Effects of Epinephrine on Firing Characteristics of Two Functionally Different Types of Carotid Baroreceptors


Sympathetic stimulation and catecholamine exposure have been shown to sensitize the arterial baroreceptors, but the extent or importance of this effect is not known. We performed this study to investigate the effects of sympathetic feedback on the carotid sinus baroreceptors, specifically examining the effect of the stimulation on the two different functional types of baroreceptors characterized in an earlier study. The existence of two baroreceptor function–response curves has suggested that the roles of the two functionally different baroreceptors may not be the same. If true, the effects of epinephrine exposure on baroreceptor firing characteristics may contribute to differential roles played by each baroreceptor type in the control of blood pressure. Single-fiber baroreceptor activity from a vascularly isolated carotid sinus was recorded during slow increases in carotid sinus pressure before and during exposure to epinephrine (10⁻⁸ to 10⁻⁶ M). Baroreceptor firing characteristics were determined from function curves plotting carotid sinus pressure versus nerve activity, with curve-fitting analysis of the hyperbolic type I and sigmoidal type II baroreceptor curves used to obtain threshold (P₉₀), and saturation (Fₙ₉₀) pressures, threshold (F₀ₙ₉₀) and saturation (Fₙ₉₀) firing rates, and sensitivity (slope) for each baroreceptor before and during epinephrine exposure. The possible mechanisms of observed changes were examined using our previously published baroreceptor computer model. Epinephrine exposure was found to significantly increase sensitivity, F₉₀, and Fₙ₉₀ of both types of baroreceptors, with a relatively greater effect on type I sensitivity and on type II F₉₀ and Fₙ₉₀. Epinephrine also was found to increase the level of spontaneous discharge for type II baroreceptors. These results indicate that sympathetic feedback can result in increased baroreceptor afferent activity in a potentially differential manner, based on baroreceptor type. This may result in differential contributions to the control of blood pressure. Computer model predictions suggest that the effect of epinephrine may be due to alterations in characteristics of potassium conductance at the baroreceptor spike-initiation zone. (Circulation Research 1991;69:1097–1105)

The close anatomical association of presumptive baroreceptors and sympathetic efferent fibers in the mediaadventitial area of the carotid sinus wall provides a potential morphological source for efferent modulation of baroreceptor output.¹ Responses of baroreceptors to changes in sympathetic efferent nerve activity to the carotid sinus²,³ or perfusion of the isolated sinus or aortic arch with epinephrine²,³ or norepinephrine¹ suggest a functional role for sympathetic feedback on baroreceptor discharge. These procedures have been found to increase baroreceptor sensitivity to varying degrees, with some studies reporting sensitization⁴,⁵ of all baroreceptors examined, and others finding sensitization of only a portion of receptors⁶,⁷ or no sensitization of any receptors.⁸ The time course of sensitization has been reported to be as short as 16–18 msec⁹ or as long as minutes.⁹,¹⁰ The mechanism of sympathetic-induced sensitization is not known, but two major theories exist. The short latency and the dissipation of changes in sinus wall properties with nerve activity changes have been cited as evidence for a direct effect of sympathetic efferent activity, epinephrine, and norepinephrine on the baroreceptor ending itself,⁴,¹¹,¹² similar to the reported effect of sympathetic stimulation on other mechanorece-
tors. The second theory of baroreceptor sympathetic sensitization, based on diameter and pressure-volume measurements of isolated sinuses and aortic arches, suggests that changes in baroreceptor activity are secondary to changes in wall tension produced by contraction of vascular smooth muscle.

The functional importance of sympathetic feedback on baroreceptor discharge is not known, but one theory suggests that this effect serves as a "braking" control on sympathetic activity during periods such as stress, excitement, or exercise. An alternate theory suggests that sympathetic feedback to the smooth muscle in the baroreceptor areas may act to maintain tension on the baroreceptors, in a manner similar to muscle spindle modulation. Changes in sympathetic feedback to the sinus, produced directly by changes in sinus sympathetic efferent nerve activity or indirectly by perfusion of sympathomimetic agents, have been found to alter sympathetic outflow to other regions. This alteration in sympathetic tone was accompanied by simultaneous changes in whole carotid sinus nerve activity, reflecting the change in baroreceptor afferent input. This evidence suggests that modulation of sympathetic tone to the sinus can produce changes in reflex control of sympathetic outflow in general.

The role of sympathetic feedback may be dependent on the functional role played by the baroreceptor under investigation. Recent studies from this laboratory have identified two functional types of baroreceptors, based on carotid sinus pressure (CSP) (stimulus)–baroreceptor activity (response) curves. Type I baroreceptors are characterized by discontinuous, sigmoidal discharge patterns produced by slow ramp increases in CSP. Type II baroreceptors have continuous, sigmoidal discharge patterns in response to similar increases in CSP. Type I baroreceptors have significantly higher rates of discharge, pressure thresholds, and sensitivities than type II baroreceptors, which have wider operating ranges and spontaneous, non-pressure-related discharge at subthreshold pressures. The characteristics of the two distinctly different firing patterns suggest that type I baroreceptors may play a greater role in buffering sudden dynamic changes in arterial pressure, whereas type II receptors may be more important in relaying information on absolute, baseline levels of arterial pressure. If sympathetic stimulation preferentially alters one discharge pattern more than the other, it may suggest that this sympathetic modulation of baroreceptor activity may contribute more to regulation of tonic versus dynamic control of sympathetic tone, or vice versa. We performed this study to examine the effects of exposure of carotid sinus baroreceptors to varying levels of epinephrine in an attempt to define the effects of physiological sympathetic feedback on baroreceptor input. Epinephrine was used in an attempt to mimic the change in plasma levels of the catecholamines during periods of stress or exercise. The range of doses used was chosen to bracket the levels of catecholamines reported for these conditions. This method of catecholamine exposure has been used by other investigators to examine the effects of sympathetic feedback on baroreceptor discharge. Differences found in the effects of epinephrine on type I and type II baroreceptor stimulus–response curves suggest that sympathetic tone may assist the baroreceptors in playing two different roles in control of the cardiovascular system. A computer model of the carotid sinus baroreceptor designed in this laboratory was used to predict the effects of epinephrine on the electrophysiological properties of the receptor that could account for the responses seen due to epinephrine exposure.

Materials and Methods

The effects of epinephrine on carotid baroreceptor discharge were studied with an isolated carotid sinus preparation in anesthetized mongrel dogs (25 mg/kg sodium thiopental plus 10 mg/kg/hr) as previously described. Briefly, the left carotid arteries were vascularly isolated to permit either a flow-through perfusion of the sinus region at constant pressure (110 mm Hg mean pressure) or a slow ramp increase in CSP (1–2 mm Hg/sec). Lactated Ringer’s solution was used as the perfusate, oxygenated with 100% O₂ to chemically denervate any chemoreceptors not physically eliminated by the isolation technique. CSP was measured by a catheter in the lingual artery and recorded along with arterial pressure with Statham pressure transducers on a Model 7D polygraph (Grass Instrument Co., Quincy, Mass.). These and all other parameters also were recorded on a Model D FM tape recorder (A.R. Vetter Co., Rebersburg, Pa.) for later data analysis. The left cervical vagosympathetic trunk was sectioned to eliminate any sympathetic efferent activity to the isolated sinus.

Single-fiber baroreceptor activity was recorded from the left carotid sinus nerve. The sinus nerve was identified, desheathed, and dissected into smaller bundles that then were covered with mineral oil; surrounding tissue was used to create a recording chamber. To record single-fiber activity, tungsten carbide recording electrodes were connected to a high-impedance differential preamplifier (gain=1,000; 0.1–10-kHz passband), followed by a filter/amplifier, which provided additional gain (up to 400) and high and low pass filtering (fourth-order Butterworth, 10 Hz to 3 kHz). Amplifier output was recorded on the FM tape recorder, averaged, and displayed on the Grass recorder. Small nerve bundles were dissected to obtain a single active fiber preparation that remained viable for the entire experiment.

The carotid sinus was perfused at a constant pulsatile pressure (mean pressure=110 mm Hg) for a minimum of 1 hour before examination of baroreceptor stimulus–response relations. Constant pressure was maintained with a servocontroller developed in this laboratory. After the control period, pump perfusion of the carotid sinus was halted abruptly and the outflow cannula was clamped, temporarily...
making the sinus a closed pouch. A syringe pump (Harvard Apparatus, South Natick, Mass.), in-line with the inflow cannula, was used to infuse Ringer’s solution into the sinus pouch at a constant rate, producing a linear increase in CSP at a rate of 1–2 mm Hg/sec from 0–225 mm Hg. The pressure ramp was repeated before the perfusion circuit was re-opened and constant CSP re-established. The response to the second pressure ramp was used to construct baroreceptor stimulus–response curves.

After control ramps, the sinus again was perfused at constant pressure for 10 minutes. The sinus then was exposed to perfusate containing $10^{-8}$, $10^{-7}$, or $10^{-6}$ M epinephrine for 1 minute, and ramp changes in CSP were repeated. Constant-pressure perfusion then was re-established for 10 minutes, and the sinus was exposed to the next level of epinephrine. For eight baroreceptors, the epinephrine level was chosen randomly to test for the effects of time and order. In those preparations, the epinephrine-containing perfusates were completely eliminated from the circuit between epinephrine exposures, and 30 minutes of constant-pressure perfusion was maintained to ensure epinephrine washout before exposure to the next epinephrine level.

To test the potential mechanism of epinephrine-induced changes in baroreceptor function, phenolamine and propranolol were used to block α- and β-adrenergic receptors, respectively. After all other procedures, the sinus was exposed to perfusate containing $10^{-6}$ M epinephrine and either $10^{-6}$ M propranolol or $10^{-7}$ M phenolamine for 3 minutes. The slow ramp changes in CSP then were performed as described earlier. The procedure was repeated after addition of the remaining adrenergic blocker.

Conduction velocities of the fibers studied were obtained to determine fiber type based on the criteria of Paintal,26 who designated all fibers with a conduction velocity greater than 3 m/sec as A fibers. Conduction velocities were determined using the technique of spike-triggered averaging,22 which uses simultaneously recorded whole-nerve activity obtained from the carotid sinus nerve immediately adjacent to the sinus and single-fiber activity from the recording electrode. Signals then were averaged using a Model 370, two-channel averaging oscilloscope (Nicolet Instrument Corp., Madison, Wis.), which was triggered when the single-fiber potential exceeded a voltage threshold set on the oscilloscope. A cursor was used to position the averaged single-fiber potential such that the averaged whole-nerve activity preceding it in time also was displayed on the second channel. After six to 12 averages, a distinct potential could be observed in the whole-nerve activity produced by the same nerve fiber observed in the single-fiber recording. By dividing the time between the peaks of the two potentials by the distance between the two pairs of recording electrodes, the conduction velocity of the single fiber was calculated.

For analysis of single-fiber baroreceptor afferent nerve activity, tape recorded raw activity was processed using a window discriminator that generated a voltage pulse for each spike whose amplitude fell between an upper and lower voltage threshold, thereby restricting analysis to spikes from only one active receptor. Pulses were fed into a digital counter/timer whose analog output was proportional to the number of spikes per unit time (1 second). The counter output, along with ramp CSP, was sampled (1 Hz) using an HP 310 computer (Hewlett-Packard Co., Palo Alto, Calif.) and was stored on a computer disk for later analysis, as follows.

Single-fiber baroreceptor activity (response) versus ramp changes in CSP (stimulus) was plotted for each baroreceptor using the HP 310 computer. Steady-state stimulus–response curves for the CSP–baroreceptor frequency relation were found to belong to one of two previously described categories22: baroreceptors showing 1) a discontinuous, hyperbolic stimulus–response curve (type I), or 2) a continuous, sigmoidal stimulus–response curve (type II). Standard nonlinear least-squares regression techniques described previously22 were used to obtain an optimum fit of the experimental data and thereby obtain the best-fit estimates of the following parameters: threshold ($F_{th}$) and saturation ($F_{sat}$) firing rates, threshold ($P_{th}$) and saturation ($P_{sat}$) pressures, and maximum gain (slope). Type I stimulus–response curves were analyzed using a hyperbolic curve-fitting regression, and type II curves were analyzed with a sigmoidal curve-fitting routine. For both types of receptors, the maximum gain (slope) of each curve was determined to quantitate the sensitivity of each receptor. The maximum gain for type I baroreceptors was the initial slope of the hyperbolic stimulus–response curve, and the maximum gain of the sigmoidal type II stimulus–response curves was the slope at the midpoint of the linear portion of the curve. These methods of determining slope will include contributions to changes in sensitivity that are both dependent on and independent of firing range.

The values for $F_{th}$, $P_{th}$, $F_{sat}$, $P_{sat}$, conduction velocity, and slope for type I or type II baroreceptors for control and each level of epinephrine or adrenergic blocker were compared within groups using a two-way analysis of variance. Significantly different means were located using Duncan’s multiple range test. The control values for firing characteristics and conduction velocities between type I and type II baroreceptors also were compared using an unpaired $t$ test. All levels of significance were set at $p<0.05$.

To investigate the possible mechanism or mechanisms behind effects produced by epinephrine exposure, we used the computer model of the type I baroreceptor previously developed in this laboratory24 and created baroreceptor stimulus–response curves under a number of conditions. The computer model combines both receptor membrane and spike-initiation zone electrophysiological properties, including nonspecific cation conductances, to generate the receptor potential. The model was based on the Hodgkin and Huxley model27 originally developed for
TABLE 1. Values for Threshold and Saturation Pressures, Threshold and Saturation Frequencies, and Slopes for Control and Epinephrine Exposures for Type I and Type II Baroreceptors

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>10⁻⁸ M EPI</th>
<th>10⁻⁷ M EPI</th>
<th>10⁻⁶ M EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I baroreceptors (n=14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P₃ (mm Hg)</td>
<td>74.0±7.8</td>
<td>75.8±8.6</td>
<td>78.4±8.3*</td>
<td>82.6±8.0†</td>
</tr>
<tr>
<td>P₄ (mm Hg)</td>
<td>170.4±9.1</td>
<td>173.7±20.2</td>
<td>167.5±10.2</td>
<td>173.8±11.7</td>
</tr>
<tr>
<td>Fₙ (spikes/sec)</td>
<td>17.6±1.4</td>
<td>18.7±1.6</td>
<td>19.7±1.3*</td>
<td>20.7±1.4‡</td>
</tr>
<tr>
<td>Fₘ (spikes/sec)</td>
<td>36.4±2.9</td>
<td>40.0±3.9*</td>
<td>40.8±1.3*</td>
<td>41.5±3.1*</td>
</tr>
<tr>
<td>Slope (spikes/sec/mm Hg)</td>
<td>1.11±0.24</td>
<td>1.27±0.26*</td>
<td>1.30±0.27*</td>
<td>1.42±0.27‡</td>
</tr>
<tr>
<td>CV (m/sec)</td>
<td>6.0±0.60</td>
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<tr>
<td>Type II baroreceptors (n=13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P₃ (mm Hg)</td>
<td>64.8±6.3</td>
<td>70.5±6.6*</td>
<td>74.7±7.3*</td>
<td>73.4±8.2*</td>
</tr>
<tr>
<td>P₄ (mm Hg)</td>
<td>155.5±9.1§</td>
<td>158.6±15.4</td>
<td>165.6±13.8*</td>
<td>165.8±12.7</td>
</tr>
<tr>
<td>Fₙ (spikes/sec)</td>
<td>1.96±0.31§</td>
<td>2.22±1.60</td>
<td>2.43±0.43*</td>
<td>2.82±0.45*</td>
</tr>
<tr>
<td>Fₘ (spikes/sec)</td>
<td>20.5±3.5§</td>
<td>23.7±4.5*</td>
<td>24.3±3.6*</td>
<td>25.5±4.0*</td>
</tr>
<tr>
<td>Slope (spikes/sec/mm Hg)</td>
<td>0.27±0.04§</td>
<td>0.32±0.05*</td>
<td>0.32±0.04*</td>
<td>0.32±0.05*</td>
</tr>
<tr>
<td>CV (m/sec)</td>
<td>1.9±0.28§</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

Values are mean±SEM. EPI, epinephrine; P₃, threshold pressure; P₄, saturation pressure; Fₙ, threshold frequency; Fₘ, saturation frequency; CV, conduction velocity.

*Significantly different from control within same fiber type (type I or type II) at p<0.05.
†Significantly different from control, 10⁻⁸, and 10⁻⁷ M EPI within the same type at p<0.05.
‡Significantly different from control and 10⁻⁸ M EPI within the same type at p<0.05.
§Significantly different from control for type I baroreceptors at p<0.05.

the squid axon and was modified to produce an axon with a resting potential of −70 mV at 37°C capable of repetitive firing and encoding graded depolarizations. The major changes were the addition of a transient potassium current, Iₖ, which contributed to the conductances at the spike-initiation zone of the receptor axon, and adjustment of time- and voltage-dependent gating parameters for the sodium (gₖ) and potassium (gₓ) conductances (h, m, and n). The firing behavior of the model baroreceptor spike-initiation zone in response to a constant injected stimulating current was determined by voltage- and time-dependent changes in membrane gₖ, outward delayed gₓ, a leakage conductance (gₒ), membrane capacitance (Cₘ), and the outward fast transient K⁺ conductance (gₓ). To simulate the stimulus–response curves obtained experimentally during epinephrine exposure of the baroreceptors, changes in gating properties and ionic conductances located at the spike-initiation zone of the baroreceptor were altered in the model. Because of the reported effects of epinephrine on other excitable cells, including a decrease in gₓ and an increase in rate of diastolic depolarization in cardiac muscle, the primary changes examined as potential epinephrine effects included decreases in 1) gₓ, 2) γ, a time constant of potassium conductance, and 3) n, a gating parameter of the potassium current.

Results

The comparison of control firing characteristics between types I and II baroreceptors reflected the differences between receptors reported previously (Table 1). Type I baroreceptors were found to have significantly greater conduction velocities, slopes, Fₘ, and Fₙ than type II receptors. The significantly greater conduction velocity for type I receptors indicates the greater size of afferent fibers for this group of receptors.

The effects of epinephrine on a single type I and type II baroreceptor are shown in Figures 1 and 2, respectively. The averaged data for epinephrine effects on the firing characteristics of all type I and type II baroreceptors studied (Table 1) were used to create the best-fit curves shown in Figures 3 and 4. These figures demonstrate the overall increases in sensitivity and receptor discharge rates produced by the sympathomimetic stimulation. As demonstrated in the figures and in Table 1, epinephrine produced an almost dose-dependent increase in type I baroreceptor sensitivity. The significant increase in sensitivity (14%) at 10⁻⁸ M epinephrine was accompanied by a change in average firing range [(Fₘ−F₃) (13%)], due to a significant increase in Fₙ. This suggests that the change in sensitivity could be accounted for by the change in range (primarily Fₘ). The changes in slope at 10⁻⁷ M (17%) and 10⁻⁶ M (22%) epinephrine were greater than the accompanying changes in firing ranges (12% and 11%, respectively), which again primarily were due to significant increases in Fₙ. At the two highest epinephrine levels, there were also significant increases in Fₘ. These results suggest that at least at the higher epinephrine levels, a range-independent mechanism may be responsible for a portion of the increase in sensitivity produced by epinephrine exposure. P₃ was significantly increased at the two highest doses of epinephrine, with P₄ at 10⁻⁸ M epinephrine significantly greater than threshold at all other conditions.
For type II baroreceptors, epinephrine exposure resulted in a significant increase in sensitivity over control that was not different among all epinephrine levels. The significant increases in sensitivity over control (19%) were accompanied by increases in average firing range (16%, 18%, and 22% respectively), which primarily were due to the significant increases in \( F_{\text{th}} \). At \( 10^{-7} \) and \( 10^{-6} \) M epinephrine, there were also significant increases in \( F_{\text{th}} \). These results suggest that there was not much range-independent change in sensitivity for type II baroreceptors, although the larger change in sensitivity relative to the change in range at \( 10^{-6} \) M epinephrine suggests that some range-independent mechanism may be operative. The pattern of effects on other firing characteristics for type II baroreceptors was similar to that for type I receptors, although the two highest epinephrine doses produced significant increases in \( P_{\text{th}} \) not seen with type I baroreceptors. All epinephrine levels produced a significant increase in \( P_{\text{th}} \) over the control value, although the increases for epinephrine exposure were not significantly different from each other. As seen in Figures 2 and 4, epinephrine also increased the level of spontaneous activity seen for most type II receptors.

Addition of propranolol did not block the effects of epinephrine (Figure 5). However, in the presence of phentolamine, the effect of epinephrine on the stimulus–response curve was indistinguishable from control (Figure 5, Table 2). This effect of phentolamine was equally effective for both type I and type II baroreceptors, indicating that the sensitizing effects of epinephrine for both were due to an \( \alpha \)-receptor mediated response.

The stimulus–response curves generated by the computer model of the type I baroreceptor indicated that the changes induced by epinephrine exposure could be partially simulated by a decrease in the repolarizing time constant of a potassium conductance (\( \gamma \)), a decrease in the depolarizing potassium conductance (\( g_K \)), and a decrease in the gaiting properties (n parameter) of the potassium current. The effects of 10% and 20% changes in each of these parameters are shown in Figure 6. The changes in the above parameters, however, could not account for the changes seen in \( P_{\text{th}} \).

**Discussion**

Some changes observed in baroreceptor firing characteristics after epinephrine exposure are similar to changes reported in response to sympathetic feedback in previous studies. However, some results from this study differ from the earlier studies. In the present study, epinephrine exposure produced an increase in \( P_{\text{th}} \) unlike the lack of change reported in earlier studies that examined the effects of norepinephrine in an isolated rat aortic arch preparation.
or isolated rabbit carotid sinus preparation. The reason for the disagreement among studies is not known but may be due to the preparation or to a species difference in the effect of epinephrine and norepinephrine. The mechanism responsible for the increase in $P_{th}$ has not been determined but appears to be related to changes in sinus wall mechanics. Although the lowest levels of epinephrine used in this study have not been found to produce changes in the pressure-volume relation of the sinus or aorta, there is evidence that these concentrations can initiate changes in contractile state of vascular smooth muscle. There may have been enough of an effect on smooth muscle tension to alter the coupling properties of the receptors within the sinus wall, or the stiffening resulting from the constrictive actions of epinephrine on sinus smooth muscle may have resulted in the need for a greater distending pressure, that is, $P_{th}$ even at the lower epinephrine levels.

The epinephrine levels used were chosen in an attempt to examine the effects of the catecholamine at doses that ranged from resting levels to those reported during exercise. As reported by Bevan et al., the synaptic concentration of norepinephrine can range from $10^{-7}$ to $10^{-4}$ M, depending on the anatomy of the synapse. Furthermore, intimal exposure to catecholamines produces only a 60% increase in extracellular catecholamine concentration in a 10-minute period. These findings suggest that even at the high epinephrine level used in the present study, the epinephrine levels at the media-ventitial border where the majority of baroreceptors are located were probably below the catecholamine level seen during actual exercise when both plasma epinephrine and synaptic norepinephrine concentrations increase.

In the present study, type I baroreceptors showed a dose-dependent sensitization to increasing epinephrine levels, whereas type II receptors responded with a significant increase in slope at all epinephrine levels that was not different among concentrations. The increase in sensitivity for all baroreceptors was associated with an increase in average firing rate, primarily because of an increase in $P_{sat}$. However, for type I baroreceptors, the increase in sensitivity at the highest epinephrine level could not be completely accounted for by the increase in firing range. The
results indicate that a portion of the increase in sensitivity for all baroreceptors was associated with the increase in $F_{\text{sat}}$, suggesting that a mechanism or mechanisms that resulted in epinephrine-induced increases in maximum firing level contribute to the increased rate of change of discharge. However, despite the mechanisms involved, epinephrine did result in enhanced sensitivity and elevated discharge rates, the extent of which were different between type I and type II baroreceptors.

The dose-dependent increases in slopes seen for type I baroreceptors also were reported by Goldman and Saum\textsuperscript{6} for baroreceptors after norepinephrine exposure. However, not all studies have reported a dose-dependent effect of sympathetic feedback.\textsuperscript{3,11} Munch et al\textsuperscript{11} identified a biphasic effect of norepinephrine on baroreceptor discharge, with decreases in discharge at low norepinephrine concentrations ($10^{-10}$ to $10^{-7}$ M) and increases at higher levels of norepinephrine exposure ($10^{-6}$ to $10^{-5}$ M). In contrast, Tomomatsu and Nishi\textsuperscript{3} reported an increase in baroreceptor sensitivity at low norepinephrine concentrations ($10^{-9}$ M) followed by a decrease at a higher level of norepinephrine exposure ($10^{-6}$ M). The earlier studies explained the biphasic responses as the results of combinations of direct receptor effects of norepinephrine, which sensitized the baroreceptors, and indirect effects via vasoconstricting actions on smooth muscle, which unloaded the baroreceptors. The reasons for the differences between studies are not known but may be due to prevailing tone in the baroreceptive area. Munch et al\textsuperscript{11} found that if a given reduction in diameter in an isolated rat aortic arch was obtained by active vasoconstriction due to norepinephrine, the decrease in baroreceptor discharge was less than if the same diameter was achieved by a passive reduction in pressure. Therefore, the degree of active tone in preparations may alter the relative effects of further changes in sympathetic feedback. In spite of differences in the pattern of sensitization, effects of sympathetic feedback on baroreceptor discharge generally have been found to be eliminated by the $\alpha$-adrenergic blocker phenolamine.\textsuperscript{6,11} Because this blocking effect was seen in an adventitial preparation devoid of smooth muscle,\textsuperscript{12} there is evidence that at least some of the $\alpha$-mediated effect is due to direct actions on the receptor.

The overall effects of epinephrine on the firing characteristics of the two functional types of baroreceptors were similar, with some important differences in the magnitudes of the effects on each parameter. The net effect of epinephrine at the higher levels of exposure resulted in sensitized type I baroreceptors (28% increase in slope), with higher $P_{\text{th}}$ values and somewhat higher discharge rates ($F_{\text{sat}}$,

\begin{table}[h]
\centering
\caption{Values for Threshold and Saturation Pressures, Threshold and Saturation Frequencies, and Slopes for Control and After Epinephrine Plus Phenolamine Exposure for Type I and Type II Baroreceptors}
\begin{tabular}{lccc}
\hline
 & Type I ($n=3$) & Type II ($n=5$) \\
\hline
 & Control & EPI+phenolamine & Control & EPI+phenolamine \\
P_{\text{th}} (mm Hg) & 72.9±3.1 & 76.9±5.7 & 75.0±10.9 & 75.1±11.2 \\
P_{\text{sat}} (mm Hg) & 140.2±9.6 & 146.3±13.3 & 214.3±15.8 & 212.5±9.7 \\
F_{\text{th}} (spikes/sec) & 17.0±5.5 & 15.4±5.1 & 2.67±0.46 & 2.21±0.41 \\
F_{\text{sat}} (spikes/sec) & 31.9±7.0 & 32.3±5.1 & 22.1±4.0 & 20.2±4.1 \\
Slope (spikes/sec/mm Hg) & 3.43±1.2 & 3.03±1.2 & 0.24±0.06 & 0.21±0.04 \\
\hline
\end{tabular}
\end{table}

Values are mean±SEM. Concentrations were $1\times10^{-8}$ M epinephrine (EPI) and $1\times10^{-5}$ M phenolamine. $P_{\text{th}}$, threshold pressure; $P_{\text{sat}}$, saturation pressure; $F_{\text{th}}$, threshold frequency; $F_{\text{sat}}$, saturation frequency.
14%; $F_{th}$, 18%). However, although epinephrine also sensitized type II baroreceptors, albeit to a lesser degree (19% increase in slope), it also resulted in a 44% increase in $F_{th}$ and a 24% increase in $F_{sat}$. The enhanced threshold discharge rate reflects the increased spontaneous activity found for all levels of epinephrine exposure. This type of increase in spontaneous activity (subthreshold pressure) discharge also has been reported by other investigators.\(^6,11,21\)

Thus, although overall increases in sensitivity after epinephrine exposure were greater for type I baroreceptors, resulting in relatively more afferent input change in pressure, the increases in $F_{th}$, $F_{sat}$, and spontaneous discharge for type II baroreceptors also would contribute to the increased afferent input reported for whole carotid baroreceptor nerve activity\(^2\) after epinephrine exposure. The epinephrine-induced increase in $F_{th}$ and spontaneous activity for type II baroreceptors may be the major components producing the decrease in baseline renal sympathetic efferent nerve activity after epinephrine exposure of a constant-pressure–perfused sinus.\(^2\) Similarly, the abrupt increase in renal sympathetic efferent nerve activity after sympathetic denervation of a constant-pressure–perfused carotid sinus may be due to a decrease in efferent activity from primarily the type II baroreceptors because of the withdrawal of sympathetically induced baroreceptors discharge.\(^2\) However, the enhanced reflex responsiveness of baroreceptor reflex changes in renal sympathetic efferent nerve activity and contralateral sinus sympathetic efferent nerve activity\(^\text{18}\) may be due more to the effects of sympathetic feedback on type I baroreceptors, in which epinephrine had the greater effects on receptor sensitivity. Obviously, both types of baroreceptors would contribute to both responses, but the degree of changes induced in the firing characteristics of each receptor type could predispose each type to provide a greater contribution to different areas of control of sympathetic outflow.

One other study has examined the differential effects of sympathetic feedback on discharge from different types of baroreceptors.\(^21\) Yao and Thoren\(^21\) found that norepinephrine exposure (10\(^{-5}\) M) and electrical stimulation of sympathetic efferent fibers to the sinus had no consistent effect on discharge of baroreceptors with myelinated A afferent fibers but did result in an increase in discharge frequency of nonmyelinated C-fiber baroreceptors. However, CSP was held constant in both studies, providing conditions that may optimize the ability for one to detect changes in the less dynamically sensitive C-fiber, and predominantly type II, baroreceptor discharge. As seen in the present study, epinephrine exposure had relatively greater effects on type II versus type I tonic discharge ($F_{th}$, spontaneous activity), whereas the epinephrine effects on pressure-induced changes in activity (slope) were greater for type I baroreceptors.

The results of the model-simulated effects of epinephrine on baroreceptor discharge indicated that small changes in conductance and gating properties of the potassium conductance at the spike-initiation zone of the receptor could produce changes in baroreceptor discharge similar to those seen for type I baroreceptors, except the shift seen for $P_{th}$. These altered potassium conductance properties could serve as a common mechanism for the changes seen in firing rate and sensitivity. Similar changes in potassium conductance have been proposed to be the mechanism of epinephrine action on Purkinje cells,\(^28\) although another study on bullfrog sympathetic ganglion cells has suggested that a decrease in a voltage-dependent potassium conductance, possibly the M-current, may be involved in the epinephrine-induced depolarization.\(^30\) Epinephrine also has been thought to play a role in the regulation of conductance of the transient potassium A-current,\(^31\) offering another possible site of action in this study. However, in an earlier study,\(^24\) the effects of a potassium A-current blocker, 4-aminopyridine, on baroreceptor discharge were not affected by the presence of epinephrine or phentolamine, suggesting that $\alpha$-adrenergic effects were not involved in regulation of the A-channel in this preparation. As stated above, the modeled data did not produce a significant change in
P\(_{th}\) with epinephrine exposure, although there was a trend toward higher pressures. The significantly higher P\(_{th}\) obtained from the actual study may reflect the indirect “stiffening” effects of epinephrine on vascular smooth muscle, which has not been included in the computer model. The effects of epinephrine on smooth muscle also may contribute to some of the changes seen in other firing characteristics of type I and type II baroreceptors, but this cannot be determined from the present model. However, if the different types of baroreceptors are coupled to different components of the vascular wall, as suggested previously,\(^1,2\) the stiffening of smooth muscle could produce differential degrees of tension on the baroreceptors, depending on the compliance of the wall component with which they are associated. This remains an area for future investigation.

In conclusion, epinephrine produced sensitizing effects on both type I and type II baroreceptors. However, the changes seen in type II spontaneous activity and baseline rates of discharge may prove to be the more important components of their response, whereas the increase in type I sensitivity may be the main contributor to changes seen in response to changes in sinus pressure. The epinephrine-induced increase in baroreceptor discharge has been shown to modulate the reflex control of regional sympathetic outflow, but the importance of this effect under physiological situations has not been determined. The results of the computer modeling study suggest that at least a portion of the epinephrine response may be due to alteration of \(g_K\), a mechanism similar to that reported for cardiac muscle. The mechanism or mechanisms responsible for the change seen in \(P_{th}\) in this study still must be determined and may lead to a better understanding of the coupling arrangements of the different types of baroreceptors within the sinus wall.

Acknowledgment

The authors would like to thank Ms. Claudia Salter for her technical assistance.

References


**KEY WORDS** • arterial baroreceptors • baroreceptor reflex • sympathetic nervous system • potassium conductance
Effects of epinephrine on firing characteristics of two functionally different types of carotid baroreceptors.

J L Seagard, J F van Brederode, C Dan, F A Hopp, E O Elegbe, L A Gallenberg and J P Kampine

Circ Res. 1991;69:1097-1105
doi: 10.1161/01.RES.69.4.1097

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/69/4/1097

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