How do the Rats of SHR Show Typical Developments of the Blood Pressure into Hypertension?

Tohoku Psychologica Folia
1993, **52**, 45-51

HOW DO THE RATS OF SHR SHOW TYPICAL DEVELOPMENTS OF THE BLOOD PRESSURE INTO HYPERTENSION ?

By

SATO TOSHIHIKO (佐藤 俊彦)[1], MIYAZAKI AKIO (宮崎 章夫)[1],
SHIMIZU KAYOKO (清水加代子)[2], and HATAYAMA TOSHITERU (畑山 俊輝)[1]

(*Tohoku University*)

A long-term measurement of systolic blood pressure (SBP) and heart rate (HR) was made with a tail-cuff method by using 9 male spontaneously hypertensive rats (SHR) and 9 male Wistar-Kyoto strain rats (WKY): the period of measurement was over 14 weeks in total, with the measurement taken once a week since 6 weeks in age. The long-term measurement of the cardiovascular indices gave us useful data for our subsequent study of the relation between blood pressure and general activity in SHRs. The results showed that a gradual increase in the SHRs' SBP was found throughout the whole period of measurement, and that it took about 10 weeks to reach to a higher steady level of blood pressures around 200 mmHg. With another cardiovascular index in this study, HR, we found that the SHRs' HR level was significantly higher than the WKYs' at all of the measurement points. The facilitated cardiac activity in the SHRs is probably an important feature produced by the hypertension. The HR values on the WKYs tended to decrease with time course of bodily development. Mean body weights of the SHRs were significantly lighter than that of the WKYs after 9 weeks in age, in which the SHRs showed a higher level of hypertension above the SBP of 180 mmHg. It was suggested that these could be related to the facilitated sympathetic activities in SHRs.

Key Words: spontaneously hypertensive rats, blood pressure, hypertension, cardiovascular regulation.

INTRODUCTION

Spontaneously hypertensive rat (SHR) is characterized by marked behavioral features such as hyperactivity in novel situations and insensitivity to a heat pain stimulus (Sato & Hatayama, 1995). Although earlier studies of SHR have focused on the relation between high blood pressure and behavioral activities, the period of blood pressure measurement was relatively short to make the nature of the relation much clear. For that purpose it is necessary to describe precisely how spontaneous hypertension develops in SHRs. The purpose of this study was to take a long-term measurement of blood pressure, heart rate, and body weight in the rats ranging in the developmental period from 6 weeks in age to 19 weeks, and to determine how the blood pressure changes would be associated with the others.

SHR has been widely used as the animal model of human essential hypertension because

1. Department of Psychology, Faculty of Arts and Letters, Tohoku University, Kawauchi Aoba-ku, Sendai 980-77, Japan.
Phone 81-22-217-6048 Fax 81-22-265-8028
2. College of Medical Sciences, Tohoku University, 2-1 Seiryomati, Sendai 980-77, Japan.

it has cardiovascular complications (Yamori, 1983), just as human beings often show.

In addition to the hypertension, SHR is characterized by some behavioral peculiarity like hyperactivity in open-field situations (Hellstrand & Engel, 1980; Van den Buuse & de Jong, 1988), hypoemotionality in fear conditioning (LeDoux, Sakaguchi, & Reis, 1983b), insensitivity to heat pain stimuli (Maixner et al., 1982; Sato & Hatayama, 1995). These studies suggest that SHRs would greatly differ in emotional reactivity from normotensive rats, or WKYs.

Concerning the blood pressure in SHRs, it is limited to a relatively shorter period just after weaning that they can show their normal systolic blood pressure. After that period, the blood pressure tends to increase, resulting in hypertension; The systolic blood pressure reaches to 200 mmHg. To grasp such a developmental course of hypertension is basically useful to understand the behavioral peculiarity.

Although Albrecht (1978) and Judy, Watanabe, Henry, Besch, Murphy and Hockel (1976) made long-term measurements of blood pressure in SHRs, they used larger inter-measurement intervals to investigate cardiovascular functions. These intervals of measurement are too long to describe precisely how the blood pressure level would increase during the developmental course of the animal life. The present study made a polygraphical long-term measurement by adding the two variables of heart rate and body weight to the blood pressure in order to understanding well how the chronic hypertensive symptom would be appear.

Method

Subjects: Nine male SHRs were used; the control group consisted of 9 normotensive Wistar-Kyoto strain rats (WKY).

Apparatus and Procedure: A measurement of systolic blood pressure (SBP) and heart rate (HR) was made non-invasively from the pulse of the tail of conscious rats with tail-cuff plethysmography (NATSUME KN-210 manometer-tachometer system). A rat was put on hot-plate with a constant temperature of 36 ± 1 ℃ for 30 minutes prior to the determination of the two cardiovascular indices. These values were acquired every week from 6 to 19 weeks in age; In addition, body weight (BW) was also measured from 5 to 19 weeks.

Results

SBP measurement: Figure 1 shows the results of SBP measurement. During the period of SBP measurement the SHRs exhibited a gradual increase in the SBP from some 160 mmHg to 200 mmHg or more, while the WKYs had relatively stable SBP values around 130 mmHg. A two-way ANOVA with repeated measures indicated highly significant main effects of strain [$F(1, 16) = 350.91$, $p < 0.0001$], and of age [$F(13, 208) = 15.06$, $p < 0.0001$]. This analysis also revealed a significant effect of interaction [strain × age: $F(13, 208) = 15.43$, $p < 0.0001$]. The subsequent multiple-comparison with the Tukey method showed that differences in the SBP values between both strain groups were significant across all ages ($p < 0.05$).

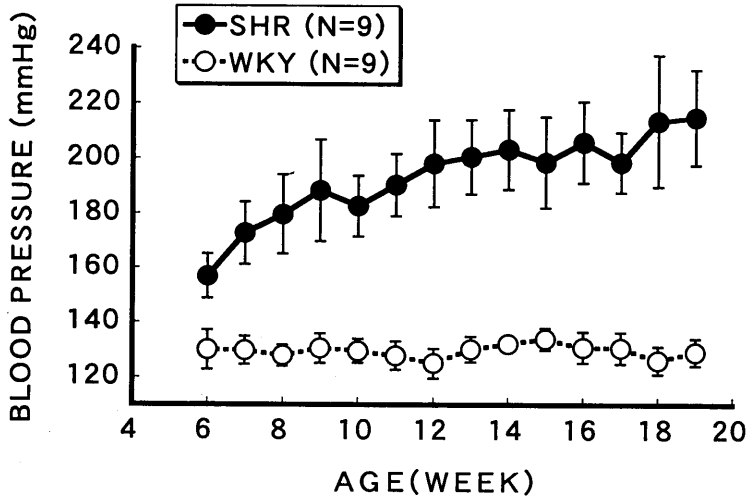

Fig. 1. Means ($\pm SD$) of the SBP values in the SHRs and the WKYs. In the SHRs, a gradual increase in the mean SBP was observed with age.

HR measurement: Figure 2 depicts the results of HR measurement. The values of HR in every age in week were significantly higher in the SHR group than in the WKY, though there might be a tendency for the values of both groups, especially those of the WKY, to decrease throughout the chronological age. The SHR's HR remained generally unchanged throughout the time course in week, which was greatly different from the SBP index. A two-way ANOVA with repeated measures indicated highly significant main effects of strain [$F(1, 16) = 39.07$, $p < 0.0001$], and of age [$F(13, 208) = 18.25$, $p < 0.0001$]. The subsequent multiple-comparison with the Tukey method showed that strain differences in the HR values were significant across all ages ($p < 0.05$).

BW measurement: The results of BW measurement are shown in Fig. 3. This figure indicated that the rate of increase in the SHR's BW was low compared to the WKY. An increase in BW was retarded in SHRs. A two-way ANOVA with repeated measures indicated highly significant main effects of strain [$F(1, 16) = 19.84$, $p < 0.0004$], and of age [$F(14, 224) = 1029.16$, $p < 0.0001$]. This analysis also revealed a significant interaction [strain $\times$ age: $F(14, 224) = 22.42$, $p < 0.0001$]. The subsequent multiple-comparison with the Tukey method showed strain differences in the BW values were significant in every week in age after 9 weeks old ($p < 0.05$).

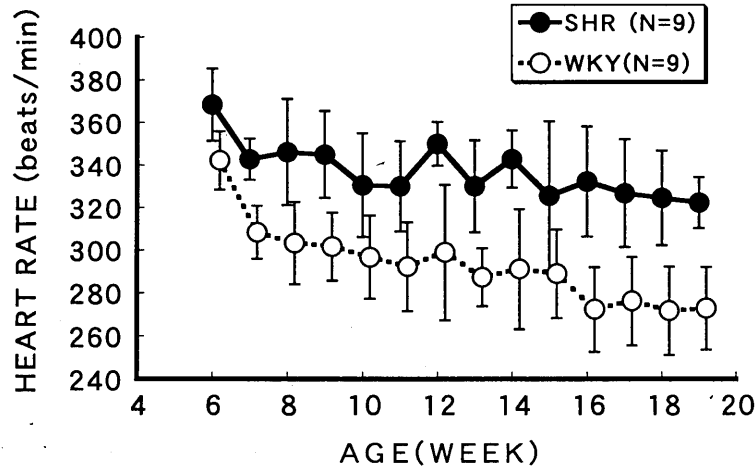

Fig. 2. means ($\pm SD$) of the HR values in the SHRs and the WKYs. The SHRs had greater value of HR than that of WKYs throughout whole period of experimental observation.

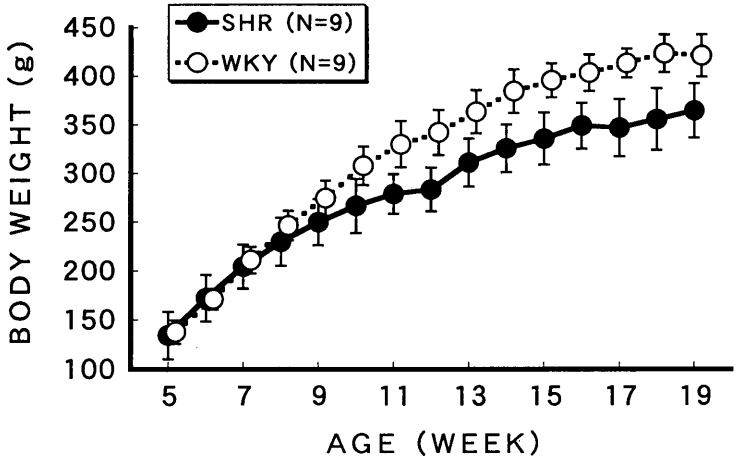

Fig. 3. Development of mean ($\pm SD$) BW in SHRs and WKYs. Mean body weights of the SHRs were significantly lighter than that of the WKYs after 9 weeks in age.

Discussion

Throughout whole period of experimental observation, the SHRs exhibited higher SBP values than those of the WKYs in all ages and showed an increase in SBP with age. Our results confirmed the findings of earlier studies (Okamoto & Aoki, 1963; Albrecht, 1974; Quock et al., 1984) about the SBP in the SHRs. Concerning the course of SBP enhancement seen in the SHRs, we found that there was a gradual increase in the SBP over the period of more than 10 weeks before reaching a higher level of hypertension above 200 mmHg.

In addition, the SHRs showed greater variances at SBP levels than the WKYs, which indicates that there were larger individual difference at the levels in the SHRs than in the WKYs.

The values of HR were also greater at the SHRs than the WKYs throughout the experimental period. This results suggest that the excessive cardiac activity in SHRs could contribute to the development of hypertension: the higher HR levels kept little changed in the SHRs across the whole period of measurement.

The HR activity may be, however, only one of the contributing factors to the gradual increase in the SHR's SBP; Some studies (Ekas, Steenberg, Woods & Lokhandwala, 1983; Juskevich, Robinson, & Whitehorn, 1978; Nagatsu, Ikuta, Numata(Sudo), Kato, Sano, Nagatsu, Umezawa, Matsuzaki, & Takeuchi, 1976; Okamoto, Nosaka, Yamori & Matsumoto, 1967; Saavedra, Grobecker, & Axelrod, 1978) pointed out that neural and neurohumoral cardiovascular control systems play an important role in the development of hypertension.

Some opioidergic mechanism, too, seem to be involved between in blood pressure control and in behavioral regulation. Quock et al. (1984) pointed out that chronic administration of an opiate antagonist, naloxone, would tend to inhibit the process of hypertension appearing in young SHRs at a dose-related manner. We have reported that insensitivity to heat pain stimulus would be observed in the SHRs, and that naloxone might make the SHRs more sensitive to the heat stimulus, although naloxone hardly lowered the level of systolic blood pressure (Sato & Hatayama, 1995). The opioidergic mechanisms play an important role in behavioral regulation on pain. The relationship between the opioidergic activity and the cardiovascular activity mechanisms, however, still remain to be unclear.

In addition to the cardiovascular indices, a strain difference in the BW appeared in consecutive weeks following 9th week after birth, in which the SHRs showed a higher level of hypertension above the SBP of 180 mmHg: the SHR's BWs were lighter than the WKYs. Because the SHR's cardiac activity is chronically facilitated, our finding about the SHR's BW supports that activity in visceral sympathetic nerves in SHRs is greater than WKYs, which Judy et al. (1976) and Judy, Watanabe, Murphy, Aprison, and Yu (1979) suggested.

The results of present study suggests that we should pay attention to the whole picture of hypertensive symptoms to study the behavior of SHRs. Studies so far mainly focused only on blood pressure level (e.g., Hendley, Atwater, Myers, & Whitehorn, 1983; LeDoux, Sakaguchi, & Reis, 1983a; Van den Buuse, Veldhuis, De Boer, Versteeg, & De Jong, 1986), rather than excessive sympathetic activity and other aspects of hypertensive disorders. An interesting

attempt to grasp collectingly the nature of the blood pressure on the SHRs is seen in studies by Castanon, Hendley, Fan, and Mormede (1993) and Hendley, Cierpial, and McCarty (1988). Considering these studies too, we need to carry out further studies to elucidate how the cardiovascular activity would play a causal role on behavioral control of SHRs.

REFERENCES

Albrecht, I. **1974** The hemodynamics of early stages of spontaneous hypertension in rats. Part I: male study. *Japanese Circulation Journal*, **38**, 985-990.

Castanon, N., Hendley, E. D., Fan, X.-M. & Mormede, P. **1993** Psychoneuroendocrine profile associated with hypertension or hyperactivity in spontaneously hypertensive rats. *American Journal of Physiology*, **265**, R1304-R1310.

Ekas, R. D., Steenberg, M. L., Woods, M. S., & Lokhandwala, M. F. **1983** Presynaptic α- and β-adrenoceptor stimulation and norepinephrine release in the spontaneously hypertensive rat. *Hypertension*, **5**, 198-204.

Hellstrand, K., & Engel, J. **1980** Locomotor activity and catecholamine receptor binding in adult normotensive and spontaneously hypertensive rats. *Journal of Neural Transmission*, **48**, 57-63.

Hendley, E. D., Atwater, D. G., Myers, M. M., & Whitehorn, D. **1983** Dissociation of genetic hyperactivity and hypertension in SHR. *Hypertension*, **5**, 211-217.

Hendley, E. D., Cierpial, M. A., & McCarty, R. **1988** Sympathetic-adrenal medullary response to stress in hyperactive and hypertensive rats. *Physiology & Behavior*, **44**, 47-51.

Judy, W. V., Watanabe, A. M., Henry, D. P., Besch, H. R., Murphy, W. R., & Hockel, G. M. **1976** Sympathetic nerve activity: role in regulation of blood pressure in the spontaneously hypertensive rat. *Circulation Research*, **38** (Suppl. II), II-21-29.

Judy, W. V., Watanabe, A. M., Murphy, W. R., Aprison, B. S., & Yu, P. L. **1979** Sympathetic nerve activity and blood pressure in normotensive backcross rats genetically related to the spontaneously hypertensive rat. *Hypertension*, **1**, 598-604.

Juskevich, J. C., Robinson, D. S., & Whitehorn, D. **1978** Effect of hypothalamic stimulation in spontaneously hypertensive and wistar-kyoto rats. *European Journal of Pharmacology*, **51**, 429-439.

LeDoux, J. E., Sakaguchi, A., & Reis, D. J. **1983a** Alpha-methylDOPA dissociates hypertension, cardiovascular reactivity and emotional behavior in spontaneously hypertensive rats. *Brain Research*, **259**, 69-76.

LeDoux, J. E., Sakaguchi, A., & Reis, D. J. **1983b** Strain differences in fear between spontaneously hypertensive and normotensive rats. *Brain Research*, **277**, 137-143.

Maixner, W., Touw, K. B., Brody, M. J., Gebhart, G. F., & Long, J. P. **1982** Factors influencing the altered pain perception in the spontaneously hypertensive rat. *Brain Research*, **237**, 137-145.

Nagatsu, T., Ikuta, K., Numata (Sudo), Y., Kato, T., Sano, M., Nagatsu, I., Umezawa, H., Matsuzaki, M., & Takeuchi, T. **1976** Vascular and brain dopamine β-hydroxylase activity in young spontaneously hypertensive rats. *Science*, **191**, 290-291.

Okamoto, K., & Aoki, K. **1963** Development of a strain of spontaneously hypertensive rats. *Japanese Circulation Journal*, **27**, 282-293.

Okamoto, K., Nosaka, S., Yamori, Y., & Matsumoto, M. **1967** Participation of neural factor in the pathogenesis of hypertension in the spontaneously hypertensive rat. *Japanese Heart Journal*, **8**, 168-180.

Oparil, S., & Cutilletta, A. F. **1979** Hypertrophy in the denervated heart: a comparison of central sympatholytic treatment with 6-hydroxydopamine and peripheral sympathectomy with nerve growth factor antiserum. *The American Journal of Cardiology*, **44**, 970-985.

Quock, R. M., Vaughn, L. K., & Kouchich, F. J. **1984** Influence of chronic naloxone treatment on development of hypertension in the spontaneously hypertensive rat. *Naunyn-Schmiedeberg's Archives of Pharmacology*, **325**, 88-90.

Saavedra, J. M., Grobecker, H., & Axelrod, J. **1978** Changes in central catecholaminergic neurons in the spontaneously hypertensive rat. *Circulation Research*, **42**, 529-534.

Sato, T., & Hatayama, T. **1995** Effects of naloxone on pain reaction threshold in spontaneously hypertensive rats. In T. Kikuchi, H. Sakuma, T. Saito, & K. Tsuboi (Eds.), *Biobehavioral self-regulation: eastern and western perspectives.* Hong Kong: Springer-Verlag, pp.540-545

Van den Buuse, M., Veldhuis, H. D., De Boer, S., Versteeg, D. H. G., & De Jong, W. **1986** Central 6-OHDA affects both open-field exploratory behavior and the development of hypertension in SHR. *Pharmacology, Biochemistry & Behavior*, **24**, 15-21.

Van den Buuse, M., & De Jong, W. **1988** Open-field behavior and blood pressure in spontaneously hypertensive rats. *Clinical and Experimental hypertension -Theory and Practice*, **A10**, 667-684.

Yamori, Y. **1983** Physiopathology of the various strains of spontaneously hypertensive rats. In J. Genest, O. Kuchel, P. Hamet, & M. Cantin (Eds.), *Hypertension: physiopathology and treatment.* 2nd ed. New York: McGraw-Hill Book Company, pp. 556-581.

(Received September 24, 1993)
(Accepted November 22, 1993)