Hypothalamic $\beta_2$-Adrenoceptor Control of Renal Sympathetic Nerve Activity and Urinary Sodium Excretion in Conscious, Spontaneously Hypertensive Rats

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SUMMARY. The contributions of $\beta_1$, $\beta_2$, and $\alpha_2$-adrenoceptors in the posterior hypothalamus to the increased renal sympathetic nerve activity and decreased urinary sodium excretion resulting from environmental stress (air jet) in conscious spontaneously hypertensive rats were examined. Air stress increased mean arterial pressure and renal sympathetic nerve activity (54% from 7.0 ± 0.7 integrator resets/min), and decreased urinary sodium excretion (44% from 2.7 ± 0.4 (μEq/min per 100 g body weight). After bilateral injection of ICI 118,551 ($\beta_2$-adrenoceptor antagonist) into the posterior hypothalamus of the same spontaneously hypertensive rats, air stress had no effect on renal sympathetic nerve activity (8% from 4.8 ± 0.7 integrator resets/min) or urinary sodium excretion (2% from 5.2 ± 0.8 (μEq/min per 100 g body weight), but still increased mean arterial pressure. Bilateral injection of isoproterenol ($\beta_2$-adrenoceptor agonist) into the posterior hypothalamus enhanced the renal sympathetic nerve activity and urinary sodium excretion (but not mean arterial pressure) responses to air stress. Air stress had no effect on renal sympathetic nerve activity or urinary sodium excretion when ICI 118,551 was given into the posterior hypothalamus before isoproterenol. Atenolol ($\beta_1$-adrenoceptor antagonist) had no effect on the renal responses to air stress when given alone or before isoproterenol. Similarly, ICI 118,551 administered into the lateral hypothalamus or lateral cerebral ventricle, or guanabenz ($\alpha_2$-adrenoceptor agonist) given into the posterior hypothalamus, had no effects on the renal or mean arterial pressure responses to air stress. Thus, $\beta_2$-adrenoceptors in the posterior hypothalamus mediate the increased renal sympathetic nerve activity and antinatriuresis resulting from environmental stress in conscious spontaneous hypertensive rats. (Circ Res 58: 241-248, 1986)

THE central nervous system and the kidneys have long been thought to be critical in the pathophysiology of hypertension (Folkow, 1982; Guyton, 1980). Indeed, the development of hypertension in spontaneously hypertensive rats (SHR) is associated with increased renal retention of sodium, and can be blocked by surgical denervation of the kidneys (Winternitz et al., 1980; Beierwaltes et al., 1982). Moreover, chronic stimulation of the central nervous system with environmental stress produces hypertension in borderline hypertensive rats (crossbred SHR × WKY) and exacerbates hypertension in SHR (Lawler et al., 1981; Ely and Weigand, 1983). The potential contributions of the central nervous system and kidneys in these models of chronic stress hypertension are suggested by studies of acute environmental stress. Acute exposure to air jet stress leads to antinatriuresis and an increase in renal sympathetic nerve activity that is much greater in conscious SHR than in conscious normotensive Wistar-Kyoto rats (WKY) (Lundin and Thoren 1982; Koepke and DiBona, 1985b). The antinatriuretic response to air stress in conscious SHR is abolished by surgical renal denervation, further implicating the renal sympathetic nerves in the renal excretory response (Lundin and Thoren 1982; Koepke and DiBona, 1985b).

The neural control of urinary sodium excretion is also demonstrated by studies in which $\alpha$- and $\beta$-adrenoceptor agonists and antagonists were injected into the central nervous system. The increased renal sympathetic nerve activity and antinatriuresis resulting from air stress in conscious SHR is prevented by intracerebroventricular administration of $\beta_2$-adrenoceptor antagonists (propranolol, timolol), $\beta_2$-adrenoceptor antagonist (ICI 118,551), or $\alpha_2$-adrenoceptor agonists (clonidine, guanabenz) (Koepke and DiBona, 1985a; Koepke and DiBona, in press). Other studies point to possible central nervous system loci where adrenoceptors may be important in the neural control of urinary sodium excretion. Natriuresis results from the administration of norepi-
nephrine into the ventromedial hypothalamus, lateral hypothalamus, septal area, or 3rd cerebral ventricle of conscious rats; this natriuresis is prevented by α₁-adrenoceptor antagonists and is potentiated by α₂-adrenoceptor antagonists (Camargo et al., 1976; Morris et al., 1977; Pillar et al., 1977; Saad et al., 1984). In contrast, an antinatriuresis follows the injection of isoproterenol into the lateral hypothalamus, septal area, or 3rd cerebral ventricle; this antinatriuresis is abolished by β₁, β₂, but not β₁, β₂, adrenoceptor antagonists (Morris et al., 1977; Pillar et al., 1977; Camargo et al., 1979). In support of these findings, radioligand-binding studies have identified both α₁- and β-adrenoceptors in the hypothalamus (Leibowitz, 1982; Petrovic et al., 1983; Unnerstall et al., 1984). The present study extends these results by examining the contribution of hypothalamic β₁, β₂, and α₂-adrenoceptors to the increased renal sympathetic nerve activity and antinatriuresis resulting from air stress in conscious SHR.

Methods

Male SHR, 14–16 weeks old, were used (Charles River Laboratories). The animals were maintained on standard laboratory rat chow and tap water. All experimental procedures were in accordance with University of Iowa College of Medicine and National Institutes of Health guidelines for the care and use of animals.

Twenty-four to 48 hours before experimentation, SHR were anesthetized with ketamine HCL (150 mg/kg; Ketaset, Bristol Laboratories). Catheters (Tygon) were implanted in the left jugular vein and carotid artery, tunneled to the back of the neck, filled with heparinized saline (100 U/ml; Elkins-Sinn), and plugged with stainless steel pins. With the skull surface level between bregma and lambda, the posterior hypothalamus, lateral hypothalamus, and lateral ventricle were stereotaxically (Kopf, model 900) cannulated in separate SHR with stainless steel cannulas (18 gauge, 12.5 cm long) according to the coordinates of Paxinos and Watson (1982). These coordinates were: posterior hypothalamus (bilateral) 4.0 mm posterior to bregma, 0.5 mm lateral to midline, 7.5 mm below skull surface; lateral hypothalamus (bilateral) 4.0 mm posterior to bregma, 1.5 mm lateral to midline, 8.5 mm below skull surface; right lateral ventricle 0.3 mm posterior to bregma, 1.4 mm lateral to midline, 4.5 mm below skull surface. Brain cannulas were held in place with stainless steel jewelers screws and cranioplastic cement. The venous cannula was used for saline infusions, the arterial cannula was used for arterial pressure and heart rate recordings, and the brain cannulas were used for drug injections.

On the day of the experiment, SHR were anesthetized with methohexital sodium (Brevital, 20 mg/kg, iv, supplemented by 10 mg/kg, iv, as needed; Eli Lilly) and were implanted with a bladder cannula and renal sympathetic nerve activity-recording electrode (Koepke and DiBona, 1985a, 1985b). Via a suprapubic incision, a stainless steel urinary bladder cannula (18 gauge, 12.5 cm long), modified from that of Gellai and Valtin (1979), was sutured into the urinary bladder, exteriorized, and secured by suturing to adjacent muscle, subcutaneous tissue, and skin. To implant the renal sympathetic nerve activity recording electrode, we exposed the left kidney through a left flank incision via a retroperitoneal approach. Using a dissection microscope (25×), we then dissected a renal nerve branch from the aortorenal ganglion and placed it on a bipolar silver or platinum wire (Cooner Wire Company; Chatsworth, CA) electrode. Renal sympathetic nerve activity was amplified (10,000–50,000×) and filtered (low, 30; high, 3000 Hz) with a Grass P511 bandpass amplifier (Grass Instrument Co.). The amplified and filtered signal was channeled to a Tektronix 5113 oscilloscope (Tektronix, Inc.) and Grass model 7DA polygraph for visual evaluation, to an audio amplifier/loudspeaker (Grass model AM 8 Audio Monitor) for auditory evaluation, and to a rectifying voltage integrator (Grass model 7P10). The integrated voltage and renal neurogram signals were displayed on the Grass polygraph. We assessed the quality of the renal sympathetic nerve signal during surgery by examining the magnitude of decrease in recorded renal sympathetic nerve activity during sinoaortic baroreceptor loading with intravenous injection of norepinephrine (3 μg) and the magnitude of increase in recorded renal sympathetic nerve activity remaining after maximum inhibition following norepinephrine administration (3 μg, iv) was similar to the background noise observed 30–45 minutes postmortem (less than one integrator reset/min) (Koepke and DiBona, in press); this value was subtracted from all experimental values of renal sympathetic nerve activity.

When an optimal renal sympathetic nerve activity signal was observed, the recording electrodes were fixed to the renal nerve branch with Wacker Sil-Gel 604 (Rüdiger et al., 1981). The electrode cable was tunneled to the back of the neck and exteriorized, the flank incision was closed in layers, and 4–6 hours were allowed for recovery.

SHR then were placed in Lucite cylinders, and a 5% dextrose Ringers solution was infused (30 μl/min) for 1 hour. Three to 5 hours after surgical preparation, an isotonic saline infusion was started (100 μl/min), the arterial catheter was flushed and attached to a pressure transducer (Statham P23Db), and a 3-cm polyethylene catheter was attached to the urinary bladder cannula and led to a collection beaker. The renal sympathetic nerve activity-recording electrode cable was connected to a high impedance probe (Grass HIP 511) which, in turn, was connected to the bandpass amplifier. The quality of the renal nerve activity recording was tested with intravenous norepinephrine (3 μg) and acetylcholine (1 μg), as above, to ensure the absence of noise due to mechanical movement, respiration, or heart rate. If the quality of the renal sympathetic nerve activity recording was the same as that observed when the electrode was implanted, then the experiment commenced.

After urine flow rate and urinary sodium excretion had stabilized (45–60 minutes), two consecutive sets of experimental periods (control, air stress, recovery; 10 minutes each) were examined. The microinjection of α₁- or β₁-adrenoceptor agonists or antagonists through the brain cannulas occurred immediately after the first recovery period and 10–20 minutes before the control period of the second set of experimental periods. In some rats, β₁-adrenoceptor antagonists were administered 20 minutes before isoproterenol (Figs. 5 and 6). Separate groups of SHR were used for each drug protocol. This design has been shown to result in increases in renal sympathetic nerve activity and arterial pressure and decreases in urinary sodium excretion during air stress of similar magnitude between the first and second sets of experimental periods in the same conscious SHR (Koepke and DiBona, 1985a). Environmental stress (air stress) consisted of an air jet delivered...
to the top of the rat's head located 4–5 cm in front of the
rat (Lundin and Thoren, 1982; Koepke and DiBona, 1985a,
1985b, in press). At the end of each experiment, the quality
of the renal sympathetic nerve activity recordings was
again assessed with intravenous injections of norepineph-
rine (3 μg) and acetylcholine (1 μg).

Drugs used for central nervous system administration
were ICI 118,551 HC1, atenolol HC1, isoproterenol HC1,
and guanabenz acetate. Vehicle was isotonic saline (1 μl).

Urine volume was determined gravimetrically. Urine so-
dium concentration was measured by flame photometry
(Instrumentation Laboratories, model 143).

At the end of each experiment, SHR were perfused
through the left ventricle of the heart with isotonic saline
until clear saline flowed from an incision in the right
ventricle. Then, about 100 ml of 10% buffered formalin
were infused via the heart. The brain, still encased in the
skull, was stored 2–3 days in 10% buffered formalin before
it was removed and cut into 40-μm sections on a cryostat.
The brain sections were mounted on a slide and stained
with cresyl violet. The placement of brain cannulas in the
hypothalamus was determined by an investigator without
knowledge of corresponding physiological measures. Only
SHR with bilateral placement of brain cannulas in the
specific hypothalamic areas were included in data analyses
(44 of 55 SHR).

Statistical analyses were conducted with repeated-
measures analyses of variance (BMDP 2PV) (Dixon et al.,
1981) for main effects and interactions, and Tukey’s HSD
test (Kirk, 1968) for pair-wise comparisons among means.
Statistical significance was defined as P < 0.05.

**Results**

Air stress in conscious SHR increased mean arte-
rial pressure and renal sympathetic nerve activity and
decreased urinary sodium excretion (Fig. 1, left
panel). In addition, air stress decreased urine flow rate (24% from 18.0 ± 4.5 μl/min per 100 g body
weight, P < 0.05) and increased heart rate (23 beats/
min from 377 ± 18 beats/min, P < 0.05) in these
SHR. During the recovery period, all measures re-
turned to control levels. After the bilateral admin-
istration of the β2-adrenoceptor antagonist, ICI
118,551 (2 × 1 μg), into the posterior hypothalamus of
the same SHR, air stress had no effect on urinary sodium excretion or renal sympathetic nerve activity, but still increased mean arterial pressure (Fig. 1, right
panel). Air stress had no effect on urine flow rate (+10% from 25.6 ± 4.3 μl/min per 100 g body
weight), but increased heart rate (21 beats/min from
389 ± 19 beats/min, P < 0.05) after ICI 118,551.

Injection of ICI 118,551 (2 μg) into the lateral
cerebral ventricle (Fig. 2) or the lateral hypothalamus
(2 × 1 μg) (Fig. 3) had no effect on the increase in
mean arterial and renal sympathetic nerve activity or
decrease in urinary sodium excretion resulting from
air stress in conscious SHR. These measures returned
to control levels during recovery periods before and after ICI 118,551 injections (Figs. 2 and
3). Urine flow rate did not change during air stress
either before or after ICI 118,551 administration into
the lateral cerebral ventricle (−8% from 22.7 ± 5.2
μl/min).

**FIGURE 1.** After injection of ICI 118,551 into the posterior hypotal-
amus, air stress (AIR) had no effect on urinary sodium excretion
(UNaV) or renal sympathetic nerve activity (RSNA). ICI 118,551 did
not alter the mean arterial pressure (MAP) response to air stress in
conscious SHR. *P < 0.05 AIR compared to control (CONT); tP <
0.05 recovery (RECOV) compared to CONT.

**FIGURE 2.** Intracerebroventricular injection of ICI 118,551 at the
same dose that was given into the posterior hypothalamus had no
effect on the MAP, UNaV, or RSNA responses to air stress in conscious
SHR. *P < 0.05 AIR compared to CONT.
and -5% from 26.1 ± 5.5 μl/min per 100 g body weight, respectively) or into the lateral hypothalamus (-15% from 22.7 ± 7.5 and -10% from 21.0 ± 5.3 μl/min per 100 g body weight, respectively). ICI 118,551 administered into the lateral cerebral

ventricle or lateral hypothalamus had no effect on baseline levels of mean arterial pressure, urinary sodium excretion, urine flow rate, or renal sympathetic nerve activity (Figs. 2 and 3).

Stimulation of β₂-adrenoceptors in posterior hypothalamus had the opposite effects of blockade. Bilateral injection of isoproterenol (2 × 5 μg) enhanced the increased renal sympathetic nerve activity and antinatriuretic responses to air stress in conscious SHR (Fig. 4). Before isoproterenol, air stress increased renal sympathetic nerve activity by 65% from 5.1 ± 0.3 integrator resets/min (P < 0.01) and decreased urinary sodium excretion by 38% from 3.2 ± 0.5 μEq/min per 100 g body weight (P < 0.01). After isoproterenol, air stress had greater effects (both absolute and percent changes; P < 0.05) on renal sympathetic nerve activity (+88% from 6.9 ± 0.6 integrator resets/min) and urinary sodium excretion (-55% from 2.0 ± 0.1 μEq/min per 100 g body weight). Urine flow rate did not change during air stress either before (+10% from 16.3 ± 2.3 μl/min per 100 g body weight) or after (+8% from 9.6 ± 1.1 μl/min per 100 g body weight). Isoproterenol decreased (P < 0.05) baseline levels of urinary flow rate (50% from 19.2 ± 3.5 μl/min per 100 g body weight) and urinary sodium excretion (38% from 3.0 ± 0.4 μEq/min per 100 g body weight), and increased (P < 0.05) baseline levels of renal sympathetic nerve activity (35% from 5.4 ± 0.6 integrator resets/min) and heart rate (36 beats/min from 365 ± 19 beats/min); isoproterenol had
no effect on baseline level of mean arterial pressure (Fig. 4).

The bilateral administration of ICI 118,551 (2 × 1 μg) into the posterior hypothalamus before isoproterenol (2 × 5 μg) prevented air stress from increasing renal sympathetic nerve activity and decreasing urinary sodium excretion, while mean arterial pressure still increased (Fig. 5). Pretreatment of the posterior hypothalamus with atenolol (2 × 15 μg) did not change the ability of isoproterenol (2 × 5 μg) to enhance the increase in renal sympathetic nerve activity and antinatriuretic responses to air stress (Fig. 6). Before atenolol and isoproterenol were administered, air stress increased renal sympathetic nerve activity 51% from 9.0 ± 1.1 integrator resets/min and decreased urinary sodium excretion 22% from 3.6 ± 0.3 μEq/min per 100 g body weight. After atenolol and isoproterenol in the same SHR, both absolute and percent changes in renal sympathetic nerve activity and urinary sodium excretion were greater during air stress (P < 0.05; +81% from 13.3 ± 0.7 integrator resets/min and −52% from 2.4 ± 0.5 μEq/min per 100 g body weight, respectively). Mean arterial pressure increased similarly before and after atenolol and isoproterenol (Fig. 6). After atenolol, isoproterenol decreased baseline urinary flow rate (from 20.8 ± 3.2 to 11.8 ± 1.6 μl/min per 100 g body weight; P < 0.05) and urinary sodium excretion, and increased baseline renal sympathetic nerve activity, without affecting baseline mean arterial pressure (Fig. 6).

Bilateral injection of the β1-adrenoceptor antagonist, atenolol (2 × 15 μg), into the posterior hypothalamus had no effect on the urinary sodium excretion, renal sympathetic nerve activity, or mean arterial pressure responses to air stress in conscious SHR (Fig. 7). Both before and after atenolol, air stress increased mean arterial pressure, heart rate (40 beats/min from 344 ± 30 beats/min, and 35 beats/min from 331 ± 31 beats/min, respectively, P < 0.05), and renal sympathetic nerve activity (Fig. 7). Whereas urinary sodium excretion decreased both before and after injection of atenolol into the posterior hypothalamus (Fig. 7), urine flow rate decreased before atenolol (−41% from 16.4 ± 3.8 μl/min per 100 g body weight, P < 0.05) but not after (−3% from 19.3 ± 4.3 μl/min per 100 g body weight). All measures returned to control levels during recovery. Atenolol had no effect on baseline levels of any variable.

Administration of the α2-adrenoceptor antagonist, guanabenz (2 × 2.5 μg) in the posterior hypothalamus had no effect on the increased mean arterial pressure, decreased urinary sodium excretion, and increased renal sympathetic nerve activity resulting from air stress in conscious SHR (Fig. 8). Both before and after guanabenz (2 × 2.5 μg), air stress decreased urine flow rate (−20% from 12.6 ± 1.5 μl/min per 100 g body weight and −19% from 17.6 ± 1.3 μl/min per 100 g body weight, respectively; P < 0.05), and increased heart rate (21 beats/min from 396 ± 30 beats/min and 18 beats/min from 397 ± 30 beats/min, respectively; P < 0.05). Guanabenz administered into the posterior hypothalamus had no effect on the baseline levels of these measures (Fig. 8).
Discussion

This study shows that \( \beta_2 \)-adrenoceptors in the posterior hypothalamus are important in the neural control of renal function in conscious SHR. This conclusion is supported by the following observations. First, pharmacological blockade of \( \beta_2 \)-adrenoceptors in the posterior hypothalamus with ICI 118,551 completely blocked the increased renal sympathetic nerve activity and antinatriuresis resulting from air stress in conscious SHR. Moreover, ICI 118,551 in the posterior hypothalamus lowered baseline renal sympathetic nerve activity and raised baseline urinary sodium excretion. Injection of the same dose of ICI 118,551 into the lateral cerebral ventricle or lateral hypothalamus had no effect on the renal responses to air stress or on baseline levels of renal sympathetic nerve activity and urinary sodium excretion. In addition, in three rats that were omitted because cannulas were positioned above the posterior hypothalamus, the same dose of these \( \beta \)-adrenoceptor antagonists, centra! nervous system \( \beta \)-adrenoceptors do not appear to contribute to the control of renal sympathetic nerve activity or urinary sodium excretion in conscious SHR. Neither the intracerebroventricular (Koepeke and DiBona, in press) nor posterior hypothalamic administration of the \( \beta_1 \)-adrenoceptor antagonist, atenolol, affects the renal sympathetic nerve activity or urinary sodium excretion responses to air stress in conscious SHR. Moreover, the increased renal sympathetic nerve activity and antinatriuresis resulting from isoproterenol in the posterior hypothalamus is unaffected by \( \beta_1 \)-adrenoceptor blockade with atenolol. Thus, a specificity for \( \beta_2 \)-rather than \( \beta_1 \)-adrenoceptors exists in the central nervous system for the neural control of renal function in conscious SHR.

Unlike \( \beta_2 \)-adrenoceptor blockade, injection of guanabenz, an \( \alpha_2 \)-adrenoceptor agonist, into the posterior hypothalamus of conscious SHR had no effect on the renal sympathetic nerve activity or urinary sodium excretion responses to air stress. This finding is in contrast to the finding that the same dose of guanabenz as used in this study, or clonidine (1 \( \mu \)g) given into the cerebral ventricles, blocks the renal responses to air stress in SHR at a central nervous system site of action; the blockade is reversed by a \( \beta_1 \)-adrenoceptor antagonist (yohimbine, rauwolscine) (Koepeke and DiBona, in press). Hence, guanabenz (intracerebroventricular, 5 \( \mu \)g) must act at a central nervous system site other than the posterior hypothalamus. In this regard, \( \alpha_2 \)-adre-
noceptors have been identified in several brainstem areas, other hypothalamic areas, and the amygdala, and stimulation of central \( \alpha_2 \)-adrenoceptors can lower blood pressure (Brody et al., 1984; Unnerstall et al., 1984), supporting the possibility that \( \alpha_2 \)-adrenoceptors in these other areas may mediate the renal sympathetic nerve activity and antinatriuretic responses to air stress in conscious SHR.

The renal mechanisms of the antinatriuretic response to air stress in conscious SHR include an increased renal tubular reabsorption of sodium, since glomerular filtration rate and effective renal plasma flow do not change (Koepke and DiBona, 1985b). The renal sympathetic nerves are critical in the antinatriuretic response to air stress in SHR, since surgical renal denervation completely abolishes the antinatriuresis (Lundin and Thoren, 1982; Koepke and DiBona, 1985b). The importance of the central nervous system in the renal response to air stress is further shown in SHR on a high sodium intake for 15 days. In these SHR, the renal sympathetic nerve activity and antinatriuretic responses to air stress are enhanced, indicating facilitation of central nervous system neurotransmission (Koepke and DiBona, 1985b). Hence, environmental stress can increase renal tubular reabsorption of sodium via a central nervous system-mediated increase in renal sympathetic nerve activity.

The posterior hypothalamus is an important central nervous system area for blood pressure control and the pathophysiology of hypertension. Electrical stimulation of the posterior hypothalamus increases blood pressure, abdominal sympathetic nerve activity, and renal vasoconstriction to a greater degree in conscious SHR than normotensive control rats (Takeda and Bunag, 1978; Berecek and Brody, 1982). The pressor response to electrical stimulation of the posterior hypothalamus in cats is reduced by \( \beta \)-adrenoceptor blockade (\( d,l \)-propranolol) and enhanced by \( \beta \)-adrenoceptor stimulation (isoproterenol) in the posterior hypothalamus (Phillipu and Stroehl, 1978). Moreover, the development of hypertension in SHR is associated with a greater noradrenergic/cholinergic imbalance in the posterior hypothalamus of SHR compared to WKY (Winteritz et al., 1984). Furthermore, electrolytic lesion of the posterior hypothalamus lowers blood pressure in SHR (Bunag and Eferakeya, 1976).

An interaction among environmental stress, dietary sodium intake, and genetic predisposition to hypertension has been shown for the neural control of renal function (Koepke, 1985). The increased renal sympathetic nerve activity and antinatriuresis resulting from exposure to air stress is much greater in conscious SHR than in normotensive WKY (Lundin and Thoren, 1982; Koepke and DiBona, 1985b). Thus, a genetic predisposition to develop hypertension may be associated with a predisposition to respond to environmental stress with increased renal sympathetic nerve activity and renal sodium retention. High dietary sodium intake, another environmental factor, enhances the increased renal sympathetic nerve activity and antinatriuretic responses to air stress in conscious SHR, but has no additional effects in WKY (Koepke and DiBona, 1985b). The development of hypertension in SHR is associated with increased renal sodium retention; surgical renal denervation reduces both the hypertension and renal sodium retention (Winteritz, 1980; Beierwaltes et al., 1982). These studies demonstrate the importance of the renal sympathetic nerves and renal sodium retention in the pathogenesis of hypertension in SHR. In addition, long-term exposure to environmental stress increases the severity of hypertension in SHR and produces hypertension in borderline hypertensive rats (crossbred SHR × WKY) (Lawler et al., 1981; Ely and Weigand, 1983). Moreover, high dietary sodium intake exacerbates the hypertension in SHR resulting from environmental stress (Ely and Weigand, 1983). Together, these studies point to the hypothesis that environmental (stress, sodium intake) and genetic factors interact to promote increased renal sympathetic nerve activity and renal sodium retention resulting in hypertension.

An antinatriuresis also results from environmental stress in conscious dogs and humans. In conscious dogs, avoidance stress decreased urinary sodium excretion in 21 of 30 dogs (Koepke et al., 1983b). This antinatriuresis is abolished by surgical renal denervation, indicating that the renal sympathetic nerves mediate the renal excretory response (Koepke et al., 1983b). Moreover, blockade of central nervous system \( \beta \)-adrenoceptors prevents the antinatriuretic response to avoidance stress in conscious dogs (Koepke et al., 1983a). In humans, stressful competitive tasks decrease urinary sodium excretion only if a positive family history of hypertension is present (Light et al., 1983). Thus, environmental stress influences the neural control of renal function not only in conscious SHR, but also in some conscious dogs, and even, perhaps, in humans with a predisposition to hypertension.

This work was supported by National Institutes of Health Grants AM15843, HL14388, and NS07610, and by grants from the American Heart Association-Iowa Affiliate, and the Veterans Administration. Address for reprint: Gerald F. DiBona, M.D., Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, Iowa 52242.

Received September 20, 1985; accepted for publication December 10, 1985.

References


INDEX TERMS: Posterior hypothalamus • Renal function • Conscious rats • Hypertension • Environmental stress • β- and α-Adrenoceptors
Hypothalamic beta 2-adrenoceptor control of renal sympathetic nerve activity and urinary sodium excretion in conscious, spontaneously hypertensive rats.

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Circ Res. 1986;58:241-248
doi: 10.1161/01.RES.58.2.241

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:
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