Effects of blood pH changes on potassium excretion in the dog

CHARLES TOUSSAINT and PIERRE VEREERSTRAETEN

Department of Experimental Medicine, Université Libre de Bruxelles and Fondation Médicale Reine Elisabeth, Brussels, Belgium

TOUSSAINT, CHARLES, AND PIERRE VEREERSTRAETEN. Effects of blood pH changes on potassium excretion in the dog. Am. J. Physiol. 202(4): 768-772. 1962.-K+ excretion rate was measured at normal as well as at rising plasma K+ concentration in intact, in K-depleted, and in acetazolamide-treated dogs submitted to acute blood pH changes. The results indicate that, for any given value of glomerular filtration rate, K+ excretion rate is determined by at least three factors: 1) plasma K+ concentration, 2) blood pH level, and 3) presumably, the H+ gradient across the luminal border of the distal tubule. The data further suggest that most of the filtered K+ is reabsorbed by the proximal tubule, even in conditions of high filtered loads.

Although the more recent data derived from micropuncture studies (1) seem to indicate that K+ reabsorption by the proximal tubule is not as complete as was initially supposed (2), it is generally assumed that distal tubular secretion plays a major role in K+ excretion by the kidney (3-6). It has further been repeatedly demonstrated that K+ excretion is strongly influenced by blood pH changes (3, 7-10). This phenomenon was explained by the competitive relationship between distal cellular K+ and H+ secretion in exchange for urinary Na+ ions (11, 12). Most of the data in support of this concept have been obtained at normal plasma K+ levels. It was therefore found necessary to investigate by conventional clearance method the effects of rising plasma K+ concentration on K+ excretion rate during acute acid-base imbalances induced in normal animals, as well as in animals submitted to other conditions known to affect K+ excretion: K depletion and carbonic anhydrase inhibition.

The data secured in such conditions of high filtered loads still indicate 1) that tubular secretion is the major process involved in K+ excretion and 2) that this transport is competitive with H+ secretion.

Received for publication 9 October 1961.

1 This investigator was aided by a grant from the Fondation Paul Govaerts.

2 Aspirant Fonds National de la Recherche Scientifique.

MATERIALS AND METHODS

Experiments were performed on female mongrel dogs weighing 10-29 kg. Pentothal anesthesia was used only in experiments involving CO2 inhalation. Exogenous creatinine clearance was used as a measure of glomerular filtration rate (GFR). Periods involving a fall in GFR exceeding 10% of control values were excluded from the data. In each experiment, K+ excretion was studied during three to six successive control, 8-12-min periods at normal plasma levels. Plasma K+ concentration was subsequently raised by 0.16 or KCl infusion, so that K+ excretion rate was measured at progressively rising plasma concentration, while blood pH was maintained within control ranges. In each experiment, in order to cancel the effect of body weight differences, K+ excretion rate was expressed in milliequivalents per liter of glomerular filtrate (mEq/liter GF).

Similar experimental procedures were applied to three different groups of animals: 1) previously normal, 2) acetazolamide-treated, and c) K depleted dogs. Tables 1-3 give the various data collected in one experiment of each of the three groups. The methods used have been described in detail elsewhere (13) and will be summarized presently.

Normal animals (26 exps., 302 clearance periods). K+ excretion rate was measured at rising plasma K+ concentration for three different blood pH ranges: 7.17, 7.41, 7.57 units.

Acidosis (9 exps.) was produced either by 0.06-0.15 M
HCl infusion, or by 0.3 mM NaHCO₃ infusion combined with 20% CO₂-80% O₂ inhalation, so that blood pH values ranged from 7.01 to 7.24.

Eight experiments were performed at normal (7.33-7.45) blood pH values with 0.1-0.34 mM NaCl infusions containing 20-40 mM NaHCO₃/liter.

Metabolic alkalosis (pH 7.52-7.65) was obtained either by priming doses of 150-250 mM NaHCO₃ followed by 0.15 mM NaHCO₃ infusion (5 exps.), or by peritoneal dialysis with isotonic NaHCO₃ (4 exps.).

Acetazolamide-treated animals (10 exps., 119 clearance periods). Carbonic anhydrase inhibition was accomplished by infusion of acetazolamide at rates of 20-50 mg/kg/hr, preceded by a priming dose of 10 mg/kg. K⁺ excretion was studied at rising plasma K⁺ level for two different blood pH ranges: 1) slight metabolic acidosis (pH 7.16-7.33) in five experiments where priming doses of 40-60 mM NaCl were followed by 0.15 mM NaCl infusion, 2) severe metabolic alkalosis (pH 7.46-7.61) produced in five experiments by priming doses of 220-300 mM NaHCO₃ followed by 0.15 mM NaHCO₃ infusion.

K-depleted animals (12 exps., 153 clearance periods). K depletion was induced in 12 dogs by 4-6 weeks of feeding a K-free diet supplemented with a sulfonic exchange resin in its sodium cycle. The degree of the deficit, assessed by repeated measurements of the K⁺ pool with K⁴²⁺, ranged from 14 to 25% of control values. K⁺ excretion was measured at rising plasma K⁺ concentrations in two different conditions: a) slight metabolic acidosis (pH 7.17-7.35) in five experiments where priming doses of 180-320 mM NaCl were followed by 0.3 mM NaCl infusion, and b) severe metabolic alkalosis (pH 7.52-7.62) produced in seven experiments by priming doses of 150-250 mM NaHCO₃ followed by 0.15 mM NaHCO₃ infusion.
RESULTS

The results are summarized in Figs. 1-3 and in Table 4. Figure 1 shows K⁺ excretion rate plotted against corresponding plasma K⁺ concentration at the three different blood pH ranges studied in the previously normal animals. The slope of this relation rises from 0.674 at a blood pH mean value of 7.17 to 0.932 for a pH of 7.41. The slope is further increased to 1.283 at a blood pH value of 7.57. The three slopes are significantly different from each other (P < 0.001).

In Fig. 2, the data obtained in the two groups of acetazolamide-treated animals are presented as in Fig. 1. As was noted for the normal animals, the slope increases from 0.950 for a pH of 7.28 to 1.248 for a pH of 7.55. The difference between these values is also significant (P < 0.001).

Figure 3 illustrates the relation of K⁺ excretion rate to plasma concentration obtained in the K-depleted animals, studied at two different blood pH levels. In this condition, alkalosis induces also an increase in the slope value, 0.728 and 1.062 at the 7.23 and 7.56 blood pH levels, respectively. The difference between the slopes is significant (P < 0.001).

The mathematical expression of the relation of K⁺ excretion rate, y, to plasma concentration, x, is y = ax + b; (b/a) represents the point of the abscissae cut by the regression line. This point might be conventionally called the “threshold” for K⁺ excretion. In the K-depleted animals (b/a) constitutes a true threshold. In the two other groups (b/a) would be an extrapolated threshold.

In the normal dogs (Fig. 1) the threshold values calculated at different blood pH levels are similar (Table 4). They are 0.95 mEq/liter in acidosis, 1.19 mEq/liter at normal blood pH level, and 1.08 mEq/liter in alkalosis. In the acetazolamide-treated group (Fig. 2), the threshold values are also similar, -0.23 mEq/liter in acidosis and 0.33 mEq/liter in alkalosis (Table 4). The same phenomenon is observed in the K-depleted animals (Fig. 3): the threshold values are 2.45 mEq/liter in acidosis and 1.85 mEq/liter in alkalosis (Table 4). The mean threshold values calculated in each of the three groups (normal, acetazolamide-treated, and K-depleted) differ significantly from each other (P < 0.02).

DISCUSSION

If it is assumed that K⁺ filtered through the glomeruli is completely reabsorbed by the proximal tubules, and reaches the final urine by some distal tubular exchange process where K⁺ competes with H⁺ for secretion (3), it is easy to conceive how the slope of a relation between K⁺ excretion rate and plasma K⁺ concentration is a direct function of blood pH in the K-loaded animals. In such a conception, changes in blood pH presumably induce H⁺ concentration changes within the distal tubular cells, making less H⁺ and more K⁺ available for secretion in alkalosis.

On the other hand, if K⁺ escaping tubular reabsorption constitutes an important fraction of K⁺ found in final urine, it must be assumed that the pH of the proximal tubular cells influences K⁺ reabsorption rate. In such a case, K⁺ uptake by the tubule would be decreased in alkalosis and increased in acidosis. Although our observations do not exclude such a possibility, this conception would be at variance with the data depicted in Fig. 4, where ΔK is plotted against corresponding blood pH for the different experiments herein described. The migration of K⁺ into the cells of the body as a whole increases markedly from acidosis to alkalosis, as was previously observed by others in similar experiments (14-18). Consequently, the influence of blood pH on
**FIG. 3.** K⁺ excretion rate plotted with plasma K⁺ concentration in acidotic ▲ and alkalotic ○ K-depleted animals.

**TABLE 4.** Characteristics of the various regressions calculated for relation of K⁺ excretion rate to plasma concentration values in three groups

<table>
<thead>
<tr>
<th>Blood pH Ranges*</th>
<th>Slope†</th>
<th>Threshold[</th>
<th>No. of Clearance Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>7.01-7.24 (7.18)</td>
<td>0.674±0.033</td>
<td>0.95±0.31</td>
</tr>
<tr>
<td></td>
<td>7.33-7.45 (7.41)</td>
<td>0.932±0.044</td>
<td>1.19±0.23</td>
</tr>
<tr>
<td></td>
<td>7.52-7.65 (7.57)</td>
<td>1.283±0.066</td>
<td>1.08±0.28</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>7.17-7.35 (7.28)</td>
<td>0.950±0.074</td>
<td>-0.23±0.52</td>
</tr>
<tr>
<td></td>
<td>7.46-7.61 (7.55)</td>
<td>1.248±0.047</td>
<td>0.33±0.17</td>
</tr>
<tr>
<td></td>
<td>7.14-7.33 (7.28)</td>
<td>0.728±0.026</td>
<td>2.45±0.24</td>
</tr>
<tr>
<td></td>
<td>7.52-7.69 (7.56)</td>
<td>1.063±0.056</td>
<td>1.85±0.30</td>
</tr>
</tbody>
</table>

* Values in parentheses are means. † ± SEM.

the slope of the relation between K⁺ excretion rate and plasma K⁺ concentration would be best explained by the assumption that, even in condition of K⁺ loading, most of K⁺ reaches the final urine by distal secretion.

Besides its slope, the relation of K⁺ excretion rate to plasma concentration is defined by the threshold value. This parameter is the theoretical plasma concentration for which K⁺ excretion equals zero. Within any of the three groups of animals investigated, the threshold is apparently not influenced by blood pH changes. On the other hand, it rises markedly, from a mean value of 0.05 mEq/liter in the acetazolamide-treated group to 0.33 mEq/liter in the normal, and to 2.08 mEq/liter in the K-depleted animals (Figs. 1-3).

If K⁺ escaping proximal reabsorption constitutes an important fraction of excreted K⁺, the increased threshold observed in K deficiency could be explained by a stimulation of proximal tubular reabsorption. The enhancement of this transport would constitute a particular aspect of the avidity for K⁺ of the K-deficient organism, as illustrated by Fig. 4. However, a preponderance of the proximal over the distal tubular transport would not explain the decreased threshold value observed in the acetazolamide treated dogs for, in such animals, “stop flow” experiments have unequivocally shown increased K⁺ concentration in distal, but not in proximal, urine samples (5). It follows that, for any given value of plasma K⁺ concentration, the depression of K⁺ excretion in K deficiency and its enhancement by acetazolamide is explained by parallel changes in distal K⁺ secretion rather than opposite changes in proximal K⁺ reabsorption.

If K⁺ is to be entirely reabsorbed in the proximal tubule during acute K⁺ loading, its distal secretion appears as a direct function of plasma K⁺ concentration. As in each experiment plasma K⁺ level was progressively raised by K⁺ infusion, it was not certain whether the main factor determining the magnitude of K⁺ excretion rate was the plasma K⁺ concentration itself or the duration of the infusion. In order to dissociate these two factors, three experiments were performed at blood pH levels ranging from 7.24 to 7.35 on three different animals. Plasma K⁺ concentration was maintained at elevated and constant level by KCl infusion for periods extending up to 120 min. Table 5 gives the mean values (for 3 successive 10-min clearance periods) of blood pH, plasma K⁺ concentration, and K⁺ excretion rate observed in these three experiments. It is readily ap-
plasma K+ concentration kept constant

<table>
<thead>
<tr>
<th></th>
<th>Blood pH</th>
<th>Plasma K+</th>
<th>Excreted K+</th>
<th>Blood pH</th>
<th>Plasma K+</th>
<th>Excreted K+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 Min elapsed</td>
<td>7.27</td>
<td>6.0</td>
<td>2.8</td>
<td>7.36</td>
<td>6.3</td>
<td>4.7</td>
</tr>
<tr>
<td>30-60 Min elapsed</td>
<td>7.25</td>
<td>6.1</td>
<td>3.4</td>
<td>7.34</td>
<td>6.4</td>
<td>3.3</td>
</tr>
<tr>
<td>60-90 Min elapsed</td>
<td>7.24</td>
<td>6.4</td>
<td>3.8</td>
<td>7.32</td>
<td>6.2</td>
<td>5.6</td>
</tr>
<tr>
<td>90-120 Min elapsed</td>
<td>7.25</td>
<td>6.4</td>
<td>4.0</td>
<td>7.31</td>
<td>6.5</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Each horizontal column represents mean values of 3 successive 10-min clearance periods. Blood pH values are in units, plasma K+ in mEq/liter, and excreted K+ in mEq/liter.

parent that K+ excretion rate increases despite the fact that plasma K+ concentration remains constant. The increment amounts to 0.7-1.2 mEq/liter, a value which represents 20-33% of the increment observed when plasma K+ level is raised from 3.0 to 7.0 mEq/liter for a comparable period of time and blood pH range. For these three experiments, simultaneously measured K+ intake and output data in the course of the infusion demonstrate a steadily positive K+ balance, despite the constancy of plasma K+ concentration and despite the increase of K+ excretion rate. This positive balance is due to the cellular penetration of K+ which probably constitutes the main factor responsible for K+ secretion by the distal tubular cells in this type of experiment.

It follows that, in the experiments involving rising plasma K+ concentration, the magnitude of K+ excretion rate is determined primarily by plasma K+ level and, to a lesser extent, by the duration of the K+ infusion. The slope of the relation between K+ excretion rate and plasma K+ level is apparently a function of the pH of the plasma and, presumably, of the distal tubular cells of the kidney.

Acidosis or alkalosis produced within any of the three groups of animals studied did not appreciably modify the threshold for K+ excretion (Table 4). Carbonic anhydrase inhibition presumably produces a decrease, and K depletion an increase (19), in H+ concentration within the distal tubular cell, without primarily affecting the pH of the extracellular fluid. It follows that both conditions could markedly influence H+ gradient between the cell and urine. This gradient would be increased in K deficiency and depressed during acetazolamide treatment. It is therefore suggested that the threshold for K+ excretion would be directly related, not to the cellular pH itself, but rather to the H+ gradient established across the luminal border of the distal tubular cell.

The authors express their thanks to Dr. R. W. Berliner and to Dr. P. P. Lambert for their comments and criticisms, and to the Lederle Laboratories for supplying the Diamox (acetazolamide) used in these experiments.

REFERENCES