Alterations in Osmotic but Not Pressor Responses to ACTH by Optic Recess Lesions in Sheep


SUMMARY This study examines whether neural structures in the region of the optic recess of the third ventricle may be involved in the genesis of adrenocorticotrophic hormone (ACTH)-induced hypertension in sheep. Five sheep were prepared with lesions in an area of the forebrain that included the organum vasculosum of the lamina terminalis (OVLT) and surrounding periventricular tissue. In these animals the dipsogenic response to systemically infused hypertonic sodium chloride (NaCl) was abolished. ACTH treatment (20 μg/kg/day) for 5 days caused an increase in mean arterial pressure (MAP) of 19 mm Hg, a response identical to that seen in normal sheep. With ACTH treatment, increases in plasma osmolality were greater than normal, but polydipsia did not occur in the lesioned sheep. In six other sheep with lesions either lateral or anterior to the optic recess of the third ventricle, the dipsogenic response to hypertonic NaCl and pressor response to ACTH were normal. These studies establish that in ACTH-treated sheep the integrity of the anterior ventral part of the third ventricle is not essential for the development of the hypertension. This is in contrast to the finding in other models of experimental hypertension in the rat. (Hypertension 4 (suppl II): II-154-II-158, 1982)

KEY WORDS • OVLT • lesions • sheep • ACTH • blood pressure

STUDIES by Brody and colleagues1-8 have established that the integrity of the anteroven-tral region of the third ventricle of the brain (AV3V) is essential for the development and maintenance of a number of different types of hypertension in the rat. AV3V lesions prevent the development of DOCA-salt hypertension,1 one-kidney or two-kidney one clip renal hypertension,1 and Dahl salt-sensitive hypertension.9 The lesions also reverse established one-kidney renal hypertension and two-kidney one clip renal hypertension.9 Further, AV3V lesions attenuate nucleus tractus solitarius (NTS) lesion hypertension,10 but do not alter arterial pressure in spontaneously hypertensive rats (SHR).11

Studies in the goat,6 rat,7 and sheep8 have shown that areas close to and including the organum vasculosum of the lamina terminalis (OVLT) play an important role in the thirst response, arginine vasopres-sin (AVP) secretion, and renal response to osmotic stimuli such as systemic hypertonic sodium chloride infusion.

Adrenocorticotrophic hormone (ACTH)-induced hypertension in sheep12 is an adrenal-dependent model of hypertension that is not primarily due to either the “mineralocorticoid” or “glucocorticoid” activity of adrenocortical steroids. It has been postulated that a novel “hypertensionogenic” class of steroid hormone action may be responsible.10 Because ACTH-induced hypertension is associated with increases in cerebrospinal fluid (CSF) and plasma osmolality, sodium concentration, urine output, and water intake, we decided to examine whether tissue in the anterior wall of the optic recess of the third ventricle is involved in the development of ACTH hypertension in the sheep.

Methods

Eleven adult crossbred merino ewes (body weight, 35-45 kg) that had been prepared at least 3 months earlier with bilateral carotid arterial loops and oophorectomy were used in this study. They were prepared with lesions in an area of the forebrain that included the organum vasculosum of the lamina terminalis (OVLT) and surrounding periventricular tissue. In these animals the dipsogenic response to systemically infused hypertonic sodium chloride (NaCl) was abolished. ACTH treatment (20 μg/kg/day) for 5 days caused an increase in mean arterial pressure (MAP) of 19 mm Hg, a response identical to that seen in normal sheep. With ACTH treatment, increases in plasma osmolality were greater than normal, but polydipsia did not occur in the lesioned sheep. In six other sheep with lesions either lateral or anterior to the optic recess of the third ventricle, the dipsogenic response to hypertonic NaCl and pressor response to ACTH were normal. These studies establish that in ACTH-treated sheep the integrity of the anterior ventral part of the third ventricle is not essential for the development of the hypertension. This is in contrast to the finding in other models of experimental hypertension in the rat. (Hypertension 4 (suppl II): II-154-II-158, 1982)
housed in individual metabolism cages to allow for separate collections of urine and feces and were fed daily 0.8 kg of lucerne/oaten chaff containing 60–120 mmoles/kg sodium and 200–300 mmoles/kg potassium with water ad libitum.

At least 30 days prior to production of the lesion, with the sheep under general anesthesia, single or paired stainless steel electrodes were implanted over or near the anterior wall of the optic recess of the third ventricle of the brain. A guide tube was also implanted over the lateral ventricle. The animals recovered quickly and took normal amounts of food and water within 2 to 3 days. Brain lesions were produced 1 to 2 months later in the conscious animal by application of radiofrequency current between the electrodes and a subcutaneous indifferent electrode.

Blood pressure and metabolic responses to ACTH administration were examined both pre- and post lesion. Animals received 20 μg/kg/day ACTH (Synacthen Depot, Ciba-Geigy) intramuscularly for 5 days.* Animals were also tested for lesion-induced disturbances in osmotic regulation of fluid balance by measuring the dipsogenic response to intracarotid 4M NaCl (1.3ml/min for 20 minutes) both before and after placement of the lesion. AVP was measured by radioimmunoassay (RIA) before and after the infusion of hypertonic NaCl. It was also measured in five normal sheep prior to and after 5 days of ACTH treatment. Results are expressed as means ± SEM.

At the conclusion of all experiments, the sheep were killed with an overdose of sodium thiopentone, and their brains perfused via the carotid arteries with 0.9% NaCl followed by 10% formal saline. Frozen serial sections were cut (40 μm) and stained with cresyl violet to assess the extent of the lesion.

**Results**

Of the 11 animals used, five had lesions that encompassed the midline tissue in the wall of the optic recess ventrally from the OVLT up to the anterior commissure and the median preoptic nucleus (ORL-sheep). Clear damage to the OVLT, the preoptic periventricular area, and the medial anterior hypothalamic region was evident (fig. 1). The six others (CL-sheep) had damage to areas above or lateral to the OVLT region, which was intact (fig. 1). The responses to dipsogenic stimuli and ACTH administration of this group of CL-sheep serve for comparison with those of ORL-sheep.

The hypertensive responses to ACTH treatment in the 11 animals tested prior to lesioning were within the range observed in normal sheep.* On Day 5 of ACTH treatment, the MAP had risen by 19 mm Hg, and HR had risen by 10 beats/min. Three weeks after lesioning and prior to the second ACTH study, MAP, HR, food and water intake, plasma Na, K, and osmolality were in the normal range. All ORL-sheep and CL-sheep had significantly elevated blood pressures within 24 hours of ACTH administration. By Day 5 of ACTH treatment, the five ORL-sheep showed rises in MAP and HR similar to prelesion values; the MAP had risen from 64.9 ± 1.6 to 84.6 ± 4.3 mm Hg, and HR from 58 ± 2 to 74 ± 5 beats/min (fig. 2). The MAP in the six CL-sheep had risen by 21 mm Hg. These increases in MAP in lesioned sheep were not statistically different than those for normal animals.

All animals exhibited typical metabolic responses to ACTH administration* prior to lesioning. After 5 days of ACTH treatment, plasma K had fallen by 1.2 mM, and plasma Na and osmolality had risen by 3 mM and 5 mOsm/kg. There was also an increase in water intake by 1.1 liter/day and urine volume by 1.1 liter/day. Urinary Na excretion fell within 2 to 3 days. By 24 hours of ACTH administration, plasma Na rose from 142.8 ± 2.4 to 158 ± 3.1 mM in the ORL-sheep.

The increase in water intake from 1.73 ± 0.17 to 2.19 ± 0.38 liter/day in ORL-sheep was not significant and was less than the corresponding rise of 1.1 liter/day seen in prelesion studies (fig. 3). The increase in urine output from 0.57 ± 0.10 to 1.22 ± 0.27 liter/day was similar to the increase of 1.1 liter/day seen in prelesion studies. There was no significant difference in the urinary Na and K excretion rates between ORL-sheep and nonlesioned animals over the period of ACTH administration.

When ORL-sheep were not being treated with ACTH, the dipsogenic and AVP secreting responses to infused hypertonic saline were tested, and nearly complete abolition of the dipsogenic response to intracarotid infusion of 4M NaCl was observed. Water intake of 27 ± 16.5 ml occurred with this stimulus compared to a mean value of 1150 ± 122 ml in prelesion trials. The CL-sheep drank 854 ± 131 ml, an amount not different from the prelesion volume. Plasma AVP rose from the basal value of < 3.5 to 15.7 ± 2.1 pg/ml after the 4M NaCl infusion in prelesion trials. In postlesion trials, plasma AVP changed from < 3.5 to 5.2 ± 1.2 pg/ml in the ORL sheep. In response to the hypertonic NaCl infusion, plasma Na rose from 142.8 ± 1.8 to 153.3 ± 2.6 mM in prelesion trials and from 147.1 ± 2.4 to 158 ± 3.1 mM in the ORL-sheep.
Discussion

In contrast to the inhibitory effect of AV3V lesions in several different types of experimental hypertension in the rat, lesions in a corresponding region of the sheep brain had no effect on the hypertensive response to ACTH. Both the rate of rise of blood pressure and the level of blood pressure reached after 5 days of ACTH treatment in ORL-sheep were similar to those found in animals without lesions. Administration of DOCA-salt in AV3V-lesioned rats resulted in a rise in blood pressure of 30 mm Hg, less than that achieved in sham-lesioned animals treated with DOCA-salt for 4 weeks. Because plasma and blood volume changes were similar in both AV3V-lesioned and sham groups, Fink and colleagues concluded that AV3V lesions prevented the development of low renin steroid-salt hypertension by mechanisms unrelated to sodium and volume status. Central angiotensin mechanisms were also unlikely to be involved. More recently it has been suggested that the AVP release in response to DOCA-salt administration may be reduced as a result of the lesion. However, other evidence to support a primary role for AVP as the cause of DOCA-salt hypertension is lacking. The increase in plasma AVP concentration is small except in animals with malignant hypertension; specific inhibitors of the pressor action of AVP do not always reverse the hypertension, and DOCA-salt can produce hypertension in diabetes insipidus rats if positive fluid balance is achieved by administration of 1-diamino-8-D-arginine vasopressin (DDAVP). An alternative hypothesis to explain the effect of the AV3V lesion in DOCA-treated rats has been proposed by Pamnani and colleagues. They suggest that the AV3V lesion may result in reduced production of an inhibitor of Na-K ATPase, thought to be involved in the development of hypertension in response to volume expansion.
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**FIGURE 2.** Effect of 5 days ACTH (20 μg/kg/d) administration on blood pressure, heart rate, plasma osmolality, [Na], and [K] in ORL-sheep (n = 5).

It is unlikely that AVP plays an important role in ACTH-induced hypertension. The increase in the plasma AVP level following ACTH administration is small in normal sheep, and the pressor responsiveness to infusions of AVP is not changed by ACTH. In many other respects the effects of the AV3V lesion are similar in the sheep and rat, with the exception of the immediate postlesion aphagia and adipsia that occurred only in the rat. In the sheep there was often a transient period of hypernatremia following placement of the lesion but no marked reductions in food or water intake. When first tested 7 to 10 days after the lesion placement and when plasma Na had returned to normal, the dipsogenic response to infused hypertonic sodium chloride was abolished. The AVP response to this osmotic stimulus was also reduced in the sheep with optic recess lesions. Dipsogenic responses to angiotensin II were more variable, a result consistent with findings in the rat. This suggests that the anatomical areas responsible for the dipsogenic response to angiotensin II may be distinct from those responsible for osmotic stimuli. No change in the pressor responsiveness to intravenous angiotensin II infusion was found in ORL-sheep (unpublished observations), a finding similar to that reported in the rabbit but in contrast to data obtained from the rat. Detailed histological analysis carried out in the lesioned animals suggests that the anatomical structures corresponding to those in rats and rabbits were ablated. In the sheep, the optic recess lesions damaged the OVLT (5/5), preoptic periventricular region (5/5), the medial anterior hypothalamic region (5/5), the preoptic medianus nucleus, the anterior commissure (3/5), hypothalamic paraventricular nucleus (3/5), the suprachiasmatic nucleus (3/5), and septum (2/5). In the rat, the AV3V lesions damaged the OVLT, the preoptic periventricular area, the anterior hypothalamic periventricular area, and the median preoptic nucleus. In contrast, CL-sheep generally had damage lateral to the optic recess region. These lesions (CL-sheep) had no effect on the hypertensive response to ACTH or the dipsogenic response to intracarotid hypertonic saline.

Although the blood pressure response to ACTH was not changed in ORL-sheep, the increase in plasma osmolality was greater than in normal animals. A similar response has also been seen in these animals when deprived of water for 3 days. It is possible that...
the exaggerated hyperosmolarity observed with ACTH may be due to the failure of the animals to increase their water intake in response to the stimulus of hyperosmolarity. This lack of response is consistent with the failure of the ORL-sheep to drink in response to a systemic infusion of hypertonic saline. The ORL-sheep failed to exhibit the increase in Na excretion that usually accompanies water deprivation in sheep.�

All these data point to the AV3V region as a major regulatory influence on water and possibly sodium regulation in the sheep.

The difference in blood pressure response in the rat and sheep may be related to the different modes of production of experimental hypertension that have been used, or to other mechanisms. In the rabbit, Bryan and Fink28 have shown that lesions in the AV3V area do not prevent the development of single kidney renovascular hypertension. A similar result has also been obtained in this laboratory in three ORL-sheep with a single kidney and in which constriction of the renal artery still caused a hypertensive response (unpublished observations). These preliminary findings in the rabbit and sheep, using a similar method of producing hypertension to that used in the rat, suggest that the failure of rats with AV3V lesions to become hypertensive is due either to a species difference or to a generalized decrease in the capacity of the lesioned rats to raise their blood pressure. This conclusion is supported by the observation that all types of hypertension studied, with the exception of genetic hypertension (SHR), and the pressor response to infused angiotensin II are prevented by AV3V lesions.14,15 It is possible that the gross disturbances in food and fluid and therefore sodium intake observed following the placement of lesions in rats may result in animals that are less responsive to hypertensive stimuli.

In summary, the present series of experiments shows that lesions of the optic recess of the third ventricle region, including areas similar to those destroyed by AV3V lesions in the rat, produce changes in body fluid homeostasis in sheep that are similar to those produced in rats. However, these lesions do not prevent or attenuate ACTH hypertension in sheep, suggesting that neural pathways involving the OVLT and adjacent tissue are not essential for the development of ACTH-dependent hypertension in this species.

Acknowledgments

Ciba-Geigy, Australia, kindly donated the ACTH.

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Alterations in osmotic but not pressor responses to ACTH by optic recess lesions in sheep.
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Hypertension. 1982;4:154-158
doi: 10.1161/01.HYP.4.3_Pt_2.154

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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