SPONTANEOUS HYPERTENSION IN RATS VERSUS ESSENTIAL HYPERTENSION IN MAN

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In search of an animal model for essential hypertension, Drs. Okamoto, Aoki and our group succeeded in establishing an inbred strain of rats with spontaneous hypertension by selective brother-sister inbreedings from a male Wistar with spontaneous hypertension and a female with relatively high blood pressure[1,2]. This strain, designated as spontaneously hypertensive rats (SHR), has been branched off into several substrains which are now maintained in our Department of Pathology. These SHR are the best animal models so far for hypertension research in the following points: (1) They develop hypertension without any obvious organic lesions, (2) Incidence of hypertension in this strain is 100%, (3) Hypertension is very severe, frequently over 200 mm Hg, and (4) Hypertensive cardiovascular diseases are observed in high incidence. They are widespread in the world and now becoming one of the most favorite experimental materials in hypertension research.

The characteristics as well as pathological factors or pathogenetic mechanisms of this hypertension mainly studied by our group up to the present are shortly reviewed in comparison with those of essential hypertension (Table I).

TABLE I

SPONTANEOUS vs. ESSENTIAL HYPERTENSION

	SPONTANEOUS HYPERTENSION	ESSENTIAL HYPERTENSION
DEVELOPMENT	"PRIMARY HYPERTENSION" WITHOUT ORGANIC LESIONS	
AGE	> 7 weeks old	> 40 years old
HEMODYNAMICS	↑ Peripheral Resistance	↑
	↑ → ↑ Cardiac Output	↑ →
	↑ → ↑ Heart Rate	→
	→ Blood Volume	→
PATHOLOGICAL FINDINGS AND COMPLICATIONS	• Cardiac Hypertrophy	•
	• Arteriosclerosis	•
	• Angionecrosis	•
	• Cerebrovascular Lesions (Softening, Bleeding)	•
	• Myocardial lesions	•
	• Nephrosclerosis	•
ANTI-HYPERTENSIVE AGENTS	Sympatholytics, Diuretics: Effective	

	SPONTANEOUS HYPERTENSION	ESSENTIAL HYPERTENSION
PATHOGENESIS	Polygenic Additive	Polygenic (or Single)
HEREDITY, ENVIRONMENT DIET(SALT) STRESS	Augmentation of Hypertension or Hypertensive Complications	
HYPERTENSIVE MECHANISMS	—not yet completely clarified—	
NEURAL	± Sympathetic Tone	↑
	• Baroceptor Resetting	•
	• Central Mechanism	?
HUMORAL	± Endocrine Factors	?
	• Renal Factors	-
VASCULAR	• Structural Change	•
	↑, Reactivity	↑
PRESCIENCE PROPHYLAXIS	Available	Future Problem

1. Development of hypertension

Both essential and spontaneous hypertensions are primary hypertensions which develop without any preceding organic lesions. SHR develop hypertension during 5 and 10 weeks of age and the development progressively became earlier with gradual augmentation of hypertension in the later generations[2]. That is, SHR F28-29 at present develop hypertension before adolescence, much earlier than man whose blood pressure gradually rises after reaching 40. This age difference may be simply because genetic factors are concentrated in SHR after many generations of inbreedings, and actually once normotensive genes are introduced in SHR by crossbreeding, development of hypertension is clearly delayed.

2. Pathological findings and complications

SHR show not only hypertension but also hypertensive cardiovascular diseases in the advanced stage. Cardiac hypertrophy is the most common gross pathological finding and main cardiovascular complications in the brain, heart and kidney such as cerebral bleeding or softening, myocardial lesions and malignant or benign nephrosclerosis are observed in SHR as well as in essential hypertension. They are similar in pathological nature to those in man except for periarteritis nodosa, which is commonly observed in any type of hypertensions in rats but not so in essential hypertension. Statistical analyses revealed that SHR with higher blood pressure over 200 mm Hg showed a greater incidence of these complications than SHR with hypertension below 200 mm Hg[3], and this result confirmed the influence of severe hypertension on the incidence of hypertensive complications as observed in man.

Moreover, our recent observation showed that not only severity of hypertension but also genetic predisposition is important for the development of cardiovascular complications, because several substrains of SHR with almost the same grade of hypertension show different susceptibilities to hypertensive lesions[4,5]. For example, substrain A_3 show severer cerebral lesions in a higher incidence (47%) in the earlier stage, while substrain C show milder lesions in a lower incidence (4%). Such substrain differences in vascular vulnerability are still observed under the loading of salt with or without high fat cholesterol diet (A:78%, C:18%). Investigation on the nature of such substrain differences in SHR is expected to throw light on the nature of the difference between benign and malignant hypertension from the predisposition of vascular diseases.

3. Pathogenesis

The fact that SHR was established by selective inbreeding indicates the importance of heredity in the etiology of this hypertension. The mode of heredity analyzed by crossbreeding between SHR and normotensive Wistar strains was an additive inheritance of a relatively small number of major genes, and the degree of genetic determination of blood pressure was extremely high, 86 to 96%[6]. In conclusion of these genetic analyses, hypertension in SHR is genetically determined to a large extent in an additive mode by a relatively small number of major genes. This conclusion helps us to understand the data on the heredity of essential hypertension, about which no final agreement is yet obtained between the majority supporting polygenic inheritance and the minority in favour of unigenic inheritance with incomplete penetrance.

On the other hand, environmental factors and their interaction with genetic factors in SHR were studied by observing the effect of extreme environmental conditions such as stress and diet on hypertension. Various stress loadings accelerated the development of hypertension, augmented the grade of hypertension and also aggravated hypertensive cardiovascular lesions in SHR[7]. Extreme changes in dietary conditions such as chronic salt excess intake also clearly augmented the hypertension[8]. Similar effects of stress and dietary conditions on essential hypertension have been observed clinically as well as epidemiologically.

4. Hemodynamics

Hemodynamic characteristics in SHR are not in conflict with those of essential hypertension. Both show an obvious increase in peripheral resistance[9]. Cardiac output and heart rate tended to increase in the early stage in some SHR but are not changed or rather decreased in the advanced stage. Neither blood volume nor viscosity of blood is altered in both hypertensions.

5. Hypertensive mechanisms

As hypertensive mechanisms are not yet completely clarified especially in man, comparison of spontaneous hypertension with essential hypertension from this aspect is not feasible. One fact is obvious that both are not Goldblatt-type hypertension. As morphological, biochemical or functional approaches on endocrine systems in SHR indicate a slight activation of hypophyseo-adrenal or thyroidal axes[10], subsidiary participation of these endocrine factos in hypertension is not completely eliminated in SHR and also in essential hypertension, although both are not simple endo-

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crine hypertensions. Parabiosis between SHR and normotensive controls showed no effect on blood pressure in control rats connected with SHR and indicated no humoral transmissible pressor factos in SHR[11].

On the other hand, removal of neural vasomotor tone by encéphale isolé or pithing resulted in a greater fall of blood pressure in SHR and indicated the importance of neural component[12]. Furthermore, artificial perfusion of hind limb revealed that a greater peripheral vascular resistance in SHR is dependent on neural vasomotor tone[13]. By the analyses of responses to various amounts of norepinephrine this neural dependency was attributed partly to increase vascular reactivity and partly to increase sympathetic vasomotor tone. Increased vascular reactivity is observed also in essential hypertension. However, an increase in vasomotor activity is only suggested by the effectiveness of sympatholytics in hypertensive patients and still remains as an unprovable thesis because of methodological limitation in clinical investigation.

As for vascular changes, histometrical study confirmed that the diameter of peripheral resistance vessels such as the 4th branches of jejunal arteries was reduced whether functionally or structurally[14], while aortic lumen was significantly dilated and the aortic wall was thickened in SHR. Consequently, the ratio of peripheral arterial diameter to aortic diameter was always smaller in SHR and decreased with age[15]. This ratio might be a morphological correlate of the greater peripheral resistance in SHR. The hemodynamic studies by Folkow *et al* also indicated structural changes of resistance vessels in SHR as well as in essential hypertension[9].

In summary, hypertensive mechanisms multifactorially inherited in SHR are neuro-humoral ones via autonomic nervous and endocrine systems, which influence the vasculature functionally as well as structurally to increase the peripheral vascular resistance. These general neuro-humoral alterations in SHR are possibly due to the deviation of central regulatory mechanisms of autonomic and endocrine systems, because some inherited lesions are detected in the brainstem of SHR, such as aromatic L-amino acid decarboxylase activity[16,17] and moreover, compensation for such genetic defects by various pharmacological procedures not only decreased blood pressure in SHR but also arrested the development of hypertension[18]. Such central mechanisms of essential hypertension remain to be solved in future.

6. Therapy, prescience and prophylaxis

SHR are sensitive to various antihypertensives which are also effective in man, so that SHR are becoming indespensable for the screening of antihypertensive agents. Although it is not possible to predict the development of hypertension in man before blood pressure rises, spontaneous hypertension is predictable even in the prehypertensive stage by the help of SHR-specific esterase isozymes in the kidney and liver[19]. Therefore, prophylactic approaches to spontaneous hypertension have been attempted[18,20] in SHR and they are important for preventing cardiovascular complications which develop subsequently after hypertension is established. Prescience and prophylaxis of essential hypertension are important problems for the future.

In conclusion, various studies on SHR up to the present confirmed the similarity of this hypertension to essential hypertension and these studies are hopefully expected to contribute to the elucidation of the pathogenesis, the exploitation of causative therapy and also to the establishment of prophylaxis in essential hypertension.

REFERENCES

1. Okamoto, K. and Aoki, K.: "Development of a strain of spontaneously hypertensive rats." Japanese Circulation Journal, 27, 282-293, 1963.
2. Okamoto, K., Yamori, Y., Ooshima, A., Park, C., Haebara, H., Matsumoto, M., Tanaka, T., Okuda, T., Hazama, F. and Kyogoku, M.: "Establishment of the inbred strain of the spontaneously hypertensive rat and genetic factors involved in hypertension." In Spontaneous Hypertension (ed. Okamoto, K.), 1-8, Springer-Igaku Shoin, New York, Berlin, Tokyo, 1972.
3. Ooshima, A., Yamori, Y. and Okamoto, K.: "Cardiovascular lesions in the selectively-bred group of spontaneously hypertensive rats with severe hypertension." Japanese Circulation Journal, 36 (in press), 1972.
4. Okamoto, K., Hazama, F., Haebara, H., Amano, S., Tanaka, T. and Ooshima, A.: "Pathology of dietary induced cerebrovascular diseases in spontaneously hypertensive rats." In Spontaneous Hypertension (ed. Okamoto, K.) 129-133, Springer-Igaku Shoin, New York, Berlin, Tokyo, 1972.
5. Okamoto, K., Yamori, Y., Ooshima, A. and Tanaka, T.: "Development of substrains in spontaneously hypertensive rat: Genealogy, isozymes and effects of hypercholesterolemic diet." Japanese Circulation Journal, 36, 461-470, 1972.
6. Tanase, H., Suzuki, Y., Ooshima, A., Yamori, Y. and Okamoto, K.: "Genetic analysis of blood pressure in spontaneously hypertensive rats." Japanese Circulation Journal 34, 1197-1212, 1970.
7. Yamori, Y., Matsumoto, M., Yamabe, H. and Okamoto, K.: "Augmentation of spontaneous hypertension by chronic stress in rats." Japanese Circulation Journal, 33, 399-409, 1969.
8. Aoki, K., Yamori, Y., Ooshima, A. and Okamoto, K.: "Effects of high or low sodium intake in spontaneously hypertensive rat." Japanese Circulation Journal, 36 (in press), 1972.
9. Folkow, B., Hallbäck, Y., Lundgren, Y., Sivertsson, R. and Weiss, L.: "The importance of adaptive changes in vasculature design for the establishment and maintenance of primary hypertension, as studied in man and in spontaneously hypertensive rat." In Spontaneous Hypertension (ed. K. Okamoto) 103-114, Springer-Igaku Shoin, New York, Berlin and Tokyo, 1972.
10. Okamoto, K.: "Spontaneous hypertension in rats." International Review of Experimental Pathology. Vol. 7, 227-270, Academic Press Inc., New York and London, 1969.
11. Yamori, Y.: "Parabiotic effect on blood pressure in spontaneously hypertensive rats." Japanese Circulation Journal, 35, 821-827, 1971.
12. Okamoto, K., Nosaka, S., Yamori, Y. and Matsumoto, M.: "Participation of neural factor in the pathogenesis of hypertension in the spontaneously hypertensive rat." Japanese Heart Journal, 8, 168-180, 1967.
13. Nosaka, S., Yamori, Y., Ohta, T. and Okamoto, K.: "Neural fraction of peripheral vascular resistance and vascular reactivity in the spontaneously hypertensive rat." In Spontaneous Hypertension (ed. Okamoto, K.) 67-72, Springer-Igaku Shoin, New York, Berlin, Tokyo, 1972.
14. Ichijima, K.: "Morphological studies on the peripheral small arteries of spontaneously hypertensive rats." Japanese Circulation Journal, 33, 785-813, 1969.
15. Kyogoku, M., Haebara, H., Ooshima, A., Yamori, Y., Ikehara, S., Ohta, T., Okuda, T. and Okamoto, K.: "Further studies on the cardiovascular system in the spontaneously hypertensive rat." In Spontaneous Hypertension (ed. Okamoto, K.) 155-159, Springer-Igaku Shoin, New York, Berlin, Tokyo, 1972.
16. Yamori, Y., Lovenberg, W. and Sjoerdsma, A.: "Norepinephrine metabolism in brainstem of spontaneously hypertensive rat." Science, 170, 544-546, 1970.
17. Yamori, Y., Ooshima, A., Nosaka, S. and Okamoto, K.: "Metabolic basis for central blood pressure regulation in spontaneously hypertensive rats." In Spontaneous Hypertension (ed. Okamoto, K.) 73-78, Springer-Igaku Shoin, New York, Berlin, Tokyo, 1972.
18. Yamori, Y., de Jong, W., Yamabe, H., Lovenberg, W. and Sjoerdsma, A.: "Effects of various drugs, especially L-DOPA on brain norepinephrine level and blood pressure in spontaneously hypertensive rats." Journal of Pharmacy and Pharmacology, 24 (in press), 1972.
19. Yamori, Y. and Okamoto, K.: "Zymogram analysis of various organs from spontaneously hypertensive rats." Laboratory Investigation, 22, 206-211, 1970.
20. Freis, E. D.: "Modification of hypertension by antihypertensive drug treatment in spontaneously hypertensive rats." In Spontaneous Hypertension (ed. Okamoto, K.) 231-237, Springer-Igaku Shoin, New York, Berlin, Tokyo, 1972.