ALDOSTERONE SECRETION DURING HIGH SODIUM CEREBROSPINAL FLUID PERFUSION OF THE BRAIN VENTRICLES

By

Suzanne F. Abraham, John R. Blair-West,
John P. Coghlan, Derek A. Denton, David R. Mouw
and Bruce A. Scoggins

ABSTRACT

Conscious sheep with permanent indwelling cannulae in the lateral ventricles and the cisterna magna were Na depleted and then perfused for 9 h with an artificial CSF solution. There were 3 experimental groups: Group I (n = 5) received perfusion with artificial CSF containing Na 170 mEq./l, Group II (n = 7) received perfusion with artificial CSF containing Na 145 mEq./l, Group III (n = 7) received no perfusion. In Group I the blood aldosterone level fell from 26.4 ± 7.4 to 8.6 ± 2.3 ng/100 ml by 9 h after perfusion. There was no significant change in plasma [Na] or [K], blood angiotensin II or plasma renin concentration. Blood cortisol and corticosterone levels rose. There was also a fall in blood aldosterone in Group II but this was not significant until 4 h post-perfusion. Group III showed no significant change in blood aldosterone concentration. Multivariate statistical analysis showed that the fall in aldosterone levels during 170 mEq./l Na perfusion could not be accounted for by changes, either alone or together, of ACTH as evi-

denced by alteration in blood cortisol or corticosterone, or by change of plasma [Na], [K] or renin concentrations. This data supports the hypothesis of an additional factor which may be of CNS origin being involved in the control of aldosterone secretion.

Four stimuli have a direct effect on the zona glomerulosa of the adrenal to cause increased aldosterone secretion. They are increase of arterial plasma concentration of K, angiotensin II and ACTH, and decrease of Na concentration. Whereas the importance of these factors is established, there is evidence that changes in them may not be sufficient to account for all changes in aldosterone secretion which occur under several experimental conditions which can be contrived during onset and rapid correction of Na deficiency in sheep (Abraham et al. 1973; Blair-West et al. 1971a; 1973). In particular, studies on Na deficient sheep with adrenal transplants show that the consummatory act of rapid satiation of salt appetite may be associated with a large evanescent fall of aldosterone secretion over 15–30 min which is not accounted for by changes in the four known stimuli systems (Abraham et al. 1973; Blair-West et al. 1965). The data suggests an unidentified central nervous influence in aldosterone control.

To further investigate the role of the central nervous system on aldosterone secretion, a colony of sheep have been prepared with permanent indwelling cannulae in the lateral ventricles, and the cisterna magna as described by Pappenheimer et al. (1962). The ventricles of the brain of conscious animals depleted of 400–500 mEq. of Na by parotid salivary loss have been perfused for 9 h with an artificial cerebrospinal fluid (CSF) of high Na concentration 170 mEq./l. Control experiments were with 145 mEq./l Na concentration artificial CSF, or where the same chemical and physiological observations were made without perfusion.

MATERIALS AND METHODS

Experiments were performed on 10 mature cross-bred Merino sheep of body weights 25–40 kg. The animals were housed in metabolism cages and maintained on 0.9 kg/day mixed (50/50) oatlen lucerne chaff containing 80–100 mEq. Na, and had free access to water. All animals had surgically prepared bilateral carotid loops. Both ewes and wethers were studied but only ewes were used for collection of urine.

Ventriculo-cisternal perfusion. – Animals were surgically prepared with stainless steel guide tubes over each lateral ventricle and the cisterna magna at least 3–4 weeks prior to the first experiment. This enabled sampling of CSF and ventriculo-cisternal perfusion of an artificial CSF solution in the conscious undisturbed animal, and constant monitoring of ventricular pressure (Mouw et al. 1974). Strict asepsis was maintained at all times. Two different artificial CSF solutions were used. The high Na CSF solution contained Na-170 mEq./l and Cl-156 mEq./l but otherwise closely re-
sembled natural sheep CSF in ionic content. Control CSF solution was prepared identically and contained Na-145 mEq/l and Cl-130 mEq/l. The artificial CSF solutions were gassed with 95% O2:5% CO2 during the experiment and for at least 30 min prior to commencement. Samples were taken to check its ionic composition.

**Analytical methods.** – Sodium and potassium were analysed using a Technicon auto analyser. Plasma renin concentration, peripheral blood aldosterone, cortisol and corticosterone concentrations and blood angiotensin II concentrations were assayed by enzyme kinetic, double isotope dilution derivative and radioimunoassay techniques as previously described (Blair-West et al. 1964b; Catt et al. 1967; Coghaln & Scoggins 1967).

**Sodium depletion.** – The animals were depleted of Na by acute cannulation of one parotid duct, 40–60 h prior to commencement of experiment. The cannula was removed 12–20 h prior to the experiment to permit a ‘steady state’ of Na depletion and blood aldosterone concentrations to be reached. The animals lost 2.2–4.2 l of saliva containing 226–676 mEq of Na. The animals were fed 16–18 h prior to the experiment, and in most, feeding was completed within the following three hours.

**Protocol.** – There were 3 experimental groups. Group I (5 experiments) received ventriculo-cisternal perfusion of ‘high Na’ CSF solution (Na 170 mEq/l). Group II (7 experiments) received ventriculo-cisternal perfusion of ‘normal’ CSF solution (Na 145 mEq/l). Group III (7 experiments) received no perfusion. The artificial CSF solution was perfused for 9 h at a rate of 1.2 ml/min using a constant rate roller pump (Paton Industries).

Prior to perfusion, food and water were withdrawn from the animal, the lateral ventricle cannulated and a 5 ml sample of Na deplete CSF taken. Blood samples were taken 60 and 90 min prior to, and 1, 3, 5 and 9 h after commencement of perfusion and 4 h post-perfusion.

Venous blood samples were taken for measurement of blood aldosterone, cortisol, corticosterone concentrations and plasma renin concentration via a polyethylene cannula (i.d. 1.57 mm) inserted at the time of parotid cannulation. Blood samples for measurement of blood angiotensin II concentrations were taken directly from a carotid artery loop. The blood angiotensin II concentration was analysed for 5 experiments in Group I, 6 in Group II and 6 in Group III. The total volume of blood taken at the time of each bleed was 50 ml.

Prior to each blood sample being taken, the CSF outflow from the cisterna magna was sampled (5–10 ml). At least two, 30–60 min collections were taken to determine the rate of outflow during perfusion. Immediately after each blood sample the blood pressure, cardiac rate and respiration rate were measured. Systolic and diastolic blood pressures were measured by carotid loop sphygmomanometry and auscultation. Urine collections were made hourly in 4 animals in each of Group I and II via a Foley (size 16) retention catheter inserted at the time of parotid cannulation. Bladder washes with 15 ml of sterile distilled water were used.

Group III, which received no perfusion, was treated in an identical manner to Groups I and II. The initial natural ventricular CSF samples were taken in only 4 of these 7 experiments.

In no experiment was there an increase in ventricular pressure at any time during the perfusion or any possibility of air entering the ventricular system. Ventriculocisternal perfusion did not influence blood pressure, respiration, cardiac rate or behaviour of the animals.
After completion of the post-perfusion period, the animals were fed and given free access to water and a NaHCO₃ solution (300 mEq/l).

Statistical analysis. – Effects of the perfusion on the variables blood aldosterone, cortisol, corticosterone and angiotensin II concentrations, plasma renin, Na and K concentrations were tested in two ways. For each experimental group the variables were compared to the pre-perfusion level, after 3, 5 and 9 h of perfusion, and 4 h post-perfusion, using Student’s t-test for paired observations. Between group comparisons of each of the variables at each time period were made using a standard Student’s t-test. The relationship between plasma [K] and blood aldosterone concentration was examined by the methods of linear regression and correlation coefficient. To establish whether the changes in blood aldosterone concentration could be explained wholly or in part by changes in the blood level of the four major known stimuli to aldosterone production, multivariate analysis (Clyde et al. 1966) was carried out using an IBM 7044 computer. Plasma renin concentration was used as an index of the blood angiotensin II level. Even though the latter hormone was measured in the majority of the experiments, data on blood angiotensin II was not available from 4 of the 19 studies, and in all experiments at 3 h perfusion so it could not be used in the multivariate analysis. In other studies we have reported a highly significant correlation between blood angiotensin II and plasma renin concentrations in Na deficiency (Blair-West et al. 1971a). In the absence of blood ACTH measurements, the blood cortisol level was used as an index of circulating ACTH levels in the analysis. Plasma [K] and [Na] were the other two variables included. Data were analysed for each group at all time periods.

Results

Na deficit. – The mean Na deficit in Group I (Na 170 perfusion) was 492 ± 57 mEq. (mean ± se). Similar deficits of 486 ± 60 mEq. and 492 ± 52 mEq. were found in Group II (Na 145 perfusion) and Group III (no perfusion) respectively.

Table 1.

| [Na] (mEq/l) of cerebrospinal fluid prior to ventriculo-cisternal perfusion as sampled from a lateral ventricle and during perfusion as sampled from the cisterna magna. Results expressed as mean ± se. Group I, 170 Na perfusion; Group II, 145 Na perfusion. |
|---------------------------------|-----------------|-----------------|
| Natural CSF                    | 148.8 ± 1.3     | 150.1 ± 0.9     |
| Artificial CSF                 | 170.7 ± 0.9     | 145.3 ± 0.7     |
| 3 h perfusion                  | 163.0 ± 1.0     | 147.3 ± 0.7     |
| 5 h perfusion                  | 163.6 ± 1.0     | 147.1 ± 0.4     |
| 9 h perfusion                  | 164.4 ± 0.8     | 147.3 ± 0.6     |

123
Corticosterone. – Table 1 shows the relationship between the Na concentration (mean ± se) of the natural CSF taken prior to perfusion, the artificial CSF before perfusion through the ventricular system, and the perfusate collected from the cisternal outflow cannula after 3, 5 and 9 h of perfusion for Group I (Na 170 perfusion) and Group II (Na 145 perfusion). During the Na 170 perfusion the mean artificial CSF [Na] decreased by 8, 7 and 6 mEq/l indicating an elevation of the ventricular [Na] of approximately 14, 15 and 16 mEq/l above natural CSF at 3, 5 and 9 h respectively. During the Na 145 perfusion the mean artificial CSF [Na] was increased by 2 mEq/l which was 3 mEq/l below that of natural CSF. The CSF outflow collections, of 30–60 min duration, made during perfusion, showed that the outflow volume equalled the volume of artificial CSF entering the ventricular system. Any variations over the short term were accounted for by changes in the level of the animal’s head relative to the tip of the outflow cannula. Changes of less than 0.5 ml/h were outside the accuracy of measurement.

Blood aldosterone concentration. – Results for the three series of experiments are shown on Table 2. Perfusion of the ventricular system with an artificial CSF solution containing Na 170 mEq/l (Group I) was associated with a pro-

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Pre</th>
<th>3</th>
<th>5</th>
<th>9</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aldosterone (ng/100 ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>26.4 ± 7.4</td>
<td>24.8 ± 8.1</td>
<td>15.3 ± 4.3</td>
<td>8.6 ± 2.3</td>
<td>10.1 ± 2.6</td>
</tr>
<tr>
<td>II</td>
<td>23.3 ± 3.6</td>
<td>26.5 ± 3.7</td>
<td>20.0 ± 2.7</td>
<td>16.7 ± 2.8</td>
<td>11.5 ± 3.7</td>
</tr>
<tr>
<td>III</td>
<td>25.1 ± 3.1</td>
<td>26.0 ± 4.7</td>
<td>31.4 ± 5.2</td>
<td>30.4 ± 7.6</td>
<td>22.2 ± 6.3</td>
</tr>
<tr>
<td><strong>Cortisol (μg/100 ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>0.91 ± 0.29</td>
<td>1.99 ± 0.48</td>
<td>2.53 ± 0.55</td>
<td>2.35 ± 0.38</td>
<td>2.74 ± 0.62</td>
</tr>
<tr>
<td>II</td>
<td>1.19 ± 0.27</td>
<td>1.78 ± 0.57</td>
<td>4.19 ± 0.96</td>
<td>4.17 ± 1.00</td>
<td>2.19 ± 0.87</td>
</tr>
<tr>
<td>III</td>
<td>1.05 ± 0.25</td>
<td>0.35 ± 0.12</td>
<td>0.42 ± 0.10</td>
<td>0.79 ± 0.35</td>
<td>0.26 ± 0.05</td>
</tr>
<tr>
<td><strong>Corticosterone (μg/100 ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>0.06 ± 0.01</td>
<td>0.10 ± 0.03</td>
<td>0.12 ± 0.04</td>
<td>0.09 ± 0.03</td>
<td>0.05 ± 0.03</td>
</tr>
<tr>
<td>II</td>
<td>0.08 ± 0.02</td>
<td>0.11 ± 0.03</td>
<td>0.25 ± 0.07</td>
<td>0.20 ± 0.05</td>
<td>0.08 ± 0.04</td>
</tr>
<tr>
<td>III</td>
<td>0.09 ± 0.02</td>
<td>0.06 ± 0.01</td>
<td>0.06 ± 0.01</td>
<td>0.06 ± 0.02</td>
<td>0.03 ± 0.01</td>
</tr>
</tbody>
</table>
The effect of ventriculo-cisternal perfusion on blood aldosterone concentration. Results (mean ± se) are shown for Group I Na 170 perfusion and Group III no perfusion.

Progressive fall in aldosterone concentration when compared to the pre-infusion level (26.4 ± 7.4 ng/100 ml) (Fig. 1). After 5 h the mean blood aldosterone concentration had fallen by 42% to 15.3 ± 4.3 ng/100 ml and by 9 h by 67% to 8.6 ± 2.3 ng/100 ml, the latter value being significantly different ($P < 0.05$) from control. Four hours post-perfusion the aldosterone level was still significantly ($P < 0.05$) decreased (10.1 ± 2.6 ng/100 ml). Perfusion of CSF Na 145 mEq/l (Group II) also decreased mean aldosterone concentration and after 9 h the level had fallen by 37% to 16 ± 2.8 ng/100 ml. However, when compared to the pre-perfusion level this fall was not significant ($P > 0.05$) and resulted from large decreases in 3 of the 7 animals. The level at the time of the post-perfusion sample is similar to that found in Group I and is significantly lower than control ($P < 0.05$). In experiments with no perfusion (Group III) there were no significant changes in blood aldosterone concentration. The no perfusion and Na 170 perfusion groups were compared at each time period and found to be statistically different ($P < 0.05$) from each other at 5 and 9 h (Fig. 1). When between group comparisons were made at each time period, Group II showed no significant differences with either Group I or Group II.

*Plasma electrolytes.* – There was no significant change in plasma [K] in the Na 170 perfusion animals (Group I) during the experiment (Table 3). In contrast, Groups II and III showed a significant decrease in mean plasma [K].
Table 3.

Effect of ventriculo-cisternal perfusion on plasma [K], [Na] renin concentration and blood angiotensin II. Results expressed as mean ± se. Group I, 170 Na perfusion (n = 5); Group II, 145 Na perfusion (n = 7); Group III, no perfusion (n = 7).

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>3</th>
<th>5</th>
<th>9</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma [K] mEq./l</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>4.2 ± 0.2</td>
<td>4.1 ± 0.2</td>
<td>3.9 ± 0.2</td>
<td>3.8 ± 0.2</td>
<td>3.8 ± 0.1</td>
</tr>
<tr>
<td>II</td>
<td>4.3 ± 0.2</td>
<td>4.2 ± 0.1</td>
<td>3.9 ± 0.2</td>
<td>3.5 ± 0.1</td>
<td>3.5 ± 0.2</td>
</tr>
<tr>
<td>III</td>
<td>4.5 ± 0.2</td>
<td>4.5 ± 0.2</td>
<td>4.4 ± 0.2</td>
<td>4.1 ± 0.1</td>
<td>3.9 ± 0.1</td>
</tr>
<tr>
<td><strong>Plasma [Na] (mEq./l)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>142 ± 2</td>
<td>142 ± 2</td>
<td>141 ± 2</td>
<td>142 ± 2</td>
<td>143 ± 2</td>
</tr>
<tr>
<td>II</td>
<td>142 ± 1</td>
<td>142 ± 2</td>
<td>142 ± 1</td>
<td>143 ± 2</td>
<td>144 ± 2</td>
</tr>
<tr>
<td>III</td>
<td>143 ± 1</td>
<td>143 ± 1</td>
<td>144 ± 1</td>
<td>144 ± 1</td>
<td></td>
</tr>
<tr>
<td><strong>Plasma renin (ng/h/ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>2.7 ± 0.5</td>
<td>2.5 ± 0.5</td>
<td>3.0 ± 0.5</td>
<td>3.4 ± 0.7</td>
<td>3.6 ± 0.6</td>
</tr>
<tr>
<td>II</td>
<td>3.2 ± 0.6</td>
<td>3.5 ± 0.5</td>
<td>3.2 ± 0.6</td>
<td>3.6 ± 0.7</td>
<td>3.5 ± 0.5</td>
</tr>
<tr>
<td>III</td>
<td>3.6 ± 0.5</td>
<td>3.9 ± 0.4</td>
<td>3.8 ± 0.5</td>
<td>3.9 ± 0.7</td>
<td>4.4 ± 0.9</td>
</tr>
<tr>
<td><strong>Blood angiotensin II (ng/100 ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>t8.3 ± 1.7</td>
<td>—</td>
<td>7.8 ± 1.5</td>
<td>10.1 ± 1.6</td>
<td>15.5 ± 1.1†</td>
</tr>
<tr>
<td>II</td>
<td>*11.4 ± 3.1</td>
<td>—</td>
<td>13.5 ± 3.8</td>
<td>12.0 ± 2.8</td>
<td>15.3 ± 3.5</td>
</tr>
<tr>
<td>III</td>
<td>*13.2 ± 2.6</td>
<td>—</td>
<td>12.4 ± 2.3</td>
<td>12.1 ± 2.5</td>
<td>13.4 ± 1.4</td>
</tr>
</tbody>
</table>

† n = 4  * n = 5  * n = 6

In the no perfusion group (Group III) plasma [K] fell from 4.5 ± 0.2 mEq./l pre-perfusion to 4.1 ± 0.1 mEq./l after 9 h observation (P < 0.001) and to 3.9 ± 0.1 mEq./l at 4 h post-perfusion (P < 0.001). The Na 145 perfusion group (Group II) fell from 4.3 ± 0.2 to 3.9 ± 0.2 mEq./l by 5 h (P < 0.05) and to 3.5 ± 0.1 mEq./l at 9 h (P < 0.001). It remained at this level for 4 h post-perfusion. Between group comparisons were made at each time period. The no perfusion group was significantly higher than both the Na 170 and the Na 145 groups at 5 and 9 h (P < 0.05). There were no significant differences for plasma sodium concentration within each group with time or between groups.

**Blood cortisol and corticosterone concentrations.** – The mean blood cortisol and corticosterone concentrations for the three experimental groups are shown on Table 2. In Group III there was no significant change in the blood cortisol or corticosterone level until 4 h post-perfusion, at which time significant de-
increases were observed \((P < 0.05)\) when compared with pre-perfusion levels. By contrast, with the Na 170 perfusion (Group I) an increase in blood cortisol occurred during the experimental period. Blood cortisol increased from \(0.91 \pm 0.29 \ \mu g/100 \ ml\) pre-perfusion to \(2.53 \pm 0.55 \ \mu g/100 \ ml\) at \(5 \ h\) and remained at this level for the remainder of the experiment. The observed increases in blood corticosterone in this group were not significant. In the Na 145 perfusion group (Group II) the blood cortisol concentration was increased at \(5 \ h\) \((P < 0.001)\), \(9 \ h\) \((P < 0.05)\) and \(4 \ h\) post-perfusion \((P < 0.05)\) when compared with the pre-perfusion level. Although all animals showed a rise in blood cortisol concentration the large rise seen in the value at \(5\) and \(9\) \(h\) is in part due to a rise from \(1.65\) to \(8.8 \ \mu g/100 \ ml\) at \(5 \ h\) and \(9.7 \ \mu g/100 \ ml\) at \(9 \ h\) in one animal. There was also a significant increase in blood corticosterone levels in this group at \(5 \ h\) \((P < 0.05)\) and \(9 \ h\) \((P < 0.05)\) when compared with pre-perfusion levels. Again the large rises in the mean levels at \(5\) and \(9\) \(h\) were primarily due to changes in one sheep.

When between group comparisons were made for blood cortisol Group III was significantly different from the Na 170 Group I at \(3 \ h\) \((P < 0.01)\), \(5 \ h\) \((P < 0.001)\), \(9 \ h\) \((P < 0.05)\) and \(4 \ h\) post-perfusion \((P < 0.001)\). Group III was significantly different from the Na 145 Group II at \(3 \ h\) \((P < 0.05)\), \(5 \ h\) \((P < 0.001)\), \(9 \ h\) \((P < 0.05)\) and \(4 \ h\) post-perfusion \((P < 0.001)\). For blood corticosterone levels there was a significant difference between the no perfusion group and the Na 145 perfusion group at \(5\), \(9\) and \(4 \ h\) post-perfusion \((P < 0.05)\).

**Plasma renin concentration.** – There was no significant difference \((P > 0.05)\) for plasma renin concentration within each group with time or between groups (Table 3).

**Blood angiotensin II concentration.** – The results for all experiments in which blood angiotensin II levels were measured are shown on Table 3. Like plasma renin concentration there were no significant differences within or between groups.

**Urine volume and urinary Na output.** – There was no detectable change in either urine volume or urinary Na output. The urinary Na excretion was 2 mEq./h or less throughout all the experiments in which it was measured.

**Multivariate statistical analysis.** – The contribution of changes in plasma [Na], [K], renin concentration and ACTH, using blood cortisol and corticosterone as an index, to the observed changes in blood aldosterone levels was examined for each group at each time period. It was found that at \(5\) and \(9 \ h\) when aldosterone levels were significantly lowered in Group I compared with Group III or the pre-perfusion level in Group I, the reduction was not due either in part or together to changes in the variables outlined above. An addi-
tional factor/s must be evoked to explain the observed changes in the blood aldosterone level.

DISCUSSION

These studies suggest that the CNS may be either the source of an additional factor affecting control of aldosterone secretion or a centre able to influence its secretion. They also confirm earlier studies from our laboratories on the sheep (Blair-West et al. 1960, 1964a) and studies on other species (Barbour et al. 1965; Ganong et al. 1959; McCaa et al. 1973a,b; Newman et al. 1958; Van der Wal et al. 1965) which suggest that the CNS may have a role in the aldosterone response to sodium deficiency.

Ventriculo-cisternal perfusion in the conscious Na depleted sheep with an artificial CSF solution containing Na at 170 mEq./l (Group I) resulted in a significant decrease in blood aldosterone levels after 9 h of perfusion. This fall in aldosterone secretion cannot be simply explained by concomitant changes in the factors known to control aldosterone secretion. The contributions of four stimuli known to directly influence aldosterone secretion were evaluated in these experiments. Plasma [Na] changes were not statistically significant and any changes too small to affect aldosterone secretion (Blair-West et al. 1971b). Similarly, neither plasma renin concentration nor the blood angiotensin II level showed a significant decrease during perfusion. In fact, there was a tendency for the levels of both hormones to increase in the latter stage of the experiments, when blood aldosterone levels were lowest. Cortisol and corticosterone blood levels were used as an index of ACTH secretion. The marked increase in blood corticosteroid levels suggests ACTH release as a result of the perfusion. In the sheep, an increase of blood ACTH level that increases cortisol secretion to about half the functional capacity of the gland to secrete the hormone may stimulate aldosterone secretion (Blair-West et al. 1962). The measured cortisol levels indicate that perhaps the ACTH rise in these experiments may have blunted the observed fall in blood aldosterone level. Plasma [K] changes in the Group I experiments were not statistically significant. Multivariate statistical analysis confirmed that the observed fall in aldosterone secretion was not due to changes in plasma electrolytes, renin-angiotensin system or ACTH secretion acting either singly or in combination. An additional influence must be evoked to explain the change in aldosterone secretion in this group.

Blood aldosterone levels also fell in the group of animals (Group II) that were perfused with a solution containing [Na] – 145 mEq./l. However, whereas changes in plasma [Na], the renin-angiotensin system and ACTH were probably not responsible for the decline of aldosterone, the fall in plasma [K] was significant and was correlated to the change in blood aldosterone level.
As was stated in Results a large fall in blood aldosterone occurred in 3 animals and this was accompanied by a large fall in plasma [K] in two of these experiments. Previous studies have shown that small changes in plasma [K] may play an important role in control of aldosterone secretion in both Na replete and deplete sheep (Funder et al. 1969). In the light of these changes in plasma [K], it is not possible to establish whether perfusion of the ventricular system with CSF of [Na] similar to that in natural CSF influences aldosterone secretion. A [Na] of 145 mEq./l in the perfusion fluid rather than 149–150 mEq./l was used in this control group to prevent any increase in ventricular CSF Na concentration. In the remaining group (Group III) the animals were not perfused and in these animals blood aldosterone levels remained elevated.

Early studies in the sheep (Blair-West et al. 1960, 1964a) involving decerebration between the mid-collicular region and the rostral border of the pons, and including hypophysectomy and pinealectomy, showed that elevated aldosterone secretion continued in the Na depleted animal. When Na was replaced by intravenous infusion, aldosterone secretion was inhibited only in those experiments in which the decerebration was in the midpulvinar region – i.e., rostral to the colliculi. The data suggested the possibility of an inhibitor factor in the aldosterone control system – though such data should be treated with the reservations appropriate to acute experimentation. Norman (1961) varied the ionic composition of artificial CSF in experiments involving ventricular perfusion of anaesthetised dogs. However, all perfusions resulted in increased adrenal steroid output not related to changes in ionic composition. In the dog, cat and rat many studies have been carried out using ablation or lesion producing techniques to examine the influence of the CNS and pineal gland on aldosterone secretion (Barbeau et al. 1969; Bartter et al. 1964; Blair-West et al. 1964a; Ganong et al. 1959, 1961, 1966; McCaa et al. 1973a,b; Newman et al. 1958; Palkovits et al. 1965, 1974; Taylor & Farrell 1962; Van der Wal et al. 1965; De Wied et al. 1972). The results are inconsistent and interpretation is complicated by undefined effects of trauma, blood loss and anaesthesia associated with acute experimentation. The most recent of these studies in the dog by McCaa et al. (1973b) suggests that a pituitary factor other than ACTH may be important for aldosterone secretion. The presence of a similar factor was proposed by Ganong et al. (1961). Studies in the rat have shown that growth hormone and perhaps other pituitary factors as well as ACTH are important for a normal aldosterone response to sodium depletion (Palmore & Mulrow 1967; Lee et al. 1968; Palmore et al. 1970; Palkovits et al. 1970, 1971). De Wied et al. (1972) have recently reviewed the role of the CNS in aldosterone regulation in the rat. In this and a more detailed study (Palkovits et al. 1974) they reported that discrete lesions in certain areas of the hypothalamus reduced aldosterone production when the rat adrenals were subsequently incubated in vitro. Lesions in the median eminence and the ven-
tromedial nucleus lowered both aldosterone and corticosteroid production, confirming earlier studies of a similar type in the dog (Ganong et al. 1959, 1966). When the lesions were in the nucleus paraventricularis then only aldosterone production was affected. Lesions in other areas did not affect adrenal steroid production. Administration of growth hormone was able to restore aldosterone production. It is possible that the hypothalamus-pituitary axis, independent of the ACTH mechanism, is important for aldosterone secretion in the rat and possibly in the dog. In man, abnormalities on the CNS have been associated with impairment of aldosterone production (Barbeau et al. 1969; Krieger & Krieger 1964).

Other convincing evidence for a role of the CNS comes from studies on conscious trained sheep where the response to repairing established Na deficiency by voluntary satiation of Na appetite has been observed (Abraham et al. 1973; Blair-West et al. 1965). In sheep, the consummatory act of rapid satiation of salt appetite often causes a highly significant fall in aldosterone secretion within 15–36 min. Aldosterone then returns to the elevated level again before falling as a result of Na absorption from the gut. This 'psychic inhibition' can occur without change in plasma electrolyte or angiotensin II level and it does not occur if the Na is given directly into the rumen. These experiments suggest the existence of a CNS mechanism affecting aldosterone secretion which is functionally associated in some way with CNS mechanism concerned with satiation of Na appetite. Whether this inhibition of aldosterone secretion is acting via the same mechanism as that seen during ventriculocisternal perfusion is not known.

Whether it is the change in Na concentration per se or removal of other component/s of natural CSF by ventriculocisternal perfusion which results in a change in aldosterone secretion cannot be determined. The 145 mEq./l group, the control series which would have established this point, showed a fall in aldosterone level, but as discussed previously this was associated with changes in plasma [K] which may have acted as a stimulus to inhibit aldosterone secretion. The finding that the no perfusion group had a similar fall in plasma K concentration but no change in aldosterone suggests that the perfusion procedure itself may be involved. The large effect on ACTH release seen in Groups I and II also suggests a response to perfusion per se. Further studies are required to establish the exact mechanism of the aldosterone inhibition.

Although the mechanism cannot at this time be defined, the present series of experiments show clearly that the CNS may play an important role in control of aldosterone secretion. Further, confirming earlier studies in the sheep (Abraham et al. 1973; Blair-West et al. 1971a, 1973) the four known factors, plasma [K] and [Na], angiotensin II and ACTH, are not adequate to explain all the changes in aldosterone secretion observed during Na deficiency.
REFERENCES

Abraham S. F., Blaine E. H., Blair-West J. R., Coghanl J. P., Denton D. A., Moww
med. (Amst.) (1973) 733.
1161.
Bartter F. C., Barbour B. H., Carr A. A. & Delea C. S. In: Baulieu E. E. and Robel P.,
Blair-West J. R., Boyd G. W., Coghanl J. P., Denton D. A., Goding J. R., Wintour
(1965) 207.
Blair-West J. R., Cain M. D., Catt K. J., Coghanl J. P., Denton D. A., Funder J. W.,
Blair-West J. R., Coghanl J. P., Denton D. A., Ging J. R., Munro J. & Wright R. D.:
J. Physiol. (Lond.) 153 (1960) 52.
381.
Ganong W. F., Lieberman A. H., Daily W. J. R., Yuen V. S., Mulrow P. J., Luetscher
169.
32 (1973a) 356.
407.
Received on December 11th, 1974.