1) Relationship between Stroke-related Behavior and Plasma Norepinephrine Concentration in Stroke-prone Spontaneously Hypertensive Rats.
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Summary
Previous study(1) has indicated that behavioral changes occur at the onset of cerebral accidents in stroke-prone spontaneously hypertensive rats (SHRSP). In the SHRSP stroke cases (SHRSP-stroke) in this study, the plasma norepinephrine concentration and blood pressure levels were higher than those in Wistar Kyoto rats (WKY) and stroke free SHRSP (SHRSP-control). These findings suggest that the increase in plasma norepinephrine level is at least in part associated with the blood pressure rise and behavioral changes in the SHRSP-stroke cases.

Introduction
In a previous study(1), we noted that after cerebral accidents, SHRSP ambulatory activity was desynchronized with water drinking activity in both light and dark phases. It was also demonstrated that the desynchronization with light and dark phases was followed by stroke. Moreover, in SHRSP stroke cases, death occurred after impairment of diurnal rhythm. The present experiment was undertaken to elucidate the relationship between stroke-related behavioral changes and plasma norepinephrine concentration in SHRSP-stroke cases.

Materials and methods
We used SHRSP and WKY kindly donated by Prof. Dr. Kozo Okamoto, Department of Pathology, Kinki University, School of Medicine. The automatic Ambulo-Drinkometer (O'HARA & CO., LTD., Tokyo) developed by Tadokoro et al.(2) was used for the simultaneous measurement of ambulation and water drinking in SHRSP and WKY. Age-matched male SHRSP and male WKY were subjected to a 12 hour light and dark alternation cycle. Other rats were anesthetized with 50 mg/kg \( \alpha \)-chloralose and 500 mg/kg urethane i.p.. Blood pressure and heart rates were recorded invasively via the left femoral artery with a pressure transducer and pen recorder. After determination of blood pressure, blood samples (up to 3.0 ml) were drawn from the femoral artery for the determination of plasma norepinephrine concentration. After blood was withdrawn, autopsies and pathological studies were carried out to clarify the etiology of cerebral accidents in all cases. The plasma catecholamine concentrations were determined by Peuler and Johnson's radioenzymatic method(3). A commercially available catecholamine assay Kit (CAT-A-KIT, Upjohn, Michigan) was used throughout this experiment.

Results
(1) With aging, ambulatory activity decreased and drinking activity increased in both SHRSP and WKY. The ambulatory activity and water drinking of SHRSP over 20 weeks old were significantly greater than those of the age-matched WKY. With aging, the activity counts of drinking behavior and ambulation in the light period progressively increased as compared with those in the dark phases.
(2) After cerebral accidents, SHRSP ambulatory activity was desynchronized with water drinking activity in both light and dark phases. Desynchronization with the light and dark phases was followed by stroke. (3) Autopsies and pathological studies revealed stroke (cerebral bleeding and cerebral infarction) at a frequency of 4 out of 53 cases (7.5%) in SHRSP less than 20 weeks old. After 20 weeks, stroke occurred in SHRSP at a frequency of 23 out of 54 cases (42.5%). There was no remarkable difference in behavior between SHRSP with cerebral bleeding and cerebral infarction. (4) Fig. 1 shows the correlation between age (weeks old) and plasma norepinephrine concentration (NE) in both
WKY and SHRSP. In 32 WKY, plasma NE correlated positively with age ($r=0.486$, $p<0.005$). In 99 SHRSP, including SHRSP-control and SHRSP-stroke, plasma NE correlated positively with age ($r=0.361$, $p<0.001$). (5) Both systolic and diastolic blood pressures rose significantly in SHRSP over 15 weeks old. Systolic blood pressure of the WKY, SHRSP-control (SHRSP with no detectable cerebral bleeding or cerebral infarction) and SHRSP-stroke cases was 135.7 ± 21.4 mmHg, 176.2 ± 32.3 mmHg and 216.3 ± 39.5 mmHg, respectively (Fig. 2a). With regard to the diastolic blood pressure, there were significant differences between the WKY (91.0 ± 12.5 mmHg), SHRSP-control (123.5 ± 35.5 mmHg) and SHRSP-stroke cases (159.1 ± 34.6 mmHg) (Fig. 2b). There were significant differences between the three groups in respect to heart rate as well (Fig. 2a). The heart rates of the WKY, SHRSP-control and SHRSP-stroke were 392.39 ± 53.38 bpm, 315.77 ± 39.49 bpm and 339.04 ± 46.11 bpm, respectively. (6) There was a significant difference in the plasma NE between the WKY, SHRSP-control and SHRSP-stroke groups. As shown in Fig. 2b, the plasma NE of WKY was 269.4 ± 115.8 pg/ml. Plasma NE levels of the SHRSP-control and SHRSP-stroke were 328.4 ± 124.4 pg/ml and 537.4 ± 233.2 pg/ml, respectively. On the other hand, significant differences were seen between the WKY and SHRSP-stroke groups in terms of plasma epinephrine concentration. The plasma epinephrine concentrations of the WKY, SHRSP-control and SHRSP-stroke were 88.5 ± 50.4 pg/ml, 97.4 ± 66.5 pg/ml and 124.2 ± 54.0 pg/ml, respectively.

**Discussion**

Using the Ambulo-Drinkometer, specific behavioral changes were observed at the onset of stroke in SHRSP. The present study was designed around the possibility that changes in plasma norepinephrine concentration may be relevant...
Fig. 2a. Systolic blood pressure, diastolic blood pressure and heart rate in WKY, SHRSP-control and SHRSP-stroke cases.

Fig. 2b. Plasma norepinephrine concentration and plasma epinephrine concentration in WKY, SHRSP-control and SHRSP-stroke cases. Values are the mean±SD. *,**: Significantly different from the WKY with p<0.05 and p<0.01, respectively. #,##: Significantly different from SHRSP-control with p<0.05 and p<0.01, respectively. SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate (beats per minutes), E=epinephrine, NE=norepinephrine.

to stroke related behavioral changes in SHRSP-stroke cases. The most important observation in this study was that the plasma norepinephrine concentration in the SHRSP-stroke cases was significantly elevated as compared with that in the SHRSP-control cases. Moreover, the plasma epinephrine concentration in SHRSP-stroke was significantly higher than that in WKY. In this study, prior to the onset of stroke, a significant increase in both plasma norepinephrine concentration and blood pressure was noted in the SHRSP-control group. It seems likely that in the SHRSP-stroke cases the activity of the peripheral sympathetic nervous system is increased, probably via an initial process that is generated within the central nervous system. It is tempting to speculate that stroke somehow produces an activating influence on the higher brain center. To date, experimental evidence for this view is lacking.

References