Aqueduct Block Markedly Reduces Mortality and Hypertension in Post–Deoxycorticosterone Acetate Dahl Salt-Resistant Rats

Jong Y. Lee and Louis Tobian

When Dahl salt-resistant (DR) rats are given mild post–deoxycorticosterone acetate (DOCA) hypertension, they will have, within 8 weeks, a 53% mortality on a high NaCl diet, without a rise of blood pressure. Forty-two DR rats were given DOCA in silicone (250 mg/kg) and 1% NaCl to drink. After 4 weeks, the DOCA and 1% saline were removed and replaced with a low NaCl diet and tap water. One week later, they were divided into two groups perfectly matched for blood pressure (154 mm Hg). One group had the aqueduct of Sylvius blocked with silicone and epoxy materials; the other group had a sham block. After 4 more recovery weeks on a low NaCl diet, blood pressure averaged 171 mm Hg in sham rats and 147 mm Hg in truly blocked rats (p < 0.0001). Thus, the aqueduct block prevented most of the post-DOCA hypertension and permitted a strong post-DOCA recovery from the acute DOCA hypertension. The rats with the sham block had an actual rise in blood pressure during the post-DOCA recovery period. The vicious cycle leading to permanent post-DOCA NaCl hypertension was broken by the aqueduct block. Then both groups began an 8% high NaCl diet, and blood pressure averaged 184 mm Hg in sham and 155 mm Hg in truly blocked rats (p < 0.0001). After 12 weeks on 8% NaCl, all sham rats had died (28 of 28), whereas only one of 14 truly blocked rats had died (93% reduction in mortality, p < 0.0001). The urinary albumin/creatinine ratio was 36 in sham rats versus only 14 in truly blocked rats (−62%, p < 0.0001). The dry heart weights averaged 431 mg in the sham rats versus 310 mg in the truly blocked rats (−28%, p < 0.05) even though the body weight of the sham rats averaged 6% less on the high NaCl diet. In the post-DOCA NaCl period, it is likely that structural changes linger on in the third brain ventricle region, leading to post-DOCA hypertension and progression of renal lesions. An aqueduct block produces hydrocephalus of the third ventricle and thereby reverses the lingering post-DOCA structural effects, thus greatly reducing blood pressure, mortality rate, cardiac hypertrophy, and urinary albumin. (Hypertension 1991;17:1197–1203)

A high NaCl diet is associated with the development of human hypertension,1 a cause of cardiovascular morbidity and mortality in industrialized countries. Although a high NaCl diet is a well-known causal factor in increased blood pressure, understanding the relation between the high dietary NaCl intake and the increased blood pressure is still controversial. The structures surrounding the third brain ventricle are vital for maintenance of normal body fluid homeostasis and cardiovascular responses. Our previous study in Dahl salt-sensitive (DS) rats showed that hydrocephalus produced by blocking the cerebral aqueduct significantly attenuates the rise of blood pressure and the mortality associated with high NaCl diets.2 Other studies have also shown that the anteroventral third ventricle (AV3V) region is a major location for sodium-related receptors and is involved in salt-sensitive hypertension.3–10 Our previous study suggested that volume receptors in the area of the upper brain ventricles respond to a high NaCl diet. A high NaCl diet might swell the tissues around the slitlike structure of the third brain ventricle and cause the ependymal cells and nerve fibers in the opposing walls of the third ventricle to touch one another. This may trigger neural signals leading to hypertension in susceptible individuals. Involvement of the central nervous system (CNS) in the pathogenesis of NaCl-induced hypertension is indicated in several studies. The paraventricular nuclei, which release vasopressin, project fibers to sympathetic neurons in the brain.

From the Department of Medicine, University of Minnesota Hospital and School of Medicine, Minneapolis, Minn.
Supported by grant HL-17871 from the National Institutes of Health and The Cargill Foundation.
Address for reprints: Louis Tobian, MD, Department of Medicine, Box 285 UMHC, University of Minnesota Hospital, 420 Delaware Street SE, Minneapolis, MN 55455.
stem and spinal cord as well as to the dorsal motor vagus nucleus. These structures play a part in regulating the cardiovascular system. The AV3V region is involved in the development of hypertension in the DS rats and in other NaCl-related hypertension.2-7 Guanethidine, 6-hydroxydopamine, or diltiazem, which induce reductions in sympathetic traffic, also prevent NaCl-induced hypertension in DS rats. Recent studies also indicate that the area postrema, at the caudal end of the fourth cerebral ventricle, is involved in angiotensin II and the renin-vagus nucleus. These structures play a part in regulating the cardiovascular system.10-13

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The experiment was designed to examine whether induced hydrocephalus would affect post-DOCA hypertension. DOCA-salt hypertension was induced in 4-week-old uninephrectomized male DR rats by implanting subcutaneously a silicone disk containing DOCA (250 mg/kg) and by giving only a 1% NaCl solution with 0.2% KCl as the drinking water. These rats were fed regular Purina chow for 4 weeks. The DOCA disk was removed after 4 weeks of implantation and rats were switched for 1 week to a 0.3% low NaCl diet and saline. At the end of the 4-week recovery period, blood pressure was measured intraraterially on each rat under methohexital (Brevital, Eli Lilly and Co., Indianapolis, Ind.) anesthesia (50 mg/kg). Using these blood pressures, the pool of post-DOCA rats was divided into two groups with precisely matching blood pressures (155 versus 153 mm Hg). The average weights of the two groups were also quite similar (213 versus 202 g). Then, the aqueduct of Sylvius was blocked stereotaxically with silicone in one group, using the same method as in our previous study.2 Pathological examinations were done on each rat.

Results were analyzed by the least-squares method and two-tailed Student’s t test. Data are expressed as mean±SEM. A value of p<0.05 was considered significant.

Results

DR rats were used to test whether hydrocephalus protects or reverses post-DOCA NaCl hypertension. One week after DOCA and saline had both been removed, DR rats with post-DOCA NaCl hypertension were divided into two matched groups with regard to blood pressure, with both groups averaging about 154 mm Hg. One of the groups underwent the aqueduct block; the other group had a sham block. These procedures were followed by 4 weeks of a very low NaCl diet for both groups. Four weeks after such procedures, both groups were switched to an 8% high NaCl diet.

In Figure 1, the sham group’s blood pressure averaged much higher than that of the true blocked rats at 4 weeks after surgery even after 4 weeks of a 0.3% low NaCl diet, 171±2.7 versus 147±6.1 mm Hg, p<0.001. Blood pressure was further increased in both groups after 4 weeks of an 8% high NaCl diet, 184±2.8 versus 155±6.0 mm Hg, p<0.001. It should be noted that many rats of the sham group were mortality were compared. Dry heart and kidney weights were ascertained. The aqueduct blocks were verified histologically using the same methods as outlined in our previous study.2 Pathological examinations were done on each rat.

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Creatinine excretion in the two groups

Silicone disks containing deoxycorticosterone acetate (250 mg/kg) were implanted at 4 weeks of age, and the rats were fed normal rat chow and were given drinking water containing 1% NaCl and 0.2% KCl. Four weeks later, the disks and the NaCl drinking water were removed, and the rats were switched to a 0.3% low NaCl diet with tap water. Rats were allowed to recover for 1 week before undergoing either aqueductal block or sham lesion. An 8% high NaCl diet was introduced 4 weeks after surgery. After 6 weeks on the high NaCl diet, 19 of 28 rats in the sham group had died, whereas none of 14 rats in the truly blocked group had died (p<0.0001).

Figure 2. Line graph showing percentile cumulative survival in Dahl salt-resistant (R) rats on an 8% high NaCl diet after either a sham (■) or a verified aqueductal block (○). Silicone disks containing deoxycorticosterone acetate (250 mg/kg) were implanted at 4 weeks of age, and the rats were fed normal rat chow and were given drinking water containing 1% NaCl and 0.2% KCl. Four weeks later, the disks and the NaCl drinking water were removed, and the rats were switched to a 0.3% low NaCl diet with tap water. Rats were allowed to recover for 1 week before undergoing either aqueductal block or sham lesion. An 8% high NaCl diet was introduced 4 weeks after surgery. After 6 weeks on the high NaCl diet, 19 of 28 rats in the sham group had died, whereas none of 14 rats in the truly blocked group had died (p<0.0001).

Table 2 gives the heart and kidney weights in the post-DOCA DR rats on the high NaCl diet. Cardiac hypertension was prominent in the sham-blocked group of rats. At the end of 12 weeks of the high salt diet, the dry heart weights were 431±41 mg in the sham-blocked rats versus 310±20 mg in the true-blocked rats, p<0.05 (a 28% reduction). However, kidney hypertension in the sham-blocked group of rats was not different from that of the blocked group. All of the rats in both groups that had not previously died were killed after 12 weeks on the 8% high NaCl diet. Thus, all of the rats were included in Table 2.

Discussion

Evidence That the Central Nervous System Is Involved in Mineralocorticoid Hypertension

There are many pieces of evidence that, when taken together, indicate that the CNS plays a very important role in DOCA-salt hypertension. Hauesler et al. were the first to show that injecting 6-hydroxydopamine in the lateral brain ventricle could prevent DOCA-salt hypertension. 6-Hydroxydopamine causes the death of catecholamine-containing neurons, and their study suggested that the presence of these neurons was necessary for the full expression of DOCA-salt hypertension. Lamprecht et al. were able to show the same phenomenon with 6-hydroxydopamine. In our own laboratory, we were able to confirm that 6-hydroxydopamine injected into the lateral brain ventricle prevented DOCA-salt hypertension in Sprague-Dawley rats.

In producing such hypertension, it is absolutely necessary to have both the mineralocorticoid excess and to have a reasonably high NaCl diet. In previous studies from our laboratory, we combined DOCA injections with a very low sodium diet and found that there was no elevation of blood pressure whatsoever. Moreover, in sheep given DOCA hypertension, the switch to a very low NaCl diet causes a drop of

Table 2. Significantly Reduced Cardiac Hypertrophy With Induced Hydrocephalus in post-DOCA Dahl R Rats on an 8% High NaCl Diet

<table>
<thead>
<tr>
<th>Organs (dry wt)</th>
<th>Sham (n=28)</th>
<th>Block (n=14)</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart (mg)</td>
<td>431±41</td>
<td>310±20</td>
<td>-28%, p≤0.05</td>
</tr>
<tr>
<td>Kidney (mg)</td>
<td>532±21</td>
<td>494±12</td>
<td>-7%, p=NS</td>
</tr>
</tbody>
</table>

wt, Weight; n, number of rats; NS, not significant.
blood pressure to normal levels and also does away with the exaggerated thirst that usually accompanies DOCA-salt hypertension. Moreover, the institution of the low salt diet also diminishes the increased NaCl appetite that the sheep had when they were taking DOCA and NaCl. Since the brain centers that control thirst and NaCl appetite are located in nuclei surrounding the third brain ventricle, these findings suggest that DOCA plus NaCl have a central effect on structures near the third brain ventricle, but DOCA minus NaCl does not have this same type of an effect. In these sheep, the level of the blood pressure and the level of thirst and NaCl appetite all increased and decreased more or less together. Since the thirst and the NaCl appetite brain regions are very definitely in the neighborhood of the third brain ventricle, these findings suggest that the mechanisms causing a rise in blood pressure are partially subserved by structures near the third brain ventricle. Along the same lines, Soltis and Bohr administered DOCA peripherally and infused the lateral ventricle with a fluid containing a normal level of NaCl. No rise of blood pressure occurred. When they switched the fluid to hypertonic NaCl perfusing the lateral ventricle, a considerable rise in blood pressure was noted. If the lateral ventricle was infused with hypertonic saline alone, without the peripheral DOCA, there was a very small rise in blood pressure to borderline levels. Such levels were much lower than the levels achieved when DOCA was given peripherally and hypertonic saline was infused into the lateral ventricle. With a somewhat different strategy, Gomez-Sanchez administered aldosterone into the lateral brain ventricle and produced hypertension, suggesting that if the mineralocorticoid is administered centrally, it can cause a rise of blood pressure. To strengthen this conclusion, Gomez-Sanchez et al then administered aldosterone peripherally along with a high salt diet in a combination that will ordinarily produce hypertension. However, when this combination of aldosterone and a high salt diet is accompanied by an infusion into the lateral brain ventricle of a compound that blocks aldosterone receptors, no hypertension can be found. Thus, if the compound that blocks aldosterone in the CNS can prevent aldosterone-NaCl hypertension when the aldosterone is given peripherally, this strongly suggests that peripherally administered aldosterone must act effectively on CNS receptors to produce the hypertension. The effects of DOCA or aldosterone on the CNS to produce hypertension might be partially accomplished by an increase in sympathetic traffic. De Champlain and van Ameringen found evidence that DOCA-NaCl increased sympathetic nerve activity. The various pieces of evidence taken together strongly suggest that DOCA and NaCl produce hypertension by an action on the CNS and particularly in the neighborhood of the third brain ventricle. Of course, the effect of the mineralocorticoid in causing the body to be stuffed with NaCl is undoubtedly an important link in the total mechanism of the hypertension.

Effect of Hydrocephalus on Post-Deoxycorticosterone Acetate Hypertension During Low NaCl Diet

In rats, after 4 weeks of administering DOCA and saline, the DOCA-NaCl hypertension often does not disappear when the DOCA and the NaCl are removed. Even in DR rats given DOCA and saline, we found that hypertension at the level of 160 mm Hg existed even after 4 weeks of no DOCA plus a very low NaCl diet. The explanation of this post-DOCA hypertension is not totally known. It is true that 4–6 weeks of acute DOCA-NaCl administration not only leads to hypertension but also leads to renal lesions. It is quite probable that these renal lesions contribute to the continuation of the hypertension even when the inciting causes, DOCA and saline, have been removed. Since we know that the DOCA and saline also have an action in the CNS near the third brain ventricle (see preceding section), it is also possible that this CNS effect somehow lingers on even after the DOCA and saline have been removed. In the present study, the silicone disk containing the DOCA was removed from its subcutaneous site, the saline administration had been stopped, and the rat had begun to eat a diet with a very low NaCl content. This post-DOCA interval continued for 1 week. This would allow time for the DOCA levels in the body to diminish to almost zero and would also allow time for the rat to come into a new sodium balance commensurate with the very low NaCl intake. At that point the pool of rats in the post-DOCA status were divided into two groups with precisely matching blood pressures. One of these groups received a block of the aqueduct of Sylvius while the other group underwent a sham block. After either the true block or the sham block of the aqueduct, 4 more weeks without DOCA and with a very low sodium diet took place to allow the blood pressure to return toward normal during this post-DOCA interval. This design permitted us to assess the influence of the aqueduct block on the course of the post-DOCA hypertension. During this 4-week post-DOCA interval in the rats with the sham block, the blood pressure rose from 155 mm Hg after 1 week post-DOCA to a level of 171 mm Hg after 5 weeks of the post-DOCA interval. This represents a definite expression of post-DOCA hypertension. However, in this same time interval, the rats that had undergone the true aqueduct block had a decrease of blood pressure from 153 mm Hg after 1 week of the post-DOCA interval to 147 mm Hg after 5 weeks of the post-DOCA interval. Thus, it appeared that the aqueduct block almost completely abolished the post-DOCA hypertension, whereas the sham block allowed a considerable rise in blood pressure in the post-DOCA period. In our previous study, we found that the block of the aqueduct causes a fourfold widening of the third ventricle slit. This same type of aqueduct block prevented most of the hypertension.
that appears in salt-fed DS rats. Moreover, a thermal lesion at the site in the aqueduct where the block usually occurred actually increased the blood pressure slightly rather than decreasing it. Thus, it appeared that it was the actual hydrocephalus produced by the block that was greatly reducing the degree of NaCl-induced hypertension in the DS rat. Hence, it seems likely that the process of hydrocephalus in the third ventricle and lateral ventricles was somehow abolishing the post-DOCA hypertension, whereas the sham block was allowing a strong expression of it.

A possible explanation for all these events would be that the effect of the DOCA and NaCl somehow tends to continue in the structures surrounding the third brain ventricle even after the DOCA has been removed and after the high NaCl intake has been changed to a very low NaCl intake. This lingering CNS effect could allow for a continuing rise of blood pressure and could also encourage a continuation of the renal lesions that had begun to appear during the acute DOCA and saline administration. This combination of a continuation or worsening of the renal lesions, which would tend to increase the blood pressure plus the continued effect of the CNS per se on raising the blood pressure, could explain the rise of the blood pressure during the post-DOCA interval. When the aqueduct is blocked after 1 week of the post-DOCA period, this lingering CNS effect of the DOCA and the saline is somehow abolished so that the blood pressure—raising influence disappears and the renal lesions also then begin to heal. This combined effect would then prevent the post-DOCA hypertension that otherwise would have occurred. The aqueduct block did not completely abolish post-DOCA hypertension since 147 mm Hg in the truly blocked group of rats represents a borderline level of hypertension. Moreover, it is possible that the blood pressure might have gone even lower in the blocked rats if the post-DOCA interval had been extended.

The third brain ventricle in the rat is shaped in the form of a slit. It is quite possible that during acute DOCA-NaCl administration, the tissues surrounding the third brain ventricle tend to become slightly edematous, thereby causing the ependymal cells and nerve fibers in the walls of the slit to touch one another as they come into contact with those on the opposite wall of the slit. When we blocked the aqueduct, we had previously noted a fourfold increase of the width of the slit. This change in the configuration of the third ventricle might somehow have a strong influence for abolishing the lingering CNS effects of DOCA and NaCl during the post-DOCA period. This would suggest that the lingering effects of DOCA and NaCl have a structural component that is somehow reversed by the hydrocephalus. One could speculate that the third ventricle slit is somehow narrowed during the acute DOCA and saline period and is not readily reversed in the post-DOCA period, a type of biological hysteresis. The block of the aqueduct would, of course, reverse this. The fact that the aqueduct block prevents the post-DOCA hypertension provides strong additional evidence that the lingering CNS effect of DOCA and NaCl in the post-DOCA period involves the upper brain ventricles. And studies by Bohr and Gomez-Sanchez also add to the likelihood that the lingering effects of DOCA and NaCl involve the upper ventricles. Structural changes in neural connections around the third ventricle are another possible structural alteration.

When the aqueduct is blocked, a hydrocephalus in the lateral ventricles is also produced and may be somehow involved in the process. A block of the aqueduct would also prevent humoral agents from being transferred in the CSF fluid from the upper ventricles to the fourth ventricle. There are many centers in the medulla that have a strong influence on the level of blood pressure, and the area postrema, which is exposed to the CSF, is an important component of these medullary actions. It is not at all certain just how the block of the aqueduct tends to abolish the post-DOCA hypertension.

**Addition of a High NaCl Diet to Post-Deoxycorticosterone Acetate Rats Previously on Low NaCl**

In our previous study of post-DOCA DR rats, the switch from a low NaCl diet to a high NaCl diet did not alter the level of blood pressure but caused a marked increase in the mortality rate of these rats. When these post-DOCA DR rats ate an 8% high NaCl diet, 53% were dead after 8 weeks of the diet; similar rats that continued on the low NaCl diet had no deaths at all. The high NaCl diet was associated with a number of small cerebral infaracts. In the present study, all of the post-DOCA DR rats were given the 8% high NaCl diet after 5 weeks of the post-DOCA interval. Those with the true aqueduct block had an average blood pressure of 147 mm Hg before the 8% NaCl diet. Four weeks on the 8% NaCl diet raised the average blood pressure only to 155 mm Hg. The rats with the sham block had an average blood pressure of 171 mm Hg before the 8% NaCl and this increased to an average of 184 mm Hg after 4 weeks on the 8% NaCl diet. Thus, both groups had a very modest rise in blood pressure when they switched from a low NaCl to a high NaCl diet. During the high NaCl diet, the rats with the true aqueduct block still had mild hypertension while those with the sham block had severe hypertension. The effects of the high NaCl diet were added to the effects of the high blood pressure in the sham-blocked group of rats. This resulted in a very high mortality rate with 100% dead after 12 weeks on the high NaCl diet. Conversely, all but one of the rats with the true aqueduct block were still alive after 12 weeks on the high NaCl diet (13 of 14). In this group of rats, the high NaCl diet was given to rats with only borderline hypertension.

On the high NaCl diet, the rats with the true aqueduct block had a 28% lower dry heart weight than those with the sham block. A great deal of this difference would be due to the difference of blood pressure in the two groups. It is also known that a high NaCl diet per se tends to produce cardiac
hypertrophy and this effect might be mitigated somewhat in the presence of the aqueduct block. There could conceivably be some effects of the high NaCl diet per se, with severe effects in the sham-blocked groups and much lesser effects in the rats with the true aqueduct block. Similarly, the albumin-to-creatinine ratio was 62% lower in the high NaCl rats with the true block compared with the high NaCl rats with the sham blocks. A good part of this difference could be related to the large difference in blood pressure of these two groups. However, a high NaCl diet can in and of itself produce some renal lesions in the absence of a rise in blood pressure. It is possible that the aqueduct block prevented this particular effect on the kidney. Such a mechanism could also partially account for the greatly diminished albumin excretion in the rats with the true aqueduct block. It is quite possible that some CNS effect of the high NaCl diet increases the tendency to renal lesions, and the true aqueduct block could reverse this CNS effect.

The deaths in the sham-operated group on the high NaCl diet were mostly related to small brain infarcts and to vasculitis in the mesenteric vascular bed. Uremia was not a cause of death. The rats with the true aqueduct block had much lower blood pressure, much lower mortality rate, and greatly diminished cardiac hypertrophy and albuminuria. Since there was such a large difference in blood pressure between rats with the true block and those with the sham block, it is difficult to determine whether the true block prevented hypertrophy and lesions by mechanisms that are unrelated to the difference in blood pressure. This remains a possibility but cannot be proven one way or the other by the data presented here.

Conclusions

Acute DOCA-NaCl hypertension has a strong CNS component with structures around the third brain ventricle playing a major role. In the post-DOCA state in which all the DOCA has been removed and all rats are on a low NaCl diet, some of the effects of the acute DOCA and NaCl administration could well linger in structures around the third brain ventricle, leading to a continuing elevation of blood pressure and a continuing progression of renal lesions. The combined effects of such hypertension and the tendency toward continuing renal lesions would be the factors most likely causing post-DOCA hypertension. The results presented here strongly suggest that the block of the aqueduct caused a hydrocephalus of the third brain ventricle. This hydrocephalus brought about an abolition of the lingering structural effects of acute DOCA and NaCl in the structures around the third brain ventricle during the post-DOCA state. When these lingering effects were reversed, the tendency to continuing high blood pressure was greatly diminished and the renal lesions ceased to progress and probably healed somewhat. Thus the aqueduct block, by reversing these lingering CNS effects of DOCA and NaCl, virtually abolished the post-DOCA hypertension and greatly reduced the high mortality rate, hypertrophied myocardium, and massive albuminuria that accompanied the combination of post-DOCA hypertension plus an 8% NaCl diet.

These findings could conceivably have pathophysiological implications that go beyond post-DOCA-NaCl hypertension. In the past, we have studied "post-salt" hypertension, in which high NaCl diets are given for a period to produce hypertension and the hypertension persists long after the high NaCl diet is switched to a low NaCl diet. In a way, essential hypertension in humans could be considered as a "post-salt" hypertension. In an individual genetically susceptible to hypertension, a lifelong low NaCl diet will prevent that hypertension from occurring. However, a generous intake of NaCl in such an individual will gradually result in an elevated blood pressure. After many years, if such an individual switches to a low NaCl diet, the blood pressure may go down somewhat but often it will not return to the normal range. This situation is typical of essential hypertension and it is reminiscent of post-DOCA-NaCl and post-NaCl hypertension in rats. In these current studies of post-DOCA-NaCl hypertension, strong evidence was presented that the effects of the DOCA-NaCl linger in the region of the upper brain ventricular system long after the DOCA and NaCl have been removed. Similarly, in essential hypertension that can not be normalized with a very low NaCl diet, there is a very good possibility that the long standing effects of the high NaCl diet in a genetically susceptible person can cause lingering structural changes in the region of the upper brain ventricular system long after the high NaCl has been removed. As with post-DOCA-NaCl hypertension in rats, these lingering CNS changes could raise blood pressure enough to aggravate renal lesions. These lingering CNS effects might explain why human hypertension can often be resistant to treatment and respond slowly to medications. In any event, if these lingering CNS effects of post-DOCA and post-NaCl hypertension can be demonstrated in the rat, and since we know that hypertension caused by an aldosteronoma can be cured over a long period in only half of those who have the adenoma removed ("post-aldosterone hypertension"), there is a distinct possibility that these lingering CNS changes occur in typical human essential hypertension.

Acknowledgments

We thank Mary Ann Johnson for technical help and assistance in the preparation of this manuscript and Judy Lange for her assistance in various aspects of this study.

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KEY WORDS  • cerebral aqueduct  • deoxycorticosterone • hypertrophy  • albuminuria • sodium chloride • hydrocephalus • hypertension
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*Hypertension*. 1991;17:1197-1203
doi: 10.1161/01.HYP.17.6.1197

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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