ON THE MECHANISM OF HYPERKALAEMIA DUE TO HYPEROSMOTIC EXPANSION WITH SALINE OR MANNITOL

D. L. MAKOFF, J. A. DA SILVA* AND B. J. ROSENBAUM†

Cedars–Sinai Medical Research Institute, and Medical and Research Service, Los Angeles Veterans Administration Center, Divisions of Medicine, Cedars–Sinai Medical Center, and UCLA School of Medicine, Los Angeles, California

(Received 12 March 1971)

SUMMARY

1. To investigate the mechanism of the hyperkalaemia that results from hyperosmotic infusions of saline or mannitol, nephrectomized dogs received hyperosmotic infusions of sodium chloride or mannitol with various amounts of sodium bicarbonate. $P_aCO_2$ was held constant. Body spaces and mean whole-body intracellular hydrogen ion activity $[H^+]_i$ were measured with tritiated water, Na$^{36}$Cl, and $[^14C]5,5$-dimethyl-2,4-oxazolidinedione (DMO).

2. The extracellular hydrogen ion activity after infusion varied, but all animals developed intracellular alkalosis ($[H^+]_i$ -35 nmol/l, SEM ± 5, $P<0.001$). There was no net movement of Na$^+$ across cell membranes. There was a significant negative correlation between the changes in extracellular hydrogen ion and that in extracellular potassium concentrations. A greater apparent cellular penetration of HCO$_3^-$ resulted in less net loss of K$^+$ from cells ($r = 0.69$, $P<0.01$).

3. The results suggest that the hyperkalaemia secondary to hyperosmolar infusion of saline or mannitol is not due to extracellular acidosis, but cellular dehydration, altered cell metabolism or altered cell-membrane function may contribute to the leak of K$^+$ from cells in these circumstances.

We have previously shown (Makoff, da Silva, Rosenbaum, Levy & Maxwell, 1970) that hyperosmotic infusion of mannitol or saline into the nephrectomized dog leads to an extracellular 'dilution' acidosis and intracellular 'contraction' alkalosis. Concomitant with the shift of water out of cells induced by a hyperosmotic infusion, there is a striking increase in total extracellular potassium content and concentration. Movement of potassium across cell membranes associated with alterations of intracellular and extracellular hydrogen ion activity has been the subject of several studies (Brown & Goott,

* Present address: Rua Baroa de Lucena, 438-Jabotao, Pernambuco, Brazil.
† Present address: USAF Hospital Tachikawa, APO, San Francisco, Calif. 96323, U.S.A.

Correspondence: Dr Dwight L. Makoff, Cedars–Sinai Medical Center, 4833 Fountain Avenue, Los Angeles, Calif. 90029, U.S.A.
and a close relationship between potassium and hydrogen ion gradients across the cell membrane has been widely appreciated. In studies of metabolic acidosis, Irvine & Dow (1968) suggested that plasma potassium shows an inverse linear relationship to transmembrane hydrogen ion gradient and to extracellular and intracellular pH.

The present study was designed to investigate the mechanism of the hyperkalaemia induced by infusion of hyperosmotic saline or mannitol. Possible factors in the genesis of the hyperkalaemia are the changes in the extracellular and intracellular hydrogen ion activity, disturbed cell-membrane function, solvent drag and altered cellular metabolism.

MATERIALS AND METHODS

All the experimental techniques and analytical methods used in this work were described or referred to in a preceding paper (Makoff et al., 1970).

Fourteen studies were performed on mongrel dogs weighing between 13·6 and 30·9 kg. The animals were starved and deprived of water for 24 h before the experiments, anaesthetized with sodium pentobarbital (30 mg/kg) and intubated; succinylcholine chloride and pentobarbital were given by continuous infusion to achieve muscle paralysis and maintain anaesthesia. The dogs were ventilated by a constant volume Harvard respiration pump adjusted frequently to keep $\text{Pa}_\text{CO}_2$ within a narrow range of control values. Body temperature was monitored by indwelling rectal or gastric probes and blood pressure measured half-hourly via an indwelling femoral artery cannula. Arterial blood samples were collected anaerobically from the femoral artery cannula. Splenic and renal pedicles were ligated. After it was determined that $\text{Pa}_\text{CO}_2$, extracellular pH, and blood pressure were stable, a blood sample was taken for background isotope counting, electrolytes and osmolality. Then, 100 $\mu$Ci of $^3$H$_2$O, 20 $\mu$Ci of $[^{14}\text{C}]$5,5-dimethyl-2,4-oxazolidinedione ($[^{14}\text{C}]$DMO) and 4 $\mu$Ci of Na$^{36}$Cl were injected for the measurement of total body water, extracellular space and mean whole body intracellular hydrogen ion activity, and allowed to equilibrate for 3 h. At this time, blood samples were taken for duplicate isotopic and chemical analyses.

After a similar control period in fourteen dogs, seven dogs received a 30 min infusion of 35 mOsm/kg body weight of a 0·75 $M$ mixture of NaCl with 0·8–3·0 mmol of NaHCO$_3$/kg body weight. A second group of seven dogs received a 30 min infusion of 35 mOsm of 1·5 $M$ solution of mannitol/kg body weight mixed with 1·8–3·0 mmol of NaHCO$_3$/kg body weight. Blood samples for radioactivity and chemical analyses were drawn 2, 3 and 4 h after completion of infusions. Arterial pH and $\text{Pa}_\text{CO}_2$ were determined at approx. 30 min intervals throughout the entire experiment. Appropriate temperature corrections for $\text{Pa}_\text{CO}_2$ and pH were made, and plasma bicarbonate concentration was calculated with the Henderson–Hasselbalch equation by using a $pK_a$ of 6·10 and solubility coefficient for CO$_2$ of 0·0301.

It has been determined from previous studies that a period of 45 min is required for chemical equilibration after hyperosmotic infusions (Makoff et al., 1970; McDowell, Wolf & Steer, 1955; Winters, Scaglione, Nahas & Verosky, 1964). Isotopic re-equilibration occurs 2 h after completion of hyperosmotic infusions (Makoff et al., 1970).

Previous studies of hyperosmotic expansion with simultaneous measurements of extracellular space with $^{35}\text{SO}_4^{2-}$ and Na$^{36}$Cl demonstrated equal apparent expansion, thus substantiating the validity of the changes measured with Na$^{36}$Cl in these studies (Makoff et al., 1970).
A series of studies on control dogs was reported in a previous paper (Rosenbaum, Makoff & Maxwell, 1969). These animals were prepared in a manner similar to the present experiments, but received no infusions, and were studied for changes in extracellular hydrogen ion activity and body fluid spaces over 7 h. No significant change in any of these parameters was found over this period of observation, which is similar to the time involved in the present studies. Therefore, it is concluded that any changes after the control period in each dog are not due to the experimental design alone, but are secondary to the infusion given.

Standard statistical methods were used (Hill, 1966). All probability values are derived from Student t test analyses for paired data. Mean values are given ±SEM.

RESULTS

Fourteen dogs were infused with hyperosmotic solutions, all receiving a total of 35 mOsm/kg body weight. Seven dogs were given hyperosmotic sodium chloride and seven dogs hyperosmotic mannitol. Both groups received various amounts of sodium bicarbonate with their infusions. A summary of the results is shown in Tables 1 and 2. Close agreement in isotope and chemical analyses between 2 and 4 h after infusion indicated the presence of a post-infusion steady state.

All dogs receiving hyperosmotic sodium chloride and sodium bicarbonate developed hypernatraemia and hyperchloraemia. Hyperosmotic mannitol with sodium bicarbonate induced a fall in extracellular sodium and chloride concentrations. Before infusion the mean plasma osmolality for the two groups was 302±4 mOsm/kg plasma water. Plasma osmolality increased in all dogs. In all dogs the post-infusion mean Pa,CO₂ varied less than ±5 mmHg from the mean pre-infusion Pa,CO₂ of 27·7±0·7 mmHg.

The change in extracellular hydrogen ion activity, [H⁺]ₑ, after the hyperosmotic infusions varied considerably within each group, depending on the apparent distribution of the infused sodium bicarbonate. Fig. 1 illustrates the variable distribution of infused bicarbonate in these experiments.

Fig. 2 shows that the change in [H⁺]ₑ after the infusions varied inversely with alterations in extracellular potassium concentration [K⁺]ₑ (r = -0·69, P<0·01). Also shown in Fig. 2 are the results of a previously reported study (Makoff et al., 1970) in which hyperkalaemia was consistently seen after infusions of hyperosmotic saline or mannitol without sodium bicarbonate.

Fig. 3 shows the relationship between the apparent entry of bicarbonate into cells and changes in cell potassium content. It is acknowledged that it is not possible to distinguish between movement of bicarbonate ions and opposite and equal movement of hydrogen ions. Intracellular hydrogen ion activity [H⁺]ᵢ decreased in all dogs. There was no relationship between the amount of bicarbonate disappearing from the extracellular space and the decrease in [H⁺]ᵢ induced by the hyperosmotic infusions. There was a fall in the [H⁺]ₑ/[H⁺]ᵢ ratio in all dogs, whereas the [K⁺]ᵢ/[K⁺]ₑ ratio (calculated on the assumption that the pre-infusion [K⁺]ₑ was 135 mEq/l of intracellular water) increased in five dogs in each group.

Analysis of the total extracellular electrolyte content in both groups reveals that thirteen of the fourteen animals had a net movement of potassium out of cells in response to the hyperosmotic infusions. It is of note that dog 12, which was the only dog that had a net decrease in the extracellular potassium content after the infusion, showed the highest apparent net
TABLE 1. Effect of acute infusions of hyperosmotic saline with sodium bicarbonate. All values represent mean results before and after infusion. In each pair of values the upper represents the initial value and the lower the change after infusion.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Dog No.</th>
<th>NaHCO₃ infused (mEq/kg body wt)</th>
<th>ΔmOsm/kg plasma H₂O</th>
<th>ΔPaeCO₂ (mmHg)</th>
<th>[Na⁺]e (mEq/l)</th>
<th>[Cl⁻]e (mEq/l)</th>
<th>[K⁺]e (mEq/l)</th>
<th>[HCO₃⁻]e (mEq/l)</th>
<th>[H⁺]e (nmol/l)</th>
<th>[H⁺]i/[H⁺]e</th>
<th>Fc/Kc</th>
<th>ECF (% body wt)</th>
<th>ICF (% body wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperosmotic</td>
<td>1</td>
<td>0.8</td>
<td>+49</td>
<td>+0.5</td>
<td>147.1</td>
<td>123.6</td>
<td>5.3</td>
<td>15.2</td>
<td>47.9</td>
<td>177.8</td>
<td>3.7</td>
<td>25</td>
<td>24.5</td>
</tr>
<tr>
<td>Saline</td>
<td>2</td>
<td>1.0</td>
<td>+66</td>
<td>-0.8</td>
<td>150.7</td>
<td>128.7</td>
<td>3.5</td>
<td>18.6</td>
<td>44.7</td>
<td>138.0</td>
<td>3.1</td>
<td>37.5</td>
<td>29.7</td>
</tr>
<tr>
<td>+NaHCO₃</td>
<td>3</td>
<td>2.0</td>
<td>+69</td>
<td>-1.6</td>
<td>147.6</td>
<td>128.3</td>
<td>3.6</td>
<td>19.0</td>
<td>32.4</td>
<td>151.4</td>
<td>4.7</td>
<td>37.5</td>
<td>25.7</td>
</tr>
<tr>
<td>4</td>
<td>1·5</td>
<td>+87</td>
<td>-0·8</td>
<td>146·0</td>
<td>129·3</td>
<td>4·5</td>
<td>18·7</td>
<td>35·5</td>
<td>138·0</td>
<td>3·9</td>
<td>30.0</td>
<td>17.5</td>
<td>28.2</td>
</tr>
<tr>
<td>5</td>
<td>2·0</td>
<td>+44</td>
<td>-1·3</td>
<td>147·7</td>
<td>131·9</td>
<td>3·6</td>
<td>19·9</td>
<td>37·1</td>
<td>210·7</td>
<td>4·9</td>
<td>37.5</td>
<td>22.2</td>
<td>40.5</td>
</tr>
<tr>
<td>6</td>
<td>3·0</td>
<td>+46</td>
<td>-2·8</td>
<td>145·0</td>
<td>129·2</td>
<td>4·3</td>
<td>17·3</td>
<td>43·1</td>
<td>199·5</td>
<td>4·6</td>
<td>31.4</td>
<td>28.9</td>
<td>35.4</td>
</tr>
<tr>
<td>7</td>
<td>2·0</td>
<td>+47</td>
<td>-2·4</td>
<td>142·0</td>
<td>120·9</td>
<td>4·1</td>
<td>19·5</td>
<td>28·8</td>
<td>138·0</td>
<td>4·8</td>
<td>32·9</td>
<td>29·8</td>
<td>40·7</td>
</tr>
</tbody>
</table>

Mean±SEM (initial) | 146.6 | 128.8 | 4.1 | 18.3 | 38.5 | 164.8 | 4.3 | 31.1 | 24.2 | 36.2 |

* [ ] = derived from electrolyte concentration in extracellular fluid (ECF) after correction for plasma water and Donnan factors by using 1:05 for anions and 0:95 for cations.
† [H⁺]i = mean whole body intracellular hydrogen ion activity.
‡ Initial [K⁺] assumed to be 135 mEq/l of cell water. The change in [K⁺] after infusion was calculated on the basis of change in total extracellular potassium and change in intracellular space.
§ Percentage change.
TABLE 2. Effect of acute infusions of hyperosmotic mannitol with sodium bicarbonate. All values represent mean results before and after infusion. In each pair of values the upper represents the initial value and the lower the change after infusion.

| Group 2 | Dog No. | NaHCO₃ infused (mEq/kg body wt) | ΔmOs/kg H₂O | ΔPaCO₂ (mmHg) | [Na⁺]ᵢ, [Cl⁻]ᵢ, [K⁺]ᵢ, [H⁺]ᵢ, [HCO₃⁻]ᵢ, [H⁺]ᵢ/H⁺Ị, [K⁺]ᵢ/[K⁺]ᵢ, ECF (% body wt), ICF (% body wt) |
|---------|---------|---------------------------------|-------------|---------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hyperosmotic | 8       | 2-0                             | +65         | -4-3          | 144-3, 110-9, 4-2, 23-3, 34-7, 177-8, 5-1, 32-9, 26-0, 37-8 |
|          | 9       | 1-8                             | +52         | +2-5          | 144-1, 111-5, 3-9, 20-5, 34-7, 123-0, 3-5, 34-6, 25-7, 31-1 |
|          | 10      | 2-0                             | +73         | +0-6          | 141-5, 116-2, 3-2, 19-1, 36-3, 114-8, 3-2, 46-5, 22-7, 28-8 |
| +NaHCO₃ | 11      | 2-0                             | +53         | -0-7          | 141-6, 113-4, 3-0, 21-1, 34-7, 120-2, 3-5, 45-0, 23-4, 30-1 |
|          | 12      | 3-0                             | +60         | +4-8          | 144-6, 117-9, 4-9, 22-2, 33-9, 107-2, 3-2, 27-0, 23-3, 30-7 |
|          | 13      | 3-0                             | +68         | +0-1          | 143-1, 110-5, 3-6, 20-1, 37-1, 162-2, 4-4, 37-5, 26-4, 31-5 |
|          | 14      | 3-0                             | +58         | +0-5          | 143-0, 113-0, 3-8, 21-7, 38-0, 151-4, 4-0, 34-6, 25-3, 39-8 |

Mean±SEM (Initial) | 143-5 ±0-5 | 113-3 ±0-7 | 3-8 ±0-4 | 21-1 ±0-3 | 35-6 ±0-5 | 136-7 ±10-2 | 3-8 ±0-3 | 36-8 ±2-6 | 24-7 ±0-6 | 32-8 ±1-6 |

* [J.] = derived from electrolyte concentration in extracellular fluid (ECF) after correction for plasma water and Donnan factors by using 1-05 for anions and 0-95 for cations.
† [H⁺]ᵢ = mean whole body intracellular hydrogen ion activity.
‡ Initial [K⁺]ᵢ assumed to be 135 mEq/l of cell water. The change in [K⁺]ᵢ after infusion was calculated on the basis of change in total extracellular potassium and change in intracellular space.
§ Percentage change.
**Fig. 1.** Apparent distribution of infused bicarbonate during acute expansion with hyperosmotic saline (△) or mannitol (●).

**Fig. 2.** Relationship between the changes in [H+] and [K+] after hyperosmotic infusions of saline or mannitol with and without sodium bicarbonate. ○ and △, results from a previous study (Makoff et al., 1970), in which nephrectomized dogs with constant Pa,CO₂ received 35 mOsm/kg body weight as hyperosmotic saline or mannitol; ● and ▲, the present studies. △, Hyperosmotic saline; ▲, hyperosmotic saline+NaHCO₃; ○, hyperosmotic mannitol; ●, hyperosmotic mannitol+NaHCO₃.
Hyperkalaemia and hyperosmotic expansion 389

movement of bicarbonate into cells (2.71 mEq/kg body weight). All dogs sustained an apparent increase in the intracellular bicarbonate content after infusion, as calculated by disappearance of bicarbonate from the extracellular space (Fig. 3). There was no significant movement of sodium across cell membranes, but there was a small shift of chloride out of cells with a mean change of $-1.22 \pm 0.26$ mEq/kg body weight ($P < 0.001$).

**DISCUSSION**

Hyperkalaemia after infusion of hyperosmotic salt solutions was described by Wolf & McDowell (1954). Sotos, Dodge & Talbot (1962) confirmed this finding in rabbits subjected to extreme degrees of hyperosmolality (400–500 mOsm/kg of H$_2$O). Moreno, Murphy & Goldsmith (1969) have since noted hyperkalaemia after infusion of hyperosmotic saline and mannitol into normal volunteers, but observed no increase in serum potassium with infusion of hyperosmotic bicarbonate solutions; it was therefore assumed that acidosis was an important cause of the hyperkalaemia in these circumstances. Previous studies in our laboratory in nephrectomized dogs have also confirmed the occurrence of hyperkalaemia when hyperosmotic saline or mannitol is infused (Makoff et al., 1970).

Consideration of the mechanism of the shift of potassium out of cells after hyperosmotic infusions of saline or mannitol involves a number of factors. The resting membrane potential of muscle is a function of the logarithm of the concentration gradient of potassium across the muscle-cell membrane (Hill, 1955; Hodgkin, 1951), it is reasonable to assume that a decrease

![Fig. 3. Relationship between the apparent entry into the cell of bicarbonate and the release of potassium from cells after acute infusions of hyperosmotic saline (△) or mannitol (●) with NaHCO$_3$. Change in cell bicarbonate is calculated from change in extracellular bicarbonate, after correcting for infused bicarbonate, and bicarbonate related to blood buffers and erythrocytes (Winters et al., 1964).](image)
of this ratio, as apparently occurs with hyperosmotic expansion with saline or mannitol (Makoff et al., 1970), may be related to an alteration in cell metabolism. There is evidence that changes in tonicity can indeed alter the metabolic function of isolated tissue, subcellular particles and partially purified enzymes (Kean, Adams, Winters & Davies, 1961; Najjar, 1954; Ullrich & Pehling, 1958; Umbriet, Burris & Stauffer, 1964).

Disturbed intracellular metabolism has a major effect on potassium gradients, since the anoxic, damaged or glucose-depleted cell leaks potassium at an accelerated rate (Fox & Baer, 1947; Harris, 1941; Sheppard, Martin & Beyl, 1951). However, since urea infusions do not produce a change in serum potassium, it is clear that hypertonicity per se, without cellular dehydration or altered hydrogen ion activity in body fluids, does not affect the \([K^+]_e/[K^+]_i\) ratio (Winters et al., 1964; Wolf & McDowell, 1954; Buckell, 1964). Therefore, it is worthwhile to examine the various consequences of expansion with hyperosmotic saline and mannitol.

In addition to hyperkalaemia, hyperosmotic expansion with saline or mannitol results in a complex and unique acid-base disturbance characterized by extracellular ‘expansion’ acidosis and intracellular ‘contraction’ alkalosis (Makoff et al., 1970). Studies of metabolic acidosis (Burnell, Villamil, Uyeno & Scribner, 1956), respiratory acidosis (Brown & Goott, 1963) and metabolic alkalosis (Grantham & Schloerb, 1965) all support the concept of a qualitative parallel movement of hydrogen and potassium ions in a wide spectrum of acid–base disorders. However, unlike the extracellular metabolic acidosis induced by infusion of mineral acid (Swan & Pitts, 1955) or of iso-osmotic saline (Rosenbaum et al., 1969), the extracellular acidosis induced by infusion of hyperosmotic saline or mannitol is directly related to the degree of expansion of the extracellular space (Makoff et al., 1970; Winters et al., 1964). Therefore, in spite of the absence of a net shift of hydrogen, bicarbonate or sodium ions across cell membranes, potassium is released from cells perhaps with chloride. Also, the extracellular acidosis in this instance is associated with an increase in the intracellular pH, which does not occur in the other types of extracellular acidosis mentioned above.

Irvine & Dow (1968), studying metabolic acidosis in nephrectomized rats receiving ammonium chloride, found a negative exponential relationship between intracellular pH and plasma potassium concentration. This relationship clearly does not apply with hyperosmotic expansion, since hyperkalaemia is occurring coincident with an increase in intracellular pH.

The present studies suggest that the rise in extracellular potassium concentration (and content) after hyperosmotic expansion with saline or mannitol is not dependent on changes in extracellular hydrogen ion activity. The variable \(\Delta[H^+]_e\) achieved in our studies made it possible to dissociate the effect of the hyperosmotic state from the acid–base alterations induced. Analysis of the results indicates that there was actually an inverse relationship between \(\Delta[H^+]_e\) and \(\Delta[K^+]_e\) in the present studies (Fig. 2). Four dogs developed a striking rise in \([K^+]_e\) (0.8 mEq/l or greater) after the infusion of hyperosmotic saline or mannitol, in spite of a decrease in \([H^+]_e\). Conversely, three dogs sustained a fall in \([K^+]_e\) coincident with an increase in \([H^+]_e\) of 8 nmol/l or greater.

When there was a net increase in total extracellular bicarbonate after infusion, \([H^+]_e\) tended to fall. In spite of the absence of extracellular acidosis in these animals, potassium was released from cells. Conversely, in spite of the development of extracellular acidosis in animals in which bicarbonate ‘disappeared’ from the extracellular fluid, the serum potassium tended to decrease. Although the apparent distribution of infused bicarbonate had a profound effect on
extracellular hydrogen ion activity, it is perhaps not surprising that apparent bicarbonate penetration into cells did not quantitatively augment intracellular alkalosis, since intracellular hydrogen ion activity is probably metabolically controlled and may not follow a typical buffer curve when titrated with an acid or base (Adler, Roy & Relman, 1965b; Relman, 1966). Although one cannot exclude the possibility that the effects of decreased bicarbonate generation or increased hydrogen ion production within cells could lead to apparent penetration of bicarbonate into cells, previous studies of this degree of hyperosmolality do not suggest that acid would be released from cells in this study (Makoff et al., 1970; Winters et al., 1964).

The probable explanation for the dissociation between $\Delta[H^+]_e$ and $\Delta[K^+]_e$ noted in these studies is illustrated in Fig. 3. The results suggest that the apparent movement of bicarbonate into cells, or perhaps the cellular release of hydrogen ions, can inhibit the cellular release of potassium that occurs secondary to intracellular dehydration and the hyperosmotic state. Previous studies have demonstrated that bicarbonate infusions lead either to penetration of cells by bicarbonate or cellular release of hydrogen ions (Adler, Roy & Relman, 1965a; Swan, Axelrod, Seip & Pitts, 1955; Singer, Clark, Barker, Crosley & Elkinton, 1955).

It is worthwhile to analyse the present studies with regard to changes in $[H^+]_i/[H^+]_e$ and $[K^+]_i/[K^+]_e$ ratios (Table 1). By using the body space measurements and assuming an initial intracellular potassium concentration of 135 mEq/l, theoretical calculations of changes in $[K^+]_i$ can be made. The $[H^+]_i/[H^+]_e$ ratio fell in all dogs, regardless of $\Delta[H^+]_e$, primarily as a consequence of the marked fall in $[H^+]_i$. However, ten of fourteen dogs sustained an increase in $[K^+]_i/[K^+]_e$ ratio. This dissociation between $[H^+]_i/[H^+]_e$ and $[K^+]_i/[K^+]_e$ ratio has not been noted with simple acid-base disturbances (Brown & Goott, 1963; Burnell et al., 1956).

It seems quite likely that a link between bicarbonate and/or hydrogen ion and potassium movement across cell membranes explains the dichotomy noted in these studies between directional changes in $[H^+]_i/[H^+]_e$ and $[K^+]_i/[K^+]_e$ ratios.

Although it seems clear that cellular release of potassium after hyperosmotic expansion with saline or mannitol is not dependent on the directional changes in serum sodium concentration, the intracellular alkalosis (which occurred in all dogs) or changes in extracellular hydrogen ion activity, the present studies do not further clarify the relative role of other factors, such as altered cell-membrane function, changes in intracellular metabolism and solvent drag in the genesis of the hyperkalaemia.

The clinical significance of this study is clear. Since hyperosmotic saline and mannitol are used in treatment of hyponatraemic and oliguric states, respectively, it is important to note that hyperkalaemia may develop, and the occurrence of extracellular acidosis is not a prerequisite to the genesis of an increase in serum potassium concentration (Kim & Brown, 1968).

Based on the present studies, it is tempting to speculate about the treatment of hyperkalaemia secondary to extracellular metabolic acidosis as seen clinically. It has long been postulated that in acidotic states the entry of hydrogen ions into cells leads to a release of potassium from cells. Subsequent treatment with an alkalinizing solution leads to a decrease in serum potassium. It has been felt that the decrease in serum potassium observed when alkali is administered is related to a re-entry of potassium into cells in exchange for hydrogen ions that diffuse out of cells as the extracellular pH increases. Alternatively, it is possible that potassium is carried back into cells with bicarbonate during therapy of metabolic acidosis, through a link in the transport of these two ions.
ACKNOWLEDGMENTS

A preliminary report of this work has been published in abstract form [Clinical Research (1969) 17, 439]. J. A. da Silva was a Kellogg Foundation Fellow and B. J. Rosenbaum a Research and Education Associate of the Los Angeles Veterans Administration Center while this work was done. This study was supported by United States Public Health Service Grants HE 11502-02, HE 5-501 and RR 05468.

REFERENCES


