Role of Anteroventral Third Ventricle and Vasopressin in Renal Response to Stress in Borderline Hypertensive Rats

Daniel C. Hatton, Susan Y. Jones, Alan Kim Johnson, and Gerald F. DiBona

The borderline hypertensive rat is the first filial offspring of the spontaneously hypertensive rat and the Wistar-Kyoto rat. In response to acute environmental stress (air jet), the borderline hypertensive rat exhibits a diuretic response, whereas the parental strains exhibit an antidiuretic response (spontaneously hypertensive rat) or no change in urine flow rate (Wistar-Kyoto rat). This study sought to investigate the role of the periventricular tissue surrounding the anteroventral third ventricle and vasopressin release in the diuretic response of the borderline hypertensive rat to acute environmental stress. Sixteen-week-old borderline hypertensive rats who had consumed a 1% NaCl diet for 10–12 weeks were given either electrolytic lesions of the anteroventral portion of the third ventricle or sham lesions. When exposed to acute environmental stress 4 weeks later, the increase in volume of dilute urine seen in the sham-lesion rats was not observed in the lesion rats. Plasma vasopressin concentration was decreased by acute environmental stress in the sham-lesion rats (15.2±4.0 to 10.9±1.7 pg/ml, p<0.05) but was unchanged in the lesion rats (12.3±2.0 to 13.4±4.0 pg/ml). In a separate group of intact borderline hypertensive rats, a constant intravenous infusion of vasopressin prevented the diuretic response to acute environmental stress. The results suggest that acute environmental stress produces a diuresis in the borderline hypertensive rats via a decrease in plasma vasopressin concentration that is dependent on the integrity of the periventricular tissue of the anteroventral portion of the third ventricle. (Hypertension 1991;17:755-762)
sodium excretion; glomerular filtration rate and renal plasma flow were unchanged, whereas urinary flow rate increased. These responses of BHR to acute environmental stress are similar to those seen in SHR except for the diuretic response of BHR; SHR show an antidiuretic response. The current investigation was performed 1) to examine the effect of AV3V lesions on the ERSNA and renal functional responses to acute environmental stress in BHR, and 2) to define the role of vasopressin in the diuretic response to acute environmental stress in BHR.

Methods

Animals

The BHR were the first-generation offspring of SHR females and WKY males purchased from Taconic Farms, Germantown, N.Y. The rats were weaned at 4 weeks of age. Standard laboratory rat chow and tap water were available to all rats.

Anesthesia

The rats were anesthetized with either a mixture of ketamine (50 mg/kg) and acepromazine (16 mg/kg) for the AV3V lesion or methohexital (Brevital, 20 mg/kg intraperitoneally, supplemented with 10 mg/kg intravenously as needed; Eli Lilly, Indianapolis, Ind.) for the other procedures.

Procedures

Renal denervation. Renal denervation was performed through bilateral flank incisions by stripping the renal arteries and veins of adventitia, cutting the renal nerve bundles, and coating the vessels with a solution of 10% phenol in absolute ethanol. This renal denervation procedure prevents the renal vasoconstrictor response to suprarenal lumbar sympathetic nerve stimulation, prevents the antinatriuretic response to environmental stress, reduces renal catecholamine histofluorescence to nondetectable levels, and reduces renal tissue norepinephrine concentration to less than 5% of control for up to 15 days after denervation.

AV3V lesion. At 12 weeks of age, rats were randomly assigned to either an AV3V-lesion or sham-lesion group. Rats in the lesion group were given electrolytic lesions of the AV3V area. A Kopf stereotaxic instrument (Tujunga, Calif.), was used to place a 24-gauge nichrome wire lesioning electrode on the midline, 0.3 mm caudal to bregma at a depth of 7.5 mm from dura. Direct anodal current of 2-3 mA was passed for 25-30 seconds with a rectal cathode. Sham-AV3V lesion animals received similar treatment, but the electrode was only lowered to a depth of 4 mm, and no current was passed. All AV3V-lesion animals used in these experiments demonstrated initial marked hypodipsia (<10 ml/day water intake) with increased plasma osmolality. They were supported through the early postoperative phase with drinking solutions of progressively lower sucrose concentration (10% to 5%) or 3% dextrose/0.3% saccharin with eventual transition to water. The overall mortality rate was less than 10%.

At the end of each experiment involving AV3V- or sham-lesion BHR, they were perfused through the left ventricle of the heart with isotonic saline until the effluent from an incision in the right ventricle of the heart was clear. Then, approximately 100 ml 10% buffered formalin was infused via the heart. The brain, still encased in the skull, was stored 2-3 days in the 10% buffered formalin before it was removed and cut into 40-μm sections on a cryostat. The brain sections were mounted on a glass slide and stained with cresyl violet. The assessment of the AV3V and sham lesions was determined by an investigator without knowledge of corresponding physiological measures. Previous studies from this laboratory have provided histological verification of AV3V lesions using these coordinates in the BHR.

Chronic catheterization. The rats were instrumented with catheters (Tygon, Fisher Scientific Inc., Chicago, Ill.) in the left carotid artery and jugular vein. The catheters were tunneled to the back of the neck, flushed and filled with heparinized saline (100 units/ml; Elkins-Sinn, Cherry Hill, N.J.), and plugged with stainless steel pins. Through a suprapubic incision, a polyethylene urinary bladder catheter (model PE-240, Fisher), modified from that of Gellai and Valtin, was flanged and sutured into the urinary bladder, exteriorized, and secured by suturing to adjacent muscle, tissue, and skin.

Renal sympathetic nerve activity recording electrode. The left kidney was exposed through a left flank incision by a retroperitoneal approach. With the use of a dissecting microscope (×25), a renal nerve branch from the aortorenal ganglion was isolated and carefully dissected free. The renal nerve branch was then placed on a bipolar platinum wire electrode (Cooner Wire Company, Chatsworth, Calif.). Renal sympathetic nerve activity was amplified (×10,000-50,000) and filtered (low, 30 Hz; high, 3,000 Hz) with a bandpass amplifier (model PS11, Grass Instrument Co., Quincy, Mass.). The amplified and filtered signal was channeled to an oscilloscope (model 5113, Tektronix, Inc., Beaverton, Ore.) and polygraph (Grass model 7DA) 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) and a frequency discharge counter (Scope Raster/Stepper model 140A, W-P Instruments, Inc., New Haven, Conn.). The integrated voltage, frequency discharge, and renal neurogram signals were displayed on the Grass polygraph. The quality of the renal sympathetic nerve activity signal was assessed by its pulse-synchronous rhythmicity and by examining the magnitude of decrease in recorded renal sympathetic nerve activity during sinoaortic baroreceptor loading with an intravenous injection of norepinephrine (3 μg). The minimum acceptable decrease in renal sympathetic nerve activity was 90%, and the average percentage decrease was 95%. The renal sympathetic
nerve activity remaining after maximum inhibition following norepinephrine administration was similar to the background noise observed approximately 30 minutes postmortem; 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 electrode was fixed to the renal nerve branch with a silicone cement (Wacker Sil-Gel 604, Wacker-Chemie, Munich, FRG). The electrode cable was then secured in position by suturing it to the abdominal trunk muscles. Finally, the electrode cable was exteriorized and the flank incision closed in layers.

The surgical success rate for the various procedures was approximately 90% and did not differ between the AV3V- and sham-lesion BHR.

**Experimental Protocols**

**AV3V lesion.** After 10–14 days recovery from AV3V- or sham-lesion surgery, groups of both rats underwent chronic catheterization with or without implantation of a renal sympathetic nerve activity recording electrode. Two to 3 hours after recovery from surgery, rats were placed in rat holders that permit forward and backward movement and collection of steady-state urines. An intravenous infusion (58 μl/min) of isotonic saline containing sufficient quantities of inulin and para-aminohippurate (PAH) for determination of inulin and PAH clearance, respectively, was then started and allowed to continue throughout the experimental protocol. Four to 6 hours after habituation and the start of isotonic saline infusion (6–9 hours after end of surgery), the arterial catheter was flushed and attached to a pressure transducer (model P23Db, Statham, Oxnard, Calif.), and the urinary bladder catheter was led to a collection beaker. After stabilization of urinary flow rate, arterial pressure, and heart rate (approximately 1 hour), the quality of the renal sympathetic nerve activity recording was again tested as above with an intravenous injection of norepinephrine (3 μg) 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, the experiment commenced.

**Intact.** Intact rats underwent chronic catheterization. After recovery from surgery, rats were placed in rat holders as described above. An intravenous infusion (58 μl/min) of isotonic saline containing sufficient arginine vasopressin (Sigma Chemical Co., St. Louis, Mo.) to deliver 143 pg/min was then started and allowed to continue throughout the experimental protocol. Four to 6 hours after habituation and the start of isotonic saline infusion, the arterial catheter was flushed and attached to a pressure transducer (model P23Db, Statham), and the urinary bladder catheter was led to a collection beaker. After stabilization of urinary flow rate, arterial pressure, and heart rate, the experiment commenced.

**Acute environmental stress.** The control period comprised two consecutive 10-minute urine collections. The acute environmental stress was applied for 20 minutes using air jet stress. Air jet stress consisted of an air jet delivered to the top of the rat's head through a tube located 4–5 cm in front of the rat. Repeated applications of air jet stress in the same rat (SHR, Dahl, BHR, or DOCA-NaCl models) result in similar increases in heart rate, mean arterial pressure, and efferent renal sympathetic nerve activity and in decreases in urinary flow rate and sodium excretion.10,11,17-23 Five minutes after the start of air jet stress (air jet stress period), two consecutive 10-minute urine specimens were collected. Five minutes after cessation of air jet stress (recovery period), two consecutive 10-minute urine specimens were collected. Venous blood samples (0.2–0.5 ml) were taken during the midpoint of the control, air jet stress, and recovery periods; the volume removed was replaced with an equal volume of isotonic saline. The quality of the renal sympathetic nerve signals was again assessed as above with intravenous injections of norepinephrine (3 μg) after completion of the protocol. The rat was then killed and postmortem renal sympathetic nerve activity was continuously recorded for 30 minutes as a measure of background noise. The kidneys were removed, decapsulated, drained, and weighed.

**Analytical**

Urine volume was determined gravimetrically. Urine sodium concentration was measured by flame photometry (model 143, Instrumentation Laboratories, Lexington, Mass.). Urine and plasma inulin and PAH concentrations were determined by the anthrone24 and ethylenediamine methods,25 respectively. Plasma and urine osmolality were measured with a vapor pressure osmometer (Wescor, Logan, Utah). Plasma vasopressin concentration was measured with a radioimmunoassay in the Cardiovascular Center Core Laboratories, University of Iowa, Iowa City, Iowa, as previously described.26 Glomerular filtration rate was measured as inulin clearance as follows: $C_{\text{IN}}=(V)(U_{\text{IN}})/P_{\text{IN}}$, where $U_{\text{IN}}$ and $P_{\text{IN}}$ are urine and plasma inulin concentrations, respectively, and $V$ is urine flow rate. Effective renal plasma flow was determined by PAH clearance as follows: $(V)(U_{\text{PAH}})/P_{\text{PAH}}$, where $U_{\text{PAH}}$ and $P_{\text{PAH}}$ are urine and plasma PAH concentrations, respectively.

Heart rate was determined with a linear cardiotachometer (Grass model 7P4) driven by the arterial pressure waveform. Data acquisition was performed with a commercially available software package (Labtech Notebook, version 4.2; Laboratory Technologies Corp., Wilmington, Mass.). Integrated renal sympathetic nerve activity is expressed as integrator resets per minute.

Statistical analyses were conducted with repeated-measures analysis of variance and post hoc comparisons were done using the Newman-Keuls test.27 Statistical significance was defined as $p<0.05$. 

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    - Statistical analyses were conducted with repeated-measures analysis of variance and post hoc comparisons were done using the Newman-Keuls test.27 Statistical significance was defined as $p<0.05$. 

**Results**

**Effects of AV3V Lesion on Responses to Air Jet Stress**

The systemic and renal neural, hemodynamic, and excretory responses to air jet stress in AV3V- and sham-lesion BHR are shown in Figures 1 and 2. Air jet stress produced significant increases in heart rate and mean arterial pressure in both AV3V- and sham-lesion BHR (p<0.05). The increase in heart rate for the AV3V lesion rats was less than that for the sham-lesion rats due to their slightly higher control heart rate. The increases in mean arterial pressure were similar for AV3V- (5 ± 1 mm Hg) and sham-lesion rats (5 ± 1 mm Hg). Air jet stress produced significant increases (p<0.05) in ERSNA (analyzed as either integrator resets per minute or percentage of control) that were not different from each other in both AV3V- and sham-lesion BHR.

While control values for glomerular filtration rate were similar between AV3V- and sham-lesion BHR, control renal plasma flow was significantly less (p<0.05) in AV3V-lesion BHR than in sham-lesion BHR. Air jet stress did not affect glomerular filtration rate, and the downward trends in renal plasma flow did not achieve statistical significance. Air jet stress produced significant decreases (p<0.05) in urinary sodium excretion that were not different from each other in both AV3V- and sham-lesion BHR. Air jet stress produced significant increases (p<0.05) in renal plasma flow in the sham-lesion BHR; this response was abolished in AV3V-lesion BHR. The diuretic response of sham-lesion BHR was associated with a significant reduction (p<0.05) in urinary osmolality, whereas there was no change in urinary osmolality in AV3V-lesion BHR. AV3V-lesion BHR had significantly higher (p<0.05) control plasma osmolality, but stress had no effect on plasma osmolality in either AV3V- or sham-lesion BHR. All variables returned to the control period levels in the recovery period after the cessation of air jet stress.

Data from experiments in which the responses of plasma vasopressin concentration to air jet stress in AV3V- and sham-lesion BHR were measured are shown in Figure 3. These rats were treated similarly to those presented in Figures 1 and 2, but they did not have renal nerve recording electrodes placed and did not receive inulin or PAH. The control values for plasma osmolality were significantly greater in AV3V- than in sham-lesion BHR, whereas the control values for urine flow rate and osmolality were similar. Air jet stress produced significant increases and decreases, respectively, in urine flow rate and urine osmolality in sham-lesion BHR; these responses were abolished by AV3V lesion. Plasma vasopressin concentration decreased significantly from 15.2 ± 4.0 pg/ml during control to 10.9 ± 1.7 pg/ml during air jet stress in sham-lesion BHR but was unchanged in AV3V-lesion BHR (control 12.3 ± 2.0 pg/ml versus air jet stress 13.4 ± 4.0 pg/ml).

Histological examination verified lesion placement in the AV3V-lesion BHR. The damage sustained by the AV3V-lesion BHR was comparable with that observed in several other rat strains as well as BHR, described and documented in numerous reports from our laboratories. Specifically, the typical lesion was confined to the periventricular tissues that surround the most rostral portion of the third ventricle. Included in all lesions were the
ventral lamina terminalis-associated structures lying beneath the anterior commissure (i.e., the ventral region of the median preoptic nucleus and the organum vasculosum of the lamina terminalis). Also consistently ablated were the periventricular preoptic nuclei, which includes the anteroventral periventricular nucleus. Caudally, lesion damage gradually declined and fell off in the periventricular nuclei at the level of the anterior hypothalamus. Laterally, the lesions did not usually extend beyond the medial third of the medial preoptic nucleus. The paraventricular nucleus usually sustained minimal, if any, direct lesion damage, and the supraoptic nucleus was not encroached upon.

**Effect of Vasopressin on Responses to Air Jet Stress**

The effects of a constant intravenous infusion of vasopressin on the responses to air jet stress in intact BHR are shown in Figure 4. These rats were treated similarly to those presented in Figure 3, but they had neither AV3V nor sham lesions. Vasopressin infusion decreased the control values for urine flow rate and increased the control values for urine osmolality in comparison with sham-lesion BHR. Like sham-lesion BHR, these intact BHR infused with vasopressin had an increase in heart rate and mean arterial pressure but no change in plasma osmolality in response to air jet stress. However, vasopressin infusion in these intact BHR prevented the increase in urine flow rate and decrease in urine osmolality seen with air jet stress in sham-lesion BHR.

**Effects of Renal Denervation on Responses to Air Jet Stress**

The effects of chronic (1-week) bilateral renal denervation on the responses to air jet stress in intact BHR are shown in Figure 5. As was observed in sham-lesion BHR, air jet stress produced significant increases in heart rate and mean arterial pressure without alterations in glomerular filtration rate, renal plasma flow, or plasma osmolality. Renal denervation did not affect the increase in urine flow rate and decrease in urine osmolality seen with air jet stress. However, after renal denervation, air jet stress no longer produced an antinatriuretic response. Rather, there was an increase in urinary sodium excretion that probably resulted from the natriuretic effects of the increase in mean arterial pressure being no longer opposed by the antinatriuretic effects of the increase in ERSNA.

**Discussion**

These studies demonstrate that AV3V lesion abolishes the diuretic and urinary dilution response but has no effect on the renal sympathoexcitatory and antinatriuretic responses to acute air jet stress in the BHR. Further, the ability of the AV3V lesion to abolish the diuretic and urinary dilution response to air jet stress is related to an interference with mechanisms that regulate the release of vasopressin.

With respect to the failure of the AV3V lesion to affect the increase in ERSNA during air jet stress, this finding is comparable with that of Sanders et al., who found that the increase in arterial pressure to foot shock was not attenuated by AV3V lesion in BHR. Similarly, the increase in arterial pressure to the air jet stress used herein was not attenuated by AV3V lesion. Thus, the central and peripheral neu-
rohormonal pathways that produce the increases in ERSNA and arterial pressure in BHR during air jet stress do not appear to be critically dependent on the AV3V.

The major differences in response to air jet stress between AV3V- and sham-lesion BHR were in urine flow rate and urine osmolality (Figure 2). There was a pronounced diuresis of dilute urine in the sham-lesion BHR that was not present in the AV3V-lesion BHR. It seems unlikely that the diuresis was caused by increased arterial pressure because the arterial pressure response to air jet stress was similar in the two groups. The pattern of a rise in urine flow rate and a decrease in urine osmolality with stable glomerular filtration rate suggests that a reduction in plasma vasopressin concentration mediated the diuretic response. The experiments in which plasma vasopressin concentration was fixed at an increased level by constant infusion of vasopressin in intact BHR provide evidence in support of this suggestion. When plasma vasopressin concentration was unable to be decreased during air jet stress, urine flow rate did not increase and urine osmolality did not decrease (Figure 4). Measurement of plasma vasopressin concentration in AV3V- and sham-lesion BHR demonstrated that air jet stress decreased plasma vasopressin concentration in association with a diuresis of dilute urine in sham-lesion BHR, whereas there was no change in plasma vasopressin concentration, urine flow rate, or urine osmolality in AV3V-lesion BHR (Figure 3). These results support the view that air jet stress produces a diuresis of dilute urine in BHR via a decrease in plasma vasopressin concentration that is dependent on an intact AV3V. These results indicate that the AV3V is critically involved in the regulation of plasma vasopressin concentration in the BHR. These results are in agreement with extensive previous studies demonstrating that abnormal regulation of vasopressin is the principal determinant of the hydromineral disturbance observed in rats and dogs with AV3V lesions.

Acute environmental stress is known to cause an inhibition of vasopressin release and an increase in urine flow rate. In rats, immobilization stress caused a biphasic response of plasma vasopressin concentration with an early increase followed by a prolonged decrease. Accordingly, urine flow rate was initially decreased, but with the prolonged reduction in plasma vasopressin concentration there was a substantial increase in urine flow rate. In another study with rats, classical conditioning was found to cause a suppression of shock-induced vasopressin release. In NaCl-loaded dogs, Anderson et al reported the development of polyuria during avoidance training that may have been related to inhibition of vasopressin release in addition to increased arterial pressure.

While these results are consonant with stress-induced inhibition of vasopressin release and increased urine flow rate, it should be pointed out that there are other reports of either no change or increased vasopressin release in response to stress. Koepke et al reported antidiuresis and increased plasma vasopressin concentration with avoidance training in dogs. Likewise, Onaka et al observed an increase in plasma vasopressin concentration to foot shock. On the other hand, Knepel et al saw no effect of 5 minutes of intermittent foot shock on plasma vasopressin concentration in rats. Both Hussain et al and Gibbs used a variety of stressors to show variation in stress-induced vasopressin release in rats. Very few of the many stressors used altered plasma vasopressin concentration. Only electric shock, manual restraint, and ether were found to elevate plasma vasopressin concentration significantly above control levels. Other stressors, such as forced swimming, noise, and wheel turning, resulted in no change in plasma vasopressin concentration.

These disparate results led Michajlovskij et al to propose that emotional stress or fear may cause an inhibition of vasopressin release, whereas physical stressors may cause an increase in vasopressin release. Stress may activate several mechanisms known to be inhibitory to vasopressin release; one of these is β-endorphin. Kneipel et al have shown that β-endorphin activity is elevated during intermittent foot shock and that use of opioid antagonists results in an increase in plasma vasopressin concentration. Similarly, Kapusta et al have shown that administration of κ-opioid agonists results in a profound diuresis.
independent of alterations in renal sympathetic nerve activity.

It has been previously demonstrated that AV3V-lesion rats, despite having normal amounts of vasopressin in the posterior pituitary, have a decreased plasma vasopressin concentration and an impaired release of vasopressin in response to dehydration. In the current studies, the control plasma vasopressin concentration of the AV3V-lesion BHR was less than that of the sham-lesion BHR despite a higher plasma osmolality. Thus, in response to a greater osmotic stimulus, AV3V-lesion BHR were unable to appropriately increase plasma vasopressin concentration. Because AV3V lesion results chronically in a decrease in blood volume (average, 10%), the plasma vasopressin concentration response to an osmotic stimulus would be expected to be even greater. Using equations for the rat that correlate the plasma vasopressin concentration response with plasma osmolality during various degrees of acute blood volume depletion, it can be calculated that, at the plasma osmolality of 315 mosm/kg found in AV3V-lesion BHR, the plasma vasopressin concentration should have been 23 pg/ml for no blood volume depletion, 40 pg/ml for a small amount of blood volume depletion (average, 6%), and 63 pg/ml for a large amount of blood volume depletion (average, 15%). The observed value was 12.2 pg/ml, which further demonstrates that AV3V lesion produces a chronic impairment in vasopressin release in BHR. Although the current experiments relate to a state of chronic adapted hypovolemia rather than acute blood volume depletion, it seems clear the plasma vasopressin concentrations are lower than expected for the plasma osmolality, particularly with accompanying blood volume depletion.

The current studies provide evidence that, in addition to an impaired ability to increase vasopressin release, AV3V lesion also produces impaired ability to decrease vasopressin release and effect a diuresis. In response to air jet stress, sham-lesion BHR decreased plasma vasopressin concentration, whereas AV3V-lesion BHR exhibited no change in plasma vasopressin concentration. Thus, AV3V lesion results in a situation where control plasma vasopressin concentration is less than that found in sham-lesion rats (especially when referenced to the stimulus of an increase in control plasma osmolality) and exhibits impaired responsiveness to maneuvers that normally increase or decrease it. Therefore, these studies support the view that the AV3V appears to be necessary for normal regulation of vasopressin release and plasma vasopressin concentration.

The ERSNA and renal excretory responses to air jet stress reveal important differences in mechanisms governing renal sodium and water handling between SHR and BHR. In the SHR, air jet stress produces an increase in ERSNA with a decrease in urine flow rate and sodium excretion; prior renal denervation abolishes the antidiuretic and antinatriuretic responses to air jet stress. In the BHR, air jet stress produces an increase in ERSNA with an increase in the flow rate of dilute urine and a decrease in urine sodium excretion (Figures 1 and 2). Prior renal denervation abolished the antinatriuretic response but does not affect the diuretic response to air jet stress (Figure 5). The diuretic response is abolished by interventions that prevent the decrease in plasma vasopressin concentration (Figures 3 and 4).

In summary, AV3V lesion abolishes the diuretic and urinary dilution response seen during acute environmental stress in BHR through interference with mechanisms involving the regulation of plasma vasopressin secretion. However, AV3V lesion does not impair the increase in arterial pressure and ERSNA or the decrease in urine sodium excretion seen during acute environmental stress in BHR. These results emphasize the multiplicity of neurohormonal pathways capable of exerting regulatory influence on renal sodium and water handling that are activated by acute environmental stress.


**KEY WORDS** • kidney • renal nerves • sodium • water • vasopressin • hypertension
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