Korean J Physiol Pharmacol
Vol 2: 573-580, October, 1998

Altered Cerebral Vasomotion with Decreased CGRP Level in Pial Arteries of Spontaneously Hypertensive Rats

Kwang Ho Lee, Jae Moon Choi, and Ki Whan Hong

Department of Pharmacology, College of Medicine, Pusan National University, Pusan 602-739, and Center for Biofunctional Molecules, Pohang University of Science and Technology, Pohang 790-600, Korea

The study aims to identify the mechanism (s) underlying the altered vasodilatory responses of the pial artery of spontaneously hypertensive rats (SHR) under a hypothesis that calcitonin gene-related peptide (CGRP) exerts a modulator role in the autoregulation of cerebral blood flow (CBF). The animals were divided into four groups: 1) Sprague-Dawley rats (SDR), 2) Wistar rats (WR), 3) SHR with high blood pressure (BP $\geq$ 150 mmHg), and 4) SHR with normotensive BP ($\leq$150 mmHg). The lower limit of CBF autoregulation in SHR shifted to a higher BP (82.8$\pm$9.3 mmHg, $P<0.05$) than that in SDR (58.9$\pm$5.7 mmHg). In SHR, whether the BP levels were high or normotensive, the vasodilator responses to a stepwise hypotension were significantly attenuated unlike with SDR and WR. When artificial cerebrospinal fluid (CSF) containing capsaicin (3×10^{-7} M) was suffused over the cortical surface, a transient increase in pial arterial diameter was observed in the SHR with high or normotensive BP. In contrast, SDR and WR showed a large increase in diameter, and the increase was sustained for over 10 minutes. In line with these results, the basal releases of CGRP-like immunoreactivity (CGRP-LI) in the isolated pial arteries from SHR with high and normotensive BP were 12.5$\pm$1.4 and 9.8$\pm$2.8 fmole/mm^2/60 min ($P<0.05$), while those from SDR and WR were 25.5$\pm$3.1 and 24.6$\pm$3.1 fmole/mm^2/60 min, respectively. The isolated basilar arteries showed similar results to those of the pial arteries in SHR. Thus, it is summarized that, in the SHR, the reduced autoregulatory vasodilator responses to stepwise hypotension and capsaicin may be, in part, ascribed to the decreased release of CGRP from the perivascular sensory nerve fibers of the pial arteries, and that altered vasomotor activity in SHR may not be related with the hypertensive tone.

Key Words: Cerebral autoregulation, CGRP, Spontaneously hypertensive rats, Cerebral blood flow, Capsaicin

INTRODUCTION

Autoregulation of cerebral blood flow denotes the intrinsic ability of cerebral vascular bed to maintain a constant perfusion pressure in the face of blood pressure changes (Fog, 1938). A number of morphological and pharmacological studies have shown that the vasomotor tone of cerebral arteries is controlled by sympathetic vasoconstrictor and non-sympathetic vasodilator nerves (Lee et al, 1978). Saito & Lee (1985) have further demonstrated a decrease in the number of non-sympathetic nerves fibers containing agranular vesicles in the cerebral microvessels of the hypertensive animals. On the other hand, the lower limit of the autoregulatory CBF shifts to a higher level of arterial blood pressure (BP) in the renal hypertensive rats and SHR, and these hypertensive animals are more susceptible to ischemic brain damage than the normotensive rats following acute hypotension (Barry et al, 1982).

It is reported that the autoregulatory capacity of the

Corresponding to: Ki Whan Hong, Department of Pharmacology, College of Medicine, Pusan National University, Ami-Dong 1-Ga, Seo-Gu, Pusan 602-739, Korea (Tel) 82-51-240-7727 (Fax) 82-51-244-1036

cerebral circulation reduces in chronic hypertension (Baumbach & Heistad, 1988; Paulson et al, 1989), and that CGRP content in the dorsal horn of spinal cord and some brain regions of the SHR are lower than that of the age-matched control rats (Lewis et al, 1990; Westlund et al, 1991). Supowit et al. (1993) have demonstrated in SHR, unlike in the case of control rats, that reduced neuronal CGRP levels are associated with significantly decreased CGRP mRNA in the dorsal root ganglion of SHR in comparison with control rats.

CGRP is involved in the vasodilator response to a stepwise hypotension of the pial arteries (Hong et al, 1994). Recently, we demonstrated the transient vasodilation in response to capsaicin and the enhanced vasodilation to CGRP in association with decreased CGRP release from the pial artery of SHR (Hong et al, 1997). In the present study, gain more information about the role of CGRP in the autoregulatory cerebral vasodilation, more efforts were made to gather quantitative information about the role of CGRP. For this purpose, by using Sprague-Dawley rats, Wistar rats, and SHR with high and normotensive BP, we determined: 1) changes in pial arterial diameter in response to hypotension and local application of capsaicin in association with change in the lower limit of CBF, and 2) capsaicin-induced CGRP- LI release from the pial and basilar arteries.

METHODS

Preparation of animals

The animals used in this study were Sprague-Dawley rats (241.1±5.9 g, 20~30 weeks old), Wistar rats (327.5±17.3 g, 20~24 weeks old) and SHR. The SHR group was divided into two subgroups: one is SHR (235.8±11.8 g, 16~24 weeks old) with higher BP (≥150 mmHg), and the other is SHR (227.3±10.9 g, 16~24 weeks old) with normotensive BP (<150 mmHg).

The animals were anesthetized with urethane (1.0 g/kg, i.p.) and placed on a heating pad to maintain a constant body temperature. After tracheostomy, each rat was ventilated by using a respirator (Model 683, Harvard, South Natick, MA). The left femoral artery was cannulated with PE-50 polyethylene tube for measurement of blood pressure (Statham P23D pressure transducer, Gould). Arterial blood sample was collected through the left carotid artery after installation of cranial window for blood gas and pH determination (NOVA Biochemicals, STAT Profile 3). The mean arterial blood gas and pH determined during experiments were as follows: pH, 7.36±0.04; P_{aCO2}, 29.8±2.2 mmHg; P_{aO2}, 102.3±3.4 mmHg. Rectal temperature was monitored continuously and was kept constant (37±0.5°C) with a heating pad.

Laser-Doppler flowmetry

The animal's head was fixed in a stereotaxic instrument and the animals spontaneously breathed room air. One small burr hole was made on the parietal skull. CBF of the pial artery in the right parietal cortex was continuously monitored by a laser-Doppler flowmeter (BLF 21, Transonic Systems Inc.) with 12 KHz of doppler signal band width, 780 nm wave length and 3.0 sec time constant. The measuring probes (1.0 mm in diameter and 0.25 mm in width of fiber) were placed extradurally over the parietal artery in the cranial window, and advanced into the CSF approximately 0.2~0.3 mm above the surface of cortex. The position was carefully chosen to avoid the large dural or pial veins. The change in cortical CBF was recorded on polygraph (Grass Instrument, Quincy MA). The laser- Doppler flowmetry outputs were regarded as arbitrary units and the changes in CBF were expressed in percentage of the baseline CBF.

Measurement of vessel diameter

Pial microvessels were visualized through an implanted cranial window as described by Hong et al (1994). Briefly, the head was fixed in prone position with a stereotaxic apparatus (Stoelting, Wood Dale, IL), and a square shape craniotomy (5×5 mm) was made over the right parietal cortex. Pial microvessels, ranging in diameter between 30 and 50 μm, were visualized through the implanted cranial window. Cerebral microvessels were allowed to equilibrate for 60 min after installation of cranial window. The window field was suffused with prewarmed artificial CSF (37°C) at a rate of 0.3 ml/min. The image of pial vessels was captured with a CCD video camera (VDC 3900, Sanyo, Japan) through a stereoscope (SMZ-2T, Nikon, Japan) and fed to a television monitor for direct observation, and the caliber was measured using a Width Analyzer (C3161, Hama-

matsu, Japan). The composition (mM) of the artificial cerebrospinal fluid was as follows: 125 NaCl, 3.5 KCl, 1.3 $CaCl_2$, 1.1 $MgCl_2$, and 25 $NaHCO_3$. The intracranial pressure was maintained at 5~6 mmHg throughout the experiment by adjusting the height of the free end of plastic tubing, which was connected to the outlet of the window. Only one artery was observed under the window in each rat.

The lowering of the arterial blood pressure was induced by bleeding of the blood into the reservoir and its reverse by infusion of the blood under suffusion with artificial CSF over the cortical surface. Each concentration of drug was suffused over the cortical surface for 5 min. To see the responses of the pial arteries to capsaicin, the cranial surface was suffused with artificial CSF containing 3×10^{-7}M capsaicin.

Measurement of CGRP-like immunoreactivity

The pial and basilar arteries isolated from the three strains of rats were equilibrated in the aerated Krebs buffer solution containing (in mM) 130 NaCl, 4.7 KCl, 1.6 $CaCl_2$, 1.18 NaH_2PO_4, 14.9 $NaHCO_3$, and 5.5 glucose (37°C) for 1 hour. Thereafter, the strips were preincubated in the Ca^{2+}-free Krebs solution containing 0.1 mM EGTA for 30 min and next they were incubated in the Krebs buffer solution (50 μl) for 60 min. The reaction was stopped by adding the assay buffer containing (in mM) 0.05 M NaCl, 0.1% bovine serum albumin, 0.01% NaN_3, and 0.1% Triton X-100 in 0.1 M sodium phosphate buffer (pH 7.4), and then the strips were removed for measurement of the surface area of the pial artery. The magnified surface areas of the microvessels were measured with planimeter (type KP-21, Kozumi, Japan). The CGRP-LI content was determined by radioimmunoassay method as described by Fujimori et al. (1989). After the sample was preincubated with rabbit anti-human CGRP serum for 16~24 hours at 4°C, the reaction mixture was incubated with (2-[^{125}I]iodohistidyl^{10}) CGRP (human) for additional 24~36 hours at 4°C. The incubation buffer for the radioimmunoassay was a 50 mM sodium phosphate buffer (pH 7.4) containing 0.1% NaCl, 25 mM Na_2EDTA, 0.05% NaN_3, and Trasylol 500 kallikrein-inhibiting units/ml.

The antibody-bound antigen was separated from free antigens by incubation for 2 hours with goat anti-rabbit IgG serum and normal rabbit serum at room temperature. After addition of the assay buffer, the samples were centrifuged and the radioactivity in the pellets was counted in a gamma counter (Wallac, Wizard 1470. Finland).

The contents of CGRP-LI in the pial arteries were determined after capsaicin *in vivo* and *in vitro* treatment. For *in vivo* treatment, at 24 hours before experiment, 50 nmole of capsaicin was intracisternally injected, and for *in vitro* treatment, the isolated pial arteries were incubated in the aerated artificial CSF containing 3×10^{-7} M capsaicin for 30 min.

Drugs

Calcitonin gene-related peptide (CGRP, Peninsula Laboratories, Inc. Belmont, CA) was dissolved in 0.1% bovine serum albumin to make a stock solution of 0.1 mM. Capsaicin (Sigma Chemical Co.) was dissolved in the mixture of Tween 80 : ethanol : normal saline (1 : 1 : 8 v/v). (2-[^{125}I]iodohistidyl^{10}) CGRP was purchased from Amersham Life Science (Buckinghamshire, UK).

Statistics

Data are expressed as mean±SEM. The percent change in diameter for each arteriole was calculated from the baseline diameter. Statistical evaluation of the data was performed either by Student's *t*-test between the results of each group, or analysis of variance with repeated measures followed by Tukey's multiple comparison test for differences in arteriolar diameter among the experimental groups. A value of $P<0.05$ was accepted as statistically significant.

RESULTS

In the SDR and WR, mean arterial BP levels were 122.5±3.5 mmHg (n=22) and 118.3±3.0 mmHg (n=6), respectively. The resting diameters of the pial arteries were 45.8±2.2 μm and 41.2±3.2 μm, respectively, which remained almost constant throughout the experiment unless there was a procedure of bleeding or suffusion of drug solution.

Mean arterial BP of SHR with high BP was 169.5 ±4.3 mmHg (n=18; $P<0.01$) and that with normotensive BP was 132.4±4.7 mmHg (n=14). The baseline diameters of the pial arteries of SHR exerted little difference between the two groups (45.2±3.8 μm and 52.8±4.2 μm, respectively)(Table 1).

Table 1. Physiological baseline variables: age, body weight, mean arterial blood pressure (BP) and pial arterial diameter before experimental procedures

	n	Age (weeks)	Body weight (g)	BP (mmHg)	Diameter (μm)
SDR	22	20~30	241.1±5.9	122.5±3.5	45.8±2.2
WR	6	20~24	327.5±17.3	118.8±3.0	41.2±3.2
SHR, high BP	18	16~24	235.8±11.8	169.5±4.3[a]	45.2±3.8
SHR, normal BP	14	16~24	227.3±10.9	132.4±4.7	52.8±4.2

n, Numbers of experiments. SDR, Sprague-Dawley rats; WR, Wistar rats; SHR, spontaneously hypertensive rats. The systemic arterial blood pressure indicates the blood pressure measured under urethane anesthesia. [a], $P<0.01$ vs. SDR.

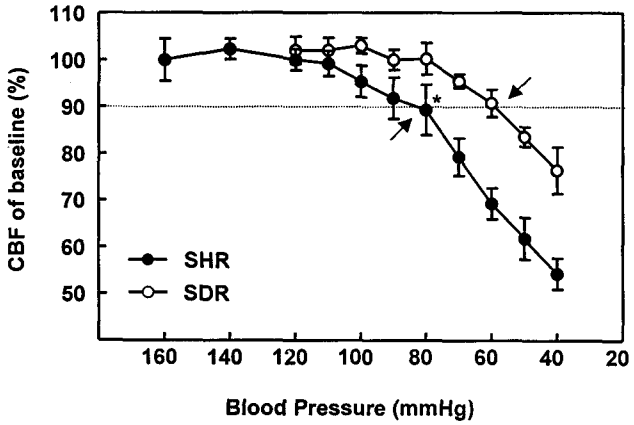

Fig. 1. Relation of mean arterial blood pressure to cerebral blood flow (CBF) in the cortical pial arteries during stepwise hypotension in the Sprague-Dawley rats (SDR) and spontaneously hypertensive rats (SHR) with high blood pressure. Arrows indicate lower limits of autoregulation defined as the mean arterial blood pressure at which CBF decreased by 10% of the baseline value. *, $P<0.05$ significantly different between SDR (n=12) and SHR (n=5).

Lower limit of cerebral blood flow autoregulation

In SDR, the CBF was well remained until the arterial BP was reduced to 80 mmHg. When BP further decreased, CBF fell steeply depending on the fall in BP thereafter. In contrast, CBF in SHR readily decreased when BP decreased to around 100 mmHg.

The lower limit of autoregulation was defined as the BP where CBF decreased by 10% of the baseline. The lower limit estimated in SHR with high BP was 82.8±9.3 mmHg (n=5), which represented a significant shift to a higher BP ($P<0.05$) in comparison with that of SDR (58.9±5.7 mmHg, n=12)(Fig. 1).

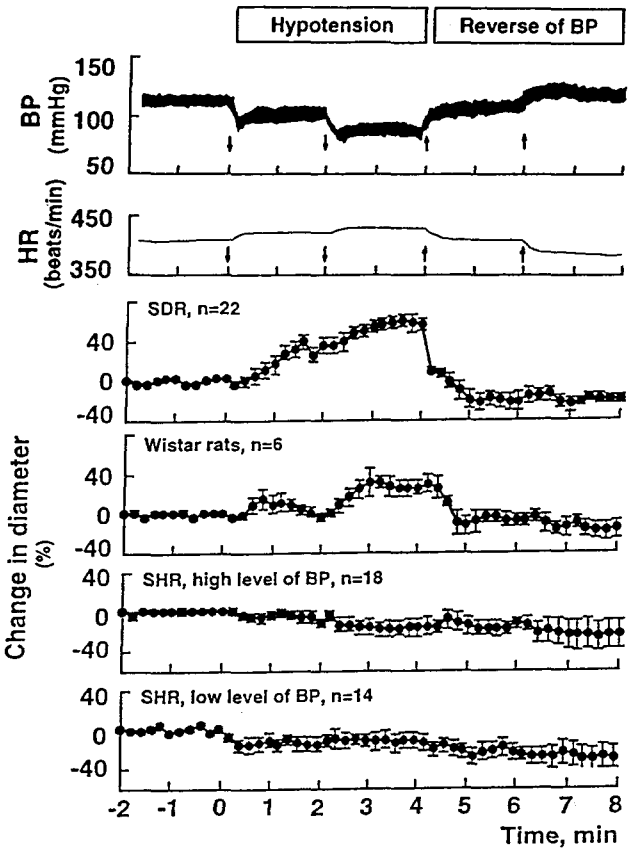

Fig. 2. Tracings showing changes in heart rate (HR) and pial arterial diameter in association with changes in systemic arterial blood pressure (BP) in Sprague-Dawley rats (SDR), Wistar rats, and spontaneously hypertensive rats (SHR) with high and normotensive BP. The results are expressed as mean±SEM from n numbers of experiment. There was no significant difference in the vasodilator responses to hypotension between SDR and Wistar rats. However, changes in diameter during hypotension in SHR with high or normotensive BP were significantly attenuated ($P<0.05$) in comparison with those in SDR and Wistar rats.

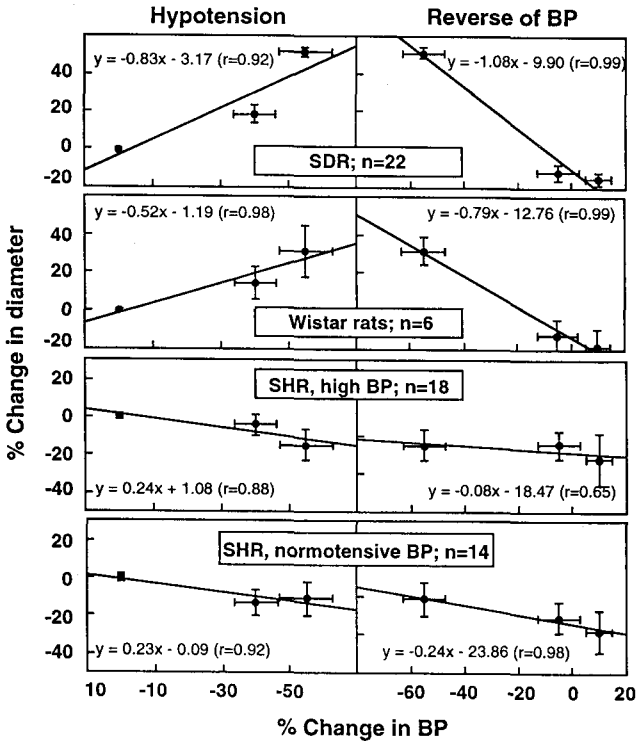

Fig. 3. Graphs showing alterations in cerebral autoregulatory responses in spontaneously hypertensive rats (SHR) with high and normotensive blood pressure (BP) in comparison with those in SDR (Sprague-Dawley rats) and Wistar rats. Changes in pial arterial diameter were plotted as a function of changes in BP observed during hypotension and reverse of BP. The slopes for vasodilation phase of the SHR were significantly decreased or turned to the opposite direction irrespective of their BP levels being high or normotensive. Each point represents mean ± SEM from n numbers of experiment.

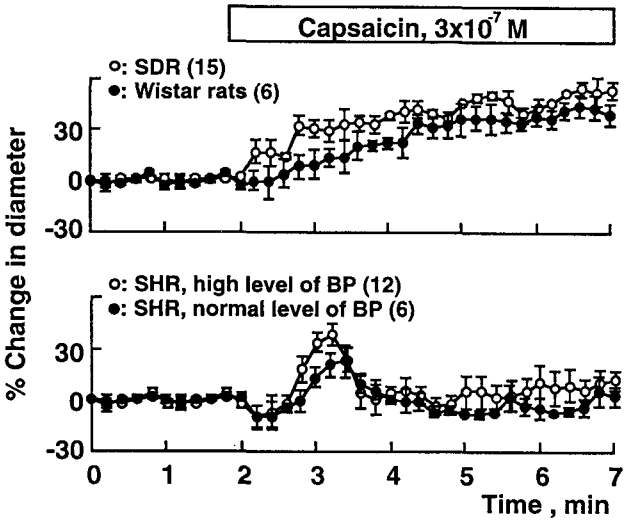

Fig. 4. Effect of capsaicin on the changes in rat pial arterial diameter upon suffusion with artificial cerebrospinal fluid containing capsaicin (3×10^{-7} M) over the cortical surface. The changes in diameter in response to capsaicin of spontaneously hypertensive rats(SHR) (both groups) were significantly reduced in comparison with those of Sparague-Dawley rats (SDR) ($P<0.05$) and Wistar rats (WR) ($P<0.05$), respectively. Each point indicates mean ± SEM from the numbers of rats in parentheses.

Alteration in cerebral autoregulation

On lowering systemic arterial BP by bleeding, the diameters of pial arteries of SDR and WR increased, and on reversing BP, the diameters decreased to the baseline or even over the baseline level as shown in Fig. 2. However, in SHR with high or normotensive BP, change in diameter during the vasodilating phase in response to stepwise hypotension was significantly low ($P<0.05$) in comparison with those of SDR or WR. In some cases, a slight vasoconstrictor response was observed in 66.7% (12 among 18 cases) during hypotensive phase. The altered features were similarly identified in the SHR with normotensive BP.

Changes in pial arterial diameter were plotted as a function of changes in mean arterial BP and analyzed with slopes of regression lines (Fig. 3). The mean slopes of the regression lines for vasodilation phase were −0.83 (r=0.92) for SDR and −0.52 (r=0.98) for WR. The slopes for vasodilation phase of the SHR showed the opposite direction whether their BP levels were high (0.24, r=0.88) or normotensive (0.23: r=0.92). The slopes for vasoconstriction phase correspondingly turned to be less steep as shown in Fig. 3.

Alterations in response to capsaicin

Fig. 4 compared the acute local effect of capsaicin on the change in pial arterial diameters of SDR and WR with those of SHR with high and normotensive BP. When cortical surface was suffused with artificial CSF containing capsaicin (3×10^{-7} M), the diameters of pial arteries of SDR and WR markedly increased and the increased diameters were sustained for more than 10 min. The significant difference was not evident between SDR and WR. In contrast, the SHR showed only a transient increase in diameter (less than 2 min) of the pial arteries whether the BP was high or normotensive. The changes in diameter in

Table 2. Release of CGRP-like immunoreactivity (CGRP-LI) in the pial and basilar arteries of the three strains of rats

Groups	CGRP-LI, fmole/mm^2/60 min	
	Pial artery	Basilar artery
Sprague-Dawley rats		
Vehicle	25.5±3.1 (19)	21.8±3.2 (9)
Capsaicin, in vivo*	10.2±1.1 (5)[a]	–
Capsaicin, in vitro**	10.0±1.0 (4)[a]	–
Wistar rats	24.6±3.1 (13)	18.9±2.1 (6)
SHR, high BP	12.5±1.4 (11)[b,c]	12.1±1.7 (7)[b,c]
SHR, normal BP	9.8±2.8 (4)[b,c]	–

Each value is mean±SEM from the numbers of experiments in parentheses. SHR, spontaneously hypertensive rats. [a], $P<0.05$ vs. vehicle group; [b], $P<0.05$ vs. vehicle group of Sprague-Dawley rats; [c], $P<0.05$ vs. Wistar rats. *, Twenty-four hours before experiment, 50 nmole capsaicin was injected intracisternally. **, The isolated cerebral arteries were incubated in the aerated Krebs buffer solution (37°C) containing 3×10^{-7} M capsaicin for 30 min and thereafter rinsed in the cold buffer solution.

response to capsaicin of the pial arteries of SHR (both groups) significantly reduced in comparison with those of SDR ($P<0.05$) and WR ($P<0.05$).

Release of CGRP-like immunoreactivity

Capsaicin-induced release of CGRP-LI from the isolated pial and basilar arteries from SDR was 25.5 ±3.1 (n=19) and 21.8±3.2 (n=9) fmole/mm^2/60 min, respectively (Table 2). Upon treatment with capsaicin *in vivo* or *in vitro* experiment in SDR groups, the CGRP-LI levels were significantly reduced to approximately 40% of the vehicle group ($P<0.05$). No significant difference in CGRP-LI release was observed between SDR and WR.

On the other hand, the CGRP-LI levels were 12.5 ±1.4 fmole/mm^2/60 min (n=11, $P<0.05$) in the pial arteries of SHR with high BP and 9.8±2.8 fmole/mm^2/60 min (n=4, $P<0.05$) in the SHR with normotensive BP. These levels in SHR were significantly lower than those in the SDR and WR. The mean surface areas of the pial and basilar arteries used for this study were in the ranges of 1.9~2.5 mm^2 and 2.2~2.8 mm^2, respectively.

DISCUSSION

The major findings of this study were that 1) the lower limit of autoregulation in SHR shifted towards higher arterial BP around 82.8±9.3 mmHg, whereas that in SDR was 58.9±5.7 mmHg, 2) the autoregulatory vasodilator adjustment in response to stepwise hypotension, which was normally observed in the SDR and WR, was markedly attenuated in the pial arteries of SHR whether their BP levels were high or normotensive, 3) local suffusion of capsaicin over the cortical surface exerts a transient vasodilatory response in the pial arteries of SHR while a sustained vasodilation was observed in SDR and WR, and 4) the capsaicin-induced release of CGRP-LI level was significantly reduced in the pial arteries of SHR unlike in SDR and WR.

Immunochemical studies (Saito et al, 1989; Edvinsson et al, 1987) have revealed that CGRP is abundantly found in the periadventitial nerve of the cerebral arteries of rats as well as other species. The CGRP-LI nerve fibers innervating in the large arteries and cortical arterioles are mainly originated from trigeminal sensory ganglia (Edvinsson 1985; McCulloch et al, 1986). In our study, the pial arteries of the SHR showed reduced autoregulatory vasodilator response to arterial hypotension, and a transient vasodilation was manifested in response to capsaicin in SHR unlike in SDR and WR. Thus, it is suggested that these findings may be closely related to the shift of the lower limit of CBF autoregulation towards a higher systemic arterial BP in SHR.

It has been reported that the active neurogenic (non-sympathetic) vasodilation is impaired in the ce-

rebral arteries of renal hypertensive rats (Saito & Lee, 1985) and SHR (Barry et al, 1982). There are some disputes regerding the plasma concentration of CGRP in the hypertensive patients. Xu et al (1989) reported that the plasma levels of CGRP decreased in patients with essential hypertension as well as in SHR, and that the decrease in CGRP content were consistently correlated with decreases in density of CGRP-containing nerve fiber in SHR (Kawasaki et al, 1990). On the contrary, Zaidi & Bevis (1991) reported high concentration of the circulating CGRP derived from perivascular nerve endings in SHR. Masuda et al (1992) also reported increased plasma CGRP levels in hypertensive patients. These controversial reports are yet to be clarified. One possible explanation is that increased levels of plasma CGRP is due to compensatory reactions in response to elevated blood pressure.

In the present study, the finding that releasable CGRP-LI levels in the pial arteries of SHR were significantly lower than those of SDR and WR was consistent with the results reported by Lewis et al (1990) and Westlund et al (1991). They said that the CGRP levels in the spinal cord and brain of the SHR were lower than those of the age-matched control rats. Supowit et al (1993) have added more evidences that, in the dorsal root ganglion of the SHR, a reduced CGRP level is associated with decreased CGRP mRNA expression. Based on these reports and our results, it appears likely that the alteration in autoregulatory vasodilator response of the pial arteries in SHR is closely related with reduced CGRP-LI level in SHR, whether the levels of BP are high or normotensive. This speculation was further supported by the result that the vasodilator response to capsaicin, a depletor of CGRP (Franco-Cereceda et al, 1988; Jansen et al, 1990; Lundberg et al, 1985), was significantly reduced in SHR. Therefore, it is considered that the decreased amount of releasable CGRP in SHR in response to capsaicin is not related to hypertension but to a genetically oriented factor, and this speculation provides a circumstantial evidence of malfunction of the sensory vasodilator system in the cerebral cortical arterioles of SHR.

Taken together, it is suggested that the content of CGRP in the perivascular sensory nerves may be genetically reduced in SHR and, thereby, the autoregulatory vasodilator adjustment is altered in response to stepwise acute hypotension and to capsaicin, leading to a shift of the lower limit of autoregulation of CBF towards a higher BP in SHR.

REFERENCES

Barry DI, Strandgaard S, Graham DI, Braendstrup O, Svendsen UG, Vorstrup S, Hemmingsen R, Bolwig TG. Cerebral blood flow in rats with renal and spontaneous hypertension: resetting of the lower limit of autoregulation. *J Cereb Blood Flow Metab* 2: 347−353, 1982

Baumbach GL, Heistad DD. Cerebral circulation in chronic arterial hypertension. *Hypertension* 12: 89−95, 1988

Edvinsson L. Functional role of perivascular peptides in the control of cerebral circulation. *Trends Neurosci* 8: 126−131, 1985

Edvinsson L, Ekman R, Jansen I, McCulloch J, Uddman R. Calcitonin gene-related peptide and cerebral vessels: Distribution and vasomotor effects. *J Cereb Blood Flow Metab* 7: 720−728, 1987

Franco-Cereceda A, Lundberg JM, Saria A, Schreibmayer W, Triihart H. Calcitonin gene-related peptide (CGRP): release by capsaicin and prolongation of the action potential in the guinea pig heart. *Acta Physiol Scand* 132: 181−190, 1988

Fog M. The relationship between the blood pressure and the tonic regulation of the arteries. *J Neurol Psychiatry* 1: 188−196, 1938

Fujimori A, Saito A, Kimura S, Watanabe T, Uchiyama Y, Kawasaki H, Goto K. Neurogenic vasodilation and release of calcitonin gene-related peptide (CGRP) from perivascular nerves in the rat mesenteric artery. *Biochem Biophys Res Commun* 165: 1391−1398, 1989

Hong KW, Pyo KM, Lee WS, Yu SS, Rhim BY. Pharmacological evidence that calcitonin gene-related peptide is implicated in cerebral autoregulation. *Am J Physiol* 266 (Heart Circ Physiol 35): H11−H16, 1994

Hong KW, Yu SS, Shin YW, Kim CD, Rhym BY, Lee WS. Decreased CGRP level with increased sensitivity to CGRP in the pial arteries of spontaneously hypertensive rats. *Life Sci* 60: 697−705, 1997

Jansen I, Alafaci C, Uddman R, Edvinsson L. Evidence that calcitonin gene-related peptide contributes to the capsaicin-induced relaxation of guinea-pig cerebral arteries. *Regul Peptides* 34: 167−178, 1990

Kawasaki H, Saito A, Takasaki K. Changes in calcitonin gene-related peptide (CGRP)-containing vasodilator nerve activity in hypertension. *Brain Res* 518: 303−307, 1990

Lee TJ-F, Hume WR, Su C, Bevan JA. Neurogenic vasodilation of cat cerebral arteries. *Circ Res* 42: 535−542, 1978

Lewis SJ, Shulkes A, Bodsworth B, Jarrot B. Regional brain concentrations of calcitonin gene-related peptide in spontaneously hypertensive and normotensive Wistar-

Kyoto rats. *J Hypertens* 8: 315−319, 1990

Lundberg JM, Franco-Cereceda A, Hua X, Hokfelt T, Fischer JA. Coexistence of substance P and CGRP-like immunoreactivities in sensory nerves in relation to cardiovascular and bronchoconstrictor effects of capsaicin. *Eur J Pharmacol* 1108: 315−319, 1985

Masuda A, Shimamoto K, Mori Y, Nakagawa M, Ura N, Iimura O. Plasma calcitonin gene-related peptide levels in patients with various hypertensive diseases. *J Hypertens* 10: 1499−1504, 1992

McCulloch JM, Uddman R, Kingman TA, Edvinsson L. Calcitonin gene-related peptide: Functional role in cerebrovascular regulation. *Proc Natl Acad Sci USA* 83: 5731−5735, 1986

Paulson OB, Waldemar G, Schmidt GF, Strandgaard S. Cerebral circulation under normal and pathologic conditions. *Am J Cardiol* 63: 2C−5C, 1989

Saito A, Lee TJ-F. Autonomic innervation of cerebral blood vessels decreases in renal hypertensive rats. *Hypertension* 7: 514−518, 1985

Saito A, Masaki T, Uchiyama Y, Lee TJ, Goto K. Calcitonin gene-related peptide and vasodilator nerves in large cerebral arteries of cats. *J Pharmacol Exp Ther* 248: 455−62, 1989

Supowit SC, Ramana CV, Westlund KN, Dipette DJ. Calcitonin gene-related peptide gene expression in the spontaneously hypertensive rat. *Hypertension* 21: 1010−1014, 1993

Westlund KN, Dipette D J, Carson J, Holland O. Decreased spinal cord content of calcitonin gene-related peptide in the spontaneously hypertensive rat. *Neurosci Lett* 131: 183−186, 1991

Xu D, Wang X, Wang J-P, Yuan Q-Z, Fiscus RR, Chang JK, Tang J. Calcitonin gene-related peptide (CGRP) in normotensive and spontaneously hypertensive rats. *Peptides* 10: 309−312, 1989

Zaidi M, Bevis PJR. Enhanced circulating levels of neurally derived calcitonin gene-related peptide in spontaneously hypertensive rats. *Cardiovas Res* 25: 125−128, 1991