The effect of sinoaortic denervation on renal wrap hypertension

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Effect of Sinoaortic Deafferentation on Renal Wrap Hypertension

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Abstract—The purpose of this study was to determine whether sinoaortic deafferentation (SAD) alters the severity of hypertension or sympathoadrenal contribution to mean blood pressure (MAP) during renal wrap hypertension. Male Sprague-Dawley rats were implanted with radiotelemetry transmitters for 24-hour recording of MAP and heart rate. All rats underwent either SAD or sham SAD (Intact) surgery and were allowed to recover for 10 to 14 days. The rats were then assigned to a normotensive (Sham) group or a hypertensive (Wrap) group in which 1-kidney figure-8 renal wrap was performed. SAD increased the acute MAP response to renal wrap (Intact-Sham=5 ± 1 mm Hg, Intact-Wrap=45 ± 3 mm Hg, SAD-Sham=3 ± 3 mm Hg, SAD-Wrap=58 ± 4 mm Hg) and increased the lability of MAP (SD of MAP; Intact-Sham=3.8 ± 0.2, Intact-Wrap=4.2 ± 0.3, SAD-Sham=9.6 ± 1.4, SAD-Wrap=9.7 ± 1.4). MAP was not different between SAD and Intact rats during 4 weeks after renal wrap or sham surgery; however, induction of hypertension produced additional MAP variability that was independent of SAD (Intact-Sham=4.6 ± 0.4, Intact-Wrap=6.2 ± 0.6, SAD-Sham=6.3 ± 0.5, SAD-Wrap=10.8 ± 1.5). In a separate group of rats, the sympathoadrenal contribution to MAP was assessed by the depressor response to ganglionic blockade and plasma norepinephrine at rest and after neuronal uptake inhibition with desipramine. The depressor response to ganglionic blockade was significantly increased by renal wrap and by SAD (Intact-Sham=-49 ± 2 mm Hg, Intact-Wrap=-73 ± 4 mm Hg, SAD-Sham=-77 ± 5 mm Hg, SAD-Wrap=-96 ± 6 mm Hg). In the 3 groups with enhanced ganglionic blockade responses, desipramine caused a significant increase in plasma norepinephrine. These results indicate that SAD does not alter the development of renal wrap hypertension but does increase the sympathoadrenal contribution to MAP in both normotensive and hypertensive animals. (*Hypertension*. 1999;33[part II]:476-481.)

Key Words: sympathetic activity ■ sinoaortic denervation ■ barodenervation ■ radiotelemetry

The arterial baroreceptor reflex buffers acute changes in blood pressure via feedback control of sympathetic and parasympathetic nerve activity. This reflex maintains relatively constant arterial pressure by altering vascular conductance and heart rate (HR). However, in chronic hypertension, the moment-to-moment blood pressure regulation resets to a higher level of pressure.[1] Because of the resetting process during the development of hypertension, this reflex does not effectively counteract mechanisms that permanently elevate mean arterial pressure (MAP). In addition to baroreflex resetting, the sensitivity of the reflex has been shown to be reduced in the hypertensive state.[2] Thus it has been suggested that impaired baroreflex function may play a permissive role in the enhancement of sympathoadrenal activity that is a hallmark of many forms of experimental hypertension.[3,4]

The goal of the present study was to determine whether altered baroreflex function contributes to the onset or maintenance of renal wrap hypertension, or both. After the acute sympathoexcitatory effects of sinoaortic deafferentation (SAD), the absence of baroreceptor input prevents baroreflex-

mediated inhibition of sympathoadrenal activity and severely suppresses baroreflex sensitivity. Consequently, it was proposed that if the baroreflex actively limited the sympathetic nervous system in hypertension, there would be a greater neurogenic component contributing to a higher arterial pressure after SAD. Because of this, sinoaortic deafferentation was used in this study to determine the role of the baroreflex in determining sympathoadrenal activity and, in turn, arterial pressure after 1-kidney figure-8 renal wrap hypertension. It was hypothesized that animals without an intact baroreflex would have augmented sympathoadrenal activity, resulting in more severe hypertension.

Methods

Subjects

Male Sprague-Dawley rats (Charles River; n=72) were kept under a constant 14-hour light/10-hour dark cycle and provided rat chow (Teklad) and tap water ad libitum throughout the duration of the study. Animals were age matched and assigned to study 1 for long-term measurement of arterial pressure with radiotelemetry or study 2 for assessment of sympathoadrenal contribution to MAP. All

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Efficacy of SAD

Parameter Tested	Intact-Sham	Intact-Wrap	SAD-Sham	SAD-Wrap
MAP response to SAD, mm Hg	3±1	1±1	31±4*	33±3*
Water intake after SAD, ml/d	35±5	37±2	6±2*	5±2*
SD of MAP	3.8±0.2	4.2±0.3	9.6±1.4*	9.7±1.4*
ΔHR/ΔMAP-PE	−2.4±0.4	−1.9±0.2	−0.4±0.1*	−0.4±0.1*
ΔHR/ΔMAP-NP	−2.4±0.2	−2.0±0.2	−0.4±0.2*	−0.4±0.2*

Efficacy of SAD was assessed with the use of four criteria: (1) the increase in MAP on the day after SAD, (2) inhibition of water intake on the day after SAD, (3) lability of MAP (using SD of MAP as an index), and (4) baroreflex-mediated alterations in HR (ΔHR) in response to changes in MAP (ΔMAP) induced by phenylephrine (PE) and nitroprusside (NP). Baroreflex control of HR was assessed 39 to 43 days after SAD surgery.

*$P<0.05$ vs respective intact group.

experimental protocols were approved by the University's Institutional Animal Care and Use Committee. Animals were treated in accordance with the American Physiological Society's Guiding Principles for the Use of Animals in Research and Testing. The University of Texas Health Science Center at San Antonio is an AAALAC International accredited institution.

Surgical Interventions

Study 1

Under gaseous anesthesia (Metofane; Mallinckrodt Veterinary), rats were surgically implanted with a TA11PA-C40 radiotelemetry transmitter (Data Sciences). From 7 to 10 days after implantation surgery and after the measurement of control arterial pressure and HR, animals were assigned to either undergo SAD or sham (Intact) surgery. For SAD, rats were anesthetized (ketamine/xylazine/acepromazine IM), and SAD was performed according to the methods of Schreihofer and Sved.[5] A chronic indwelling catheter was inserted into the femoral vein for measurement of cardiac baroreflex function to test the efficacy of SAD. From 10 to 14 days later, rats were returned to the laboratory for induction of hypertension by 1-kidney figure-8 renal wrap, or Sham renal wrap (unilateral nephrectomy alone). For these procedures, the rat was anesthetized (Metofane), and the kidneys were approached through a flank incision. Renal wrap was performed according to the methods of Grollman et al.[6] MAP and HR measurements were continuously made throughout the periods after SAD and renal wrap until 4 weeks after the wrap.

Study 2

A separate group of age-matched rats were prepared in a manner similar to those used in study 1. However, radiotelemetry transmitters were not implanted. Instead, at the end of the third week after renal wrap, the rats were anesthetized (Metofane) and implanted with a chronic indwelling arterial catheter for measurement of MAP and collection of blood samples, and a venous catheter was used for injection of drugs.

Experimental Protocols and Data Collection

Study 1

Animals prepared with radiotelemetry transmitters were housed in individual wire mesh cages containing an RLA-3000 radiotelemetry receiver (Data Sciences International). Every 10 minutes, a 20-second measurement of MAP and HR was acquired, and the data were averaged to obtain a single hourly value for each parameter (DataQuest A.R.T.; DSI International). Body weight and fluid intake were measured daily. To test for complete SAD, bolus injections of phenylephrine hydrochloride (1 and 2 μg/kg; Sigma) and sodium nitroprusside (2 and 4 μg/kg; Sigma) were administered. During baroreflex control of HR testing, MAP and HR were measured continuously via telemetry at a sampling rate of 0.5 Hz. The peak responses were expressed as changes from the control period, and a

ratio of ΔHR/ΔMAP was used to determine whether SAD surgery was effective.

Study 2

Catheterized animals were housed individually in Plexiglas cages with wire mesh bottoms. The day before data collection, they were brought to the laboratory for 4 to 5 hours and placed in round opaque containers to become acclimatized to the environment to be used for data collection. Resting MAP and HR were recorded using a computer-based data collection system (Maclab; AD Instruments). Efficacy of SAD was tested by injection of phenylephrine and nitroprusside as described for study 1. The sympathetic contribution to MAP was assessed by the acute MAP response to ganglionic blockade using a bolus injection of hexamethonium (20 mg/kg; Sigma) and methyl atropine (0.1 mg/kg IV; Sigma). The peak change in MAP was taken within 2 minutes after administration.[7] On a second day of data collection (separated by ≥2 days), blood samples were collected for assay of plasma catecholamines before and after desipramine (1 mg/kg bolus followed by 30- to 45-minute infusion at 1.6 μg · kg^{-1} · min^{-1}; Sigma).

Data Analysis

Study 1

Six values for MAP and HR were acquired every hour with radiotelemetry. These values were averaged to obtain an hourly mean, which was used to calculate a daily mean. The 1-hour values were averaged each day for a daily mean. The SD of this daily mean was taken as an index of MAP lability. The statistical program SuperANOVA (Abacus Concepts) was used to generate 3-factor ANOVA (Intact/SAD×Sham/Wrap×Time) for MAP, HR, MAP lability, body weight, and fluid intake. Two-factor ANOVA (Group×Time) was used for pairwise comparisons when a main effect or interaction reached statistical significance. The acute effects of Wrap/Sham surgery were assessed by comparing MAP and HR during a 48-hour control period with values during a 16-hour post–wrap/sham period (the hours of 7:00 AM to 3:00 PM were not included in the postmean to allow for surgery and recovery from anesthesia). From these values, a change in MAP and HR was calculated for pre-to-post comparison using ANOVA. Significance was accepted at $P<0.05$. All data are expressed as mean±SEM.

Study 2

A 30-minute recording of MAP, SD of MAP, and HR was made each day of data collection. These values were averaged and compared using 2-factor ANOVA (Intact/SAD×Sham/Wrap). The peak change in MAP and HR responses within 2 minutes after ganglionic blockade were compared with preganglionic blockade MAP and HR using 3-factor ANOVA. Significance was accepted at $P<0.05$. All data are expressed as mean±SEM.

Results

The efficacy of SAD was assessed according to several criteria (shown in the Table). Animals without complete SAD
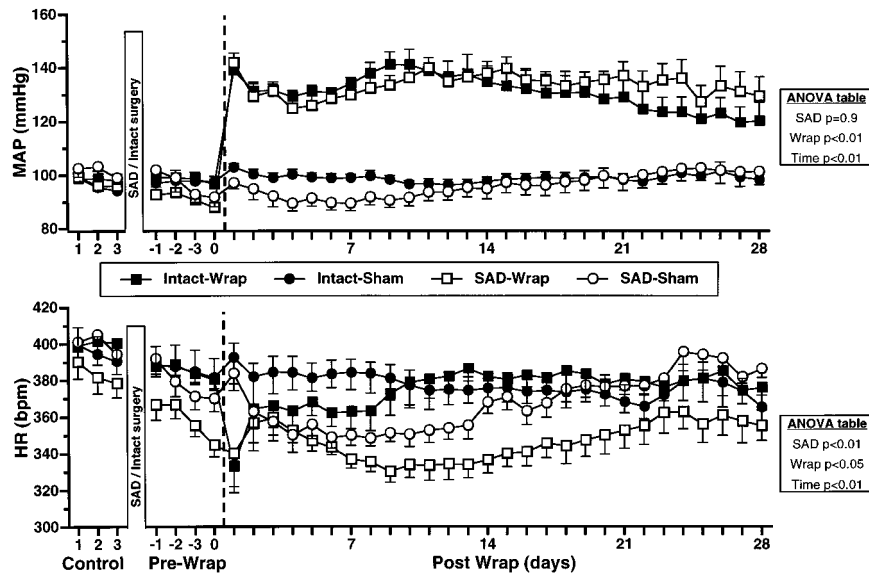
Figure 1. MAP and HR are shown during the control period before SAD surgery, the period before renal wrap, and continuously for 28 days after renal wrap. MAP was not different between SAD and intact animals.

during the final test session were removed from the study. For animals in study 2, a 30-minute estimate of the lability of arterial pressure was taken during a 3- to 4-hour recording session. In addition, baroreflexes were tested. Only animals with increased MAP lability and a deficit in reflex function were included in study 2. Differences in MAP, HR, and SD of MAP among groups in study 2 were similar to the differences seen among groups in study 1.

Study 1
Body weight was not different among groups of animals during the control period. Growth rates of the rats in each group were similar as indicated by parallel increases in body weight through the study; however, animals undergoing SAD and renal wrap lost more weight after surgery than the respective sham-operated animals. After surgical recovery (typically 2 days), all animals were healthy and gaining weight throughout the study. Fluid intake did not differ among groups during the control period. However, SAD rats consistently drank less water over the duration of the study. Although renal wrapped animals increased their fluid intake in response to reduced renal function, the fluid intake of the SAD-Wrap rats remained less than in the Intact-Wrap animals.

MAP and HR measured throughout the study are shown in Figure 1. Arterial pressure was not different among groups during the control or prewrap period (Figure 1A). Three-factor ANOVA indicated that the renal wrap procedure resulted in an increase in arterial pressure over the 4-week postwrap period; however, the denervation of the baroreceptors did not affect the course of the hypertension. HR was not different among groups during the control period (Figure 1B). Baroreceptor denervated animals had a lower HR. Although the wrap/sham surgery did not affect HR in SAD rats, there was a significant decrease in Intact renal wrapped animals.

The magnitude of the changes in arterial pressure after induction of hypertension were greater in SAD animals. Renal wrap produced significant increases in arterial pressure compared with rats that underwent unilateral nephrectomy

alone (5 ± 1 versus 46 ± 3 mm Hg). The rise in MAP during the first 24 hours after renal wrap surgery was greater in the SAD animals than in Intact animals (46 ± 3 versus 58 ± 4 mm Hg). The reason for the exaggerated increase in MAP after renal wrap in the SAD animals presumably was the absence of a reflex response to the pressor stimulus (-60 ± 15 bpm in Intact animals versus -14 ± 15 bpm in SAD animals).

The lability of MAP throughout the study is shown in Figure 2. ANOVA revealed a significant increase in the variability of MAP after baroreceptor denervation. After the renal wrap procedure in these animals, arterial pressure lability increased dramatically and then stabilized at a level that was higher than that of the other groups of rats. Intact animals subjected to renal wrapping also experienced an increase in the lability of MAP immediately after wrap, which then fell to a level that was still significantly elevated. As shown in the inset of Figure 2, the SD of arterial pressure was significantly elevated in both hypertensive groups of rats relative to their respective control animals; however, the lability of MAP was consistently greater in the SAD rats.

Study 2
The sympathoadrenal contribution to MAP was studied in Intact and SAD normotensive and hypertensive rats. The magnitude of the hypertension was similar in Intact and SAD renal wrapped animals in this study compared with study 1 (Intact-Sham, 123 ± 3 mm Hg; Intact-Wrap, 150 ± 4 mm Hg; SAD-Sham, 116 ± 9 mm Hg; SAD-Wrap, 153 ± 4 mm Hg). As shown in Figure 3, MAP decreased significantly after ganglionic blockade. The fall in arterial pressure was greater in the 2 groups of hypertensive animals (Intact-Wrap, -73 ± 4 mm Hg; Intact-Sham, -49 ± 2 mm Hg; SAD-Wrap, -97 ± 6 mm Hg; SAD-Sham, -77 ± 5 mm Hg). In addition, the fall in arterial pressure was greater in both groups of SAD animals, resulting in a significantly lower final MAP after blockade of the autonomic nervous system compared with Intact rats.
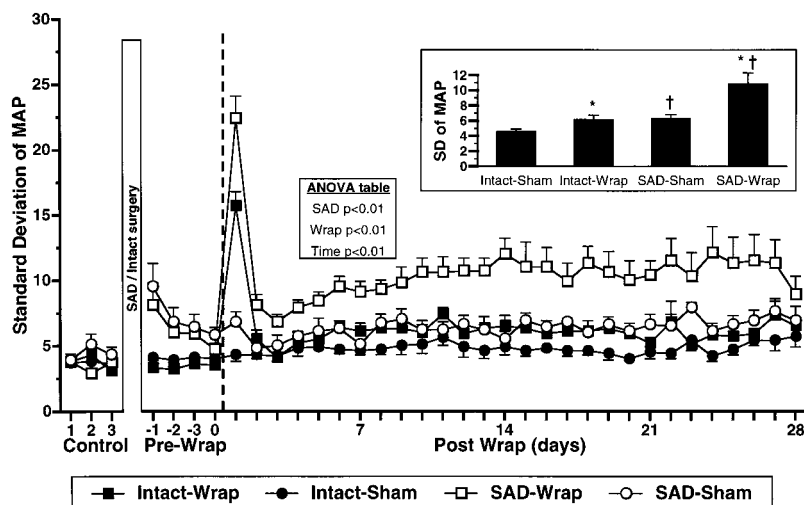
Figure 2. SD of 1-hour blood pressure values were used as an index of lability of MAP. Inset, Weekly average of the lability of MAP after Wrap or Sham surgery. *$P<0.05$ vs Sham. †$P<0.05$ vs Intact.

Resting levels of plasma norepinephrine (NE) were significantly higher in the Intact renal wrap animals than in with sham-operated rats (Figure 4). In contrast, the hypertensive SAD rats had lower resting plasma NE levels relative to both normotensive SAD and hypertensive Intact animals. Plasma epinephrine was not different among the 4 groups of rats. Animals were challenged with desipramine to block neuronal uptake of catecholamines to determine whether an enhanced uptake of NE influenced circulating levels of the biogenic amines. ANOVA revealed a significant effect of desipramine; however, plasma NE increased only in the SAD groups and the Intact hypertensive group of rats, not in the Intact normotensive animals.

Discussion

This study had 2 principal findings. First, SAD significantly augmented sympathoadrenal component maintaining arterial pressure compared with intact rats. This enhanced sympathetic nervous system function was present in both normotensive and hypertensive rats. Second, despite the marked increase in sympathoadrenal function associated with SAD, long-term levels of resting arterial pressure were similar in Intact and SAD animals whether normotensive or hypertensive.
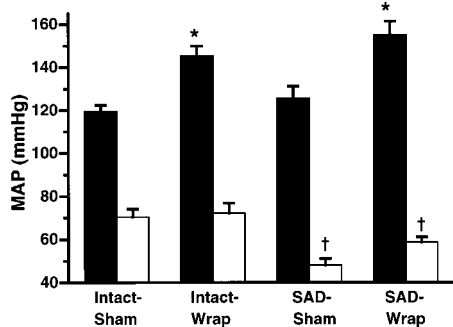
SAD results in acute increases in sympathetic activity causing an increase in MAP. Physiological[8–11] and biochemical[12,13] evidence indicates that the hypertension within the first 1 to 4 days after SAD is produced by sympathetic hyperactivity. However, the initial level of hypertension after SAD does not appear to be maintained.[10,14–16] Some studies have shown that chronic SAD produces moderate increases in resting MAP relative to Intact animals,[12,17–19] whereas others have reported that arterial pressure is not elevated chronically.[10,15,20] In the present study, an elevated MAP was not observed in chronic SAD animals (5 to 6 weeks after SAD) through the use of radiotelemetry or recording MAP with chronic catheters. Many explanations may contribute to differences in MAP reported in baroreceptor denervated animals, including recording conditions, time of day, strain of rat, and degree of stress that the animal may experience.[20,21]

Figure 3. MAP is shown during a control period before (filled bars) and after (open bars) ganglionic blockade. Ganglionic blockade was achieved by bolus intravenous injection of 20 mg hexamethonium and 0.1 mg atropine. *$P<0.05$ vs respective Sham. †$P<0.05$ vs respective Intact.
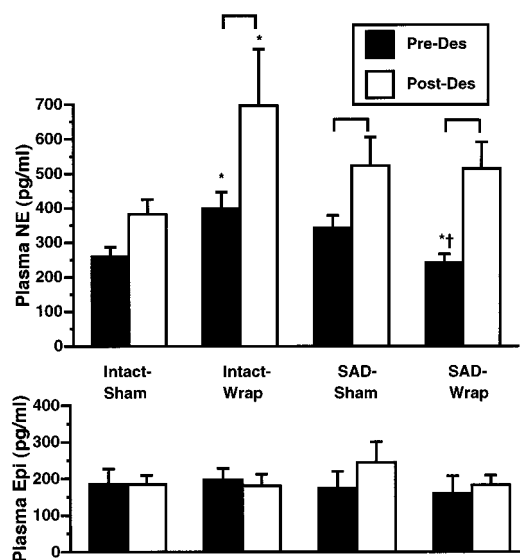

Figure 4. Plasma NE and epinephrine (Epi) are shown during a control period before (Pre-Des) and after (Post-Des) neuronal uptake inhibition with desipramine (1 mg/kg bolus and then 1.6 μg · kg^{-1} · min^{-1} infusion). *$P<0.05$ vs respective Sham. †$P<0.05$ vs respective Intact. Brackets above the pairs of bars represent significant increases in plasma NE.

The level of activity of the sympathetic nervous system chronically after SAD also is unclear. Some indexes of sympathetic activity, such as plasma dopamine β-hydroxylase and NE[12] and ganglionic blockade responses,[10] have been shown to be sustained when MAP return toward normal, whereas other indicators, such as renal sympathetic activity[11] and adrenal catecholamine synthesis,[13] are not chronically elevated. In the present study, a persistent increase in sympathoadrenal activity was observed in sham wrapped SAD rats. Sympathoadrenal activity was assessed in the present study using the MAP response to ganglionic blockade and plasma catecholamine levels at rest and after uptake inhibition with desipramine. Neural support of MAP was clearly increased in the SAD rats. Resting NE values were not different between normotensive SAD and intact rats, but there was a significant increase in plasma NE in the SAD rats after uptake inhibition. Although many factors at the neuroeffector junction affect overflow of NE into plasma, a significant increase in plasma NE after desipramine suggests that neuronal uptake mechanisms in the SAD rats may be enhanced.

An increase in the sympathoadrenal contribution to arterial pressure was observed in SAD hypertensive animals relative to the Intact renal wrapped animals. The MAP response to ganglionic blockade was greater in the SAD-Wrap animals, suggesting an increased sympathetic activity. Although resting plasma NE levels were not significantly greater in the hypertensive SAD rats, plasma NE increased significantly after NE uptake inhibition in both hypertensive groups of rats. There is evidence from other studies that uptake of NE increases with the level of sympathetic nerve activity.[22] In the present study, the 3 groups of rats demonstrating an exaggerated response to ganglionic blockade also experienced a significant enhancement of plasma NE after desipramine. These findings suggest that the severe long-term reduction in baroreflex sensitivity produced by SAD leads to an activation of the sympathetic nervous system. However, even after the baroreflex resets to a higher level in renal wrap hypertension, there does not appear to be alterations in reflex control of renal nerve activity (S. Mifflin, personal communication). This suggests that mechanisms besides reduced baroreflex sensitivity are important in the hypertensive process.

Although SAD resulted in greater levels of sympathetic function in the hypertensive rats, the resting level of arterial pressure was not different compared with Intact animals. The absence of reflex bradycardia and sympathoinhibition after renal wrap in SAD animals resulted in a greater initial rise in MAP. However, this augmented hypertension was not sustained for >24 hours despite the greater sympathoadrenal activation. A similar observation has been made in SAD dogs in which anephric animals were challenged with a volume infusion.[23] In these animals, arterial pressure rose to a higher level than was observed in intact animals, but within 24 hours, the arterial pressure was similar in both groups of dogs. Although other studies have shown that SAD animals may develop a more rapid rise in MAP when renal hypertension in induced,[24,25] only 1 study has demonstrated an exaggerated and sustained MAP after renal hypertension in SAD animals.[26]

The reason for the equivalent levels of MAP between SAD and Intact animals was not examined in the present study. Based on work by others, a pressure natriuresis and diuresis may be responsible for reducing extracellular fluid and blood volumes after baroreceptor deafferentation. As Hall et al[27] have shown, pressure natriuresis serves to limit the degree of hypertension. Support for this has also been shown in baboons. When renal arterial pressure is servo-controlled to maintain normotensive renal perfusion after SAD, the increase in peripheral arterial pressure is enhanced.[28] In contrast, Osborn and England[15] were not able to show that pressure natriuresis contributed to the normalization of MAP after SAD in the rat. In that study, resting MAP returned to normal levels after SAD even though >50% of the daily water intake was administered by intravenous infusion. Reduced water intake after SAD has also been suggested to contribute to reductions in MAP by reducing body fluid volume.[29] In the present study, 2 observations suggest that both normotensive and hypertensive SAD animals may have reduced extracellular fluid and blood volumes. First, water intake decreased after SAD and remained suppressed. Second, after ganglionic blockade, the minimum arterial pressure was significantly lower in SAD rats at a time before other compensatory mechanisms such as renin release would likely be activated. Collectively, we hypothesize that pressure natriuresis and diuresis reduce pressure despite sympathetic hyperactivity.

In conclusion, sinoaortic denervation produces persistent activation of the sympathetic nervous system. In both normotensive and hypertensive groups, augmented depressor responses to ganglionic blockade and increased plasma NE levels after uptake inhibition were observed in SAD animals. However, the enhanced sympathetic activation did not alter resting levels of MAP in either normotensive or hypertensive animals. These results indicate that alterations in baroreflex sensitivity may cause alterations in sympathetic activity, but other compensatory mechanisms may preclude a sustained influence on MAP.

Acknowledgments

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