Renal sodium transport and oxygen consumption

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Renal sodium transport and oxygen consumption. Am. J. Physiol. 201(3): 511-516. 1961.—Glomerular filtration rate and renal blood flow were increased in dogs by infusion of 270 mEq/min of glycine and hypertonic NaCl at rates of 8 ml/min. This procedure resulted both in an increased rate of sodium reabsorption and in increased oxygen consumption. Approximately six equivalents of sodium were transported per equivalent oxygen consumed, a ratio similar to that obtained by others when glomerular filtration rate had been reduced. These observations strongly suggest that a large part of renal oxygen consumption is related to the transport of sodium. When the rate of sodium reabsorption was reduced during mannitol diuresis, arteriovenous oxygen difference decreased, but renal oxygen consumption remained unchanged. It is suggested that the active sodium transport in the proximal tubules continues at an unchanged rate during mannitol diuresis but that net reabsorption is reduced owing to increased passive influx into the tubular lumen when the transtubular concentration gradient increases. Other interpretations are discussed.

It is widely assumed that transport of sodium ions is the primary event in the reabsorption of the bulk of the glomerular filtrate. It would, therefore, seem reasonable that the active transport of sodium is the reabsorptive process which requires most oxygen. This belief has been strengthened by the observation of a stoichiometric relationship between extra oxygen consumption and active sodium transport over a wide range of transport rates in the isolated amphibian skin (1-3). In analogy with these findings oxygen consumption has been used as a measure for the transport rate of sodium in kidney slices (4). Munck (5) pointed out that if the oxygen consumption of the anuric kidney is representative of the metabolic demand of processes other than tubular transport, 4 ml of oxygen/100 g of kidney might be used for tubular transport of sodium. This gives a ratio of sodium transport to excess oxygen uptake (both measured in mEq/min) of 3 or more (6), which is higher than the ratio obtained in studies of the isolated frog skin (3). Hess Thaysen et al. (7, 7a) and Kramer and Deetjen (8) reduced the glomerular filtration rate in dogs roughly parallel to renal blood flow and confirmed that there was a parallel reduction in oxygen consumption. Assuming that the reduction in oxygen consumption was due to reduction in sodium transport, the ratio of sodium transport to excess oxygen uptake was found to be 6.9 and 6. The main objection to such experiments is that more and more nephrons may be nonfunctioning when the perfusion pressure is reduced (9). The reduction in oxygen consumption might, therefore, solely result from reduction in functional tissue. We have studied the relationship between oxygen consumption and sodium transport when the rate of sodium reabsorption was increased above normal levels. This was accomplished by the administration of glycine (10) and hypertonic saline (11).

If there exists a close relationship between oxygen consumption and sodium transport, oxygen consumption might be expected to be reduced when net sodium reabsorption is reduced by the induction of large diuresis. Van Slyke et al. (12) studied in dogs the relationship between diuresis and oxygen consumption and arrived at the conclusion that both renal blood flow and oxygen consumption increased in response to metabolic demands not directly related to excretory work. The range of urine flow in their studies, however, was not more than 1.6 ml/min. There are no available data about the renal oxygen consumption over a wide range of sodium transport in the intact animal. With the large errors involved in the estimation of renal oxygen consumption, large variations in solute excretion are required.

We have, therefore, studied the relationship between oxygen consumption and sodium transport by reducing the sodium chloride reabsorption by 20-40% by induction of osmotic diuresis.

METHODS

Experiments were performed on five female dogs weighing 13-24 kg, and a total of 54 clearance periods...
forms the basis of this report. One of the dogs had been nephrectomized (left kidney) 1 month prior to the experiment. Anesthesia was induced by sodium pentobarbital, 30 mg/kg body wt. intravenously, and maintained by small additional doses. The renal pedicle was approached through an abdominal midline incision. Care was taken to ligate ovarian veins entering the renal vein. A cardiac catheter of size 7 or 8 F, inserted into the jugular vein, was guided into the renal vein. The position of the catheter was controlled at the end of the experiment. In order to maintain free air passage, the dogs were intubated, but oxygen was not administered. Arterial samples were obtained through an indwelling short plastic tube from the brachial artery. A brachial vein was used for infusions. After obtaining blood samples for determination of blood blanks, intravenous priming injections of creatinine and para-amino-hippurate (PAH) were followed by continuous administration at rates which ensured optimal extraction of PAH. In the dog with one kidney, urine was collected through a bladder catheter. In the other dogs a polyethylene tube was inserted into the ureter of the experimental kidney through the abdominal incision and tied in place at the pelviureteral junction. A 0.45% NaCl solution was administered by drip until a constant water diuresis of approximately 2 ml/min was obtained. An equilibration period of at least 40 min elapsed before the start of three to four clearance periods, each of 10 min duration. Blood samples from the brachial artery and the renal vein were obtained in the middle of the period in the same order in all clearance periods. The saline heparin solution in the catheters in the artery and in the renal vein and 2 ml blood were withdrawn gently and discarded before the collection of blood samples for analysis.

The timed urine samples were collected consecutively from the ureteral catheter. Emphyzing by suprapubic pressure and rinsing with water were performed in the experiment where urine was collected from the bladder.

When an increase in the rate of sodium reabsorption was desired, glycine was administered after the control periods at a rate of 160 mg/min. In order to increase further the rate of sodium reabsorption hypertonic saline was administered as indicated in the tables.

When a reduction in the rate of sodium reabsorption was desired, large diuresis was induced by the additional infusion of 20% mannitol in saline at rates of 20-38 ml/min. In one of the experiments mercuhydrin (Mercuhydrin, Astra) was also administered. Because of the large urine flow the clearance periods were reduced to 5 min in some of the experiments.

Physically dissolved oxygen was calculated by means of the oxygen dissociation curves in dogs (13). For oxygen determinations 4.5 ml blood was collected anaerobically in a 5-ml Luer glass syringe with the dead space filled with heparin solution. After collection of a blood sample a small amount of mercury was drawn into the syringe (for mixing); the syringe was anaerobically in a 5-ml Luer glass syringe with the dead space filled with heparin solution. After collection of the blood sample, the syringe was anaerobically sealed by means of a short piece of rubber tubing and a glass plug and placed in ice water.

After vigorous shaking for 1 min and discarding the blood in the tip of the syringe, 2.5 ml of blood was transferred to a test tube. In this sample triplicate determinations of the hemoglobin concentration were performed by the cyanmethemoglobin method (14), using an extinction coefficient of 10.8. The hemoglobin oxygen saturation was determined spectrophotometrically (15). Readings were performed in three cuvettes. Spectrophotometric constants were determined for the actual blood. Blood for the determination of PAH was also immediately cooled and centrifuged in a cold room at 4°C and the plasma carefully siphoned off.

Sodium and potassium were determined by means of a Baird indirect flame photometer. The rate of reabsorption of sodium and potassium was calculated as the difference between the plasma sodium and potassium concentrations in arterial and renal vein plasma. Renal sodium and potassium excretion were calculated as the difference between arterial and renal plasma sodium and potassium concentrations and the rate of glomerular filtration rate. Renal sodium and potassium excretion were calculated as the difference between arterial and renal plasma sodium and potassium concentrations and the rate of glomerular filtration rate.
RESULTS

In this study as well as in preliminary experiments performed on three unanesthetized dogs it was shown that the infusion of glycine consistently increased the glomerular filtration rate.

Table 1A contains data from one experiment where sodium reabsorption was increased in two steps. Glomerular filtration rate was first raised by the administration of glycine. Further increase in both glomerular filtration rate and plasma sodium concentration was achieved by the intravenous administration of hypertonic saline. The result of this procedure was an increase in both excretion and reabsorption rates of sodium. Considerable time was allowed to elapse between control periods and experimental periods in order to reach a new equilibrium. When mean values for the last three periods are compared with mean values of control periods, oxygen consumption increased by 34% and sodium reabsorption by 27%, whereas arterial blood flow increased by 79%. Fig. 1 shows the relationship between oxygen consumption and sodium reabsorption in this experiment and in another one where oxygen consumption increased by 70% and sodium reabsorption by 57% during the combined administration of glycine and hypertonic sodium chloride.

In well-hydrated animals given adequate infusion of saline filtered load and sodium excretion increased in parallel during mannitol diuresis, so that the rate of sodium reabsorption remained virtually unchanged. In order to produce a reduction in sodium reabsorption, sodium was not administered. Serum sodium levels were low, and the acute sodium depletion induced by mannitol diuresis counteracted increase in filtration rate. Table 1B shows one of the experiments where the rate of sodium reabsorption was reduced by more than 40% of the control values. During mannitol administration and in the last four periods during additional infusion of metalluride, the plasma sodium concentration dropped markedly, and the rate of urine flow exceeded the rate of infusion. The glomerular filtration rate remained constant or fell slightly, whereas the renal blood flow increased considerably. Arteriovenous oxygen difference was reduced so that the renal oxygen consumption remained essentially unchanged compared with control periods.

In all experiments there was a consistent reduction in arteriovenous oxygen difference when the rate of blood flow was increased by the administration of mannitol. In one experiment (Table 2) renal blood flow was first increased by the administration of glycine and hypertonic saline, and the arteriovenous oxygen difference remained nearly constant. When the renal blood flow was further increased by the administration of mannitol there was a reduction in arteriovenous oxygen difference so that the oxygen consumption remained constant compared with the preceding periods in spite of reduction of sodium reabsorption.

Fig. 2 shows the relationship between oxygen consumption and sodium reabsorption when the latter was reduced during mannitol diuresis. In three of the experiments, the oxygen consumption remained essentially unchanged, and in the fourth one oxygen consumption increased when the rate of sodium reabsorption was reduced. Accordingly, contrary to expectation, no reduction in oxygen consumption occurred in any of the experiments in spite of a reduction of sodium reabsorption to 40% of control values.
The observation that renal oxygen consumption increased in the pump-lung kidney preparation when the rate of sodium reabsorption was increased by a rise in arterial pressure \((zI)\) may be regarded as supporting evidence. The failure to maintain a constant creatinine clearance showed that there is a close correlation between renal oxygen consumption and sodium reabsorption when the rates of glomerular filtration and renal blood flow are increased. Oxygen consumption and the rate of sodium reabsorption can be increased more than 50\%, and it is probable that this does not represent maximal values. Attempts to relate oxygen consumption to tubular mass or kidney weight were therefore not made.

If it is assumed that the increased oxygen consumption was used solely to increase the rate of sodium reabsorption, it can be calculated from the data shown in Fig. 1 that an average of 5.9 equivalents sodium were transported per equivalent oxygen consumed, i.e., more than 20 sodium ions with their anions were transported per molecule oxygen consumed. The sodium-to-oxygen ratio is accordingly as high as or higher than in the short-circuited frog skin where anions are not transported.

The ratio between sodium reabsorption and oxygen consumption was of the same order of magnitude as those found by reducing glomerular filtration rate \((7,7a,8)\). This adds new evidence in support of the hypothesis that there exists a relationship between oxygen consumption and reabsorptive function.

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The results of the second part of this study showed that oxygen consumption remained unchanged when sodium reabsorption was reduced during mannitol diuresis. This observation seems at first sight to be at variance with the hypothesis that a large part of the renal oxygen consumption is used for tubular transport processes. It therefore seems appropriate in connection with the results obtained in this study to discuss other current hypotheses which have been advanced in order to explain the essentially unchanged arteriovenous oxygen difference over a wide range of blood flow \((12,23,24)\).

Pappenheimer and Kinter \((25)\) introduced the cell-separation hypothesis which implies that renal tubular cells are supplied by blood with a very low erythrocyte concentration and therefore at normal flow rates receive a barely adequate supply of oxygen. Therefore, a significant reduction in flow leads to a relative deficiency of oxygen. Levy and Sauceda \((26)\) introduced the hypothesis that oxygen diffuses from arterial to venous segments of the renal capillaries. As a consequence, this diffusion would partly account for the constancy of the arteriovenous oxygen difference which is assumed to be reduced in medulla and augmented in cortex, so that over-all changes in oxygen differences are absent.

The present studies, however, demonstrated that the arteriovenous oxygen difference remained grossly constant only as long as large diuresis was not induced. When the rate of blood flow increased following mannitol administration, however, there was a considerable increase in oxygen consumption. The renal blood flow per sc is accordingly not related to the oxygen consumption, and the kidney does not behave as

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**DISCUSSION**

The first part of this study when glycine was administered showed that there is a close correlation between renal oxygen consumption and sodium reabsorption when the rates of glomerular filtration and renal blood flow are increased. Oxygen consumption and the rate of sodium reabsorption can be increased more than 50\%, and it is probable that this does not represent maximal values. Attempts to relate oxygen consumption to tubular mass or kidney weight were therefore not made. If it is assumed that the increased oxygen consumption was used solely to increase the rate of sodium reabsorption, it can be calculated from the data shown in Fig. 1 that an average of 5.9 equivalents sodium were transported per equivalent oxygen consumed, i.e., more than 20 sodium ions with their anions were transported per molecule oxygen consumed. The sodium-to-oxygen ratio is accordingly as high as or higher than in the short-circuited frog skin where anions are not transported.

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a “flow-limited” tissue as suggested by Pappenheimer and Kinter. The results presented in this study also show that the renal oxygen consumption is not a function of the glomerular filtration rate per se.

Recently Levy and Imperial (27) presented data for the existence of shunting of oxygen in both the renal cortex and medulla of isolated, perfused canine kidneys. The relative constancy of A-V oxygen differences under most experimental conditions when renal blood flow is changed necessarily reflects similar changes in aerobic renal metabolism. The “shunting effect” in the renal cortex and medulla is therefore a function of the blood supply to these parts of the kidney and their aerobic metabolic requirements. The over-all low A-V oxygen difference is accordingly due to a higher ratio between blood flow and oxygen consumption than in other organs whether shunting of oxygen is present or not. There is no evidence for the alternative view that oxygen shunting regulates aerobic metabolism of the kidney.

Lassen and Longley (28) recently showed that highly diffusible gases such as Kr and presumably also oxygen are excluded from the renal papilla to a higher extent than less diffusible substances such as radioactively iodinated protein. The arrangement of the renal capillaries allows for shunting of oxygen both in the cortex and especially in the medulla, where oxygen concentration of blood in ascending capillaries probably is low. However, it should be emphasized that tracer studies or a sudden increase in arterial oxygen concentration induces a non-steady-state with large concentration gradients between descending and ascending limbs. Under steady state conditions the concentration differences between descending and ascending limbs are not known for any blood constituent. The actual shunting of oxygen (and sodium and water, etc.) can therefore not be evaluated by this technique.

Oxygen may be used for purposes not related to excretory functions. It is well known that a number of compounds may be synthesized in the kidney. The rate of synthesis may increase with increasing rates of blood flow, but even very liberal estimates of oxygen requirements for this function do not account for the high oxygen consumption of the kidney. In spite of apparent inconsistencies, the hypothesis that a major part of the renal oxygen consumption is used for tubular transport processes therefore seems to be the most attractive one.

In analogy with the results obtained in experiments on the isolated frog skin, changes in the rate of sodium reabsorption might not immediately be followed by corresponding changes in oxygen consumption (29). It might be imagined that energy was accumulated in the kidney on account of constant oxygen consumption in spite of the reduced tubular performance during mannitol diuresis. Since 30–60 min elapsed between control periods and mannitol periods, this interpretation does not seem likely. The lag time in the frog skin was not more than 15 min (29) and in kidneys was possibly much shorter (8). Furthermore, oxygen consumption would be expected to remain constant when sodium reabsorption was changed by increasing the glomerular filtration rate. The lack of correlation between sodium reabsorption and oxygen consumption during mannitol diuresis does not, however, rule out the hypothesis that the main part of the renal oxygen consumption is used for tubular transport processes. Several hypotheses may be proposed to explain the discrepancy.

1) Oxygen may be used in the transport of ions other than sodium. The reabsorption of bicarbonate, for instance, increases when the glomerular filtration rate increases but remains essentially unchanged during mannitol diuresis, where the increase in sodium excretion mainly is associated with a similar increase in chloride excretion.

There is increasing evidence for the hypothesis that bicarbonate is reabsorbed as water and CO2 following exchange of intracellular hydrogen ions for intraluminal sodium ions. The energy requirement for this process is not known, but it is assumed to be of a low order (50).

2) A large part of renal oxygen consumption might be used for the transport of organic urinary constituents such as glucose and amino acids, whereas the energy requirements of sodium transport might be considered small. Although the idea of passive sodium transport has been advocated recently (11), there is growing evidence, as summarized by Leaf (31), against this belief.

3) Ulrich (4) demonstrated that oxygen consumption increased in slices from the outer zone of medulla but not from the cortex or inner zone of medulla when external sodium concentration was increased. The increase in oxygen consumption when the filtered load was increased above normal levels suggests that active processes are stimulated, but the site and the mechanism of the increased sodium reabsorption remain unknown. If the thick ascending limb were the only segment which reacts to increased sodium concentration with increase in oxygen consumption, the additional sodium transport during glycine-hypertonic saline administration would take place in this segment and not in the proximal tubules. As apparent from this study, the rate of sodium reabsorption may be nearly doubled when the glomerular filtration rate is increased acutely. It does not seem likely, although it is not ruled out, that so large an additional sodium reabsorption is confined to the thick ascending limb. According to this hypothesis the proximal tubules would not change their oxygen consumption when the rate of sodium reabsorption was reduced as during mannitol diuresis.

4) It might be assumed that both an increase in sodium reabsorption and an increase in renal blood flow are associated with an increase in oxygen consumption. When sodium reabsorption is reduced and the rate of renal blood flow is increased, as during mannitol diuresis, oxygen consumption might remain essentially unchanged in accordance with the present findings. If this were correct the sodium-to-oxygen ratio would be considerably higher than 6.

5) During mannitol diuresis sodium is reabsorbed against a concentration gradient in the proximal tubules,
and larger expenditures of energy might be required in order to overcome the concentration gradient. According to Ussing (32) the work required for the transport of sodium may be divided into three components: the work required to overcome a) the concentration gradient, b) the potential gradient, and c) the internal sodium resistance. According to Zerahn (3) the sodium-to-oxygen ratio remained unchanged whether sodium was transported through the frog skin between identical solutions at zero potential or whether sodium was transported against an electrochemical gradient. Micropuncture studies performed during mannitol diuresis have shown that the sodium concentration in the proximal tubules of rats may drop to 0.75 of plasma values (33), and stop-flow studies in dogs suggest that maximal concentration gradient is already reached during free flow. The forces involved in the active sodium transport in the proximal tubules may therefore be weak (31). In the frog skin, however, net sodium reabsorption proceeds until the sodium concentration in the outside solution is 1 mM (32). So far the frog skin may more conveniently be related to the reabsorptive function of the tubules (4).

REFERENCES


4 During this study it was shown that the extraction of PAH decreased when renal blood flow increased even when arterial hematoctit values did not change. This observation (as well as the titration curve of PAH) may be interpreted in terms of Michaelis-Menten kinetics (35), but seems to have no direct relation to the problem discussed in the present paper. Details are therefore not included.