Aldosterone acts centrally to increase brain renin-angiotensin system activity and oxidative stress in normal rats

Zhi-Hua Zhang,1 Yang Yu,1 Yu-Ming Kang,1 Shun-Guang Wei,1 and Robert B. Felder1,2
1Department of Internal Medicine, Roy J. and Lucille A. Carver College of Medicine, University of Iowa; and Department of 2Veterans Affairs Medical Center, Iowa City, Iowa

Submitted 29 September 2007; accepted in final form 27 December 2007

Aldosterone acts centrally to increase brain renin-angiotensin system activity and oxidative stress in normal rats. Am J Physiol Heart Circ Physiol 294: H1067–H1074, 2008. First published December 27, 2007; doi:10.1152/ajpheart.01131.2007.—Aldosterone acts upon mineralocorticoid receptors in the brain to increase blood pressure and sympathetic nerve activity, but the mechanisms are still poorly understood. We hypothesized that aldosterone increases sympathetic nerve activity by upregulating the renin-angiotensin system (RAS) and oxidative stress in the brain, as it does in peripheral tissues. In Sprague-Dawley rats, aldosterone (Aldo) or vehicle (Veh) was infused for 1 wk via an intracerebroventricular (ICV) cannula, while RU-28318 (selective mineralocorticoid receptor antagonist), Tempol (superoxide dismutase mimetic), losartan (angiotensin II type 1 receptor (AT1R) antagonist), or Veh was infused simultaneously via a second ICV cannula. After 1 wk of ICV Aldo, plasma norepinephrine was increased and mean arterial pressure was slightly elevated, but heart rate was unchanged. These effects were ameliorated by ICV infusion of RU-28318, Tempol or losartan. Aldo increased expression of AT1R and angiotensin-converting enzyme (ACE) mRNA in hypothalamic tissue. RU-28318 minimized and Tempol prevented the increase in AT1R mRNA; RU-28318 prevented the increase in ACE mRNA. Losartan had no effect on AT1R or ACE mRNA. Immunohistochemistry revealed Aldo-induced increases in dihydroethidium staining (indicating oxidative stress) and Fra-like activity (indicating neuronal excitation) in neurons of the hypothalamic paraventricular nucleus (PVN); RU-28318 prevented the increases in superoxide and Fra-like activity in PVN; Tempol and losartan minimized these effects. Acute ICV infusions of sarthran (AT1R antagonist) or Tempol produced greater sympathoinhibition in Aldo-treated than in Veh-treated rats. Thus aldosterone upregulates key elements of brain RAS and induces oxidative stress in the hypothalamus. Aldosterone may increase sympathetic nerve activity by these mechanisms.

Address for reprint requests and other correspondence: R. B. Felder, Univ. of Iowa College of Medicine, E318-GH, 200 Hawkins Dr., Iowa City, IA 52242 (e-mail: robert-felder@uiowa.edu).

http://www.ajpheart.org H1067
samples were separated and stored at 

Trunk blood was collected in chilled EDTA tubes, and plasma studies, rats were deeply anesthetized with urethane (2.0 g/kg ip). The tissue was processed for mRNA expression of ACE and AT1R, as of the mammillary bodies as the posterior limit, and the lateral posterior part of the optic chiasm as the anterior limit, the anterior part (MAP) and HR were derived from the AP tracing. MAP and HR data Plus computer interface coupled with a personal computer. Mean AP chart recorder was fed into an online data-acquisition system consist-

record and monitor AP with a Hewlett-Packard 7754A chart recorder collection. The femoral artery cannula was flushed with 0.1 ml Rats were put in a small cage and allowed 20 min to adapt before data

back of the neck. When not in use, the cannula was plugged with a stainless steel obturator. Buprenorphine (0.03 mg/kg sc) was adminis-

tered immediately after surgery for management of postoperative pain.

**Drugs Infused**

Aldosterone, sarthran, Tempol, and RU-28318 were purchased from Sigma-Aldrich (St. Louis, MO), and losartan was obtained from DuPont Pharmaceuticals (Wilmington, DE). All drugs were dissolved in artificial cerebrospinal fluid. The doses of aldosterone (22.5 ng in 0.5 μl/h), Tempol (25 μg in 0.5 μl/h), losartan, and RU-28318 (1 μg in 0.5 μl/h) for continuous intracerebroventricular (ICV) infusion were derived from previous reports (5, 15, 18, 19, 26, 49). Previous studies have reported that the dose of aldosterone used here, when given centrally, has no effect on plasma electrolytes (37, 49) or aldosterone (37). It is substantially lower than the doses of aldosterone that induce hypertension when given peripherally (21). The dose of RU-28318 used here blocks the hypertension induced by chronic systemic infusion of aldosterone when given centrally but not when given peripherally (18).

**Hemodynamic Measurements**

Arterial pressure (AP) and heart rate (HR) were sampled every other day at the same time of day (9:00 a.m.–1:00 p.m.) for 1 wk during the ICV infusion of drug(s) or vehicle (artificial cerebrospinal fluid). Rats were put in a small cage and allowed 20 min to adapt before data collection. The femoral artery cannula was flushed with 0.1 ml heparinized saline (50 U/ml) and connected to a pressure transducer to record and monitor AP with a Hewlett-Packard 7754A chart recorder (HP Medical Products Group, Andover, MA). The AP signal from the chart recorder was fed into an online data-acquisition system consisting of a Cambridge Electronics Design (CED, Cambridge, UK) 1401 Plus computer interface coupled with a personal computer. Mean AP (MAP) and HR were derived from the AP tracing. MAP and HR data were collected for 30 min and averaged.

**Study Groups**

After 1 wk of ICV drug or vehicle infusion, rats were assigned to one of four study groups.

*Group 1.* To collect blood and hypothalamic tissue for molecular studies, rats were deeply anesthetized with urethane (2.0 g/kg ip). Trunk blood was collected in chilled EDTA tubes, and plasma samples were separated and stored at −80°C until assayed for nor-

epinephrine (NE) levels. The hypothalamus was removed using the posterior part of the optic chiasm as the anterior limit, the anterior part of the mammillary bodies as the posterior limit, and the lateral hypothalamic sulci as the lateral limits, as described previously (12). The tissue was processed for mRNA expression of ACE and AT1R, as described previously (51, 53). Collection of blood and hypothalamic tissue was completed within 5 min after induction of anesthesia.

*Group 2.* To collect PVN tissue for immunohistochemical studies, rats were deeply anesthetized with urethane (2.0 g/kg ip) and tran-

cordially perfused with 4% paraformaldehyde in 0.1 M PBS. Brains were removed and kept in the fixative for a further 12 h, then transferred to 30% sucrose in 0.1 M PBS overnight. The fixed forebrain region containing PVN was sliced into 16-μm coronal sections with a cryostat. Sections were mounted on the slides and stored at −80°C for later immunohistochemical studies. These studies examined the degree of chronic neuronal excitation in PVN.

*Group 3.* To collect PVN tissue for in situ detection of superoxide production, rats were deeply anesthetized with urethane (2.0 g/kg ip). The brain was removed and immediately frozen at −80°C for 1 h, blocked in the coronal plane, and sectioned into 30-μm slices with a cryostat for dihydroethidium (DHE) staining.

*Group 4.* For terminal electrophysiological studies, rats were anesthetized with urethane (1.5 g/kg ip, supplemented as necessary by 0.1 to 0.3 g/kg iv) and prepared for hemodynamic and sympathetic recordings at baseline and during acute ICV administration of sarthran, an AT1R antagonist, and Tempol, a superoxide dismutase mimic.

**Molecular Measurements**

Detection of hypothalamic mRNA expression of AT1R and ACE with real-time PCR. Total RNA was reverse-transcribed into cDNA, and 50 ng of RNA equivalent of cDNA were taken for a PCR reaction. The sequences for primers and probes used were as follows: AT1R, forward primer, 5′-GTAGCCAAAGTCACCTGCATCA-3′; reverse primer, 5′-GGTAGATGACGCGTCGCAAA-3′; probe, 5′-CATCT-

GGCTAATGGCTGGCTTGGC-3′; and ACE: forward primer, 5′-

GGAGACGACTTACGTGATGCC-3′; reverse primer, 5′-CA-

CACCCAAAGCATTCTTT-3′; probe, 5′-AATGGCCAAGTC-

CCGGAAAT-3′. Primers and probe for GAPDH were purchased from Applied Biosystems (Foster City, CA). Real-time PCR was performed using the ABI Prism 7000 Sequence Detection System (Applied Biosystems). The final results of real-time PCR were ex-

pressed as the ratio of mRNA of interest to GAPDH.

**Measurement of plasma NE by ELISA.** Plasma NE was measured using high-sensitivity ELISA kits (Rocky Mountain Diagnostics, Colorado Springs, CO) as previously reported (51). The minimum detectable concentration of NE is 2.7 pg/ml.

**Immunofluorescent and Immunohistochemical Studies**

Detection of superoxide in PVN. Superoxide generation was deter-

mined in the sections at the level of the PVN by fluorescent-labeled DHE (2 μmol/l, Molecular Probes, Eugene, OR) staining for 30 min at 37°C in a light-protected humidified chamber, as previously de-

scribed (34). Images were visualized with laser confocal microscopy and analyzed with National Institutes of Health (NIH) image software. Fluorescent intensity in dorsal parvocellular, ventrolateral parvocel-

lular, and magnocellular subregions of PVN was analyzed separately by examining tissue within a window superimposed over each region of interest. The subregions of PVN were defined as described in a previous study by others (44).

Detection of Fra-like activity in PVN. Brain sections were pro-

cessed for Fra-like (Fra-LI, fos family gene) activity using the avidin-

biotin-peroxidase complex (ABC kit, PK-6101, Vector, Burlingame, CA) technique, as previously described (28, 51, 53). The sections were incubated for 24 h at 4°C with a rabbit anti-rat polycyclonal anti-Fos antibody (K-25, 1:2,000, Santa Cruz Biotechnology, Santa Cruz, CA). Sections were incubated with the secondary antibody (1:5,000, biotinylated anti-rabbit IgG, PK-6101, Vector) for 4 h at room temperature. The Fra-LI-positive neurons were colored with DAB kit (SK-4100, Vector). In each animal, Fra-LI-positive neurons within a window superimposed over dorsal parvocellular, ventrolat-

eral parvocellular, and magnocellular subregions of PVN were counted manually in two representative 16-μm transverse sections approximately −1.80 mm from bregma and were averaged to obtain a value for data analysis.

**Electrophysiological Recordings**

Recording sessions began at least an hour after completion of the surgical preparation. AP, HR, and renal sympathetic nerve activity (RSNA) were recorded at baseline and during bolus ICV injections of sarthran (20, 40, and 80 μg) and ICV infusion of Tempol (16.6
A previously implanted cannula was used for ICV drug administration. The general methods for recording and data analysis have been described previously (55, 56). At the end of each experiment, the net value of renal nerve activity was determined by subtracting the background noise recorded after injection of the ganglion blocker hexamethonium (30 mg/kg iv) from baseline MAP, HR, and RSNA immediately preceding an experimental intervention was used as a control for peak responses to drug injections, averaged over 1-min intervals. Absolute values were used to calculate the changes in MAP and HR, and a percent change from baseline was used to calculate changes in integrated RSNA.

Statistical Analysis

All data are expressed as means ± SE. For the physiological studies, the significance of differences within groups (peak response vs. baseline) and interactions among groups (treated vs. untreated) was analyzed using repeated-measures ANOVA followed by multiple comparison with a post hoc Tukey test. For other unpaired data, a Student’s t-test was used for comparison between groups. A probability value of $P < 0.05$ was considered to be statistically significant.

RESULTS

Peripheral Responses to Central Aldosterone Infusion

Rats receiving aldosterone + vehicle (Aldo + Veh) had a small but significant ($P < 0.05$) increase in MAP (7.5 ± 2.7 mmHg) at day 7 compared with rats receiving Veh alone (Fig. 1A). HR was not affected. MAP and HR did not differ in rats treated with Aldo + RU-28318, Aldo + Tempol, Aldo + losartan, or Veh. Plasma NE increased significantly ($P < 0.05$) in rats treated with Aldo + Veh (258.5 ± 8.4 pg/ml) compared with Veh alone (187.2 ± 7.5 pg/ml) (Fig. 1B). The increase in plasma NE was abrogated ($P < 0.05$ vs. Aldo + Veh) in rats treated with Aldo + RU-28318 (204.6 ± 6.7 pg/ml) and Aldo + Tempol (208.5 ± 7.7 pg/ml) and minimized in rats treated with Aldo + losartan (216.1 ± 7.4 pg/ml).

Effects of Central Aldosterone on AT1R and ACE mRNA in Hypothalamus

Rats receiving Aldo + Veh had significantly ($P < 0.05$) higher hypothalamic AT1R (+117%) and ACE (+34%) mRNA compared with rats receiving Veh alone (Fig. 2). Rats receiving Aldo + RU-28318 had significantly ($P < 0.05$) lower hypothalamic AT1R and ACE mRNA compared with rats receiving Aldo + Veh. ACE mRNA expression was normalized. Rats receiving Aldo + Tempol had significantly ($P < 0.05$) lower hypothalamic AT1R mRNA than rats receiving Aldo + Veh. AT1R mRNA was normalized, but ACE mRNA expression was not affected. Hypothalamic AT1R and ACE mRNA were similar in rats receiving Aldo + losartan and rats receiving Aldo + Veh.

![Fig. 1. A: hemodynamic effect of simultaneous intracerebroventricular (ICV) infusion of aldosterone (Aldo; 22.5 ng/h) and ICV vehicle (Veh), RU-28318 (mineralocorticoid receptor antagonist, 1 μg/h), Tempol (a membrane-permeable superoxide dismutase mimetic, 25 μg/h), or losartan [ANG II type 1 receptor (AT1R) antagonist, 2.5 μg/h] on mean arterial blood pressure (MAP) and heart rate [HR, in beats/min (bpm)] in conscious rats. B: grouped data showing plasma level of norepinephrine (NE) after 1 wk of ICV Aldo infusion with concomitant infusion of Veh, RU-28318, Tempol, or losartan. Values are expressed as means ± SE. *$P < 0.01$ vs. Veh; †$P < 0.05$ vs. Aldo + Veh; n, number of animals.](http://ajpheart.physiology.org/)

![Fig. 2. Real-time PCR analysis of hypothalamic tissue mRNA expression of AT1R (A) and angiotensin-converting enzyme (ACE; B) in rats centrally infused with Veh, Aldo + Veh, Aldo + RU-28318, Aldo + Tempol, or Aldo + losartan for 1 wk. *$P < 0.05$ vs. Veh; †$P < 0.05$ vs. Aldo + Veh; n, number of animals.](http://ajpheart.physiology.org/)
Effects of Central Aldosterone on Superoxide Production in PVN

When compared with rats receiving Veh alone, rats receiving Aldo + Veh had a significant ($P < 0.05$) increase in superoxide production in all three regions of PVN that were examined, as indicated by the intensity of DHE staining (Fig. 3). In rats receiving Aldo + RU-28318, DHE staining in PVN was no different from that in Veh-treated rats. Rats receiving Aldo + Tempol and Aldo + losartan had more ($P < 0.05$) DHE staining in all examined regions of PVN than rats treated with Veh alone but significantly ($P < 0.05$) less than rats receiving Aldo + Veh (Fig. 3).

Effects of Central Aldosterone on Neuronal Excitation in PVN

Fra-LI activity increased significantly ($P < 0.05$) in neurons throughout the PVN in rats receiving Aldo + Veh compared with rats receiving Veh alone (Fig. 4). Areas outside PVN, at the same stereotaxic level, had scattered Fra-LI expression. However, there was no difference in these areas between Aldo + Veh and Veh-treated rats. There was no difference in Fra-LI activity between rats treated with Aldo + RU-28318 and Veh alone. Rats treated with Aldo + Tempol and Aldo + losartan had significantly ($P < 0.05$) less Fra-like activity than the Aldo + Veh rats in all regions examined but still more than the rats treated with Veh alone (Fig. 4).
Contribution of Central AT1R and Superoxide to Aldosterone-Induced Increases in Sympathetic Activity

There was a nonsignificant (P > 0.05) trend toward higher baseline HR (355.4 ± 7.4 vs. 339.5 ± 7.1 beats/min), RSNA (11.7 ± 1.3 vs. 10.4 ± 1.4 mV), and MAP (102.4 ± 2.2 vs. 98.9 ± 2.4 mmHg) in anesthetized Aldo + Veh versus Veh-treated rats. A bolus ICV injection of the AT1R antagonist sarthran decreased HR, RSNA, and MAP in a dose-dependent manner in both Aldo + Veh- and Veh-treated rats (Fig. 5A). However, the responses to acute ICV injections of sarthran were substantially (P < 0.05) larger in rats that had received Aldo + Veh than in rats that had received Veh alone (Fig. 5B). The responses began immediately and peaked ~5 min after injection, with a duration of ~10–15 min, depending on the dose. A 30-min ICV infusion of Tempol gradually reduced HR, RSNA, and MAP in both groups, but the responses were larger (P < 0.05) in Aldo + Veh rats compared with Veh-treated rats (Fig. 6).

DISCUSSION

This study demonstrates for the first time that aldosterone acts upon mineralocorticoid receptors within the brain to up-regulate the brain RAS and induces oxidative stress in a key cardiovascular regulatory region of the brain. These effects may account for much of the central influence of aldosterone on sympathetic drive.

It has been known for many years that the systemic infusion of aldosterone increases sympathetic nerve activity and induces hypertension (16, 20) and that these effects are mediated by mineralocorticoid receptors located within the central nervous system. How this occurs has remained a mystery, since mineralocorticoid receptors are located intracellularly and mediate their effects—at least those effects that can be blocked by traditional mineralocorticoid receptor antagonists—primarily via gene transcription. Previous in vitro studies have shown that aldosterone increases local tissue RAS activity (22, 38, 46, 50). Similarly, in the present in vivo study, a central infusion of aldosterone increased mRNA for ACE and AT1R in hypothalamic tissue. Prior work by others has suggested that such a mechanism might exist in brain tissue. Thus aldosterone up-regulates the expression of ouabain-like compounds in the hypothalamus (25, 26), and an increase in ouabain-like compounds increases ACE and AT1R binding densities in PVN.

Fig. 5. A: representative recordings showing responses of HR, renal sympathetic nerve activity (RSNA), and arterial pressure (AP) to ICV bolus injection of increasing doses of sarthran in Aldo- and Veh-treated rats. B: grouped data showing dose-dependent reductions in HR, RSNA, and MAP in Aldo-treated rats (black bars, n = 7) compared with Veh-treated rats (hatched bars, n = 7). *P < 0.01 vs. baseline; †P < 0.01 vs. Veh treated.
An intermediary role for ouabain-like compounds was not investigated in the present study.

A molecular marker of increased brain RAS activity, and a potential mechanism to explain aldosterone-induced increases in sympathetic nerve activity, is the increased superoxide production in the paraventricular nucleus. ANG II activates NAD(P)H oxidase to generate reactive oxygen species (15, 27), and increased superoxide production is clearly associated with increased sympathetic drive in pathophysiological states like heart failure (15, 30, 58, 59) and hypertension (5–7, 24, 36, 43). In the present study, DHE staining for superoxide was less in the rats that received losartan along with aldosterone, blocking the effects of ANG II on the AT1R. However, the mineralocorticoid receptor antagonist RU-28318 was even more effective than losartan in reducing the DHE staining in PVN induced by the aldosterone infusion. Both findings are consistent with the view that superoxide production in this region of the brain is largely dependent on ANG II-induced NAD(P)H oxidase activity: as shown here, aldosterone upregulates expression of ACE mRNA, presumably promoting the production of ANG II, as well as mRNA expression of the AT1R that mediates the effects of ANG II. Moreover, aldosterone is known to upregulate the binding of ANG II to AT1R receptors (38, 42). On the other hand, aldosterone may increase NAD(P)H oxidase activity independently (4), and the greater inhibition of superoxide production by RU-28318 than losartan suggests an independent aldosterone effect. However, the methods employed in this study cannot convincingly differentiate between a direct aldosterone-induced superoxide production versus an indirect aldosterone-facilitated ANG II-induced superoxide production. Both mechanisms may contribute to aldosterone-induced oxidative stress.

The immunohistochemical and electrophysiological studies strongly support a role for the paraventricular nucleus in mediating the sympathetic responses to aldosterone. The central infusion of aldosterone increases the expression of ACE and AT1R mRNA and superoxide production in this region of the brain, exciting neurons in a general way but also specifically affecting neurons in the ventrolateral area where presympathetic neurons are located. Concomitantly, circulating NE is increased along with MAP. All of these findings are minimized in rats receiving RU-28318 along with aldosterone. Thus, at least in this representative presympathetic region of the brain, aldosterone acts in a manner wholly consistent with the hypothesis that it increases sympathetic nervous system activity by upregulating the brain RAS. Other presympathetic regions like the rostral ventrolateral medulla, though not examined in this study, may be similarly affected.

Finally, the electrophysiological studies provide functional support for the hypothesis that aldosterone increases sympathetic nerve activity by upregulating brain RAS activity and superoxide production. Chronic administration of losartan did not prevent the increased ACE or AT1R mRNA expression induced by the chronic ICV infusion of aldosterone but did

---

Fig. 6. A: representative recordings showing responses of HR, RSNA, and AP to continuous ICV infusion of Tempol in Aldo- and Veh-treated rat. B: grouped data showing decreases in HR, RSNA, and MAP in Aldo- compared with Veh-treated rats. *P < 0.01 vs. baseline; †P < 0.01 vs. Veh treated; n, number of animals.
prevent the increase in MAP induced by aldosterone without affecting heart rate. However, acute ICV administration of the AT\textsubscript{1}R antagonist sarthran had a dramatic dose-dependent effect on RSNA, HR, and AP in the rats treated chronically with ICV Aldo + Veh, compared with the rats treated with vehicle alone. Similar responses were observed when Tempol was administered acutely ICV to counter the effects of reactive oxygen species. These studies clearly demonstrate that upregulation of the brain RAS and reactive oxygen species plays a major role in supporting the arterial pressure in aldosterone infused rats. They also confirm that the changes in brain renin-angiotensin arterial pressure and superoxide production are causative factors to, rather than responses to, the aldosterone-induced increase in arterial pressure.

This study was performed in normal rats to examine the effects of central aldosterone on brain RAS in the absence of other factors that are usually operative in high aldosterone states and might have similar effects. In hypertension and heart failure, changes in circulating and brain tissue concentrations of other neurochemical substances (10, 31, 59, 61), changes in input from cardiovascular sensory receptors (14, 59, 60), and changes in sodium chloride consumption (25, 57) may all affect the activity of the brain RAS. However, these observations in normal rats have important implications for the pathophysiology of high renin states. Previous work has demonstrated that aldosterone appears in the brain in proportion to circulating levels in normal rats (17) and is increased in the brain in rats with heart failure (52). The present study adds the important new observation that, upon entering the brain, aldosterone can upregulate the brain RAS and increase superoxide production. This mechanism likely contributes to the increased sympathetic nerve activity typical of high renin states.

Limitations of the Study

The NE measurements used as a surrogate indicator of sympathetic drive were obtained after the administration of urethane anesthesia, which reduces basal sympathetic drive (32) as well as the sympathetic response to the stress associated with collecting brain tissues (39). Although blood and tissues were obtained very soon after induction of anesthesia, the effects of anesthesia and stress may have altered our results. Nevertheless, all groups were subjected to the same procedures, and yet we observed an increase in plasma NE in the aldosterone-infused rats that was minimized in a predictable manner by all three of our treatment interventions. Thus, in contrast to a previous study (37), the present study suggests that central infusion of this dose of aldosterone increases circulating NE. A potential consequence is that renal renin release and circulating ANG II, not measured in this study, might also be increased and that circulating ANG II might contribute to the upregulation of the brain RAS indirectly via effects on circumventricular organs. Arguing against that hypothesis is the finding that mRNA for ACE and AT\textsubscript{1}R were substantially reduced by chronic central administration of the mineralocorticoid receptor antagonist but unaffected by chronic central administration of the AT\textsubscript{1}R antagonist.

Perspectives

Activity of the brain RAS is upregulated in heart failure and some forms of hypertension. It is generally believed that increased production of ANG II leads to NAD(P)H-dependent generation of reactive oxygen species in critical presym pathetic regions of the brain, resulting in increased sympathetic discharge that further compromises cardiovascular function. However, the factors driving upregulation of the brain RAS under these conditions have not been identified. The present study suggests that aldosterone plays such a role. Aldosterone is released from the adrenal gland in response to blood-borne ANG II, crosses the blood-brain barrier in proportion to plasma levels (17, 52), and, as shown here, increases the expression of key components of the brain RAS. Thus either reducing the synthesis (11) and release of aldosterone from the adrenal glands or blocking its central effects may reduce the augmented brain RAS activity that leads to increased sympathetic drive in hypertension and heart failure.

GRANTS

This work was supported by the American Heart Association Grant-in-Aid 0750164Z, a Department of Veterans Affairs Merit Review Award; the National Heart, Lung, and Blood Institute Grant ROI-HL-0073986 and an institutional fund for the University of Iowa.

REFERENCES


Lignification: ALDOSTERONE AND OXIDATIVE STRESS IN RAT BRAIN