Rate of Change in Sodium and Potassium Excretion After Injection of Aldosterone Into the Aorta and Renal Artery of the Dog

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ABSTRACT

GANONG, WILLIAM F. AND PATRICX J. MULROW. Rate of change in sodium and potassium excretion after injection of aldosterone into the aorta and renal artery of the dog. Am. J. Physiol. 195(2): 337-342. 1958.—The rate of change in sodium and potassium excretion and reabsorption following the intra-arterial injection of single 2-, 5- or 10-μg doses of aldosterone was compared with the effect of similar doses injected directly into one renal artery, in nine adrenalectomized female mongrel dogs off replacement therapy for 48 hours. After a delay of 5-30 minutes, the hormone produced decreased sodium and increased potassium excretion, and a rise in sodium and a fall in potassium reabsorption associated with no consistent change in glomerular filtration rate. The magnitude of the response was greater with larger doses but the onset and rate of development of the changes were not changed. Direct injection into the renal artery produced changes which did not differ in their timing or magnitude from the effects of the same doses injected intra-arterially. The effect on the uninjected kidney was not significantly different from that on the injected side. PSP and Pitressin produced more profound effects on the injected side.

Aldosterone administration is followed by sodium retention and potassium diuresis in a variety of species (1-3). There is little doubt that this hormone plays a role in electrolyte homeostasis (4). However, its role in acute changes in sodium and potassium excretion has not been settled, partly because little information is available concerning its rate of action. The present experiments were designed to study the rate of change in sodium and potassium excretion after injection of aldosterone into the aorta and renal artery of adrenalectomized dogs. Part of the data obtained has been presented in an abstract (5).

METHODS

Nine female mongrel dogs weighing 7.5-15.5 kg were studied. The right adrenal was removed through a flank incision after resecting the last rib. Right nephrectomy was performed at the same time in one dog (177-59). In seven of the dogs, the left adrenal was removed 6-14 days later and, at the same time, a PE-10 polyethylene catheter was inserted transaortically into the left renal artery by a modification of the technique of Barger, Rudolph, Rokaw and Yates (6). In two dogs these procedures were carried out immediately after right adrenalectomy. The cannula was led through a stab wound in the flank, where it was held in place by a plastic spindle and cap.

Postoperatively, the animals were maintained on 5 mg of cortisone acetate and 0.2 mg of desoxycorticosterone acetate in oil daily, and fed a commercial dog food with sufficient supplementary salt to provide a
TABLE I. RATE OF EFFECT OF ALDOSTERONE ON SODIUM AND POTASSIUM EXCRETION

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Dose of Aldosterone, µg</th>
<th>Route of Administration</th>
<th>Time From Aldosterone Injection to Beginning and End of Collection Period, min.</th>
<th>Initial effect</th>
<th>Maximal effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left kidney</td>
<td>Right kidney</td>
<td>Left kidney</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Na</td>
<td>K</td>
<td>Na</td>
</tr>
<tr>
<td>20-57</td>
<td>2</td>
<td>IA</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>162-57</td>
<td>2</td>
<td>IA</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>177-56</td>
<td>5</td>
<td>IA</td>
<td>10-20</td>
<td>30-40</td>
<td>5-10</td>
</tr>
<tr>
<td>307-56</td>
<td>10</td>
<td>IA</td>
<td>15-20</td>
<td>25-30</td>
<td>75-90</td>
</tr>
<tr>
<td>133-57</td>
<td>2</td>
<td>LRA</td>
<td>None</td>
<td>30-35</td>
<td>t</td>
</tr>
<tr>
<td>238-56</td>
<td>5</td>
<td>LRA</td>
<td>30-40</td>
<td>20-30</td>
<td>10-20</td>
</tr>
<tr>
<td>246-56</td>
<td>10</td>
<td>LRA</td>
<td>5-10</td>
<td>10-15</td>
<td>75-90</td>
</tr>
<tr>
<td>237-56</td>
<td>10</td>
<td>LRA</td>
<td>35-40</td>
<td>30-35</td>
<td>30-45</td>
</tr>
</tbody>
</table>

Periods selected were those showing first consistent change or maximum change, and those in which change in percentage of filtered electrolyte reabsorbed confirmed changes in excretion. IA: intra-aortic; LRA: injected in left renal artery.

* Unilateral nephrectomy. † Right ureteral catheter obstructed.

Sodium intake of 200 mEq/day. The cannula was kept patent by flushing it with heparin every 3-4 days.

The experimental studies were performed 11-71 days after the insertion of the left renal artery cannula. Two days prior to each study, maintenance steroid therapy was stopped and a single intramuscular dose of 50 mg of cortisone acetate administered. On the experimental day, the dogs were lightly anesthetized with pentobarbital. The ureters were catheterized through an abdominal incision, and plastic cannulae were inserted through the femoral artery and vein into the aorta and the inferior vena cava. After a priming dose of creatinine, a sustaining infusion of creatinine in isotonic saline was infused at a constant rate of approximately 5 ml/min. After 60-90 minutes of equilibration, timed urine collections were begun from each of the ureteral catheters. Appropriately timed arterial blood samples were also collected. After 25-30 minutes of control collections, aldosterone, diluted with saline to a volume of 1 ml of isotonic solution, was injected over a period of 1 minute into either the renal artery or the aorta. The cannula was rinsed with 2 ml of isotonic saline. The length and total number of collection periods varied from animal to animal, although in all dogs, collections were continued for 2-3 hours after injection of aldosterone. In seven of the dogs, 5-minute periods were continued from the start of the experiment until 1 hour after injection of aldosterone, while in two dogs, 2-minute periods were run for 4 minutes before and 10 minutes after hormone injection. These short periods were followed by 10-30-minute collection periods.

All five animals receiving aldosterone directly into the renal artery were also given, either before or just after the completion of the collections outlined above, 6 mg of phenolsulphonphthalein into the renal artery while 1-minute urine collections were being made from each ureter. A rough estimate of the amount of PSP present in the specimens was made visually and in one dog the values were checked photometrically. In two animals, after the aldosterone studies were completed, Pitressin (Parke, Davis & Company) was injected into the renal artery and urine volume measured from each kidney at 1-minute intervals for 5-10 minutes.

All animals were killed at the end of the clearance studies and the positions of the various cannulae verified at autopsy. The kidneys were examined grossly and microscopically.

Sodium and potassium determinations were performed on a flame photometer, using lithium as the internal standard. Creatinine was determined by the method of Bonsnes and Taussky (7).
RESULTS

The times of the initial and maximal effect of aldosterone on sodium and potassium excretion in eight of the nine dogs are shown in Table 1. The other dog received 10 μg of aldosterone into the renal artery and appeared to show sodium retention and potassium diuresis of the same order of magnitude and timing as the other dogs. However, since sodium excretion was falling and potassium excretion rising during the control periods in this dog, it was impossible to fix with certainty the times of onset and maximal effect. One of the dogs had a transient fall in creatinine clearance (Fig. 1), and two showed a gradual decline in clearance during the experiment of 2-4 ml/min. In the remaining dogs, creatinine clearance did not change appreciably.

Four dogs were given aldosterone intravenously. No change in sodium and potassium excretion was detected in either of the two dogs which received a 2-μg dose by this route. The dog which received 5 μg of the hormone had been unilaterally nephrectomized. The results obtained in this animal are illustrated in Figure 1. The dog receiving 10 μg intra-arterially showed changes which were of greater magnitude, but similar in time of onset and maximal effect. In the latter two animals, no change in potassium or sodium excretion occurred for 10-20 minutes. Thereafter, sodium excretion declined while potassium excretion rose, the maximal effect on sodium excretion occurring in about 1½ hours.

Aldosterone was injected directly into the renal artery in five dogs. The animal which received 2 μg of aldosterone by this route showed no change in sodium excretion. Potassium excretion, on the other hand, was moderately increased, beginning 30-35 minutes after the aldosterone was injected. The catheter in the right ureter of this dog became clogged during the posthormone collection periods, so conclusions about the events in the right kidney cannot be made. However, when the patency of this catheter was restored 75 minutes after aldosterone injection, the sodium and potassium values on the right side were practically identical with those on the left.

The data from the animal receiving 5 μg of aldosterone into the left renal artery is illustrated in Figures 2A and 2B. In this dog, the delay in onset of the changes in sodium and potassium excretion was even more prolonged than it was in the animal receiving the same dose intra-arterially. Creatinine clearances remained constant until the last collection period. It is clear that neither during the 2-minute clearance periods following aldosterone administration nor thereafter was any difference manifest between the two kidneys with regard to the timing and extent of the changes produced.

The changes in sodium and potassium excretion produced by injecting 10 μg of aldosterone into the left renal artery also followed similar time courses in both kidneys except in dog 246-50. This animal showed a moderate fall in sodium excretion in the 0-5-minute collection period after hormone administration, but otherwise, like the other animals, the changes produced were similar on the two sides. Generally, the 10-gamma dose produced effects of greater magnitude on electrolyte excretion than the smaller doses, but the maximum effect occurred at about the same time.

These results are in contrast to those obtained when PSP was injected into the left
renal artery in the same animals. In all cases, PSP appeared in the urine from the left kidney in either the 1st or the 2nd minute after its injection, and in the right kidney 1 minute later. Its concentration was always greater on the injected side initially, and the total amount excreted on the injected side was higher.

In two animals, injection of Pitressin had a more profound effect upon the injected side. Each of the animals tested received a 2- and a 20-μg dose. In one dog (fig. 3), the 20 μg dose caused a 90% reduction in urine volume on the injected side for 2 minutes, but by the 3rd minute after injection, volume was again normal. The simultaneous effect on the un.injected kidney was slight. The 2-μg dose produced a 15% reduction in urine volume lasting 2 minutes on the injected side in both dogs, with no effect on the opposite kidney. The 20-μg dose produced a 50% decrease in urine volume for 2 minutes in the other dog tested.

**DISCUSSION**

In the present experiments, 2 μg of aldosterone had no clear-cut effect on sodium and potassium excretion when injected into the aorta. The one animal in which it was injected into the renal artery showed a potassium diuresis with no effect on sodium excretion or reabsorption. Liddle, Cornfield, Casper and Bartter (8) report that the adrenalectomized dog shows detectable changes in sodium and potassium excretion following the intravenous injection of as little as 1 μg of aldosterone. Howcvcr, their experiments were performed on unanesthetized animals.

It should be noted that the doses of Pitressin used in the present experiments are considerably larger than the minimal amounts to which the dog is said to be capable of responding (9). However, our dogs were adrenalectomized, off replacement therapy and acutely traumatized prior to the injection of Pitressin.

A delay in the onset of the renal effects of aldosterone following the injection of a single dose of the hormone was repeatedly observed. Sartorius and Roberts reported a delay of about one-half hour before continuous intravenous infusion of desoxycorticosterone acetate produced effects on electrolyte excretion (10). In our experiments, a delay was still present when free aldosterone was injected directly into the renal artery. It would be interesting to know if other adrenocortical steroids which effect sodium and potassium excretion exhibit a similar latent period before their effects become manifest. This problem does not seem to have been studied directly, but in one of the published reports of the effects of hydrocortisone administered by continuous intravenous infusion, changes in electrolyte excretion were not apparent for an hour or more (4).

The other remarkable features of the present results are the lack of a greater or more rapid effect of the hormone on the injected side, and the similarity between the effects produced by injection into the renal artery and intra-aortic injection. In contrast, PSP
appeared more rapidly and in greater concentration on the injected side, and Pitressin produced a very prompt and mainly unilateral effect when injected into the renal artery. Injection of digoxin (11), mercurial compounds (11, 12) and various solutes (13) directly into one renal artery has been shown to produce a marked unilateral effect on water and electrolyte excretion. Most of these experiments involved acute surgical manipulation of one kidney, yet all the substances except digoxin produced a unilateral effect within the first postinjection collection period.

Barger, Berlin and Tulenko have recently reported experiments in which they have constantly infused various substances for several hours into one kidney through a chronically implanted renal artery catheter (14). Their results with Pitressin are essentially the same as ours. With aldosterone, they have also observed a delay in the onset of changes in electrolyte excretion. However, by perfusing small amounts of aldosterone into one kidney for long periods of time, they produced effects on sodium and potassium excretion which were mainly unilateral. The lack of a preferential effect on the injected kidney in the present experiments may therefore be related to the more rapid injection of the hormone.

The reasons for the delay in the onset of the effects of aldosterone are unknown. The possibility that the hormone must be altered somewhere else in the body before it acts on the kidney is unlikely in view of the report of Barger et al. cited above (14) that unilateral effects can be produced by prolonged injection into one kidney. The delay is probably not related to a slow transport of aldosterone from blood to its site of action because the half-life of aldosterone after intravenous injection is short (15). It seems likely, therefore, that the system in the kidney effected by aldosterone responds slowly to the hormone. This site of action is unknown. Previous work with other hormones does not indicate an obvious ion exchange mechanism. Ammonia and titratable acidity are not effected by acute administration of desoxycorticos- terone (16). Moreover, the present experiments indicate that sodium and potassium excretion may vary independently, since the time of onset and maximum effects of aldosterone on the excretion of these ions are not the same. Further work in this field is therefore necessary before the delay in the onset of the effects of aldosterone can be explained.

In view of the present experiments, it does not seem likely that physiological quantities of aldosterone play a role in the rapid changes in electrolyte excretion observed after such procedures as changes in posture (17). Some other mechanism must be involved, as indicated by the studies of Rosenbaum, Papper and Ashley on adrenalectomized human beings (18).

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REFERENCES