Journal of Steroid Biochemistry, 1972, Vol. 3, pp. 143–149. Pergamon Press. Printed in Great Britain

EFFECT OF ALDOSTERONE ON MAMMALIAN INTESTINE

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SUMMARY

The distal part of the large intestine is the part of the gut most affected by aldosterone, and in man, the rectum offers a simple epithelium for studying aldosterone effects. The transmucosal P.D. (potential difference) of rectal mucosa rises considerably after aldosterone is given and its magnitude becomes markedly dependent on the luminal sodium concentration. Sodium influx (lumen to plasma) and absorption rate are increased and the concentration of sodium in the lumen is reduced to much lower levels than in untreated individuals. Potassium secretion rate is increased but at present the evidence is against any close link of sodium and potassium movements.

The sodium content of the epithelial cells is relatively high and unaffected by aldosterone. Studies of sodium kinetics in the epithelium indicate that the absorbed sodium does not mix with the cell sodium. A simple model of the sodium transporting system of colonic epithelium is proposed in which only a small fraction of the cell sodium is involved in the transepithelial movements.

INTRODUCTION

ALTHOUGH there is some evidence that aldosterone can affect ionic movements in the small intestine[15, 17, 18], it is the large intestine which appears to be the part of the gut most influenced by the hormone. In species as diverse as toad[3], rat[8] and man[13], increased sodium absorption has been shown to follow aldosterone administration. In the rat, for example, we found that after aldosterone administration there was a rise in the transmucosal electrical potential difference (P.D.) of the colon particularly evident in the descending colon and that this was associated with a parallel rise of the short circuit current, tissue conductance being unchanged[8, 9]. The increase of short circuit current appeared to be almost entirely due to increase in the active transfer of sodium from the lumen towards the blood, that is in sodium absorption.* Since in animal experiments the distal colon was shown to be mainly involved, it was not surprising that we could demonstrate a similar phenomena in human rectum[7]. Studies on the rectum thus provide an excellent means of examining directly the responses of a relatively simple human epithelium to aldosterone[11].

ALDOSTERONE EFFECTS ON HUMAN RECTUM

Transmucosal P.D. was measured in man using specially designed electrodes incorporating silver–silver chloride junctions and the ionic movements were measured using a dialysis method[6]. Aldosterone was given as two intravenous injections of 0·5 mg at a 2 h interval. Sodium, potassium and hydrogen are the principal anions normally crossing the rectal and colonic epithelium. With a solu-

*In this account, absorption means that the net flux is directed from lumen to plasma, and secretion means the direction is from plasma to lumen.

tion in the lumen of similar composition to extracellular fluid, sodium is absorbed and potassium secreted, both processes being markedly influenced by mineralocorticoids. Hydrogen ions are also secreted although usually this property is masked by the much greater secretion of bicarbonate ions. Hydrogen ion secretion can however be shown by modifying the technique. We have not been able to demonstrate any definite effect of mineralocorticoids on the secretion rate of either bicarbonate or hydrogen ions but chloride absorption rate is increased.

Electrical potential difference

The transmucosal P.D. of the rectum and sigmoid colon rises during a period of a few h following aldosterone administration and within 6 h has usually reached values considerably higher than are ever observed in untreated subjects [7]. In man and animals the results of faecal analysis suggest that large intestine, in contrast to kidney, does not 'escape' from the action of aldosterone [2, 5, 14]. Our observations on animals given prolonged aldosterone infusions intravenously [19] and on one human volunteer given fludrocortisone for about two weeks [12] showed persistent elevation of the P.D. consistent with the absence of an intestinal 'escape' phenomenon. It was because of these findings that we suggested the possible value of the measurement of rectal P.D. in screening hypertensive subjects for pathological hyperaldosteronism [12].

In normal subjects the P.D. changed only to a small extent when the sodium concentration of the luminal solution was reduced (Fig. 1). In aldosterone treated subjects, there was in contrast a striking dependence of the P.D. on the luminal sodium concentration while changes of the luminal concentrations of potassium, chloride or bicarbonate had little influence.

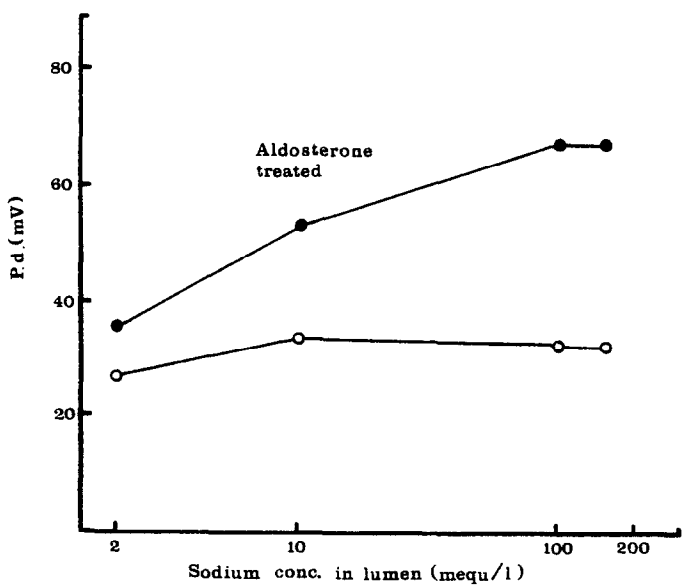

Fig. 1. The effect of altering the luminal sodium concentration on the transmucosal P.D. of the rectum of a normal subject before and after aldosterone administration. All solutions were rendered isotonic by the addition of mannitol.

Sodium fluxes

Flux measurements showed that sodium absorption was increased by aldosterone, a result of a rise in the sodium influx (lumen-to-plasma) rate with the efflux rate being not significantly affected (Table 1). These effects were most obvious when the luminal sodium concentration was low. At high luminal sodium concentration we have found it difficult to demonstrate a significant increase in the sodium influx rate. Since however in these circumstances changes in volume of the luminal solution become critically important (and are difficult to measure with sufficient accuracy), our difficulty here may simply reflect an inadequacy of the experiments. With an initial luminal sodium concentration of 10 meq/l. and usually also 20 mequ/l. the efflux rate exceeded the influx rate so that the luminal sodium concentration rose (Table 1, Fig. 2). After aldosterone treatment, the influx rate was increased and exceeded the efflux rate so that the luminal sodium concentration fell. If the experiment was prolonged the latter often fell to as low as 3–4 mequ/l.

Potassium secretion

A substantial rise of the potassium secretion rate accompanied the increased sodium absorption rate and the question arises as to whether they depend on each other. This is a question we are presently investigating and it cannot yet be completely answered. Although we have not so far found a way of substantially reducing potassium secretion while leaving sodium absorption unchanged, the evidence available does suggest that the sodium and potassium movements are to a considerable extent independent. Thus, we have not been able to demonstrate a good correlation between the amounts of sodium absorbed and of potassium secreted. Furthermore potassium secretion still occurs, and its rate is markedly increased by aldosterone, even when the luminal sodium concentration is zero or

Table 1. Effect of aldosterone on sodium and potassium transport by human rectum

Initial concentration in lumen		Net rates (μmoles/8 cm length. 30 min)			
		Before aldosterone		After aldosterone	
Sodium	Potassium	Sodium	Potassium	Sodium	Potassium
120	20	+58	−1·2	+79	−10·7
		±5·5	±4·6	±12·6	±2·9
20	20	+4·8	+3·5	+19·7	−8·6
		±1·6	±2·4	±1·3	±0·9
10	20	−2·0	−2·5	+10·4	−12·5
		±1·3	±1·1	±0·7	±4·1
		Sodium flux rates			
		J_{LS}	J_{SL}	J_{LS}	J_{SL}
10	20	17·6	20·4	34·6	22·5
		±3·2	±1·8	±2·8	±1·7

The results (given as mean ± 1.S.E.) are taken from a study on a normal subject and are based on three experiments with each solution. Sodium − 22 was added to the luminal solution to allow measurement of the sodium flux rates. The positive sign indicates absorption, the negative indicates secretion.

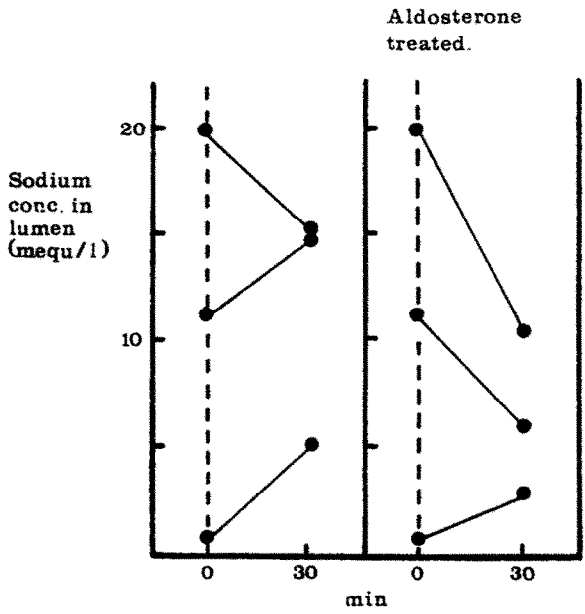

Fig. 2. The change of sodium concentration in solutions placed in human rectum before and after aldosterone treatment. The initial sodium concentration was 2, 10 or 20 mequ/l, potassium was 20 mequ/l and mannitol was present to render all solutions isotonic.

very low (Table 1). The movements of sodium and potassium do not therefore appear to be closely linked although they may well influence each other indirectly to some extent by altering the electrical charge on the epithelium.

SODIUM CONTENT OF THE EPITHELIAL CELLS

The remarkable effect of aldosterone in stimulating the epithelium of the rectum and colon to reduce the luminal sodium concentration to a very low level needs further consideration. In the transport of sodium across an epithelium it is usually supposed that the ions enter the epithelial cells passively, dependent on the electrochemical gradient between the lumen and cell contents. Thus, in order that a net sodium flow from the lumen into cell would continue even when the luminal sodium concentration was low, it might be expected that the intracellular sodium concentration would be at a very low level. We investigated this possibility in studies on rat descending colon by measuring the amounts of sodium and other ions in the epithelial cells. The cells were obtained by gentle scraping of the mucosa, the animals being earlier injected with [^{14}C]-inulin so that the amount of extracellular fluid present in the scrapes could be estimated. No significant differences in water or ionic composition could be demonstrated between the control and the aldosterone-treated animals. Furthermore the intracellular sodium concentration as calculated from the amounts of sodium and water averaged 47 mequ/kg of cell water thus considerably exceeding the luminal sodium concentration over much of the range associated with sodium absorption. Net flow of sodium into the cell appeared therefore to take place against the concentration gradient. This could not be easily explained by postulating a diffusion P.D. across the luminal face of the cell. In the first place it was difficult to see what ionic movements could account for the diffusion P.D. Secondly, variations in the luminal

content of potassium, chloride and bicarbonate appeared not to exert any significant influence on the sodium absorption rate in these experiments.

KINETICS OF SODIUM ABSORPTION

The likely explanation is suggested by the results of experiments that we have been carrying out using miniaturized radionuclide measuring devices for studying the epithelial kinetics of various ions during absorption *in vivo* [1, 10]. In the case of sodium we have found that on removing the luminal solution which contained [^{24}Na] and replacing it by a nonradioactive solution, the radionuclide was very rapidly removed from the tissue, $T_{1/2}$ being less than two min. (Fig. 3). As stopping the blood flow largely prevented this, it seemed likely that the radionuclide pool we were observing was beyond some barrier which prevented much back diffusion to the lumen. It may have represented sodium which had already been pumped

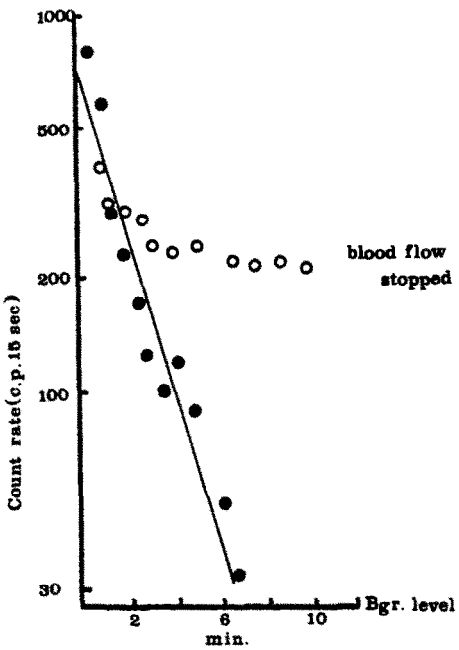

Fig. 3. The rate of removal *in vivo* of [^{24}Na] from the wall of the rat colon. Initially for 15 min. a solution containing ^{24}Na was in the lumen. It was removed at time zero and replaced by radioisotope free solution. The blood supply was stopped by a clamp on the aorta.

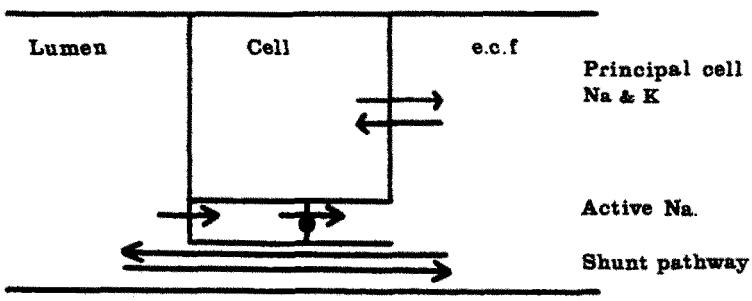

Fig. 4. Hypothetical representation of sodium transport across colonic epithelium.

into the intercellular spaces. In any case it seems very unlikely that the radionuclide had exchanged into the main mass of sodium within the epithelial cells. If this were so, then the sodium fluxes across the serosal face would have to be very great to account for the short half time.

We suggest that the scheme represented diagrammatically in Fig. 4 is more likely. In this scheme, it is supposed that the active absorption of sodium occurs through a sodium pool which constitutes only a small and separate part of the epithelial cell sodium. There is some evidence from other tissues for the possibility that sodium within cells may be compartmentalized[16, 20]. In addition, there is probably a shunt pathway through which sodium, potassium and probably other ions can diffuse across the intestinal epithelium[1]. Since the tissue electrical conductance is unchanged by aldosterone[9], this pathway is presumably unaffected by the hormone. It seems likely therefore that aldosterone influences the movement of sodium through the epithelium without involvement of more than a very small fraction of the sodium present.

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DISCUSSION

Leaf: I would like to support Dr. Edmonds's view of the compartmentation of the sodium transport pool because in the bladder the transport pool is about 25% of the total sodium within the cell.

Edmonds: Yes.

Crabbé: Morphologically, is the colon epithelium rather homogeneous or do you deal with a lot of mucus-secreting cells?

Edmonds: There are many mucus-secreting cells in the crypts but apart from this it seems to be fairly homogeneous with few superficial goblet cells.

Edelman: Did aldosterone produce an increase in the transepithelial electrical potential difference?

Edmonds: Yes, that's right. The first measurable P.D. increases are about 2–3 h later to a reach a maximum about 6 h after aldo addition. If repeated injections are given to keep aldosterone effect high we can keep the P.D. at a high level for a long time.

Edelman: Is it possible that accumulation of K^+ in the luminal fluid is a consequence of the increase in the potential difference?
Edmonds: This point of view is certainly possible. However, if we reduce the sodium concentration to very low, almost zero level, e.g. by substituting choline chloride solutions in the lumen, a P.D. still remains but is similar whether aldosterone has or has not been given. But even when we do this, we still get a considerable rise of potassium flux into the lumen. This seems inconsistent with the interpretation that the increased P.D. is the driving force responsible for the increased potassium flux into the lumen.
Edelman: Is the latent period of the K^+ effect the same as that of the Na^+ effect?
Edmonds: I can't really answer that. I haven't got the measurements. It would certainly be worth measuring this.
Leaf: Did you do any controls with inhibitors?
Edmonds: No we haven't. We have studied some patients while on spirolactone using comparable procedures. But most of our patients were not given any other drugs than aldosterone nor maintained under special conditions—not on special diets or at controlled temperature for example.
Handler: May I just make a suggestion along the line of Dr. Edelman's question? Have you tried the effect of actinomycin D on the sodium and potassium transport in the colon? In the kidney this drug blocks the effect on sodium and not the effect on potassium.
Edmonds: Yes. We have done this kind of study with animals; at least, we have tried, but have found it very difficult to block the aldosterone effect without killing the animals. By just measuring the P.D. we compared the effect of actinomycin D on the hormone thyroxin and on aldosterone. It is quite easy to block thyroxin action in the gut—one can show this simply with non toxic doses of the drug—but aldosterone action is very resistant and P.D. together with sodium reabsorption is extremely difficult to stop rising, so we were all rather disappointed about this and gave up.
Porter: I am not sure how you are preparing your patients. Do they receive the aldosterone-blocking agent spirolactone?
Edmonds: We have been using spirolactone in some of the patients but I haven't mentioned this group of data because we had not enough time. The patients the results of which were shown here were all patients without any particular preparation beforehand. The patients were all patients coming to the hospital for some kind of bowel investigation to be done and then they would receive aldosterone.
Porter: Would the spirolactone block your effect?
Edmonds: Yes, to some extent, though possibly not completely. Spirolactone even in normal individuals has some action on the colon. One can easily demonstrate this simply by observing the lowering of P.D. and decrease of sodium absorption which occurs when the drug is given.