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The cardiovascular response of normal rats to dual lesion of the subfornical organ and area postrema at rest and to chronic losartan

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Abstract

The subfornical organ (SFO) and the area postrema (AP), two of the sensory circumventricular organs (CVO), are known to play a role in the chronic central control of blood pressure. In previous studies in which these regions were independently lesioned, the chronic hypotensive effects of the AT₁ receptor blocker losartan (10mg/kg/day) were attenuated by ~15mmHg. In the present study, we sought to investigate the effect of concurrent lesion of both the SFO and the AP on the cardiovascular effects of chronic losartan infusion in order to test the hypothesis that a greater attenuation of the hypotensive effects of losartan would be observed in rats with dual lesions. To do so, arterial pressure and heart rate responses to 10 day infusion of losartan were compared in sham rats and those with dual lesions of the AP and SFO. Two important findings resulted from this study. First, dual lesion rats exhibited a sustained and significant decrease in resting blood pressure (83 ± 1 mmHg vs. 104 ± 1 mmHg, respectively) and heart rate (356 ± 3 bpm vs. 398 ± 6 bpm, respectively) compared to sham animals. Secondly, rats with concurrent lesion of both the AP and the SFO demonstrated a significantly attenuated response to losartan compared to sham animals but showed no greater attenuation of losartan's chronic hypotensive effects than animals with lesion of either the SFO or the AP (~15mmHg). Although these results do not support the stated hypothesis, they do suggest redundancy and compensatory roles of the AP and SFO in basal cardiovascular control.

Keywords

subfornical organ; area postrema; losartan; hypertension

Introduction

The hormone Angiotensin II (AngII) has been well documented as having a prominent role in the regulation of blood pressure and pathogenesis of hypertension, although we still do not fully understand the myriad of effects of this hormone on the central nervous system. However, two of the circumventricular organs (CVO), the subfornical organ (SFO) and the area postrema (AP), have received much attention as regions in the brain central to the regulation of blood pressure and actions of AngII (Simpson, 1981, Fink et al., 1987; Ferguson and Bains, 1997,

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Zimmerman et al., 2004). Both of these CVO are well situated to play important roles in this regard, as they lack the blood/brain barrier (and thus are easily accessible to peptides like AngII), house a dense supply of AT₁ receptors (Phillips et al., 1993; Tsutsumi and Saavedra, 1991), and have been shown to project to major CNS cardiovascular control centers such as the hypothalamic paraventricular nucleus (PVN) and the rostral ventral lateral medulla (RVLM) (Ferguson and Bains, 1996; Johnson and Gross, 1993; Osborn et al., 2007). In fact, by utilizing lesion of either the SFO or AP, we have previously characterized the roles of both of these CVO in the chronic hypertensive effects of AngII (Hendel and Collister, 2005; Nahey and Collister, 2007).

With regard to the effects of endogenous AngII, our lab has consistently shown a profound and slowly developing decrease in blood pressure of approximately 30 mmHg in rats chronically administered the AT₁ antagonist, losartan (10 mg/kg/d IV) (Collister et al., 1996). This suggests a major role of the endogenous RAS in the maintenance and regulation of normal blood pressure, yet we still do not fully understand the mechanism(s) mediating this response. It seemed reasonable that, like the effects of exogenously administered AngII, the chronic hypotensive effects of losartan are similarly mediated in part via CVO, such as the SFO and AP. In that regard, our lab has demonstrated an attenuation of this chronic hypotensive effect of losartan by ~15 mmHg in rats with lesion of either the SFO (Collister and Hendel, 2003) or the AP (Collister and Osborn, 1998).

Interestingly, lesion of either the AP or SFO did not completely abolish the effects of losartan but merely attenuated them. We cannot explain these results solely based on the idea of blockade of AT₁ receptors at a given CVO, as complete removal of CVO AT₁ receptors (via lesion of the CVO) should conceivably have the same effect as CVO AT₁ blockade, and although blood pressure transiently falls in animals with lesion of the AP (Collister and Osborn, 1998), we do not see any long term changes in arterial pressure in animals with lesion of either the SFO (Collister and Hendel, 2003) or the AP (Collister and Osborn, 1998). Indeed, we acknowledge the fact that other (non-AT₁ related) mediators of the RAS such as Ang(1–7) do appear to be playing a role in this chronic response (Collister and Hendel, 2003). However, the possibility remains that there could be redundant pathways involving these CVO, in that either of these CVO could compensate for the loss of the other during chronic AT₁ receptor blockade. We thus hypothesized that under conditions of chronic losartan infusion, rats with dual lesions of both the SFO and the AP would demonstrate a further attenuation, or near abolishment of the hypotensive effects of losartan compared to rats with lesion of either the SFO or the AP. To test this hypothesis, rats underwent sham or SFO/AP co-lesion surgery and MAP and HR responses were continuously measured during 10 days of losartan infusion.

Results

Cardiovascular response to losartan

As shown in figure 1, after dual lesion of the SFO and AP, rats demonstrated a significantly lower baseline MAP and HR compared to sham animals. The effects of chronic losartan treatment on MAP and HR are shown in figure 2. Animals with lesions of both the SFO and AP demonstrated an attenuated hypotensive response to losartan compared to sham animals; by day 2 of losartan infusion, MAP in SFOAPx rats had only decreased 13 ± 1 mmHg while MAP in SFOAPshm rats had decreased by 20 ± 2 mmHg. The difference in this attenuation was found to be significant and continued through the protocol, reaching -22 ± 3 mmHg in SFOAPx and -32 ± 2 mmHg in SFOAPshm rats by day 10 of treatment. When compared to their respective control data, MAP values were found to be significantly different on days 2 – 10 of losartan infusion in SFOAPx rats, and on all days of losartan infusion in SFOAPshm rats (statistics not shown).

With regard to the HR response, no difference was observed between sham and lesion groups during losartan infusion. There were, however, significant differences seen in both groups when comparing values during losartan infusion to baseline values (statistics not shown). Heart rate in SFOAPx rats was significantly higher during losartan than control values on days 2 through 9 of treatment, and in SFOAPshm rats on days 2, 4–6 and 10 of treatment.

Food intake and sodium and water balance responses

Food intake (FI) of both groups is shown in figure 3. Although rats with dual lesions were observed to have eaten less than sham animals throughout the experimental treatment, this difference was not significant, nor was consumption of food within groups altered compared to control values.

Sodium and water data are shown in figure 4 and figure 5, respectively. As expected with a slightly lower FI, the sodium intake (NaI) of SFOAPx rats appeared to be lower than that of sham animals throughout the experimental protocol, but was never statistically significant. Likewise, sodium excretion (NaE) was slightly lower in the SFOAPx group than the sham group on most days of the experimental phase, but again, not significantly. Values were not significantly different from baseline control levels in either group for all Na measurements.

No significant difference was observed in water intake (WI), urine output (UO), nor total water balance (WB) between SFOAPx rats and SFOAPshm rats throughout the protocol. Likewise, values were not significantly different from baseline measurements in either group for all water measurements.

Discussion

Although much evidence has been collected supporting the importance of the central nervous system in the long term control of BP, much has yet to be discovered about this regulatory pathway and its individual components. The present study aimed to provide further insight as to the roles of the SFO and the AP in the neural control of blood pressure by simultaneously removing both areas from the brains of rats and subjecting these rats to chronic infusion of the AT₁-receptor blocker losartan. Based on previous studies showing an attenuation of the hypotensive effects of losartan of ~15 mmHg in animals with lesion of either the SFO (Hendel and Collister, 2005) or the AP (Collister et al., 1996), we hypothesized that the hypotensive effects of losartan in dual lesioned animals (SFOAPx) would be even more attenuated or eliminated than in those with single lesions. The observed results do not support this hypothesis as SFOAPx rats exhibited approximately the same magnitude of attenuation of hypotension in response to chronic losartan as those with lesion of either the SFO or AP alone.

Two important findings were observed in the current study. First, resting MAP and HR were significantly reduced in animals with lesion of both the SFO and AP in contrast to control animals. Second, SFOAPx rats exhibited similar responses to chronic losartan as animals with a sole lesion of either of these structures.

Baseline MAP and HR

Of particular interest in the current study is the observation that SFOAPx rats had significantly lower baseline MAP and HR than sham rats. This sustained “resetting” of baseline pressure and HR has not previously been reported. With regard to the SFO, we and others have never reported altered baseline MAP or HR after lesion of this CVO (Bruner et al., 1985; Collister and Hendel, 2005). In contrast, with regard to the AP, chronic hypotension has been reported in AP lesioned dogs (Ferrario et al., 1979) and Skoog and Mangiapane (1988) showed a significant decrease in MAP for 5 out of the first 7 days post-lesion in rats, although using less

accurate methods of measurement. Similarly, Collister et al. (1996) reported a transient decrease in MAP of ~10mmHg in APx rats for three weeks post-operatively. However, in that study the decrease in MAP in APx rats was similar to that of rats on a food restricted diet (to match the transient decreased food intake typical of APx rats), which alone has been shown to affect basal BP (Curtis et al., 2003). Our lab has since reported no change in baseline MAP in rats with AP lesions after months of recovery (Collister and Osborn, 1998; Collister and Osborn, 1998). Regarding HR, our group has reported a significantly slower HR in APx rats even after 3 months post-lesion surgery (Collister and Osborn, 1998). Skoog and Mangiapane (1988) similarly reported significant bradycardia for 7 days post-AP lesion. This suggests a permanent alteration in autonomic control in APx rats and has been attributed to an increase in vagal tone after destruction of the AP (Skoog and Mangiapane, 1988). Yet even compared to past studies that reported a transient decrease in BP, the drop in basal MAP observed in the current study is of a greater magnitude. It is therefore reasonable to suggest, based on the data from the present study, that baseline input from both the SFO and the AP is necessary for the support of normal chronic basal blood pressure and heart rate levels. This idea is further supported by the observation that dual lesion animals with only partial lesion of the SFO demonstrated baseline MAP levels between that of complete SFOAPx animals and shams (results not shown). Specifically, rats with complete lesion of the AP but with remaining anterior portions of an incompletely lesioned SFO exhibited baseline MAP levels of approximately 10 mmHg lower than sham rats but 10 mmHg higher than SFOAPx rats.

Again, the fact that neither lesion of the SFO nor AP caused long term changes in MAP, while combined lesions produced a large and sustained decrease provides support for not only some redundancy but compensatory function between the two CVO. Double lesion alone greatly reduced MAP in these animals (approximately 20mmHg) while losartan treatment in shams lowered MAP approximately 30mmHg. Ultimately, double lesion plus losartan treatment caused a drop in MAP of 40 mmHg. It is interesting to speculate that perhaps much of the hypotensive actions of losartan are mediated through both the AP and SFO and a majority of this reduction in pressure is seen upon removal of AT₁ receptors from lesion of both CVO. While compelling, this is difficult to explain by the fact that our previous studies showed no long term change in baseline pressure after lesion of either CVO alone. These data would suggest that both CVO are necessary for control of baseline blood pressure, but removal of only one CVO allows for some level of compensation by the other to support arterial pressure, potentially either through angiotensinergic or other hormonal systems, or changes in neural messaging.

Response to losartan

In previous studies, our lab showed an attenuation of the hypotensive effects of losartan of approximately 10 – 15 mmHg in SFOx rats (Collister and Hendel, 2003) and approximately 15 mmHg in APx rats (Collister and Osborn, 1998). A similar magnitude of attenuation was observed in the present study in rats lacking both regions. A 2-factor ANOVA analysis comparing MAP values from our lab's previous SFOx study (during which rats received the exact same treatment) and MAP values from the current SFOAPx study showed no significant difference in the change in MAP between these two groups. (A similar test comparing APx and SFOAPx was not performed due to the fact that MAP measurements in APx rats in the previous study did not employ telemetry). Therefore, SFO and AP co-lesion had no further effect on the attenuated response to losartan than that from SFOx alone.

Lastly as stated, it is notable that animals with dual lesions of the SFO and AP responded with yet a further drop in pressure in response to losartan treatment, suggesting other peripheral system involvement, non-AT₁ mediated explanations, or likely involvement of other areas of central AT₁ blockade. Of these possibilities, we do not suspect that these effects are mediated

peripherally as we have shown that this dose of losartan causes no immediate change in blood pressure, but does completely block the acute vasoconstrictor effects of AngII (Collister et al., 1996). It is likely though that RAS non-AT₁ receptor mediated effects do contribute to the hypotensive response to losartan. For example, some of the anti hypertensive effects of blockade of the RAS have been attributed to the peptide, Ang-(1–7) (Iyer et al., 1998, Iyer et al., 2000). Indeed, we have previously shown that part of the blood pressure lowering effect of losartan is mediated by Ang-(1–7), as the hypotensive response to losartan was attenuated by concomitant administration of the Ang-(1–7) antagonist, A-779 (Collister and Hendel, 2003). Lastly, apart from the pathway discussed here, studies have shown evidence for actions of AngII at AT₁ receptors in the NTS (Tan et al., 2007) and the RVLM (Dampney et al., 2007), and, as losartan can readily cross the blood brain barrier (Li et al., 1993; Wang et al., 2003) and thus access these and other brain sites, it must be considered that observed effects could be mediated through blockade of some of these AT₁ receptors as well that would never be accessible to normal circulating AngII. This potential consequence of receptor blockade behind the blood brain barrier at further integral AT₁ laden sites must not be overlooked and requires further investigation as a potentially contributing factor to the results of the present study.

Experimental procedures

Adult male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) with initial weights between 250 – 300 g were used in all experiments. Throughout the experiments, rats were individually housed in metabolic cages (Harvard Apparatus, Holliston, MA) and kept on a 12 hour light/dark cycle. All procedures were conducted in accordance with institutional and National Institutes of Health guidelines, complied with the Guide for Care and Use of Laboratory Animals (NIH Pub No. 85-22, Revised 1996), and were approved by the Institutional Animal Care and Use Committee of the University of Minnesota.

Surgical procedures

For all surgeries, rats were preanesthetized with pentobarbital (32.5 mg/kg, IP) and atropine (0.2 mg/kg IP), and surgical anesthesia was achieved with a second intramuscular injection containing a combination of anesthetic agents (acetylpromazine, 0.2 mg/kg; butorphanol tartrate, 0.2 mg/kg; ketamine, 25 mg/kg). Rats were given an intramuscular antibiotic injection of 2.5 mg gentamycin and a subcutaneous injection of 0.075 mg butorphanol tartrate for analgesic purposes postoperatively. During recovery periods, all rats were allowed water and standard rat chow ad libitum.

Rats were randomly assigned to either the lesion (SFOAPx, n = 6) or the sham (SFOAPshm, n = 6) group. Due to transient hypophagia observed in AP lesioned rats (Bishop and Hay, 1993; Hyde and Miselis, 1983) for approximately 3 weeks after the procedure, AP lesions were performed first. Briefly, rats were placed in a stereotaxic device with the head flexed. An incision was made from the occipital crest to the first vertebrae, and the underlying muscle and tissue were dissected away to allow visualization of the AP. The AP was removed via suction using a blunt 23-gauge needle attached to a vacuum line. The musculature was closed using 3.0 chromic gut and the skin incision closed using 3-0 surgical silk. Sham operations were identical except for the use of the vacuum line. Rats were allowed one week of recovery before SFO lesion or sham SFO operation.

For SFO lesions, rats were again placed in a stereotaxic device and the head was leveled. An incision was made in the top of the head and a 3 mm hole drilled in the skull immediately caudal to the bregma landmark. As previously described (Hendel and Collister, 2005), a tungsten electrode was lowered into the brain at 4 pre-determined coordinates and an electrical current of 1 mA was passed for 8 seconds. After the lesion, bone wax was used to fill the hole

in the skull and 3-0 silk suture was used to close the incision. Sham operations were performed identically, except the electrode was lowered 2mm less to avoid puncturing the SFO and no current was passed. All rats were allowed one week of recovery before transmitter and catheter implantation.

For the continuous monitoring of BP and HR, and for continuous vehicle infusion, rats were instrumented with radiotelemetric pressure transducers (model no. TA11PA-C40, Data Sciences International, St. Paul, MN) and venous catheters, respectively, as previously described (Nahey and Collister, 2007). Briefly, a midline abdominal incision was made and the descending aorta was exposed. The aorta was clamped and the catheter of the transducer was introduced distal to the clamp and glued in place. The transmitter unit was attached to the abdominal wall with 3-0 surgical suture during closure of the abdominal cavity. For the venous catheter, a small ventral incision was made in the left leg of the animal and the underlying tissue dissected away to expose the femoral vein. The vein was tied off and the catheter was inserted into the vein approximately 9 mm and tied in place. The catheter was guided subcutaneously to an exit location between the scapulae, and passed through a flexible spring connected to a single-channel hydraulic swivel. Rats received intravenous antibiotics consisting of 15 mg ampicillin for three days following the surgery.

Experimental protocol

Throughout the experiment, rats were infused with 7 ml/day 0.9% sterile saline. In order to most accurately match the normal salt intake of rats allowed standard rat chow ad libitum (approximately 2 mEq/day), rats were fed a 0.4% NaCl diet (Research Diets, New Brunswick, NJ) to compliment the saline infusion. To normalize sodium and water balance, rats were given the 0.4% NaCl diet and saline infusion was begun at least three days before the initial baseline measurements were taken.

To begin the experiment, data were collected over a 3 day control period. On day 2 of the control period, rats were weighed to calculate losartan quantities to be infused. After the control period, losartan infusion (10 mg/kg/day) was begun and continued for 10 days, after which losartan infusion was terminated.

Food, water, urine and sodium measurements

Food intake, water intake and urine output were measured gravimetrically daily at approximately hour 6 of the daily light cycle. Total water intake was calculated as the sum of voluntary drinking and infused volume. Sodium intake was calculated as the sum of sodium received in the daily infusion and the product of food intake and sodium content of the food. Urine sodium concentration was analyzed using the Nova 1 Analyzer (Nova Biomedical, Waltham, MA), and urine sodium excretion was calculated as the product of urine sodium concentration and daily excreted urinary volume. Balances were calculated as the difference between intake and output.

Histological verification

After conclusion of the experimental protocol rats were anesthetized (as above) and perfused intracardially with 4% paraformaldehyde. Whole brains were removed and kept refrigerated in 4% paraformaldehyde, then transferred to a 30% sucrose solution for three days. Coronal serial sections (50 μ m) were sliced using a freezing microtome and mounted on treated slides. Slides were stained with cresyl violet and examined using light microscopy for confirmation of an intact or lesioned AP and/or SFO. All lesioned rats included in the study were confirmed to have undergone complete AP and SFO ablation with minimal damage to the surrounding tissue.

Statistical Analyses

All values are reported as mean $\pm$ SEM. Statistical comparison between experimental groups was performed by two-way ANOVA for delta data sets and repeated measures ANOVA for all other data. The Geisser-Greenhouse adjusted *P* value was used to account for violations that accompany this experimental design, and in cases where significance was observed post hoc analysis was done using Fisher's LSD multiple-comparison test. A value of $P < 0.05$ was considered statistically significant for all tests.

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Figure 1. Baseline averages of mean arterial pressure (top) and heart rate (bottom) in SFOAPx and SFOAPshm rats during control period. * $P < 0.05$ between groups.

Figure 2.

Daily averages of change in mean arterial pressure (top) and heart rate (bottom) relative to baseline control averages of SFOAPx and SFOAPshh rats during chronic infusion of losartan (10/mg/kg/d). * $P < 0.05$ between groups.

Figure 3.
Daily averages of total food intake in SFOAPx and SFOAPshh rats during control period and chronic infusion of losartan (10 mg/kg/d).

Figure 4. Daily averages of total sodium intake (top), sodium excretion (middle) and sodium balance (bottom) for SFOAPx and SFOAPshh rats during control period and chronic infusion of losartan (10 mg/kg/d).

Figure 5. Daily averages of total water intake (top), urine output (middle) and water balance (bottom) for SFOAPx and SFOAPshh rats during control period and chronic infusion of losartan (10 mg/kg/d).