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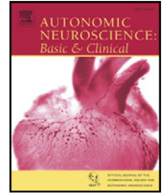

Acute effects of arterial baroreflex on sympathetic nerve activity and plasma norepinephrine concentration

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ABSTRACT

Arterial pressure (AP) elevates as a logarithmic function of exogenously administered dose of norepinephrine (NE). In contrast, AP is nearly linearly correlated with efferent sympathetic nerve activity (SNA) during acute baroreflex intervention. The present study aimed at quantifying the relationship between SNA and plasma NE concentration during acute baroreflex intervention. Carotid sinus regions were isolated from systemic circulation in five Wistar Kyoto rats, and carotid sinus pressure was changed among 60, 100, 120, 140, and 180 mm Hg every 2 min. Arterial blood (0.2 ml) was obtained at each pressure level for plasma NE measurement. Maximum AP and minimum AP were 153.34 ± 6.28 and 67.31 ± 4.92 mm Hg, respectively, in response to pressure perturbation. Plasma NE correlated linearly with SNA for individual animal data (slope: 0.957 ± 0.090 $pg \cdot ml^{-1} \cdot \%^{-1}$, intercept: 46.57 ± 7.22 pg/ml, r^2: ranged from 0.923 to 0.992) and also for group averaged data (NE = 0.956 × SNA + 47.97, $r^2 = 0.982$). Blockade of neuronal NE uptake by intravenous desipramine (1 mg/kg) administration increased the slope (2.966 ± 0.686 $pg \cdot ml^{-1} \cdot \%^{-1}$, $P < 0.05$) and the intercept (168.73 ± 28.53 pg/ml, $P < 0.01$) of the plasma NE–SNA relationship. These results indicate that the relationship between SNA and plasma NE concentration was nearly linear within the normal physiological range of acute baroreflex control of AP. While plasma NE concentration can reflect changes in SNA, it may also overestimate the sympathetic outflow from the central nervous system when neuronal NE uptake is impaired systemically.

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1. Introduction

The arterial baroreflex is an important negative feedback system that stabilizes arterial pressure (AP) during daily activities. The sympathetic nervous system plays a dominant role in the acute baroreflex control of AP. Studies using an isolated carotid sinus baroreceptor preparation have revealed that AP correlates almost linearly with efferent sympathetic nerve activity (SNA) when examined by a staircase-wise pressure input protocol in anesthetized rats (Kawada et al., 2009, 2010, 2011, 2014; Yamamoto et al., 2013). Norepinephrine (NE) is a neurotransmitter released into the synaptic cleft at sympathetic nerve endings. Although a large portion of NE is removed from the synaptic cleft by neuronal and extraneuronal NE uptake mechanisms (Eisenhofer, 2001; Nicholls, 1994; Shimizu et al., 2010), a fraction of NE is diffused into the bloodstream and can be measured as plasma NE. While it is conceivable that plasma NE concentration reflects the level of SNA, an exact relationship between SNA and plasma NE concentration during an acute baroreflex intervention remains unknown. In contrast to the almost linear AP response to SNA observed in acute baroreflex studies, AP elevates with the logarithm of exogenously administered dose of NE (Yamaguchi and Kopin, 1980) or the logarithm of plasma NE concentration during electrical spinal cord stimulation in pithed rats (Yamaguchi and Kopin, 1979). On the other hand, administration of calcium antagonists exhibits good inverse correlations between AP and the logarithm of plasma NE concentration (Imai et al., 1994). If plasma NE concentration is logarithmically associated with AP, the linearity between SNA and AP would indicate that plasma NE concentration exponentially increases as a function of SNA. To test this hypothesis, the present study aimed to quantify the relationship between SNA and plasma NE concentration during acute baroreflex intervention. In addition, the effect of neuronal NE uptake blockade on the relationship between SNA and plasma NE concentration was explored to quantitatively understand the importance of neuronal NE uptake in the determination of plasma NE concentration.

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2. Materials and methods

Animal care was provided in strict accordance with the *Guiding Principles for the Care and Use of Animals in the Field of Physiological*

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Sciences, approved by the Physiological Society of Japan. All protocols were reviewed and approved by the Animal Subject Committee of National Cerebral and Cardiovascular Center.

Male Wistar Kyoto rats (330–380 g) were anesthetized with an intraperitoneal injection (2 ml/kg) of a mixture of urethane (250 mg/ml) and α-chloralose (40 mg/ml), and mechanically ventilated with oxygen-supplied room air. Anesthesia was maintained by continuous intravenous infusion of a diluted solution of the above anesthetic mixture. An arterial catheter was inserted into the right femoral artery to measure AP. Another arterial catheter was inserted into the left common carotid artery to obtain arterial blood samples. Body temperature of the animal was maintained at approximately 38 °C using a heating pad and a lamp.

A postganglionic branch of the splanchnic sympathetic nerve was exposed retroperitoneally through a left flank incision for the measurement of splanchnic SNA (spSNA). A pair of stainless steel wire electrodes (Bioflex wire, AS633, Cooner Wire, CA, USA) was attached to the nerve, and were secured with silicone glue (Kwik-Sil, World Precision Instruments, FL, USA). A preamplified nerve signal was band-pass filtered at 150 − 1000 Hz, and then full-wave rectified and low-pass filtered at a cut-off frequency of 30 Hz using analog circuits. A ganglionic blocker hexamethonium bromide (60 mg/kg) was given intravenously at the end of the experiment to confirm the disappearance of spSNA and to measure the noise level (Kawada et al., 2010).

The aortic depressor nerves and the vagus nerves were sectioned bilaterally to minimize reflex effects from the aortic arch and cardiopulmonary regions. Bilateral carotid sinuses were isolated from system circulation according to previously reported procedures (Sato et al., 1999; Shoukas et al., 1991). The isolated carotid sinuses were filled with warmed Ringer's solution through catheters inserted into the common carotid arteries. Carotid sinus pressure (CSP) was controlled using a servo-controlled piston pump. Heparin sodium (100 U/kg) was given intravenously to prevent blood coagulation. After completing the above surgery, a stabilization period of at least 60 min was allowed before data acquisition.

2.1. Protocol 1 ($n = 5$)

To determine the time course of plasma NE response to carotid sinus baroreflex, CSP was first set at 100 mm Hg. After AP reached a steady state, CSP was increased to 140 mm Hg. Arterial blood (0.2 ml) was sampled at 80, 50, and 20 s before the step change in CSP and at 30, 60, 90, 120, 150, and 180 s after the step change in CSP. Each blood sampling procedure took approximately 15 s. To avoid contamination of the blood within a catheter, an initial 0.2-ml blood was withdrawn into a temporary syringe that had been filled with 0.2-ml saline, the following 0.2-ml blood was taken as a sample, and then the initial blood, admixed with saline, was returned into the artery. The blood samples were immediately iced to 4 °C. After the end of the protocol, the blood samples were centrifuged and plasma NE concentrations were measured using a high-performance liquid chromatography system (Eicom, Kyoto, Japan) after an alumina adsorption procedure.

2.2. Protocol 2 ($n = 5$)

To determine the relationship between spSNA and plasma NE over a wide input pressure range of the carotid sinus baroreflex, CSP was first decreased to 60 mm Hg for 4 min. CSP was then increased to 100, 120, 140, and 180 mm Hg in a staircase manner. Each step was maintained for 120 s. Based on the time course of plasma NE response obtained in *Protocol 1*, arterial blood (0.2 ml) was sampled at 100 s in each CSP step. The blood sampling procedure took approximately 15 s, as described in *Protocol 1*, and had finished before the next CSP change occurring at 120 s. After obtaining control data, a neuronal uptake blocker desipramine (1 mg/kg) was administered intravenously. Twelve minutes later, the staircase-wise CSP input was repeated and corresponding data were obtained.

2.3. Protocol 3 ($n = 5$)

As a supplemental protocol, the effect of exogenous NE administration on AP was examined. Carotid sinuses were not isolated, and the aortic depressor nerves and vagus nerves were untouched in this group. Instead, ganglionic transmission was blocked by intravenous bolus injection of hexamethonium bromide (60 mg/kg). After 30-min stabilization, the AP response to intravenous continuous administration of NE was examined. The dose of NE was changed every 15 min in an increasing order at 0.05, 0.1, 0.5, 1, 5, 10, 50, 100, 500, and 1000 $\mu g \cdot kg^{-1} \cdot h^{-1}$.

2.4. Data analysis

CSP, spSNA, and AP were recorded at 1000 Hz using a 16-bit analog-to-digital converter. In *Protocol 1*, mean spSNA recorded during CSP of 100 mm Hg was assigned to 100%, and mean spSNA measured after the ganglionic blockade was assigned to 0% in each animal. For plasma NE data, baseline NE concentration was determined from an average of three data points before the step input in each animal. In addition to the absolute NE concentration, the decrease in plasma NE concentration from the baseline value was expressed as a percentage relative to the decrease observed at the nadir (90 s after the step input). In *Protocol 2*, mean spSNA and AP were obtained by averaging spSNA and AP values from 90 to 100 s, just before the arterial blood sampling, at each CSP level. The mean spSNA corresponding to 60-mmHg CSP was assigned to 100%, and mean spSNA measured after the ganglionic blockade was assigned to 0% in each animal. In *Protocol 3*, the AP value corresponding to each NE dose was derived from an average during the last 1 min of the 15-min administration period.

2.5. Statistical analysis

All data are presented as mean and SE values. In *Protocol 1*, plasma NE concentrations at 30, 60, 90, 120, 150, and 180 s after the step input were compared using one-way repeated-measures analysis of variance (ANOVA). In *Protocol 2*, slope and intercept values were determined in each animal by linear regression, and the parameters were compared before and after the desipramine administration using a paired-t test. Differences were considered significant when $P < 0.05$ (Glantz, 2002). In *Protocol 3*, the relationship between exogenously administered dose of NE and AP was examined using a semilog plot (a linear ordinate versus a logarithmic abscissa) and linear scatter plots.

3. Results

Time series of CSP, AP, and spSNA obtained in *Protocol 1*, and corresponding plasma NE concentrations are shown in Fig. 1. CSP and AP are presented as 10-Hz resampled signals, and spSNA is presented as a 2-s moving averaged signal. Before the step increase in CSP, there were transient AP drops caused by arterial blood sampling for the measurement of plasma NE concentration. After CSP was increased, AP showed a sustained reduction. While spSNA was stable before the step input, it ceased at the onset of the step input. Thereafter, spSNA gradually recovered to approximately 35% of the baseline level after 210 s. The baseline plasma NE concentration was approximately 120 pg/ml. After CSP was increased, plasma NE concentration decreased to approximately 80 pg/ml. While there were no statistically significant differences in plasma NE concentration from 30 to 180 s, a slight nadir was observed at 90 s. If decreases from baseline are expressed as percentages relative to the decrease observed at the nadir, percent decreases were 67.1 ± 8.8% at 30 s, 82.9 ± 4.1% at 60 s, and 100% at 90 s. Thereafter, percent

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