linkage, Yamori, 1975)^{6,7,36,40}

d) Central Mechanisms: Because of the methodological limitation, the central mechanisms which increase vasomotor tone to initiate hypertension are not yet completely clarified. However, enzyme alterations in the central nervous system and some aberrations of central responses to the exogenously administered neurotransmitters have been observed in SHR.^{41,44}

Among various enzymes examined, when SHR were compared with ordinary Wistar strains,^{41,42} a clear decrease in aromatic L-amino acid decarboxylase activity was noted in the brain and also in the heart. However, Wistar-Kyoto rats, the ancestor strain of SHR, which still develop hypertension sporadically, showed the same low decarboxylase level as SHR.⁴⁴ Both of these strains with low decarboxylase activity showed different responses to peripherally administered L-DOPA. That is, they showed prolonged depressor responses following initial pressor responses as compared with other Wistar or Sprague-Dawley rats which mainly showed pressor responses.⁴ These depressor responses to L-DOPA were confirmed to be the centrally mediated α -effect of noradrenalin. The depressor

response to the peripherally administered L-DOPA in SHR and WK was probably due to the increased penetration of L-DOPA into the brain; this is partly because of the attenuation of the decarboxylase barrier in the cerebral vessels, or partly because of the reduced decarboxylation of L-DOPA in the peripheral circulation. However, intraventricularly administered L-DOPA and clonidine also elicited a greater depressor response in SHR than in WK. Thus, the central mechanism to respond to an α agonist is presumed to be altered in SHR even compared with WK.⁴² Such an increased central depressor response to L-DOPA or clonidine was noted not only in SHR, but also in DOCA hypertension in the subacute stage, but it was not so marked in renal infarction hypertension one month after operation.⁴

On the other hand, enzyme activity related to the cholinergic mechanism, that is, acetylcholinesterase activity, was increased in the brainstem of SHR as compared with the 3 normotensive control strains, but not in the other parts of the brain.^{4,42} Choline acetylase activity was also slightly increased in the brainstem of SHR. Moreover, an intraventricularly administered cholinergic agent, carbachol, or cholinesterase inhibitor elicited a greater pressor response in SHR. This pressor response to a cholinergic agent was increased also in renal infarction hypertension.

These findings, together with the alteration of enzyme activities in the brainstem, indicate the possible existence of cholinergic pressor and noradrenergic sympatho-inhibitory or depressor mechanisms in the brainstem, and they suggest that these mechanisms might be involved in hypertension. Increased central depressor response to L-DOPA or clonidine in SHR and DOCA hypertension might be due to the primary or secondary disturbance of the α -adrenergic depressor mechanism of the brainstem in these hypertensive rats. However, increased pressor response to cholinergic agents might be partly related to the activation of the cholinergic pressor mechanism in SHR and renal hypertension. Under such an imbalance between cholinergic pressor and noradrenergic depressor mechanisms, the pressor drive to the periphery may tend to be increased in these hypertension. The data obtained up to the present indicates that a part of the noradrenergic mechanisms in the brainstem is related to the depressor mechanism, which seems to work inadequately in SHR

Fig.1. Initiation and maintenance mechanisms of spontaneous hypertension and their therapeutic intervention. (Yamori, 1976)⁵ (reproduced by the cautey of C. C. Thomas Publisher)

Fig.2. Interaction of neural and nonneural factors in the pathogenesis of spontaneous hypertension. (Yamori, 1976)⁶ (reproduced by the cautey of Grune & Stratton, Inc.)

and DOCA hypertension. Recently Nagatsu et al. reported in SHR the decreased dopamine β -hydroxylase activity of the locus coeruleus, one of the main sources of noradrenergic neurones.⁴⁵

Moreover, Grobecker et al. reported that the adrenalin synthesizing enzyme, PNMT, was activated in the A₁ and A₂ areas of the brain of young SHR.⁴⁶ Further analysis is necessary to

clarify in SHR the intricate involvement of the aminergic mechanisms in pathological blood pressure regulation.

4. Neuro-Vascular Interaction in Hypertension

The outline of the neural and nonneural pathogenesis in SHR revealed up to the present is summarized in Fig. 1 and 2. Spontaneous hypertension is genetically determined by a relatively small number of major genes. Under the genetic influence metabolic deviation in the central nervous system is induced primarily or secondarily, and it results in an imbalance which tends to increase sympathetic outflow intrinsically or in response to environmental stimuli, and it neurogenically raises peripheral vascular resistance in the initial stage of hypertension. Thus, this increased pressure load to the vascular wall together with increased vasomotor tone itself enhances noncollagenous protein metabolism which leads to medial hypertrophy — that is, structural vascular changes. On the other hand, the pressure load activates collagenous protein metabolism — that is, fiber formation, which results in hypertensive arteriosclerosis. Therefore, such a metabolic change is a biochemical adaptation of the vasculature to high pressure load, (“adaptive metabolic change”) it precedes “adaptive structural changes”, and gradually increases the nonneural component of hypertension. Both of these adaptive metabolic and structural changes seem to be the final common mechanisms of hypertension. The consecutive relay from the neural or any primary cause of hypertension to these final common mechanisms seems to be the universal process in the development and maintenance of various hypertension. It is this which is thought to be the main reason why it has been so difficult to pinpoint the primary cause of hypertension, especially in essential hypertension in man.

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