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Changing dietary sodium alters the chronic cardiovascular effects of losartan in rats

John P Collister, David B Nahey

Abstract

Introduction. We have previously demonstrated a profound hypotensive response to the angiotensin II type 1 (AT1) receptor antagonist losartan in rats consuming a normal salt diet that is not seen in salt-loaded rats, presumably due to a suppression of the renin-angiotensin system (RAS) by high sodium levels. The purpose of the present study was to examine the cardiovascular effects of changing dietary sodium intake during chronic treatment with losartan. We hypothesised that during blockade of AT1 receptors by chronic losartan infusion, when renin levels would be elevated regardless of dietary sodium, changing diets from high to normal or normal to high salt would have no effect on mean arterial pressure (MAP).

Materials and methods. To test this hypothesis, groups of rats instrumented with radiotelemetry transducers for MAP monitoring and venous catheters for infusion were initially placed on either a 0.4% salt content diet, referred to as Losartan Normal diet (LosN, n = 7), a 4.0% salt content diet referred to as Losartan High salt diet – Normal diet (LosN-HI, n = 9). After a three-day control period, infusion of losartan was begun in all rats (10 mg/kg/day in 7 ml/day isotonic saline i.v.). After 10 days, data were collected for another 10 days after which losartan infusion was terminated for a 10-day recovery period.

Results. At the start of losartan infusion MAP was observed to be similar between LosN-HI rats (101±2 mmHg) and LosN-HI rats (101±2 mmHg). By day seven of the first 10 day protocol, MAP in LosN-HI rats had fallen to 71±4 mmHg while decreasing to 90±2 mmHg in LosN-HI rats. Five days after switching diets, MAP in LosN-HI rats had risen back to 85±3 mmHg, while MAP in LosN-HI rats had fallen to 75±2 mmHg.

Conclusions. These results do not support our hypothesis, suggesting that changing dietary sodium can alter the chronic hypotensive response to losartan regardless of the initial state of the RAS.

Introduction. The role of the renin-angiotensin system (RAS) in the long-term regulation of arterial pressure remains to be completely understood. Much of our understanding of this system has been gained by utilising pharmacological tools such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin (AT1)-receptor antagonists to block the system. Specifically, chronic infusion of the AT1 antagonist losartan in normotensive rats has been valuable in assessing the role of angiotensin II (Ang II) at AT1-receptors in basal blood pressure (BP) maintenance. A chronic hypotensive response in normal rats to losartan has been well documented by our laboratory, having consistently demonstrated a chronic depressor response of 25–30 mmHg to losartan (10 mg/kg/day IV) in normotensive, salt replete rats with normal plasma renin activity (PRA) levels.1 These findings suggest that the RAS is more involved in the maintenance of arterial pressure during normal physiological conditions than was previously believed. We have been investigating the mechanism of this response for some time as it is difficult to ascertain which actions of Ang II could cause such a dramatic decrease in BP after chronic blockade. We do not believe this effect is mediated through blockade of the peripheral vasconstrictor effects of Ang II because the acute effects of Ang II are blocked very rapidly at this dose of losartan long before any BP-lowering effect is observed. Secondly, we have never observed any profound diuresis or natriuresis and therefore do not feel that blockade of Ang II effects in the kidney are playing a prominent role in the response to losartan.

On the other hand, much evidence supports central nervous system actions of Ang II and we feel blockade of these could play a role in mediating the hypotensive response to losartan. Indeed, we have reported roles of two circumventricular organs (the area postrema and subfornical organ) in this response, as lesions of either of these structures markedly attenuated the chronic hypotension produced by losartan.1 It is also possible that non-AT1-receptor mediated events could be playing a role in this response. We have demonstrated that this observation appears to be mediated in part by the peptide Ang (1-7) as combined infusion of the Ang (1-7) antagonist D-Ala attenuated the hypotensive effects of losartan. Alternatively, AT2-receptors do not appear to be playing a role in this response as combined
administration of the AT$_2$-receptor antagonist PD123319, and losartan had no effect on the chronic hypotensive effects of losartan.$^5$

Interestingly, this response is attenuated with increased dietary salt, and blocked completely when rats are placed on a high salt diet.$^7$ Rats consuming a high salt diet that did not respond to losartan had marked suppression of the endogenous RAS as demonstrated by very low levels of basal PRA. This suggests that this response is the result of specific blockade of the RAS and that initial PRA is a predictor of the chronic hypotensive response to losartan in normal rats. This was further evidenced in rats treated with losartan in which the sympathetic nervous system was clamped with hexa-methonium. These rats had the same sodium intake as control rats, but a lower basal PRA and an attenuated hypotensive response to losartan.$^5$ Since sodium intake is linked to basal PRA, we wished to determine if a change in dietary sodium can alter the chronic response to losartan or if the initial state of the RAS solely predicts the chronic effects of losartan. Presumably, regardless of diet, after 10 days of AT$_1$-receptor blockade one would predict elevated PRA in all animals, and we wished to determine at that point the effects of altering sodium intake on the steady state response to losartan treatment.

We hypothesised that during blockade of AT$_1$-receptors by chronic losartan infusion, when renin levels would be elevated regardless of dietary sodium, changing diet from high to normal or normal to high salt would have no effect on mean arterial pressure (MAP). In order to test this hypothesis, BP was measured via telemetry in two groups of rats given either normal or high NaCl. The BP lowering effects of 10 days of losartan treatment were measured and then the diets of the two groups were switched. The rats were then maintained on losartan for an additional 10 days followed by a 10-day recovery period.

Methods

Adult male Sprague-Dawley rats (250–275 g, Charles River Laboratories, Wilmington, MA) were used in all experiments. All rats were housed in Nalgene metabolic cages (Harvard Apparatus, Holliston, MA) and maintained in a controlled environment with 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

All rats were instrumented with radiotelemetric pressure transducers (model no. TA11PA-C40, Data Sciences International, St. Paul, MN) for continuous sampling of MAP and heart rate (HR), and venous catheters for delivery of Ang II. Rats were preanaesthetised with pentobarbital (32.5 mg/kg. IP) and atropine (0.2 mg/kg IP) and surgical anaesthesia was achieved with a second intramuscular injection containing a combination of anaesthetic agents (acetylpromazine, 0.2 mg/kg; butorphanol tartrate, 0.2 mg/kg; ketamine, 25 mg/kg). The telemetry device was implanted as previously described.$^4$ Briefly, a midline incision was made through the abdominal wall to gain access to the descending aorta. Once isolated, with the descending aorta clamped, the arterial wall was punctured distal to the renal veins and the catheter of the transmitter was advanced cranially and glued into place. The body of the transmitter was secured to the abdominal wall with 3-0 silk sutures during closure of the abdominal cavity and the skin was closed with surgical staples. For implantation of the venous catheter, a medial incision was made in the left leg to expose the femoral vein. A small incision was made in the vein and flexible tubing (Helix Medical, silicone tubing, Fisher Scientific, Pittsburgh, PA) was advanced cranially approximately 9 cm and anchored using 3-0 silk sutures. The catheter was passed subcutaneously to an exit location between the scapulae and passed through a flexible spring connected to a single-channel hydraulic swivel. Each rat received a post-surgical subcutaneous injection of 0.075 mg butorphanol tartrate for analgesic purposes and received intravenous antibiotics consisting of 15 mg ampicillin for three days following surgery. Rats were given a 7-day recovery period post-surgery, during which distilled water was provided ad libitum. To ensure that sodium and water balance had been re-established prior to data collection, rats were placed on their respective diets and continuous infusion of 0.9% sterile saline (7 ml/day i.v.) was begun at least three days before collecting control data.

Experimental protocol

Rats were randomly selected for placement in a group that initially was fed either 0.4% (normal) NaCl diet (LosN-HI, n = 7) or a 4.0% (high) NaCl diet (LosHI-N, n = 9) (Research Diets, New Brunswick, NJ). A 0.4% NaCl diet was referred to as “normal” in the current study as the combination of this diet and the infusion vehicle results in a sodium intake of approximately 2 mEq/day, which is equivalent to normal sodium intake on standard (1.0% NaCl) rat chow. To begin the protocol, baseline control levels were recorded for three days during which rats were fed their respective diets and infused with 0.9% sterile saline (7 ml/day). Rats were weighed to calculate infusion concentrations of losartan the day before losartan infusion was begun. On days 1–10 of the experimental phase, losartan (10 mg/kg/day dissolved in 0.9% sterile saline) was infused at a

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rate of 7 ml/day for all rats. On day 11 of the experimental phase, diets were switched between groups while losartan treatment remained unchanged. Infusion of losartan was terminated while all other variables remained unchanged for a 10-day recovery period to complete the protocol. During the protocol MAP and HR were monitored 24-hours per day. Data points reported are 24-hour averages.

**Food, water, urine and sodium measurements**

Food and water intake and urine output were measured gravimetrically daily at approximately hour six 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 analysed 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.

**Statistical analysis**

All values are reported as mean±SEM. Statistical comparison between experimental groups was performed by two-way ANOVA. 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.

**Results**

**Cardiovascular effects of losartan**

The effects of infused losartan on MAP during the two levels of dietary sodium are shown in figure 1. The average MAP during the control period was not significantly different between groups (LosN-HI; 100±1 mmHg, LosHI-N; 103±1). By day 3 of losartan infusion, MAP had decreased to 78±1 mmHg in LosN-HI rats and 91±2 mmHg in LosHI-N rats. This difference was found to be significant, a trend that continued throughout the first stage of the experimental protocol. MAP decreased to 71±4 mmHg and 89±2 mmHg in LosN-HI and LosHI-N, respectively, during this stage.

Upon switching diets for the second stage of the experimental protocol a rapid increase in MAP was observed in LosN-HI rats, paralleling an observed rapid decrease in MAP in LosHI-N rats. By day three of phase 2 of the experimental protocol a rapid increase in MAP was observed in LosN-HI rats, paralleling an observed rapid decrease in MAP in LosHI-N rats. The effects of losartan on HR are also shown in figure 1. Despite a spike in HR accompanying the sharp decrease in MAP in LosN-HI rats on day two to four of the first stage of the experiment, a significant difference was observed between groups on only three additional days of the protocol.

**Water and sodium balance and food intake responses**

Water balance data are shown in figure 2. During the control period, water intake (WI) and urine output (UO) averages were 28±1 ml and 10±1 ml, respectively, in LosN-HI rats and 59±1 ml and 41±1 ml, respectively, in LosHI-N rats. During the first stage of the experiment, WI and UO for LosN-HI rats averaged 25±0.5 ml and 9±0.5 ml, respectively, and 5±0.7 and 36±0.7 ml, respectively, for LosHI-N rats. After switching diets for stage 2 of the experimental protocol, WI and UO for LosN-HI rats averaged 55±0.9 and 36±2 ml, respectively, and 31±0.6 and 14±0.5 ml, respectively, for LosHI-N rats. Both WI and UO were significantly higher in the group being fed the high salt diet compared to the group being fed the normal salt diet on all days of the experiment. Water balance was generally higher in the group being fed the high sodium diet, although a significant difference was observed only on days 2, 7 and 8 of the first phase of the experimental protocol and days 2, 4 and 7 of phase 2.
Similar results were observed regarding sodium balance data, shown in Figure 3. During the control period, sodium intake (NaI) and sodium excretion (NaE) averages for LosN-HI rats (being fed a 0.1% NaCl diet) were 3±0.1 mEq and 2±0.1 mEq, respectively. Over the same period, levels for LosHI-N rats (being fed a 4.0% NaCl diet) averaged 17±0.4 mEq and 14±0.5 mEq, respectively. During the first phase of the experiment, while rats remained on their original diets, NaI and NaE averaged 3±0.1 mEq and 2±0.1 mEq, respectively, for LosN-HI rats and 17±0.2 mEq and 14±0.2 mEq, respectively, for LosHI-N rats. During the second phase of the experimental protocol, NaI and NaE averaged 16±0.2 mEq and 14±0.3 mEq for LosN-HI rats and 3±0.1 mEq and 2±0.1 mEq, respectively, for LosHI-N rats. Both NaI and NaE levels were observed to be significantly higher in rats being fed the high sodium diet on all days of the experiment. With regard to sodium balance, a significantly higher balance was observed on all control and most experimental days in the group consuming the high sodium diet, with no observed significant difference on days 5, 6, 8 and 10 of the second phase of the experimental protocol. Sodium balance was also observed to be significantly higher in LosN-HI rats on days three, six and eight of the recovery period. No differences were observed in food intake between the groups throughout the protocol (data not shown).

**Discussion**

In the present paper, we have demonstrated a chronic hypotensive response to losartan treatment in the rat that is markedly attenuated in animals consuming a high salt diet. We have previously explained this observation with the fact that these animals have lower starting PRA.
and therefore a suppressed RAS, and are thus less responsive to the hypotensive effects of endogenous AT1-receptor blockade. We reasoned that after reaching the steady state response to losartan, when all animals – regardless of sodium intake – would presumably have high levels of PRA due to AT1-receptor blockade, the response to losartan would not be altered by a change in dietary sodium. The results were the opposite of what was expected in that animals consuming normal levels of sodium and demonstrating a hypotensive response to losartan had an increase in arterial pressure when switched to a high sodium diet. Likewise, rats consuming a high salt diet that responded to a much lesser degree to losartan had a large fall in arterial pressure when placed on a normal sodium intake while continuing losartan treatment.

Clearly, there was a shift in sodium and water balance when rats were switched to the opposing diets that could account for the changes in BP at that point. The LosN-HI rats had a transient retention of both sodium and water during the rise in pressure, while LosHI-N rats experienced the opposite. Interestingly, as previously demonstrated, the initial responses to losartan are not associated with concomitant changes in sodium and water balance. Therefore, clearly the response to losartan after changing dietary sodium in this experiment has a different underlying mechanism. One possibility is an expected difference in AT1-receptor expression between the groups as higher dietary sodium has been shown to increase the expression of AT1-receptors.6 We do not believe that this would contribute to the change in pressure, when the diets were switched as AT1-receptor blockade of additional or fewer receptors at this point should not have an effect.

It is possible that aldosterone could account for some of the observations in the present experiment. Increased circulating Ang II stimulates the release of aldosterone, and although aldosterone levels do not appear to stay elevated during chronic Ang II administration,7 it does appear that aldosterone levels are low and remain lower than normal during chronic ACE-inhibition.11 One would expect aldosterone levels to be low in both groups throughout the initial losartan treatment, as losartan has been shown to block the aldosterone response to Ang II, especially during low dietary salt.12 However, others have shown that decreased sodium affects the responsiveness of adrenal secretion of aldosterone.13,14 In isolated dog adrenal glands, for example, slight decreases in the sodium concentration or osmolality of the perfusate greatly increased aldosterone secretion, suggesting a direct effect of ionic concentration on adrenal secretion of aldosterone.15,16 Even though aldosterone levels are probably low in both groups, low dietary sodium could possibly cause higher levels of aldosterone in the LosN-HI group. The slightly increased level of aldosterone in this group could account for the sodium/water retention when switched to high salt that subsequently could account for the rise in pressure. Although this is a possibility, others have shown that even returning aldosterone levels to normal during chronic ACE-inhibition did not restore arterial pressure to normal levels.17

Lastly, other non-AT1-receptor mediated events could play a role in this response. Decreased dietary sodium has been shown to increase expression of AT2-receptors,18,19 and there are several reports demonstrating vasodilatory properties of AT2-receptors,20-23 as well as other opposing effects of Ang II actions at AT1-receptors.24,25 Indeed, it has been reported that the BP lowering effect of AT1-receptor antagonist Losartan in salt restricted rats was reversed by delivery of the AT2-receptor antagonist PD123319.26,27 It is possible that the change in MAP observed after switching the diets (after 10 days of losartan treatment) in the present study was related to altered AT2-receptor expression at this point in the experiment. For example, when switched to a lower sodium diet, LosHI-N rats would potentially have increased activity of the RAS, leading to higher levels of Ang II able to act on increased numbers of AT2-receptors. While this possibility exists, we do not believe AT2-receptors to be involved in the chronic hypotensive response to losartan in rats consuming a normal salt diet (LosN-HI rats). We have previously shown that simultaneous administration of losartan and the AT2-receptor antagonist PD123319 did not attenuate the chronic hypotensive effects of losartan in rats with a normal sodium intake.4 Regardless, it is still possible that AT2-receptors could be involved with the further fall in MAP after switching to the lower salt diet in the LosN-HI rats in the present study.

Consideration should be given to the fact that other components of the RAS could be contributing to the observations in the present study. Recent research has focused on the angiotensin metabolite Ang (1-7), an active peptide which is formed from either angiotensin I (Ang I) or Ang II.28-31 This peptide has been shown to possess vasodilatory properties29,30 and it has been shown that Ang (1-7) levels are increased during treatment with either ACE-inhibitors or AT1-receptor antagonists, owing to increased levels of either Ang I or both Ang I and Ang II.34,35 In the spontaneously hypertensive rat...
it has been shown that the antihypertensive effects of ACE-inhibitors are lessened when the effects of Ang (1-7) are blocked with specific antagonists or antibodies. More importantly, we have shown that the chronic hypotensive response to losartan is mediated in part by Ang (1-7), as the hypotensive effects are attenuated when rats were simultaneously administered an antagonist to Ang (1-7). Therefore, Ang (1-7) could likely be playing a role in the responses seen in the present experiments when the diets were switched. For instance, switching LosHI-N rats to a lower sodium diet presumably could have further activated the RAS in these animals, thus leading to even greater increases in Ang I and Ang II levels, the known precursors of Ang (1-7). The vasodilatory effects of Ang (1-7) could be further investigated in this model.

This study does not support our hypothesis that the initial elevated state of the RAS, due to chronic AT1-receptor blockade, would prevent BP changes in response to an increase or decrease in dietary salt in normal rats. These findings suggest that there are other mechanisms at work in addition to the RAS in the relationship between dietary sodium and BP.

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