Is Compensatory Vasoconstrictor Tone in the Hindquarter Vascular Region Induced by Hemorrhage in Conscious Spontaneously Hypertensive Rats?

Yasuhiro Teranishi1*, Noriko Iida1, Norio Ishioka2, Hiroshi Sugino2 and Taku Amano3

1Department of Physiology, 2First Department of Internal Medicine and 3Department of Pharmacology, Hiroshima University, Faculty of Medicine, Minami-ku, Hiroshima 734-8551, Japan

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ABSTRACT—We investigated whether a compensatory vasoconstrictor action would be induced by a hypotensive intervention in the hindquarter vascular region of conscious spontaneously hypertensive rats (SHRs). Mean arterial pressure and hindquarter blood flow were recorded. After hemorrhage (withdrawing blood, 0.3 ml/100 g body weight), hindquarter resistance (HQR) was increased significantly. The decrease in HQR induced by the administration of a ganglionic blocker (C6; 25 mg/kg, i.v.) was significantly greater in SHRs with hemorrhage than in those without hemorrhage. The present results suggest that a detectable hindquarter compensator tone occurs due to hemorrhage in SHRs, although an abnormal substantial vasoconstrictor tone already exists in the hindquarters.

Keywords: Hemorrhage, Hindquarter compensator, Spontaneously hypertensive rat

Although there was no substantial vasoconstrictor tone in the hindquarter vascular region supplied by the terminal aorta (most of which is thought to cover vessels of the lower extremity muscle) in conscious normotensive control rats, some hypotensive interventions induced sympathetic vasoconstrictor tone in this vascular region (1). We reported that this hindquarter vasoconstrictor tone produced by sodium pentobarbital was for the most part ascribable to the baroreceptor reflex as a compensator for the depressor effect of this anesthetic (2). More recently, we reported further evidence that this compensatory vasoconstrictor tone in the hindquarter vascular region is controlled by efferent fibers, including those in the lumbar sympathetic nerves (3). In addition, new generation of this sympathetic vasoconstricting tone to compensate hypotension is not only ascribable to pentobarbital anesthesia but is also a common phenomenon occurring in the hindquarters under conditions in which moderate hypotension is induced; e.g., after treatment with a nitrous acid agent (4) and after hemorrhage (5). This common compensator phenomenon in the hindquarters always disappears after ganglionic blocking by treatment with hexamethonium bromide (C6).

We doubted that this compensatory phenomenon in the hindquarters would be activated in conscious spontaneous-hypertensive rats (SHRs), because an abnormal sympathetic tone existed in the hindquarter vascular region in conscious SHRs (6). However, there is only one report on the skeletal muscle blood flow in SHRs during hemorrhage, and this report suggests that hemorrhage causes a greater decrease in skeletal muscle blood flow in SHRs than in Wistar-Kyoto (WKYs) control rats (7). In the present study, therefore, we examined whether compensatory vasoconstrictor action in the hindquarters was induced by a hypotensive intervention, i.e., hemorrhage, in conscious SHRs.

The present study was approved by the Animal Welfare Committee of the Hiroshima University Faculty of Medicine. SHRs and Wistar rats (normotensive control rats (NCRs)) were purchased from Charles River Japan, Inc. (Yokohama).

Male SHRs and NCRs at 14 – 17 weeks of age were anesthetized with 50 mg/kg of thiamylal sodium (Isozol; Yoshitomi Pharmaceuticals, Osaka) by intraperitoneal (i.p.) injection, and a probe (2.0 mm in inside diameter) attached to an electromagnetic flowmeter (Nihon Kohden Co., Tokyo) was implanted around the terminal region of the abdominal aorta (most of the blood flow measured there considered to be that of the lower-extremity muscles). At the same time, a cannula (PE-50) for arterial pressure measurement was inserted from the right common carotid artery to near the aortic arch. Another cannula (PE-10 fused to PE-20) for intravenous (i.v.) injection of drugs was
inserted into the right jugular vein. The opposite end of each tube was exteriorized at the neck.

After the instrumentation operation described above, the rats were housed separately in plastic cages measuring \(35 \times 30 \times 17\) (depth) cm and lined with wood chips. The rats were allowed free access to food pellets and drinking water. Three days after implantation of the electromagnetic flowmeter probe and cannulation, arterial pressure and blood flow of the terminal abdominal aorta (hereafter referred to as hindquarter) were measured simultaneously. First, to examine hemodynamics in the resting state, each rat was allowed to behave freely and was observed for 20–30 min in its home cage. After baseline values had been obtained, 0.3 ml of blood per 100 g body weight was withdrawn over a period of 1–2 min with a syringe through the arterial catheter. At \(5-10\) min after hemorrhage, hindquarter flow (HQF) and mean arterial pressure (MAP) were noted, and then a 2.5% (w/v) solution of C6 (Nacalai Tesque, Kyoto) was infused at a rate of 0.8 mg/min to a total dose of 25 mg/kg for ganglionic blockade. The arterial pressure and HQF values were recorded by pen-writing oscillography (RJG-4024, Nihon Kohden) after smoothing with a resistance and capacitance (RC) filter with a time constant of 1 s. The smoothed arterial pressure values were taken as the MAP. Hindquarter resistance (HQR) was calculated as MAP divided by HQF. The flow probe was regularly calibrated before implantation by passing known amounts of saline through excised arteries of other rats. The blood flow and local vascular resistance data were normalized to values per 100 g of body weight for comparison.

In the second series of experiments, to determine whether sympathetic tone exists in the hindquarter vascular bed of SHRs, we observed the effects of ganglionic blockade without hemorrhage in SHRs and NCRs. All of the rats were killed with an overdose of thioumyal sodium at the end of the experiments.

All values are expressed as means ± S.E.M. Analysis of variance of contrast tests in repeated measures ANOVA (by SAS Release 6.12) was used to evaluate the changes after successive treatments (hemorrhage and C6). Statistical analysis was performed using the t-test to determine the significance of the differences between SHRs and NCRs for each parameter (MAP, HQF and HQR) in the resting state and the differences between changes in each parameter produced by treatment with C6 and changes in each parameter produced by treatment with C6 plus hemorrhage. The significance level was set at \(P<0.05\).

The values of MAP, HQF and HQR in the resting state in SHRs (\(n = 13\)) and NCRs (\(n = 16\)) were compared. MAP was significantly higher in SHRs than in NCRs (MAP for SHRs = \(159 \pm 4.3\) vs MAP for NCRs = \(113 \pm 1.7\) mmHg, \(P<0.001\)); HQF was significantly lower in SHRs than in NCRs (HQF for SHRs = \(3.27 \pm 0.1\) vs HQF for NCRs = \(5.13 \pm 0.3\) ml·min\(^{-1}\)·100 g\(^{-1}\), \(P<0.001\)); and HQR was significantly higher in SHRs than in NCRs (HQR for SHRs = \(50.0 \pm 2.5\) vs HQR for NCRs = \(22.8 \pm 1.2\) mmHg/(ml·min\(^{-1}\)·100 g\(^{-1}\)), \(P<0.001\)). These results agree with those of our previous study (8).

Examples of the results of the experiments in an NCR (top) and an SHR (bottom) are presented in Fig. 1. In the period during which tracing of MAP was interrupted, 0.3 ml/100 g body weight of blood was withdrawn from the arterial catheter. The MAP and HQF were minimally affected by the bleeding and both reached new levels in about 10 min. Subsequently, C6 was infused (during the underlined period shown in Fig. 1).

A summary of the data obtained from the above experiments in NCRs and SHRs is presented in Fig. 2. After the hemorrhage, there was almost no change in MAP, and HQF in the SHRs (closed circles) decreased significantly, resulting in a significant increase in HQR. In contrast, there was almost no change in HQF in the NCRs (open circles) following the hemorrhage, resulting in a significant increase in HQR. According to Lombard and Roman (7), hemorrhage causes a greater decrease in skeletal muscle (gracilis muscle) blood flow in SHRs than in WKYs. The results of their study agree partially with our results showing that hemorrhage caused HQF to decrease only in SHRs (Fig. 2, middle). However, in their study using laser-Doppler flowmetry in anesthetized SHRs and WKYs (sodium pentobarbital 60 mg/kg, i.p.), reduction in skeletal muscle blood flow and the magnitude of hypotension induced by the first hemorrhage (1 ml) are strikingly greater in both rat groups when compared with the changes in each parameter in the conscious rat groups after hemorrhage treatment (approximately 0.9 ml) in the present study. Kawaue and Iriuchijima (9) reported that intravenous injection of sodium pentobarbital at 30 mg/kg in NCRs reduced arterial pressure by about 15% and the cardiac index by about 30% on average. HQF was decreased by about 25%, resulting in a significant increase in HQR. Taken together, these different magnitudes not only of decrease in skeletal muscle blood flow but also of hypotension due to hemorrhage may have been caused by different physiological conditions, i.e., conscious state or anesthetized state. The intravenous infusion of C6 after the hemorrhage induced significant decreases in MAP and HQR in both groups. However, the changes in these cardiovascular parameters in the SHRs caused by the infusion of C6 were similar to those in NCRs (ΔMAP post C6 for SHRs = −29.3 ± 3.20% vs ΔMAP post C6 for NCRs = −24.6 ± 1.21%, not significant; ΔHQF post C6 for SHRs = +31.9 ± 10.6% vs ΔHQF post C6 for NCRs = +13.2 ± 4.69%, not significant; ΔHQR post C6 for SHRs = −48.2 ± 3.54% vs ΔHQR post C6 for NCRs = −32.4 ± 2.80%, \(P<0.01\)). HQR was lower in the SHRs after hemorrhage plus C6 infusion than in the SHRs before treatment (basal), whereas the levels of
As shown in Fig. 3, the infusion of C6 significantly decreased MAP in both NCRs and SHRs. However, the changes in HQF and HQR induced by C6 (without hemorrhage) were markedly different in NCRs and SHRs. The increase in MAP was more pronounced in SHRs compared to NCRs. The decrease in HQF and HQR in both NCRs and SHRs was also more significant in SHRs. The changes in HQF and HQR in SHRs (closed circles) were more pronounced than in NCRs (open circles). The data are means ± S.E.M.; *P<0.05, **P<0.01; basal value vs hemorrhage value or hemorrhage value vs C6.
fusion of C6 produced no change in HQF in SHRs, which with the significant decrease in MAP, resulted in a significant decrease in HQR (closed circles). In contrast, in the NCRs, C6 significantly decreased HQF, which, with the significant decrease in MAP, resulted in almost no change in HQR (open circles). These results agree with previous observations (6), suggesting again that abnormal sympathetic tone in the hindquarter vascular region usually exists in conscious SHRs but not in NCRs.

In SHRs, cardiac output is within the normal range and total peripheral resistance is higher than that in NCRs (10–12). Many studies have shown that sympathetic activity in SHRs is enhanced (13–16). The resistance of certain regional vascular beds is significantly higher in SHRs than in NCRs, and basal sympathetic tone exists not only in the carotid and renal arteries but also in the hindquarter artery in SHRs (6). In the present study, we also found that the resistance of the hindquarter artery in the conscious resting state was significantly higher in SHRs than in NCRs and that ganglionic blockade decreased HQR in SHRs but not in NCRs (Fig. 3). These results suggest that basal sympathetic tone exists in the hindquarters of SHRs and that no sympathetic tone exists in hindquarters of NCRs.

We have already observed that after hemorrhage (withdrawing of blood, 0.3 ml/100 g body weight) in NCRs, ganglionic blockade with C6 significantly decreased HQR, suggesting that sympathetic vasoconstrictive tone is newly generated only in the hindquarters of NCRs after hemorrhage (5). In contrast, compensatory vasoconstrictive tone is not generated in NCRs at least in the visceral (i.e., superior mesenteric) vascular regions, by hypotensive interventions (4, 5). In a preliminary study, the superior mesenteric resistance (SMR) in SHRs was almost unchanged even after hemorrhage plus C6 infusion (ΔSMRpost C6 + hemorrhage for SHRs = +2.48 ± 7.03%, n = 10), suggesting that no compensatory vasoconstricting tone is generated in the superior mesenteric vascular regions in SHRs as well as in NCRs (e.g., Y. Teranishi et al., unpublished data). However, the magnitude of the percent decrease in HQR induced by C6 was significantly greater in SHRs with minor hemorrhage than in SHRs with no hemorrhage (ΔHQRpost C6 for SHRs = −28.8 ± 5.49% vs ΔHQRpost C6 + hemorrhage for SHRs = −48.2 ± 3.54%, P<0.01), although the percent decreases in MAP induced by C6 in SHRs with hemorrhage and those with no hemorrhage were similar (ΔMAPpost C6 for SHRs = −36.3 ± 5.64% vs ΔMAPpost C6 + hemorrhage for SHRs = −37.1 ± 3.44%). The present findings suggest that compensatory vasoconstrictor tone is activated within the limits of the hindquarters to compensate for hypotensive intervention, although an abnormal substantial vasoconstrictor tone already exists in resistance vessels of the hindquarters in conscious SHRs.

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