Baroreflex Control of Renal Sympathetic Nerve Activity in Hypertensive Miniature Swine

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SUMMARY The baroreceptor reflex control of renal nerve activity was examined in seven normotensive and 14 deoxycorticosterone acetate–treated anesthetized Yucatan miniature swine. Pressor responses evoked by the administration of phenylephrine were used to assess reflex control. The mean absolute threshold for inhibition of renal nerve activity was higher but not significantly different between the deoxycorticosterone acetate–treated and normotensive group. However, the mean relative threshold for inhibition of renal nerve activity was significantly greater in the deoxycorticosterone acetate–treated group (p < 0.05). Responses from five deoxycorticosterone acetate–treated and five normotensive swine were used to examine the time course of the baroreflex inhibition of renal nerve activity. During the initial rise in pressure the percent inhibition of renal nerve activity was similar for the two groups. During the recovery phase of the response, renal nerve activity in the deoxycorticosterone acetate–treated group returned to baseline while renal nerve activity remained attenuated below baseline in the normotensive group. The gain of the reflex was significantly lower in the deoxycorticosterone acetate–treated group compared with the control group (p < 0.05). The results of this study clearly indicate that baroreceptor reflex control of renal nerve activity is altered in anesthetized deoxycorticosterone acetate–treated hypertensive swine. (Hypertension 7: 879-885, 1985)

KEY WORDS • kidney • baroreceptors • Yucatan swine • adrenergic

It has been consistently shown that baroreflex control of heart rate is attenuated in clinical1,2 and experimental hypertension.3-6 The degree to which baroreflex dysfunction is generalized to the neural control of other vascular beds is less clear. For example, Guo and Thames7 recently reported that baroreflex control of heart rate is impaired while control of lumbar sympathetic nerve activity is preserved in renal hypertensive rabbits. Such findings are consistent with the view discussed by Abboud2 that efferent sympathetic nerve activity to different regions of the vasculature can be controlled independently of each other.

The sympathetic nerves that innervate the kidneys appear to have an important role in various forms of experimental hypertension.9-11 Renal nerve activity in states of hypertension, however, has been extensively examined only in spontaneously hypertensive rats (SHR). In this model of hypertension, the baseline renal nerve activity appears to be elevated12,13 and the volume reflex control of renal nerve activity appears to be enhanced,14 while the arterial baroreflex control of renal nerve activity is reported to be impaired.12,13,15

Recent studies in our laboratory have provided evidence that the renal sympathetic nerves play an important role in regulating kidney function in the deoxycorticosterone acetate (DOCA)–treated hypertensive Yucatan miniature swine.16 Specifically, these studies demonstrated that acute surgical or pharmacological denervation of the kidneys increased renal blood flow and glomerular filtration rate and caused a natriuresis in DOCA-treated hypertensive swine but not in normotensive controls. These findings strongly suggest that renal sympathetic nerve activity is elevated in the established phase of hypertension in DOCA-treated swine, in contrast to that in other models of hypertension, which appear to demonstrate a decrease in renal sympathetic nerve activity with time. These results are consistent with the concept that DOCA-induced hypertension involves the central nervous system and that increased sympathetic activity and possibly vasopressin are responsible for maintaining the hypertension.

More recently, we began a series of studies to directly measure renal nerve activity in DOCA-treated hypertensive swine. Because it is difficult to measure and
compare the absolute nerve activity between animals, our initial approach was to compare baroreflex control of renal nerve activity in normal and DOCA-treated hypertensive animals.

Materials and Methods

Twenty-one male Yucatan miniature swine (age, 8–12 mo; weight, 40–70 kg) were used in this study (Bucksire Corp., Perkasie, PA, USA). The DOCA-impregnated strips were implanted under sterile conditions and halothane anesthesia in 14 animals according to the procedures of Terris and Simmonds. The DOCA-treated animals were studied 3 to 4 months after implantation. The remaining seven animals were used as controls.

Conscious Measurements of Blood Pressure

The animals were anesthetized with halothane anesthesia. Catheters were placed in the femoral artery and jugular vein and exteriorized on the dorsal surface of the lower neck region. After a 1- to 2-week recovery period, the animals were suspended in a hammock sling to record conscious baseline pressure. The arterial pulsatile pressure, measured from the arterial catheter with a pressure transducer (Statham Instruments, Oxnard, CA, USA), was electronically “meaned” to obtain mean arterial pressure (MAP).

Renal Nerve Recordings

For the final studies, the animals were anesthetized with ketamine hydrochloride (3.3 mg/kg) and pentobarbital (33 mg/kg), intubated, and mechanically ventilated. The kidney was approached through a flank incision. Branches of the renal nerve plexus were exposed along the dorsal surface of the renal artery and vein. Nerve branches selected for recordings were isolated from the surrounding connective tissue for a length of 2 to 3 cm. A bipolar silver/silver chloride hook electrode attached to a high impedance probe was used to record the renal nerve activity. The recorded signal was amplified with a preamplifier (Model 7P10L, Grass Instruments, Quincy, MA, USA) with band pass filters set at 100 and 3000 Hz. The amplified signal was then simultaneously integrated (Grass Model 7P10), displayed on an oscilloscope, and monitored with an audio system. The integrated and amplified nerve recording, along with MAP and pulsatile pressure, were displayed with a pen recorder. The electrode and nerve branch were covered with a petroleum jelly–mineral oil mixture to prevent dehydration.

Baroreceptor–renal nerve reflexes were studied by evoking graded pressor responses with phenylephrine. Doses ranged from 50 to 200 μg of phenylephrine, produced increments in MAP ranging from 5 to 50 mm Hg, and were administered randomly. Three to five responses were evaluated in each animal. To quantitatively compare the functional differences in baroreflex control of renal nerve activity between DOCA-treated and control swine, we analyzed the pressor responses of individual animals that resulted in at least a 4-second period of continuous inhibition of renal nerve activity. The peak MAP of these responses was defined as the absolute baroreflex threshold (BRT), while the relative change in pressure from baseline MAP was referred to as the relative BRT.

The time course and gain of baroreflex control of renal nerve activity were determined by evaluating three responses from each of five DOCA-treated and five control swine. Animals and trials were selected to achieve a comparable mean value for pressure rises between the DOCA-treated group and the control group. The selection was conducted by evaluating data only from those animals that had a mean pressor response for three trials in the range of 25 to 35 mm Hg. This process of selection was necessary to prevent the bias of the greater pressor responses typically evoked in DOCA-treated animals and to ensure that the comparison of renal nerve activity responses between the two groups was based on pressure responses of similar magnitude. For the DOCA-treated group, the mean pressor response was 34 ± 2 mm Hg, while for the control animals the mean was 32 ± 3 mm Hg.

Results in the text, tables, and figures are expressed as means ± SEM. Values from the control and DOCA-treated animals were evaluated for significant differences using the nonparametric Mann-Whitney test. A p level less than 0.05 was used to determine significant differences between group means.

Results

After 12 to 16 weeks of DOCA treatment the MAP was significantly greater in the 14 conscious DOCA-treated swine (167 ± 4 mm Hg) relative to that in the seven untreated control animals (134 ± 7 mm Hg). In the DOCA-treated group, pentobarbital anesthesia decreased MAP to 134 ± 6 mm Hg. The effect of anesthesia on the MAP of the DOCA-treated group varied among individuals: the decrease in MAP between the conscious and anesthetized state ranged from 2 to 68 mm Hg. The MAP in anesthetized control swine was 138 ± 5 mm Hg.

Several criteria were used to verify the validity of our nerve recording techniques. In each animal, renal nerve activity was determined to be pulse synchronous with heart rate, elevated following a nitroprusside-evoked depressor response (Figure 1), attenuated following transient pressor responses evoked by phenylephrine (Figures 2 and 3), and eliminated following administration of hexamethonium bromide (Figure 1). These results indicated that the recorded activity was baroreceptor dependent (pulse synchronous), sympathetic (polarity of response to pressor/depressor responses), and postganglionic (elimination by hexamethonium bromide).

Baroreflex Threshold for Inhibition of Renal Nerve Activity

Acute transient elevation in MAP resulted in attenuation or complete transient inhibition of renal nerve activity for both DOCA-treated and control swine (Figures 2 and 3). Relative to the normotensive controls, however, the DOCA-treated animals required
greater increments in MAP to achieve similar degrees of inhibition of renal nerve activity.

To compare the reflex control of renal nerve activity of DOCA-treated and control swine, we evaluated those pressor responses that evoked inhibition of renal nerve activity for a 4-second period and referred to this pressor response as the BRT. Although the mean absolute blood pressure required to inhibit renal nerve activity (absolute BRT) was higher for the DOCA-treated swine (176 ± 6 mm Hg) than for the control group (161 ± 8 mm Hg), this difference did not achieve statistical significance. It is apparent from Figure 4, however, that for a given baseline pressure the absolute BRT was always greater in DOCA-treated animals. For both groups of animals, there was a strong correlation between the absolute BRT and baseline MAP (controls, r = 0.96; DOCA-treated swine, r = 0.95). The slope of the relation (controls, 1.32; DOCA-treated swine, 0.95) indicated that the absolute BRT varied directly with baseline MAP.
FIGURE 3. Recordings of graded pressor responses evoked by phenylephrine in an individual deoxycorticosterone acetate (DOCA)-hypertensive animal. From left to right, the three responses resulted in pressure changes of 24 mm Hg (50 μg phenylephrine), 32 mm Hg (75 μg phenylephrine), and 48 mm Hg (100 μg phenylephrine). This animal's response to 100 μg of phenylephrine (third panel) was typical of that selected for analysis of the baroreflex threshold. Abbreviations as in Figure 1.

The relative change in pressure for the reflex threshold (relative BRT) was significantly greater in DOCA-treated swine (42 ± 2 mm Hg) compared with that of the control group (22 ± 3 mm Hg). The relative BRT was not correlated with baseline MAP for either the DOCA-treated group (r = 0.24) or the control group (r = 0.66), and the slope of the relationship (controls, 0.32; DOCA-treated swine, −0.07) indicated that the relative BRT was independent of the baseline blood pressure.

Time Course of Baroreflex Inhibition of Renal Nerve Activity

Baroreflex inhibition of renal nerve activity was examined in greater detail by quantifying the percent change in voltage-integrated renal nerve activity over the time course of the pressor responses of three trials from each of five DOCA-treated and five control swine. Trials that had similar increments in MAP were selected for analysis (see Methods). For these animals, baseline MAP was significantly greater for the DOCA-treated swine (144 ± 2 mm Hg) as compared to the controls (124 ± 3 mm Hg). The mean relative BRTs for these DOCA-treated swine (42 ± 14 mm Hg) and controls (29 ± 4 mm Hg) were similar to the respective group means for all animals.

The reflex inhibition of renal nerve activity was similar for the DOCA-treated and control groups during the initial rise in pressure (Figure 5). Inhibition of renal nerve activity preceded the initial rise in MAP, and the greatest percent inhibition of renal nerve activity occurred an average of 4 to 6 seconds before the mean peak in blood pressure. Following the peak response, however, there was a difference between the two groups: the renal nerve activity of DOCA-treated animals returned to baseline, while the nerve activity of the control animals remained attenuated.

Inspection of the pressure curves of Figure 5 indicates that blood pressure returned to baseline more...
RENAL NERVE ACTIVITY IN HYPERTENSIVE SWINE/Notvest and Zambraski

Figure 5. Mean phenylephrine-evoked pressor response curves from three trials from each of five control and five deoxycorticosterone acetate (DOCA)-treated swine (n = 15 trials for each group). The mean arterial pressure (MAP) response curves show the absolute change in MAP during the phenylephrine-evoked response. The renal nerve activity response curves represent the percent change in integrated voltage relative to the baseline period (1–10 sec). Trials were aligned by their peak pressures (vertical dashed line).

Figure 6. Relation between the mean percent change in renal nerve activity and the change in mean arterial pressure (MAP) for each 2-second interval of the phenylephrine-evoked responses shown in Figure 5. Both control and deoxycorticosterone acetate (DOCA)-treated animals showed a similar degree of renal nerve activity inhibition during the rising phase of the pressor response. During the extinction phase of the response, there was less inhibition of renal nerve activity for the DOCA-treated animals relative to that of the controls for a given change in pressure. Lines shown were approximated.

Discussion

The results of this study clearly indicate that baroreceptor reflex control of renal nerve activity is altered in anesthetized, DOCA-treated hypertensive swine relative to that in normotensive controls. This conclusion is supported by the finding that the threshold of the reflex relative to baseline blood pressure (relative BRT) was significantly greater in DOCA-treated hypertensive swine. Although the peak pressure necessary to inhibit renal nerve activity may not actually represent a "threshold" pressure, since the rate of pressure rise could affect the actual pressure threshold, the use of this parameter as an index of baroreceptor function does demonstrate differences between normal and DOCA-treated hypertensive swine. The second basis for this conclusion is that for pressor responses of similar magnitude, the gain of the reflex was 50% lower in the DOCA-treated group.

Our results also imply that the effect of anesthesia on baseline blood pressure of the DOCA-treated swine cannot fully account for the difference in the relative BRT between the DOCA-treated and control groups. This point is supported by the finding that three DOCA-treated swine had minimal changes in blood rapidly in the DOCA-treated group relative to that in the control group. To determine whether this difference in the extinction of the pressure rise could account for the late differences in renal nerve activity between the DOCA-treated and control groups, we compared the relationship between the percent change in renal nerve activity and the change in MAP for the two groups (Figure 6). For a given change in MAP during the initial rise in pressure, inhibition of renal nerve activity was similar for the two groups. During the recovery phase from the pressor responses, the renal nerve activity of the DOCA-treated group was less inhibited relative to the control group for a given change in pressure.

Baroreflex Gain for Control of Renal Nerve Activity

Baroreflex control of renal nerve activity was quantified by measuring the gain of individual trials from the data in Figure 5. The gain of the reflex was calculated as the ratio of the percent change in renal nerve activity and the change in MAP. The mean gain calculated over the entire 0 to 80 seconds of the DOCA-treated hypertensive swine, 1.96 ± 0.16, was significantly lower than the 4.06 ± 0.37 gain of the control group. The gains were also calculated for three segments of this period. Values for the control and DOCA-treated animals, respectively, were 4.71 ± 0.33, 3.43 ± 0.13 (0–30 sec); 2.88 ± 0.33, 0.69 ± 0.42 (32–40 sec); and 4.10 ± 0.80, 0.04 ± 0.36 (42–80 sec). These differences in gain between the control and DOCA-treated animals were significant for all three time periods.
pressure following anesthesia yet had relative BRT values above those of all the control animals.

As a group, the relative BRT of the DOCA-treated animals appeared to be only slightly elevated by changes in baseline blood pressure following anesthesia. This latter point suggests that the reflex control of renal nerve activity is reset to the new baseline pressure of the anesthetized state in DOCA-treated animals. Results from several studies have shown that during short-term changes in baseline blood pressure (<20 min) baroreceptors adapt toward the new baseline.18-20 The resetting of the baroreceptors is never complete, however, and ranges from 23 to 40%.19 Other studies have also shown that the baroreflex control of systemic blood pressure21 and heart rate20 can reset to a much greater degree than can be accounted for by adaptation of the baroreceptors. Munch et al.20 suggested that other components of the reflex pathway contribute to acute resetting of the baroreflex; however, further studies will be required to test this hypothesis.

Goldman and Saum22 recently indicated that norepinephrine and phenylephrine may directly activate baroreceptors. Although phenylephrine could have differentially affected control and not DOCA-treated animals, which would have influenced our results, it should be noted that there is not a clear consensus or understanding of the exact effects of phenylephrine on baroreceptors.22 An early effect of phenylephrine at the baroreceptor — altering wall tension or other factors — may explain why the decrease in renal nerve activity tended to precede the actual increase in arterial pressure (Figure 5).

When the inhibition of renal nerve activity was examined over the time course of the pressor responses of selected DOCA-treated and control swine (Figures 5 and 6), during the initial rise in pressure the percent inhibition of renal nerve activity was similar between the two groups. The greatest difference in the inhibition of renal nerve activity between the two groups occurred during the recovery phase of the response, when pressure was rapidly falling, and during the late (50-80 sec) phase of the response (Figure 5), when the decline in pressure was more gradual. The reduced inhibition of renal nerve activity throughout the period, but especially prominent during the recovery and late phase of the response of the DOCA-treated animals, accounts for the 50% lower reflex gain in this group relative to that of the normotensive controls.

The differential inhibition of renal nerve activity over the time course of the response between the DOCA-treated and control groups implies that the dynamic component of the reflex is relatively normal while the static component is impaired in DOCA-treated hypertensive swine. This implication would seem to contradict the finding that the relative BRT was elevated in the DOCA-treated group, since the relative BRT was measured during dynamic changes in pressure. The discrepancy between these two points can be resolved if the relative BRT is considered to be a composite of not only the dynamic component (initial rise in pressure) but also a static component of the reflex, which first appears during the extinction phase of the responses. During the extinction phase of the response renal nerve activity returned more rapidly to baseline in DOCA-treated hypertensive swine. Greater pressor responses would therefore be required to achieve an equivalent sustained (4 sec) inhibition of renal nerve activity. Thus, the measurement of the relative BRT would be greater in DOCA-treated animals because of the attenuated static component.

In 1977, Coote and Sato13 reported that baroreflex control of renal nerve activity is attenuated in SHR. In this study, phenylephrine-evoked pressor responses were used to examine the duration of inhibition of renal nerve activity in anesthetized animals. Coote and Sato13 reported that the absolute threshold for inhibition of renal nerve activity was elevated in the SHR, while for pressor responses of similar magnitude, the duration of inhibition of renal nerve activity was less. However, these authors did not discuss the possibility that the greater change in baseline blood pressure in the SHR following anesthesia (from 179 to 132 mm Hg) might have contributed to the altered reflex control of renal nerve activity observed in this group of rats. Thoren and Ricksten14 and Judy and Farrell12 have also examined baroreflex control of renal nerve activity in SHR. In the study by Thoren and Ricksten,14 the responses of single renal nerve fibers were recorded from anesthetized animals. They reported that reflex control of percent, but not absolute, renal nerve activity was attenuated in the SHR. The effect of anesthesia on baseline blood pressure was not reported in their study. Judy and Farrell12 examined baroreflex control of renal nerve activity in anesthetized SHR by recording steady state changes in renal nerve activity during brief aortic occlusions. Their results implied that baroreflex control of renal nerve activity was attenuated in older SHR (40 wk old) during the static phase of the response.

Baroreflex control of renal nerve activity in DOCA-treated hypertensive swine appears to be similar to reflex control in the spontaneously hypertensive rat model of hypertension. In both models, baroreflex control of percent renal nerve activity is impaired.13,15 Our finding that the static component was impaired in DOCA-treated hypertensive swine is in agreement with the finding by Judy and Farrell12 for the SHR. We have also provided evidence that the dynamic component of the reflex is relatively normal in DOCA-treated swine. Although the mechanism(s) responsible for the reflex dysfunction of the SHR or DOCA-treated swine is not known, it is attractive to speculate that the impairment resides in the afferent limb of the reflex arc. Relevant to this possibility are reports by Brown et al.,23,24 which indicate that the static characteristic of aortic baroreceptor discharge is impaired in the SHR23 while the dynamic characteristic is similar to normotensive control rats.24

In conclusion, our results indicate that baroreflex control of percent renal nerve activity is impaired in anesthetized, DOCA-treated hypertensive swine. Our analysis also suggests that baroreflex control of renal nerve activity is likely to be impaired in conscious DOCA-treated animals. Although these studies dem-
onstrate that differences exist between normal and DOCA-treated hypertensive swine, further studies will be required to directly determine whether the absolute level of renal nerve activity is elevated in DOCA-treated hypertensive swine.

Acknowledgments
The technical assistance of Charles Ciccone is gratefully acknowledged.

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_Hypertension_. 1985;7:879-885
doi: 10.1161/01.HYP.7.6.879

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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