A derivative-sigmoidal model reproduces operating point-dependent baroreflex neural arc transfer characteristics

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Kawada, Toru, Kazunori Uemura, Koji Kashihara, Atsunori Kamiya, Masaru Sugimachi, and Kenji Sunagawa. A derivative-sigmoidal model reproduces operating point-dependent baroreflex neural arc transfer characteristics. Am J Physiol Heart Circ Physiol 286: H2272–H2279, 2004. First published February 12, 2004; 10.1152/ajpheart.00787.2003.—A cascade model comprised of a derivative filter followed by a nonlinear sigmoidal component reproduces the input size dependence of transfer gain in the baroreflex neural arc from baroreceptor pressure input to efferent sympathetic nerve activity (SNA). We examined whether the same model could predict the operating point dependence of the baroreflex neural arc transfer characteristics estimated by a binary white noise input. In eight anesthetized rabbits, we isolated bilateral carotid sinuses from the systemic circulation and controlled intracarotid sinus pressure (CSP). We estimated the linear transfer function from CSP to SNA while varying mean CSP among 70, 100, 130, and 160 mmHg (P70, P100, P130, and P160, respectively). The transfer gain at 0.01 Hz was significantly smaller at P70 (0.61 ± 0.26) and P160 (0.60 ± 0.25) than at P100 (1.32 ± 0.42) and P130 (1.36 ± 0.45) (in arbitrary units/mmHg; means ± SD; P < 0.05). In contrast, transfer gain values above 0.5 Hz were similar among the protocols. As a result, the slope of increasing gain between 0.1 and 0.5 Hz was significantly steeper at P70 (17.6 ± 3.6) and P160 (14.1 ± 4.3) than at P100 (8.1 ± 4.4) and P130 (7.4 ± 6.6) (in dB/decade; means ± SD; P < 0.05). These results were consistent with those predicted by the derivative-sigmoidal model, where the deviation of mean input pressure from the center of the sigmoidal nonlinearity reduced the transfer gain mainly in the low-frequency range. The derivative-sigmoidal model functionally reproduces the dynamic SNA regulation by the arterial baroreflex over a wide operating range.

The arterial baroreflex system is one of the important negative-feedback systems that stabilize arterial pressure (AP) against pressure disturbances during daily activity. A systematic analysis of baroreflex dynamic characteristics is essential for better understanding of physiological AP regulation, leading to the development of a bionic baroreflex system that can replace a failed vasomotor center (25, 26). We have analyzed the arterial baroreflex system by breaking its sympathetic limb down into neural and peripheral arc subsystems (8, 21, 24). The dynamic SNA response to baroreceptor pressure input becomes greater as the frequency of input perturbation increases in the frequency range between 0.01 and 1 Hz in anesthetized rabbits and rats (8, 15, 23), suggesting derivative characteristics of the baroreflex neural arc. In contrast, the dynamic AP response to SNA becomes smaller as the modulation frequency of SNA increases in the same frequency range, indicating the low-pass characteristics of the baroreflex peripheral arc. The fast neural arc effectively compensates for the slow peripheral arc to accelerate dynamic AP regulation by the baroreflex negative-feedback loop (8).

The static input-output relationship between baroreceptor pressure input and AP determined under open-loop conditions approximates a nonlinear sigmoidal curve with threshold and saturation (1, 2, 16, 22, 28). Under closed-loop conditions, the baroreceptor pressure input equilibrates with AP. The closed-loop operating pressure thus determined is near the center of the sigmoid curve in anesthetized rabbits and rats (4, 24). The baroreflex dynamic characteristics frequently have been estimated by using the mean input pressure around the closed-loop operating pressure (8–10, 14, 15, 19, 20). Accordingly, the baroreflex dynamic characteristics have not yet been elucidated over a wide operating range.

In a previous study, we (14) demonstrated that a cascade model consisting of a linear derivative filter followed by a nonlinear sigmoidal component (a class of Wiener model) can serve as a first approximation of neural arc transfer characteristics. Using this model, we simulated how differences in mean input pressure affect the linear transfer function from pressure input to SNA. On the basis of results of simulation using a binary white noise input, we hypothesized that deviation of the mean input pressure from the closed-loop operating pressure would decrease the neural arc transfer gain mainly in the low-frequency range, while not affecting that in the high-frequency range. To test this hypothesis, we performed an open-loop experiment on the carotid sinus baroreflex in anesthetized rabbits. The previous investigation (14) focused on developing a proper model for the overall transfer characteristics of the baroreflex neural arc based on a particular set of data, whereas the present investigation focused on verifying the model by predicting system behavior in response to input signals that had not been examined during the model construction. The results of the present study supported our hypothesis that the deviation of mean input pressure from the closed-loop operating pressure affects neural arc transfer gain in a frequency-dependent manner.

MATERIALS AND METHODS

Simulation study. Figure 1A illustrates a cascade model consisting of a derivative filter followed by a nonlinear sigmoidal component...
(see APPENDIX for numerical descriptions). This model was able to reproduce the input size dependence of baroreflex neural arc transfer characteristics from carotid sinus pressure (CSP) to SNA in a previous study (14). We calculated the linear transfer function of this model in the frequency range between 0.01 and 1 Hz by using a binary white noise input. The mean input pressure was deviated from the center (PC) of the sigmoidal nonlinearity by ±20, ±40, and ±60 mmHg (P_{C±20}, P_{C±40}, and P_{C±60}, respectively).

Surgical preparations. Animals were cared for strictly in accordance with the Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences approved by the Physiological Society of Japan. Eight Japanese white rabbits weighing 2.6–3.6 kg were anesthetized by intravenous injection (2 ml/kg) of a mixture of urethane (250 mg/ml) and α-chloralose (40 mg/ml) and mechanically ventilated with oxygen-enriched room air. Supplemental anesthetics were injected as necessary (0.5 ml/kg) to maintain an appropriate level of anesthesia. AP was measured with a high-fidelity pressure transducer (Millar Instruments, Houston, TX) inserted via the right femoral artery. We isolated bilateral carotid sinususes from the systemic circulation by ligating the internal and external carotid arteries and other small branches originating from the carotid sinuses regions. The isolated carotid sinususes were filled with warmed physiological saline through catheters inserted via the common carotid arteries. CSP was controlled by a servo-controlled piston pump. Bilateral vagal and aortic depressor nerves were sectioned at the neck to minimize re-ex effects from the cardiopulmonary arc. We exposed the left cardiac sympathetic nerve through a midline thoracotomy and attached a pair of stainless steel wire electrodes (Bioflex wire AS633; Cooner Wire) to record SNA (13). The nerve bundle peripheral to the electrodes was sectioned to eliminate afferent signals from the heart. The nerve and electrodes were covered with curing silicone glue (Kwik-Sil; World Precision Instruments) for insulation and fixation. The preamplified nerve signal was band-pass filtered at 150–1,000 Hz, and then full-wave rectified and low-pass filtered with a cutoff frequency of 30 Hz to quantify nerve activity. Pancuronium bromide (0.1 mg/kg) was administered to prevent contamination of muscular activity in the SNA recording. Body temperature was maintained at ~38°C with a heating pad.

Protocols. To estimate dynamic characteristics of the carotid sinus baroreflex at different operating points, we perturbed CSP with the mean input pressure set at 70, 100, 130, and 160 mmHg. These protocols are hereafter denoted as P_70, P_100, P_130, and P_160, respectively. In each protocol, CSP was assigned at either 20 mmHg above or below the mean input pressure every 500 ms according to a binary white noise signal. The four protocols were performed in random order. After mean SNA and AP had reached a steady state in each protocol, CSP, SNA, and AP were recorded for 10 min. Data were sampled at 200 Hz with a 12-bit analog-to-digital converter and stored on the hard disk of a dedicated laboratory computer system.

Data analysis. The neural arc transfer function from CSP to SNA, the peripheral arc transfer function from SNA to AP, and the total loop transfer function from CSP to AP were estimated by the following procedure. The input-output data pairs were resampled at 10 Hz and segmented into eight sets of 50%-overlapping bins of 1,024 points each (6). For each segment, a linear trend was subtracted and a Hanning window was applied. A fast Fourier transform was performed to obtain the spectra of the data segments (3). The ensemble averages of input [S_{XX}(f)] and output [S_{YY}(f)] and cross-spectra between the input and output [S_{XY}(f)] were estimated over the eight segments. Finally, the transfer function [H(f)] from the input to the output was calculated as (18)

$$H(f) = \frac{S_{YY}(f)}{S_{XX}(f)}$$ (1)

To quantify the linear dependence between the input and output signals in the frequency domain, a magnitude-squared coherence function [\text{Coh}(f)] was calculated as (18)

$$\text{Coh}(f) = \frac{|S_{XY}(f)|^2}{S_{XX}(f)S_{YY}(f)}$$ (2)
Fig. 2. Representative time series for CSP, SNA, and arterial pressure (AP) obtained from the 4 protocols. CSP was perturbed according to a binary white noise sequence. The mean levels of SNA and AP decreased as the mean input pressure increased. P70, P100, P130, and P160, protocols with mean input pressure at 70, 100, 130, and 160 mmHg, respectively; au, arbitrary units.

The coherence value ranges from zero to unity. A unity coherence value indicates perfect linear dependence between the input and output signals, whereas a zero coherence value indicates total independence between the two signals. Possible sources for lowering the coherence values include physical noise in signal measurements, biological noise in the output signal unrelated to the input signal, and nonlinear system responses.

Statistical analysis. All data are presented as means ± SD. Because the absolute amplitude of SNA varied depending on recording conditions, SNA is presented in arbitrary units (au). We calculated a normalization factor for the neural arc transfer function in each animal so that the average value of transfer gains obtained from the four protocols became unity at 0.01 Hz. Because we multiplied the same normalization factor to the transfer gain values at all frequencies, the gain plot did not change its frequency distribution. The inverse of the normalization factor was then applied to the peripheral arc transfer function in each animal. The total loop transfer function was not normalized. To compare the transfer functions among the P70, P100, P130, and P160 protocols, with mean input pressure at 70, 100, 130, and 160 mmHg, respectively; au, arbitrary units.

RESULTS

Figure 1B shows the linear transfer function from CSP to SNA estimated from the simulation data with a derivative-sigmoidal cascade model (see APPENDIX for details). Gain plots, phase plots, and coherence functions are presented. When the mean input pressure was at the center of the sigmoidal nonlinearity, the transfer gain increased slightly with increasing frequency. The phase approached −π rad at the lowest frequency and lagged with increasing frequency. The coherence values were close to unity in the frequency range from 0.01 to 1 Hz. The deviation of mean input pressure at P_{C=20} and P_{C=60} decreased the transfer gain mainly in the low-frequency range. The derivative characteristics became more enhanced as the deviation of mean input pressure increased. Although the phase plot did not change markedly across the four conditions, the phase values led slightly between 0.04 and 0.3 Hz at P_{C=60}. The deviation of mean input pressure decreased coherence values in the lower frequencies.

Figure 2 shows typical time series of CSP, SNA, and AP in one animal. CSP was perturbed by a binary white noise sequence. An identical binary sequence with a different pressure level was imposed on CSP. Although the series are arranged in Fig. 2 in order of ascending CSP level, the actual protocols were performed in random order. The elevation of CSP level suppressed mean SNA and AP. Despite the same amplitude of CSP perturbation, changes in AP appeared to be greater in the P100 and P130 protocols than in the P70 and P160 protocols.

Mean levels of SNA and AP obtained from all animals are summarized in Table 1. The mean SNA and AP values during the CSP perturbation were significantly higher in the P70 protocol than in the other three protocols. The mean AP value was significantly lower in the P160 protocol than in the P100 protocol.

Figure 3 shows the neural arc transfer functions averaged from all animals. Gain plots, phase plots, and coherence functions are presented. The transfer gain increased with increasing frequency in each protocol, indicating the derivative characteristics of the neural arc. The gain values at lower

Table 1. Mean levels of sympathetic nerve activity and arterial pressure

<table>
<thead>
<tr>
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<th>P70</th>
<th>P100</th>
<th>P130</th>
<th>P160</th>
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<tr>
<td>SNA, au</td>
<td>1.17±0.30*†+</td>
<td>0.85±0.37</td>
<td>0.73±0.33</td>
<td>0.72±0.28</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>113±13*†+</td>
<td>93±15</td>
<td>82±16</td>
<td>77±13§</td>
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</tbody>
</table>

Data are means ± SD. SNA, sympathetic nerve activity; au, arbitrary units; AP, arterial pressure; P70, P100, P130, P160, input pressure of 70, 100, 130, and 160 mmHg, respectively; *P < 0.01, †P < 0.05, ‡P < 0.01 vs. P100, P130, and P160, respectively; §P < 0.05 vs. P100.
frequencies were smaller in the P70 and P160 protocols than in the P100 and P130 protocols. In contrast, the gain values above 0.5 Hz were similar among the four protocols. As a result, the slope of the increasing gain was steeper in the P70 and P160 protocols than in the P100 and P130 protocols. The phase approached $-\pi$ rad at the lowest frequency in the P100 and P130 protocols, reflecting the out-of-phase relationship between CSP and SNA. The phase values in the lower frequencies were dispersed, and mean phase values were deviated from $-\pi$ toward 0 rad in the P70 and P160 protocols. The coherence values were <0.5 below 0.1 Hz in the P70 protocols. The coherence values appeared to be greater in the P100 and P130 protocols than in the P70 and P160 protocols.

Figure 4 shows the peripheral arc transfer functions averaged from all animals. The transfer gain decreased with increasing frequency in each protocol, indicating the low-pass characteristics of the peripheral arc. The transfer gain values below 0.03 Hz were smaller in the P70 protocol than in the other three protocols. A sharp peak around 0.6 Hz corresponded to the frequency of artificial ventilation. The phase approached 0 rad at the lowest frequency in each protocol, reflecting the fact that an increase in SNA increased AP at steady state. The phase lagged significantly with increasing frequency in each protocol. The coherence values were <0.5 below 0.4 Hz in the P70 protocol. The coherence values appeared to be greater in the P100 and P130 protocols than in the P70 protocol. The coherence values were similar in the P100 and P160 protocols.

Figure 5 depicts the total loop transfer function averaged from all animals. The transfer gain decreased as the frequency increased in each protocol, indicating the low-pass characteristics of the total baroreflex loop. The gain values below 0.1 Hz were smaller in the P70 and P160 protocols than in the P100 and P130 protocols. The phase approached $-\pi$ rad at lowest frequencies in the P100 and P130 protocols, reflecting the negative feedback attained by the total baroreflex loop. The phase
values in the lower frequencies were dispersed and mean phase values were deviated from $-\pi$ toward 0 rad in the P 70 and P 160 protocols. The coherence values were $<0.5$ below 0.08 Hz in the P 70 protocol and $<0.5$ below 0.02 Hz in the P 160 protocol. The coherence values appeared to be greater in the P 100 and P 130 protocols than in the P 70 and P 160 protocols.

Table 2 summarizes the statistical analysis of the obtained data. In the neural arc, $G_{0.01}$ and $G_{0.1}$ were significantly smaller in the P 70 and P 160 protocols than in the P 100 and P 130 protocols. Slope 0.1 did not differ among the four protocols. In the total loop transfer function, $G_{0.01}$ was significantly smaller in the P 130 protocol. $G_{0.1}$ and Slope 0.1–0.5 did not differ among the four protocols. In the peripheral arc, $G_{0.01}$ was significantly smaller in the P 70 than in the P 130 protocol. $G_{0.1}$ and Slope 0.1–0.5 did not differ among the four protocols. In the peripheral arc, $G_{0.01}$ was significantly smaller in the P 70 protocol than in the P 100 and P 130 protocols. $G_{0.1}$ was significantly smaller in the P 70 and P 160 protocols than in the P 100 and P 130 protocols. Slope 0.1–0.5 was significantly less negative in the P 70 than in the P 100 protocol.

**DISCUSSION**

We have demonstrated that differences in mean input CSP significantly affect the linear transfer function of the baroreflex neural arc estimated by a binary white noise input (Fig. 3). Changes in the neural arc transfer function observed in the animal experiment were qualitatively consistent with predictions made by the derivative-sigmoidal cascade model (Fig. 1B), reinforcing the validity of this model as a first approximation of baroreflex neural arc transfer characteristics.

**Operating point dependence of baroreflex transfer characteristics.** In a previous study, we (14) postulated a simple model of the baroreflex neural arc consisting of a linear derivative filter followed by a nonlinear sigmoidal component based on the input size dependence of the neural arc transfer characteristics. The same model predicted that deviation of the mean input level from the center of sigmoidal nonlinearity would decrease the gain of signal transduction mainly in the low-frequency range (Fig. 1B). The midpoint pressure for the static input-output relationship between CSP and SNA was $\sim 110–115$ mmHg in anesthetized rabbits (12, 13). Hence, significant deviation of the mean input CSP from the midpoint pressure in the P 70 and P 160 protocols resulted in decreased transfer gain in the lower frequencies compared with the P 100 and P 130 protocols (Fig. 3). Generally, the interpretation of the estimated transfer function in the frequencies associated with low coherence values is difficult. This is because the low

<table>
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<tr>
<th>Parameters of neural arc, peripheral arc, and total loop transfer functions</th>
<th>P 70</th>
<th>P 100</th>
<th>P 130</th>
<th>P 160</th>
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<tr>
<td><strong>Neural arc</strong></td>
<td></td>
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<tr>
<td>$G_{0.01}$, au/mmHg</td>
<td>0.61±0.26†§</td>
<td>1.32±0.42</td>
<td>1.36±0.45</td>
<td>0.60±0.25†§</td>
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<tr>
<td>$G_{0.1}$, au/mmHg</td>
<td>0.86±0.31†§</td>
<td>2.34±0.77</td>
<td>2.46±0.96</td>
<td>1.30±0.59†§</td>
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<tr>
<td>Slope 0.1–0.5, dB/decade</td>
<td>17.6±3.6†§</td>
<td>8.1±4.4</td>
<td>7.4±6.6</td>
<td>14.1±4.3†§</td>
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<tr>
<td><strong>Peripheral arc</strong></td>
<td></td>
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<tr>
<td>$G_{0.01}$, mmHg/au</td>
<td>0.54±0.26‡</td>
<td>0.76±0.43</td>
<td>0.96±0.30</td>
<td>0.85±0.41</td>
</tr>
<tr>
<td>$G_{0.1}$, mmHg/au</td>
<td>0.22±0.11</td>
<td>0.19±0.08</td>
<td>0.22±0.09</td>
<td>0.16±0.10</td>
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<tr>
<td>Slope 0.1–0.5, dB/decade</td>
<td>$-31.5±11.5$</td>
<td>$-35.6±5.2$</td>
<td>$-34.7±6.7$</td>
<td>$-33.4±7.9$</td>
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<tr>
<td><strong>Total baroreflex loop</strong></td>
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<tr>
<td>$G_{0.01}$</td>
<td>0.46±0.24‡</td>
<td>1.40±0.80</td>
<td>1.55±0.72</td>
<td>0.73±0.39</td>
</tr>
<tr>
<td>$G_{0.1}$</td>
<td>0.28±0.09‡</td>
<td>0.53±0.22</td>
<td>0.52±0.14</td>
<td>0.24±0.12†§</td>
</tr>
<tr>
<td>Slope 0.1–0.5, dB/decade</td>
<td>$-17.3±7.3*$</td>
<td>$-28.3±5.5$</td>
<td>$-26.0±11.2$</td>
<td>$-21.8±7.7$</td>
</tr>
</tbody>
</table>

Data are means ± SD. $G_{0.01}$, $G_{0.1}$, transfer gain at 0.01 Hz and 0.1 Hz, respectively; Slope 0.1–0.5, average slope of transfer gain between 0.1 and 0.5 Hz. *$P < 0.05$, †$P < 0.01$ vs. P 100; ‡$P < 0.05$, §$P < 0.01$ vs. P 130.
coherence values indicate that the output signal contained significant noise unrelated to the input signal and/or nonlinear system response, which may hamper the accurate estimation of the transfer function. However, in our experience, the continuous phase shift over the frequency range of interest is indicative of true system dynamics in physiological systems. In addition, the decreases in the transfer gain and coherence values in the low frequencies were observed even in the noiseless simulation (Fig. 1B: P$_{C=40}$ and P$_{C=60}$). Therefore, we judged that what we observed in Fig. 3 reflected the true reality rather than the limitations in analysis. These results indicate that the derivative-sigmoidal model was able to predict operating point-dependent changes in baroreflex neural arc transfer characteristics.

In the peripheral arc transfer function, although $G_{0.01}$ was significantly smaller in the $P_{70}$ protocol than in the $P_{130}$ protocol, other parameters did not differ markedly among the protocols. The peripheral arc transfer functions were almost unchanged among the $P_{100}$, $P_{130}$, and $P_{160}$ protocols. The static input-output relationship between SNA and AP is much more linear than that between CSP and SNA under normal physiological conditions (24). In addition, changes in mean SNA might have been limited, despite large changes in mean CSP, because of the significant nonlinearity in the baroreflex neural arc. Therefore, the differences in mean SNA among the $P_{100}$, $P_{130}$, and $P_{160}$ protocols might have been sufficiently small for the peripheral arc to show a piecewise linearity in the AP response. The results are consistent with previous studies demonstrating that the peripheral arc transfer function was unchanged regardless of differences in the operating point and input power (11, 14). The difference between the $P_{100}$ and $P_{160}$ protocols was significant in mean AP but not in mean SNA (Table 1). We think that we could not detect the difference in mean SNA between the $P_{100}$ and $P_{160}$ protocols because of the large variance in SNA data.

The operating point difference affected the total loop transfer function mainly at frequencies <0.1 Hz (Fig. 5). The significant decrease in the neural arc transfer gain in the lower frequencies (Fig. 3) contributed to the decreased gain in the total loop transfer function. In contrast to the low-frequency range, the gain values above 0.3 Hz in the total loop transfer function were similar among the four protocols (Fig. 5). The fact that the transfer gain manifested different modulations between low- and high-frequency ranges implies a pitfall in the assessment of the baroreflex function with ordinary pressure perturbations as follows. In many basic and clinical settings, the baroreflex function is frequently evaluated by using a ramp pressure disturbance induced by pharmacological intervention. With such a method, the baroreflex function is evaluated only in a limited frequency bandwidth determined by the ramp speed of pressure disturbance. The baroreflex gain thus estimated may not necessarily correlate with the steady-state gain or dynamic gain in the lowest frequency, which is a most important parameter in determining the steady-state performance of the negative-feedback system.

A possible mechanism for operating point dependence in neural arc transfer characteristics. Clearly, changes in the characteristics of the linear dynamic component would also account for the operating point-dependent changes in the neural arc transfer function. However, the low coherence values associated with the decreased transfer gain in the low frequencies in the $P_{70}$ and $P_{160}$ protocols suggest that the nonlinear system response had increased under these conditions. If the characteristics of the dynamic component alone changed, coherence values might not have changed significantly regardless of the difference in the mean input levels. A possible mechanism for the operating point dependence of the neural arc transfer characteristics is discussed below. Figure 6 schematically illustrates signal transduction through the derivative-sigmoidal cascade model. In Fig. 6, $A$–$F$, the input sinusoid at CSP (a) is first processed by the derivative filter. The filtered output (b) is then fed into the sigmoidal component and converted into the output sinusoid at SNA (c).

![Schematic diagrams of signal transduction through the derivative-sigmoidal model shown in Fig. 1A. The input sinusoid (a) is first processed by the derivative filter. The filtered signal (b) is then fed into the sigmoidal nonlinearity and converted into the output sinusoid (c). A–C: signal transduction at a low-frequency range. D–F: signal transduction at a high-frequency range. The operating point dependence of the signal transduction becomes unclear in the high-frequency range owing to the large amplitude of the filtered signal (b).](https://www.ajpheart.org)
Figure 6, A–C, depicts signal transduction at a low-frequency range. The amplitude of the output sinusoid is maximal when the mean input level is at the center of sigmoidal nonlinearity (Fig. 6A). Either an increase (Fig. 6B) or a decrease (Fig. 6C) of the mean input level makes the signal transduction saturated through the sigmoidal nonlinearity, resulting in the attenuated output sinusoid. Therefore, the mean input level would critically affect the gain of the signal transduction at low frequencies.

Figure 6, D–F, depicts the signal transduction at a high-frequency range. The amplitude of the filtered sinusoid (b) becomes much greater than that at a low-frequency range, owing to the derivative filter preceding the sigmoidal nonlinearity. The large amplitude of the filtered sinusoid makes the signal transduction saturated when the mean input level is at the center of sigmoidal nonlinearity (Fig. 6D). On the other hand, either an increase (Fig. 6E) or a decrease (Fig. 6F) of the mean input level covers the steeper portion of sigmoidal nonlinearity compared with Fig. 6, B and C, respectively, making the saturation effect insignificant. As a result, the gain of the signal transduction becomes insensitive to the mean input level at high frequencies compared with that at low frequencies.

Limitations. First, we investigated the carotid sinus baroreflex in anesthetized rabbits. Because the anesthesia affects SNA, the results might have differed had the experiment been performed in conscious animals (27). However, the operating point dependence of the neural arc transfer characteristics may be attributable to sigmoidal nonlinearity between baroreceptor pressure input and SNA and not to the absolute value of the transfer gain. Therefore, the present results are relevant for understanding neural arc transfer characteristics under conscious conditions as well.

Second, we used a binary white noise input to estimate the baroreflex transfer characteristics. A Gaussian white noise input can yield a linear transfer function proportional to the linear part of the derivative-sigmoidal model (7). If we had used the Gaussian white noise input, therefore, the differences in mean input pressure might have demonstrated only a frequency-independent influence on the transfer gain of the baroreflex neural arc. Although the binary white noise input was useful to demonstrate the possible frequency-dependent bias in the ordinary assessment of baroreflex gain, Gaussian white noise input might be necessary for simultaneous identification of the static and dynamic characteristics of the baroreflex neural arc. Much work has been done on the identification of Wiener models (7, 17). Clearly, these identification approaches should be applied to the analysis of the transfer characteristics of the baroreflex neural arc in the future.

Finally, we sectioned vagi to remove the influences of low-pressure baroreflexes on the carotid sinus baroreflex neural arc. Accordingly, the transfer function of the total baroreflex loop shown in Fig. 5 disregarded the vagal limb of the baroreflex. Although we focused on the sympathetic limb of the carotid sinus baroreflex in the present study, further studies are clearly required to identify the neural and peripheral arcs of the vagal limb of the baroreflex.

In conclusion, the deviation of mean input pressure from the midpoint of sigmoidal nonlinearity in the CSP-SNA relationship reduced transfer gain mainly in the low-frequency range. The results obtained from the animal experiments qualitatively matched predictions based on a model consisting of a linear derivative filter, followed by a nonlinear sigmoidal component. Although simplistic, the derivative-sigmoidal cascade model functionally reproduces SNA regulation by the arterial baroreflex over a wide operating range. The present study represents an example showing the utility and strength of proper modeling in studying physiological systems.

APPENDIX

We used the MatLab Simulink toolbox (MathWorks, Natick, MA) to simulate the effects of operating point on the linear transfer function of the derivative-sigmoidal cascade model (a class of Wiener model) shown in Fig. 1A. We modeled the sigmoidal nonlinearity in the baroreflex neural arc by a four-parameter logistic function using Eq. A1 (16).

\[
y = \frac{p_1}{1 + \exp[p_2(x - p_3)]} + p_4
\]  

where \(x\) and \(y\) are input (in mmHg) and output (in au) values of the sigmoidal nonlinearity, \(p_1\) is the response range (in au), \(p_2\) is the coefficient of gain, \(p_3\) is the midpoint of input range (in mmHg), and \(p_4\) is the minimum output value (in au). We set \(p_1\) to be 100 au and the maximum negative gain to be \(-1\). These settings yielded \(p_2\) of \(-0.04\) because the maximum negative gain equaled \(p_4p_2/p_4\) at \(x = p_3\). We left \(p_3\) as 0 mmHg without loss of generality, because the simulation was performed around \(p_3\) (i.e., \(p_3 = 20, p_3 = 40, \) and \(p_3 = 60\)). We also left \(p_4\) as 0 au, because the transfer function was calculated after subtracting the mean SNA and hence the absolute value of \(p_4\) was meaningless. The center of the sigmoidal nonlinearity (PC) in Fig. 1B corresponds to \(p_3\).

We modeled the derivative characteristics with Eq. A2 according to a previous study (15).

\[
H(f) = \frac{1 + \frac{f}{f_{c1}}}{1 + \frac{f}{f_{c2}}} \exp(-2\pi f L)
\]  

where \(f\) and \(j\) represent frequency (in Hz) and imaginary units, respectively, \(f_{c1}\) and \(f_{c2}\) (\(f_{c1} < f_{c2}\)) are the corner frequencies (in Hz) for derivative and high-cut characteristics of the neural arc, respectively, and \(L\) is the dead time (in s). We set \(f_{c1}, f_{c2}\), and \(L\) at 0.08 Hz, 0.8 Hz, and 0.2 s, respectively. The parameter values came from the previous study (15). Note that a negative sign for negative feedback was unnecessary, as the sigmoid curve to be connected (Eq. A1) inverts the signal.

We simulated the SNA response to CSP perturbation according to a binary white noise sequence with a switching interval of 500 ms. The input amplitude was 20 mmHg, and the mean input level was varied from \(-60\) to \(60\) mmHg around \(PC\) with an increment of 20 mmHg. The transfer functions were calculated with the 10-Hz sampled time series data obtained from the simulations. To reduce the variance of the transfer function estimation, 100-min input-output data were provided. The deviation of mean input pressure decreased coherence values in the lower frequencies despite the noiseless nature of the simulation, indicating that the nonlinear system response reduced the coherence values.

GRANTS

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REFERENCES