Predominant Role of Neural Arc in Sympathetic Baroreflex Resetting of Spontaneously Hypertensive Rats

– Analysis of an Open-Loop Baroreflex Equilibrium Diagram –

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Background: There is ongoing controversy over whether neural or peripheral factors are the predominant cause of hypertension. The closed-loop negative feedback operation of the arterial baroreflex hampers understanding of how arterial pressure (AP) is determined through the interaction between neural and peripheral factors.

Methods and Results: A novel analysis of an isolated open-loop baroreceptor preparation to examine sympathetic nervous activity (SNA) and AP responses to changes in carotid sinus pressure (CSP) in adult spontaneously hypertensive rats (SHR) and normotensive Wistar Kyoto rats (WKY) was conducted. In the neural arc (CSP-SNA relationship), the midpoint pressure (128.9±3.8 vs. 157.9±8.1 mmHg, P<0.001) and the response range of SNA to CSP (90.5±3.7 vs. 115.4±7.6%/mmHg, P=0.011) were higher in SHR. In the peripheral arc (SNA-AP relationship), slope and intercept did not differ. A baroreflex equilibrium diagram was obtained by depicting neural and peripheral arcs in a pressure-SNA plane with rescaled SNA (% in WKY). The operating-point AP (111.3±4.4 vs. 145.9±5.2 mmHg, P<0.001) and SNA (90.8±3.2 vs. 125.1±6.9% in WKY, P<0.001) were shifted towards a higher level in SHR.

Conclusions: The shift of the neural arc towards a higher SNA range indicated a predominant contribution to baroreflex resetting in SHR. Notwithstanding the resetting, the carotid sinus baroreflex in SHR preserved an ability to reduce AP if activated with a high enough pressure. (Circ J 2015; 79: 592–599)

Key Words: Equilibrium diagram; Hypertension; Norepinephrine; Phenylephrine; Sympathetic nervous activity

The arterial baroreflex control of arterial pressure (AP) is known to reset to a higher input pressure range in hypertension. To cope with the resetting, carotid baroreflex activation is proposed as a potential treatment of drug-resistant hypertension. Involvement of both neural and cardiovascular factors has been proposed in the pathophysiology of hypertension. Previous studies have demonstrated that sympathetic outflow from the central nervous system is increased in spontaneously hypertensive rats (SHR). Peripheral factors such as cardiac hypertrophy and increased vascular resistance are also considered responsible for high AP in SHR. Abnormality in vascular function is also reported in hypertensive patients.

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Device-based neuromodulation therapy has increasingly drawn scientific interest. While the arterial baroreflex has been classified as a short-term blood pressure control system, carotid baroreflex activation therapy has succeeded in reducing blood pressure in patients with resistant hypertension for more than 1 year, suggesting a potential role of the arterial baroreflex in the long-term regulation of blood pressure. Considering the multifactorial and complex nature of hypertension, further research is needed to understand how sympathetic nerve activity (SNA) and AP are determined in hypertension.

The arterial baroreflex system constitutes a key link between the autonomic nervous system and the cardiovascular system. The reflex arc of baroreflex can be divided into 2 principal arcs: the neural arc from pressure input to SNA, and the peripheral arc from SNA to AP. Under normal physiological conditions, because the arterial baroreflex operates as a closed-loop feedback control system, it is difficult to separately quantify neural and peripheral arc characteristics.

The behavior of a system might be described by dynamic and static characteristics. The dynamic characteristics determine...
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The response speed and stability of the system. An open-loop gain (G) is an important parameter of a negative feedback system, and an exogenous disturbance (D) is theoretically attenuated to D/(1+G). This expression, which does not include dynamic characteristics, indicates that a larger gain is always better to attenuate the disturbance. In reality, because of the dynamic characteristics, too large a gain causes an oscillatory response. In this regard, the baroreflex dynamic characteristics are optimized to achieve both stability and quickness. In previous studies, the baroreflex dynamic characteristics are shown to be preserved in SHR, which means that the arterial baroreflex of SHR retains the ability to stabilize AP against exogenous disturbances in spite of high prevailing AP.

Although dynamic characteristics are important to understand the stability, they do not provide information regarding the determination of AP. Why is AP higher in SHR than in Wistar Kyoto rats (WKY) despite the preserved dynamic characteristics? To answer this question, identification of static characteristics becomes necessary. After a certain amount of time, the system response reaches a steady-state value (if the system is stable). The static characteristics describe a set of steady-state responses to a wide range of inputs. The static characteristics of the neural arc approximate an inverse sigmoidal curve, and those of the peripheral arc approximate a straight line. If we superimpose the neural and peripheral arcs on a pressure-SNA plane (a baroreflex equilibrium diagram), the 2 arcs intersect. Under baroreflex closed-loop conditions, the system response or AP is settled at this intersection point, which is referred to as an operating point. These sets of information are unavailable for SHR and remain to be investigated.

The aim of the present study was to obtain the baroreflex equilibrium diagram and to compare the arterial baroreflex function between WKY and SHR. Calibration of SNA in the SHR group against SNA in the WKY group will also be discussed.

Methods

Animals were cared for in strict accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. All experimental protocols were reviewed and approved by the Animal Subjects Committee at the National Cerebral and Cardiovascular Center.

Common Surgical Preparation

Male adult WKY (18±3 weeks) and SHR (20±4 weeks) were used. Each rat was anesthetized with an intraperitoneal injection of a mixture of urethane (250 mg/ml) and α-chloralose (40 mg/ml), and mechanically ventilated with oxygen-enriched room air. A venous catheter was inserted, and 20-fold diluted anesthetic mixture was administered continuously. An arterial catheter was inserted in the femoral artery to measure AP.

Protocol 1 (Acute Baroreflex Study, n=8 for Each Group)

Bilateral vagal and aortic depressor nerves were sectioned to avoid reflexes from the cardiopulmonary region and aortic arch. The carotid sinus regions were isolated bilaterally. A post-ganglionic branch of the splanchnic sympathetic nerve was approached retroperitoneally to record SNA.

To estimate open-loop static characteristics of the carotid sinus baroreflex, carotid sinus pressure (CSP) was reduced to 60 mmHg for 4–6 min, and then increased stepwise from 60 to 180 mmHg in WKY and to 220 mmHg in SHR. The increment and duration of each CSP step were 20 mmHg and 60 s, respectively. SNA was normalized in each animal such that the noise level of SNA recorded after the ganglionic blockade (hexamethonium bromide 60 mg/kg, i.v.) was zero, and the SNA value corresponding to the CSP level of 60 mmHg was 100%.

Protocol 2 (Phenylephrine Administration, n=6 for Each Group)

To compare vascular responsiveness between WKY and SHR, native ganglionic transmission was blocked by an intravenous bolus injection of hexamethonium bromide (60 mg/kg). After a 30-min stabilization, the AP response to intravenous continuous administration of an α1-adrenergic agonist, phenylephrine, was examined. The doses were increased every 15 min at 100, 250, 500, 1,000, 2,000, and 4,000 μg·kg⁻¹·h⁻¹. A further increase in the dose did not increase AP in WKY. Additional doses of 8,000, 16,000, and 32,000 μg·kg⁻¹·h⁻¹ were examined in SHR.

Protocol 3 (Norepinephrine [NE] Measurements, n=10 for Each Group)

To establish closed-loop feedback control conditions of the carotid sinus baroreflex alone, aortic depressor nerves and vagal nerves were sectioned bilaterally. After a 30-min stabilization, 0.3-ml arterial blood was sampled to measure plasma NE concentration, and the same volume of saline was infused. Hexamethonium bromide was then injected in bolus (60 mg/kg) to block ganglionic transmission. After a 30-min stabilization, another blood sample (0.3 ml) was obtained. Plasma NE concentrations were measured using high performance liquid chromatography (HPLC; Eicom, Kyoto, Japan).

Data Analysis

Data were sampled at 200 Hz. In Protocol 1, the mean values of SNA and AP during the last 10 s at each CSP step were obtained from 2 consecutive stepwise input trials. The open-loop static characteristics of the baroreflex total loop (CSP-AP relationship) and neural arc (CSP-SNA relationship) were quantified by using a 4-parameter logistic function:

\[ y = \frac{P_1}{1 + \exp[P_2(x - P_3)]} + P_4 \]

where x and y denote the input (CSP) and output (SNA or AP), respectively; \( P_1 \) is the range response of output; \( P_2 \) is the slope coefficient; \( P_3 \) is the midpoint input pressure; and \( P_4 \) is the minimum value of output. The maximum gain or the maximum slope was calculated as \( P_4/P_3 \).

The static characteristics of the baroreflex peripheral arc (SNA-AP relationship) were analyzed by linear regression as follows:

\[ AP = a \times SNA + b \]

where a and b represent the slope and intercept, respectively.

In Protocol 2, the mean AP was measured during the last 10 s of each dose of infusion. The pooled data from the WKY and SHR groups were compared using a linear regression analysis as follows:

\[ AP = a \times \log_{10}(\text{dose of phenylephrine}) + b \]

where a and b represent the slope and intercept, respectively.
Results

Protocol 1

Typical recordings of 10-Hz resampled CSP, SNA, and AP obtained from WKY and SHR are shown in Figure 1. The white lines in the SNA plots indicate 2-s resampled signals. The green dashed lines in the SNA plots indicate 100% of SNA corresponding to the CSP level of 60 mmHg. SNA was normalized so that the value at the CSP level of 60 mmHg became 100%.

Statistical Analysis

All data are presented as mean and SE values. In Protocols 1 and 3, baroreflex parameters, NE concentrations, and AP values were compared by using an unpaired t-test between WKY and SHR. In Protocol 3, regression lines were compared between WKY and SHR. Differences were considered significant when \( P < 0.05 \).

Figure 1. Typical recordings of 10-Hz resampled carotid sinus pressure (CSP), sympathetic nerve activity (SNA), and arterial pressure (AP) obtained from Wistar Kyoto rats (WKY) (A) and spontaneously hypertensive rats (SHR) (B). Stepwise increments in CSP reduced SNA and AP. The white lines in the SNA plots indicate 2-s resampled signals. The green dashed lines in the SNA plots indicate 100% of SNA corresponding to the CSP level of 60 mmHg. SNA was normalized so that the value at the CSP level of 60 mmHg became 100%.

Figure 2. (A) Relationship of arterial pressure (AP) vs. carotid sinus pressure (CSP). The CSP-AP relationship moved upward and rightward in spontaneously hypertensive rats (SHR) compared with that in Wistar Kyoto rats (WKY). (B) The relationship of percent sympathetic nerve activity (SNA) vs. CSP. The maximum slope was reduced in SHR compared with that in WKY. (C) The relationship of AP vs. percent SNA. The slope was steeper in SHR than in WKY. Data are presented as mean and SE values. The green dashed lines in (B) and (C) indicate 100% of SNA corresponding to the CSP level of 60 mmHg. SNA was normalized so that the CSP level of 60 mmHg became 100%.

Statistical Analysis

All data are presented as mean and SE values. In Protocols 1 and 3, baroreflex parameters, NE concentrations, and AP values were compared by using an unpaired t-test between WKY and SHR. In Protocol 2, regression lines were compared between WKY and SHR. Differences were considered significant when \( P < 0.05 \).
Baroreflex Equilibrium Diagram in SHR

Figure 5A depicts the baroreflex equilibrium diagram constructed from the neural and peripheral arcs, as shown in Figures 2B and 2C. The operating-point AP was higher in SHR than in WKY (145.9 vs. 111.3 mmHg, the horizontal gray dashed lines). The operating-point SNA was lower in SHR than in WKY (82.0% vs. 90.8%, the vertical gray dashed lines) when the SNA data were derived from percent values in each animal.

Figure 5B depicts a putative baroreflex equilibrium diagram where the SNA axis of SHR is translated into the units of % in WKY based on the pressor response to phenylephrine (see Figure 2A).

Both WKY and SHR.

The open-loop static characteristics of the carotid sinus baroreflex are depicted by averages in each group (Figure 2A). In the total loop (Figure 2A), the increase in CSP decreased AP. The midpoint input pressure and the minimum AP were significantly higher, and the response range was significantly greater in SHR than in WKY (Table 1). The maximum gain did not differ between WKY and SHR.

In the neural arc (Figure 2B), the increase in CSP decreased SNA. In SHR, the response range of percent SNA was significantly narrower with a higher trough than in WKY (Table 2). The maximum slope was significantly smaller in SHR than in WKY.

In the peripheral arc (Figure 2C), AP increased linearly with percent SNA. The slope was significantly steeper in SHR than in WKY, whereas the intercept did not differ between the 2 groups (Table 2).

Protocol 2

After the ganglionic blockade, the AP response to intravenous phenylephrine infusion was examined, as shown in Figure 3. The regression line on the pooled data was AP=64.5x−71.7 for WKY and AP=71.2x−88.2 for SHR, where x indicates the log-dose of phenylephrine. The slope (P=0.23) and intercept (P=0.19) were not different between WKY and SHR.

Protocol 3

Before the ganglionic blockade, plasma NE (149.9±47.0 vs. 315.0±32.8 pg/ml, P=0.014) and mean AP (104.0±5.9 vs. 153.5±7.6 mmHg, P<0.001) were significantly higher in SHR than in WKY (Figure 4). After the ganglionic blockade, both plasma NE (5.2±2.4 vs. 10.5±4.5 pg/ml, P=0.166) and AP (63.4±3.2 vs. 62.2±5.4 mmHg, P=0.853) decreased, and there were no significant differences between WKY and SHR.
A comparison of multifiber SNA between different animal groups often suffers from the fact that the absolute amplitude of recorded SNA could vary among animals. In Protocol 1 (Figures 2B and 2C), SNA was normalized in each animal so that the SNA value corresponding to the CSP level of 60 mmHg became 100%. This normalization hampers, for instance, the comparison of the maximum SNA between WKY and SHR. To circumvent this problem, we quantified the AP response to exogenous phenylephrine in Protocol 2 (Figure 3), which allowed the conversion of a given AP value into the corresponding log dose of phenylephrine. By converting the AP value in Protocol 1 into the corresponding log dose of phenylephrine, we obtained the relationship between SNA and log dose of phenylephrine separately for WKY ([y=0.0114x1+1.853], where x1 is SNA of WKY, and y is the log dose of phenylephrine) and SHR.

**Discussion**

The open-loop static characteristics of the carotid sinus baroreflex were identified in WKY and SHR. The major finding was that the resetting of the carotid sinus baroreflex towards a higher pressure range in SHR was mainly attributable to changes in the neural arc when SNA was calibrated based on thepressor response to phenylephrine (Figure 5B). Notwithstanding the resetting, the carotid sinus baroreflex preserved the ability to suppress SNA and reduce AP to within a normal AP range if activated with high enough pressure.

**Conversion of SNA in SHR Into the Units of % in WKY**

A comparison of multifiber SNA between different animal groups often suffers from the fact that the absolute amplitude of recorded SNA could vary among animals. In Protocol 1 (Figures 2B and 2C), SNA was normalized in each animal so that the SNA value corresponding to the CSP level of 60 mmHg became 100%. This normalization hampers, for instance, the comparison of the maximum SNA between WKY and SHR. To circumvent this problem, we quantified the AP response to exogenous phenylephrine in Protocol 2 (Figure 3), which allowed the conversion of a given AP value into the corresponding log dose of phenylephrine. By converting the AP value in Protocol 1 into the corresponding log dose of phenylephrine, we obtained the relationship between SNA and log dose of phenylephrine separately for WKY ([y=0.0114x1+1.853], where x1 is SNA of WKY, and y is the log dose of phenylephrine) and SHR.
Baroreflex Equilibrium Diagram in SHR

The input-output relationship between SNA and AP approximated a straight line (Figure 2C). The slope of the peripheral arc was steeper in SHR than in WKY when SNA is expressed in percent changes (Table 2). However, when SNA is expressed in the units of % in WKY, the slope in SHR was not different from that in WKY. The pressure intercept of the peripheral arc did not differ between WKY and SHR, indicating that AP will fall to a similar level if SNA is completely blocked. In fact, AP levels acquired after the ganglionic blockade were not significantly different between WKY and SHR in the present study and in a previous study.4 In contrast, the AP level is slightly higher in SHR than in WKY after total spinal destruction.36,37 The AP level of SHR remains higher than that of WKY following hexamethonium in the conscious state.38 The possibility that the anesthesia used in the present study had masked a potential difference in the AP levels in the absence of sympathetic tone between WKY and SHR cannot be ruled out.

Baroreflex Equilibrium Diagram in WKY and SHR

The baroreflex equilibrium diagram indicated that the neural arc in SHR moved towards higher input pressure and higher SNA compared with that in WKY (Figure 5B). While the peripheral arc in SHR moved towards higher AP and higher SNA compared with that in WKY, the peripheral arcs of WKY and SHR lay along a single line. The similar peripheral arc between WKY and SHR may be in line with the fact that the frequency-pressure response curves obtained from the spinal cord stimulation were not distinguishable between WKY and SHR, excepting the maximum response.37 The intersection of the neural and peripheral arcs, that is, an operating point, occurred at higher AP and higher SNA in SHR than in WKY. The baroreflex control of SNA in SHR is therefore responsible for the reduced baroreflex control of SNA in SHR.

The possible mechanism for the shift of the neural arc towards higher SNA in SHR is the imbalance between nitric oxide and reactive oxygen species (ROS) in the brainstem; the former suppresses SNA and the latter activates SNA.39-42 Central angiotensin II increases nicotinamide-adenine dinucleotide phos-
the pressure-diameter relation towards higher input pressure.

In contrast, a mechanism for the shift of the neural arc towards higher input pressure in SHR is less clear. A reduced distensibility of the arterial wall at the baroreceptor regions can change the pressure-diameter relation towards higher input pressure. This mechanism may be secondary to hypertension because the resetting of the non-myelinated aortic baroreceptor afferent fibers in SHR does not occur at 16 weeks of age when SHR exhibits established hypertension.

Plasma Catecholamine Concentrations in WKY and SHR

Based on the baroreflex equilibrium diagram (Figure 5B), SNA at the operating point was predicted to be 1.4-fold higher in SHR than in WKY. In the present experimental conditions, the plasma NE concentration measured before the ganglionic blockade was approximately 2-fold higher in SHR than in WKY (Figure 4). Single fiber activity of renal SNA is reported to be approximately 2.2-fold higher in SHR than in WKY. Although the relationship between SNA and plasma NE was nearly linear in WKY, it was not identified in SHR. Therefore, it remains inconclusive whether the difference in the NE concentration between WKY and SHR was consistent with the predicted difference in the operating-point SNA. With respect to AP, there was no significant difference between the operating-point SNA predicted from the equilibrium diagram (Table 3) and the AP value measured before the ganglionic blockade in Protocol 3, in either WKY or SHR.

Clinical Implication

We selected SHR as the most common model for essential hypertension. While the present study is not directly relevant to long-term AP control, the fact that the neural arc has a predominant role in determining the operating-point SNA and AP in SHR may be compatible with a therapeutic approach targeting the brain in this type of hypertension. Other models of hypertension might exhibit changes in the peripheral arc alone or both the neural and peripheral arcs, which would help determine therapeutic targets depending on the types of hypertension.

Baroreflex activation therapy has demonstrated a significant reduction of blood pressure in patients with resistant hypertension. Because baroreflex activation therapy directly stimulates the baroreceptor afferent fibers, resetting at the baroreceptor level might not interfere with the treatment effect. The sustained sympathetic inhibition during the baroreflex activation therapy also indicates that the central compensations, although possible, do not diminish the chronic suppression of SNA and AP in response to baroreceptor afferent stimulation.

Although short-term regulation of AP by the arterial baroreflex is mediated by changes in peripheral vascular resistance and cardiac output, long-term regulation of AP might require changes in renal excretory function and total body fluid volume. Lohmeier and Iliescu suggested that renal nerves link suppression of central sympathetic outflow to increased renal excretory function during baroreflex activation. At the same time, they suggested that renal nerves are not the only mechanism because renal denervation does not abolish sustained reduction in AP during baroreflex activation. While electrical activation of the carotid baroreflex does not seem to disrupt the native baroreflex function, examining the baroreflex equilibrium diagram after baroreflex activation therapy in an animal model of hypertension might provide further information as to the effect of long-term baroreflex activation on the short-term AP regulation by the native baroreflex.

Study Limitations

First, because we examined the carotid sinus baroreflex under anesthetic conditions, the results are not directly extendable to the conscious state. McKeown and Shoukas have succeeded in isolating the carotid sinus regions in conscious state. Unfortunately, however, they only tested the extreme input pressures of 50 and 200 mmHg, which did not allow characterization of the sigmoidal nature of the carotid sinus baroreflex.

Second, baroreflex control of SNA and pressor responses to electrical stimulation of the spinal cord or the pharmacological interventions are known to be different, depending on the ages of WKY and SHR. Although we used only adult WKY and SHR, studies on younger rats may be required to understand the development of hypertension. The difficulty associated with the carotid sinus isolation in young and small animals needs to be resolved.

Third, because time windows of estimating the peripheral arc characteristics were different between Protocols 1 (1 min per each CSP level) and 2 (15 min per each dose of phenylephrine), the contribution of pressure-diuresis to the steady-state AP response might have been different. Although an increase in AP itself acts to increase diuresis, concurrent sympathetic activation or α-adrenergic stimulation has antinatriuretic effects. Further studies are required to quantify the time-courses of the respective and combined effects of increased AP and adrenergic stimulation on diuresis during baroreflex-mediated AP regulation.

Finally, the duration of baroreceptor pressure input (1 min per each CSP level) might be too short to extrapolate the results to interpret the long-term therapeutic mechanism of baroreflex activation therapy. Rather, this study would explain why the baroreflex activation can reduce AP in the beginning of the therapy. Once AP is decreased, adaptation or resetting of the arterial baroreflex towards the decreased level of AP would act to maintain the depressor effect through the arterial baroreflex. This speculation also needs to be tested in the future.

Conclusions

The resetting of the carotid sinus baroreflex towards a higher pressure range observed in SHR was mainly attributable to changes in the neural arc when SNA was expressed in the units of % in WKY, based on the AP response to exogenous phenylephrine. Notwithstanding the resetting, the carotid sinus baroreflex in SHR preserved the ability to suppress SNA and reduce AP to within a normal pressure range if activated with high enough pressure. These results might provide a rationale for the use of carotid baroreflex activation as an alternative therapy for drug-resistant hypertension.

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Disclosures

None.

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