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. This strain, designated as spontaneously hypertensive rats (SHR), has been branch- ed 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>
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<th>TABLE I</th>
<th>SPONTANEOUS VS. ESSENTIAL HYPERTENSION</th>
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<tr>
<td>DEVELOPMENT</td>
<td>PRIMARY HYPERTENSION</td>
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<td>Portosystemic shunt</td>
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<td>60 years of age</td>
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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 cross-breeding between SHR and normotensive Wistar strain 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%. 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 favor 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. Extreme changes in dietary conditions such as chronic salt excess intake also clearly augmented the hypertension. 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. 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 hypertension.

5. Hypertensive mechanisms

As hypertensive mechanisms are not yet completely clarified, especialy 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 hypophyseal-adrenal or thyroidal axes, subsidiary participation of these endocrine factors in hypertension is not completely eliminated in SHR and also in essential hypertension, although both are not simple endo-

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

On the other hand, removal of neural vasomotor tone by encephalide isole or pithing resulted in a greater fall of blood pressure in SHR and indicated the importance of neural components.12 Furthermore, artificial perfusion of hind limb revealed that a greater peripheral vascular resistance in SHR is dependent on neural vasomotor tone.3 By the analyses of responses to various amounts of noradrenphrine this neural dependency was attributed partly to increased vascular resistivity and partly to increase sympathetic vasomotor tone. Increased vascular resistivity 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 an unprovable thesis because of methodological limitations in clinical investigations.

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 structurally14, 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 vascular functionally as well as structurally to increase the peripheral resistance. These general neuro-humoral alterations in SHR are possibly due to the deviations 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 indispensable 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. Therefore, prophylactic approaches to spontaneous hypertension have been attempted 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


