The contribution of the kidney to the removal of a lactic acid load under normal and acidotic conditions in the conscious rat

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Summary

1. The rate of removal from the circulation of an intravenous lactic acid load has been studied in conscious rats, previously subjected either to bilateral nephrectomy or to a sham operation.

2. In rats with normal blood pH, the apparent contribution of the kidneys to removal of the lactic acid load is 30%; less than 12% of the renal contribution is attributable to urinary excretion.

3. In bilaterally nephrectomized rats made acidotic by administration of ammonium chloride, the rate of removal of a half-neutralized lactic acid load is progressively decreased with increasing severity of acidosis. No such effect is seen in sham-operated animals.

4. An increase in the ability of the kidney to remove lactate during acidosis compensates for approximately half of the simultaneous fall in the capacity of the remainder of the body for lactate assimilation.

5. Basal blood lactate concentrations fall in the presence of metabolic acidosis.

Key words: lactate load, renal lactate metabolism, acidosis, lactic acidosis.

Introduction

Anaerobic metabolism of carbohydrate produces lactate and hydrogen ions. These are removed from the circulation predominantly by the liver and kidneys. The liver has received much attention as the prime organ responsible for lactate removal; in the isolated perfused rat liver, severe metabolic acidosis impairs lactate uptake (Lloyd, Ills, Simpson, Strunin, Layton & Cohen, 1973), but the behaviour of the kidney in this respect has been little explored. The object of the present experiments was to assess the role of the kidney under normal and acidotic conditions in the removal of a lactic acid load in the fully conscious animal.

Methods

Experimental design

Experiments were performed on male Sprague-Dawley rats weighing between 200 and 350 g. There were no significant differences in mean weight in the various groups of animals studied. The animals were maintained on a standard laboratory diet (Dixon's Rat Cake type 41B; E. Dixon and Sons, Ware, Herts.) and were permitted free access to food and water until the time of administration of lactic acid. For 1 week beforehand, the animals were accustomed daily to restraining cages, so that they remained still during the studies. Operative procedures were performed under ether anaesthesia. One to 3 days before the experiment, two right atrial cannulae, prepared from Portex polypropylene tubing, were inserted, one in each jugular vein, and the ends brought out in the nuchal region (Weeks & Davis, 1964). On the morning of the experiment, the rats were subjected to either a bilateral nephrectomy or a sham operation through a midline dorsal incision; the sham operation involved exposure of the kidneys, stripping the capsule, and momentarily clamping...
the pedicle before replacing the kidney. One group of animals was made mildly to severely acidotic by oral administration of ammonium chloride solution (1.87 mol/l) in doses of 15–40 mmol/kg body weight at the same time as nephrectomy or sham operation. The animals were then allowed to recover; 4–6 h later, the rats were placed in restraining cages and allowed to settle for 15 min; a basal blood sample (0.15 ml) was then taken. A load of 8.9 mmol/kg body weight of L(+)-lactic acid (3.6 mol/l; Sigma Chemical Co.) was then infused through the cannula in the left jugular vein. The load was given over 10 min with a constant-infusion pump. In the acidotic animals, the lactic acid was administered as a solution which had previously been half-neutralized with 4 mol/l sodium hydroxide. The total volumes infused were 0.5–0.9 ml of 3.6 mol/l lactic acid and 0.7–1.3 ml of half-neutralized solution. After the infusion sequential small blood samples (0.1–0.2 ml) were taken at intervals from the cannula in the opposite jugular vein for estimation of lactate and pH. Blood was replaced with equal volumes of sodium chloride solution (154 mmol/l). The total volume of blood removed was approximately 1.2 ml.

In a further group of rats the infusion studies were performed without either sham operation or nephrectomy. Ammonium chloride was not administered to this group.

In several experiments, either an aortic polypropylene cannula tipped with Vivosil (Browning, Ledingham & Pelling, 1970) or a polypropylene inferior vena cava cannula (inserted through a lumbar vein; Lucas & Floyer, 1973), was placed at the same time as a single right atrial cannula; the preparation and infusion were carried out as before, but frequent small samples were taken from the aortic or inferior vena caval cannula for lactate estimation.

Renal lactate clearance

This was measured in a separate group of animals (both normal and acidotic). The cannulations were arranged either as two atrial cannulae or as a single atrial cannula with an inferior vena caval cannula. The rats were fed and trained as before but no renal operation was performed. A diuresis was induced by infusion of dextrose solution (0.278 mol/l) to which various amounts of L(+)-lactic acid had been added; this delivered, at the same volume rate of infusion as before, between 0.33 and 0.07 mmol min⁻¹ kg⁻¹ of lactic acid in stepwise decrements. Infusion at each lactic acid concentration was continued for a minimum of 30 min and constant blood concentrations of lactate were achieved after 10 min. Timed urine collections were made and blood was taken at the beginning and end of each urine collection. When the sample was obtained from a right atrial cannula, the infusion was stopped for 10 s before obtaining the sample; after this interval, no cross-contamination from the infusion cannula was demonstrable. Lactate was estimated in blood and urine samples; renal lactate clearance was calculated by standard formula, the mean of the blood lactate concentrations at the beginning and end of each urine collection period being used.

Blood pressure and pulse measurements

Measurements of systolic arterial blood pressure were made in other groups of nephrectomized and sham-operated animals undergoing identical lactic acid infusion. Two methods were employed. In the first, the rat was lightly anaesthetized with ether and the tail plethysmograph method used (Lucas, 1971). A second method of blood pressure measurement was used for the rats in which the effect of pH changes on blood pressure was assessed, since tail plethysmography in acidotic animals gives results which correlate poorly with direct measurements (unpublished observations). For these rats, a carotid cannula was inserted under light ether anaesthesia immediately before blood pressure recording with a semi-conductor strain-gauge transducer (type S.E. 3/81; S.E. Laboratories Ltd) and ultraviolet recorder (type S.E. 2005). Heart rate was measured from the blood pressure trace.

Analytical methods

Blood pH was measured with a blood micro-system acid–base analyser (model BMS-3; Radiometer, Copenhagen) standardized with buffers of nominal pH 6.841 and 7.383. Blood lactate concentration was determined as follows. Between 0.05 and 0.2 ml of blood was added to previously weighed tubes containing 1.0 ml of 0.6 mol/l perchloric acid; the tubes were thoroughly mixed, re-weighed and
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Supernatant lactate concentration was determined by an autoanalyser adaptation of the method of Hohorst (1962) using rabbit muscle L-lactate dehydrogenase (Boehringer). The lactate concentration in blood water was calculated in mmol/kg from the lactate concentration of the supernatant. The contribution of total blood water to the supernatant volume was assumed to be 0.83 ml/g blood weight. This factor was derived by assuming a constant packed cell volume (PCV) of 0.42 and a total blood water content of 81.4% in unoperated rats (Spector, 1956); mean PCV was 0.429 ± 0.014 (n = 5) in sham-nephrectomized rats and 0.416 ± 0.015 (n = 5) in nephrectomized rats at normal pH. In severe acidosis a mean rise of PCV of 0.057 and 0.047 occurred in the two groups respectively, unaccompanied by alteration of total blood water content (unpublished observations) and the same factor has been used. During any experiment, if the volume of blood removed exceeded 1 ml, the factor was then increased by 0.01 for each millilitre of blood taken. The term 'blood lactate' is used throughout this paper in the sense of blood water lactate.

An estimate of the within-assay coefficient of variation of repeated measurements of lactate concentration on the same blood sample was 2.4%. The mean recovery of lactate added to blood to cover the range of concentrations in the present experiments was 95.5% (SD 2.70%, n = 18). Urine lactate was estimated in the same way as blood lactate, volumes used being appropriate to the lactate concentrations.

Statistical methods

Curves of the form $y = Ae^{-kt}$ and $y = Ae^{-kt} + B$ were fitted by computer to the points of the decay curve, after subtraction of basal lactate concentration, by minimizing the sum of squares of deviations. Statistical analysis of the data was performed by non-paired Student's t-tests and by simple linear regression analysis. Means are expressed ± 1 SEM.

Results

Non-acidotic animals

Blood lactate decay curves in nephrectomized and sham-operated rats. The mean decay curves of blood lactate after lactic acid infusion are shown for a group of sham-operated rats and a group of nephrectomized rats (Fig. 1). The overall curves are better fitted by a double than by a single exponential line. The first component is very rapid and has a negligible effect on blood lactate concentration after 2.5 min. The second component returns towards the base line exponentially and is therefore believed to represent the major metabolic phase of lactate removal. The blood lactate half-life and fractional turnover rate ($k_L$) were calculated from the single exponential fitted to the 5–20 min portion of each curve by least squares.

Mean blood lactate half-life in sham-operated animals was 5.28 ± 0.209 min (n = 9) and in nephrectomized animals 7.10 ± 0.476 min (n = 10). These values are significantly different ($P < 0.01$). There was a small but significant difference in the mean pre-infusion right atrial blood pH in the two groups (sham-operated rats 7.475 ± 0.010; nephrectomized rats 7.432 ± 0.007; $P < 0.005$).

During the infusion, blood pH fell in the sham-operated group to 7.26 ± 0.013 and in the nephrectomized group to 7.18 ± 0.012. In eight sham-operated and eight nephrectomized animals the rate of return of blood pH to within normal limits was observed; this occurred at a similar rate in the two groups and in both groups blood pH was greater than 7.40 within 10 min of the end of the infusion.

Renal lactate excretion. In order to determine the proportion of renal lactate removal resulting from urinary excretion of lactate ion, the lactate clearance was measured in three rats. The results
Fig. 2. Relation of renal lactate clearance to blood lactate concentration (a) at normal pH and (b) in acidotic rats (pH 6.87–7.26). Each symbol represents a different rat. The animals weighed 324–342 g, with the exception of ▲ (230 g), whose clearance values have therefore been corrected proportionally to a weight of 330 g. ▲ and ○, Blood samples for these acidotic animals were obtained from the inferior vena cava.

are shown in Fig. 2(a). Glomerular filtration rate in rats of this size is approximately 3 ml/min (Harvey & Malvin, 1965). Clearance rose from about 0.03 ml/min at a blood lactate concentration of 1 mmol/l to approximately 0.5 ml/min at a blood concentration of 10 mmol/l.

Blood pressure and pulse measurement. The mean blood pressure in the sham-operated rats, as measured by tail plethysmography under light ether anaesthesia, was 110.3 ± 2.72 mmHg (n = 12) and in the nephrectomized animals 108.5 ± 2.58 mmHg (n = 10). The difference between these values is not significant (P > 0.6). After lactic acid infusion there was a similar slight rise in the two groups (mean rise 4–8 mmHg at different times after infusion) and at no time did the difference attain significance.

Calculation of absolute rate of removal of lactate. This requires a knowledge both of the fractional removal rate of lactate, obtained from the fitted exponentials, and of the magnitude of the lactate space, i.e. the volume from which lactate is removed exponentially. The method of calculation of lactate space is described in the Appendix. The decay curve of blood lactate is double-exponential; in order to calculate the lactate space it must be assumed that the parameters of these two exponentials also apply to lactate removal during the infusion. Fig. 3 presents evidence that this assumption is valid. It shows mean blood lactate concentrations in three rats (measured on aortic or inferior vena caval blood to avoid cross-contamination during infusion) both during and after lactic acid infusion through a right atrial cannula. The fitted mean double-exponential decay curve is shown. The lactate space is calculated for each rat by using the parameters of the two exponentials of the decay curve in that animal. With the same values used for lactate space and the two exponentials, a theoretical curve for blood lactate concentration during the infusion can be calculated for each rat; the mean theoretical concentration curve is shown and is seen to correspond well to the experimental observations.

Mean lactate space in the sham-operated rats was 337 ± 23.1 ml/kg body weight and in nephrectomized animals 318 ± 24.8 ml/kg body weight. The difference between these values is not significant (P > 0.6).

The total lactate removal rate per minute at blood lactate concentration L is \( k_L V_L L \), where \( k_L \) is the fractional removal rate of blood lactate and \( V_L \) is the lactate space. The portion of blood lactate which is presumably in direct relationship with the lactate space is the plasma water lactate. Since the concentration of lactate in erythrocyte water is approximately 27% less than in plasma water (Huckabee, 1956), the use of blood water lactate can be shown to result in a 11% underestimate of the lactate removal rate at normal pH. We have not made a correction for this systematic error. At a blood lactate con-
Fig. 3. Blood lactate concentrations during and after lactate infusions in three rats. The broken line during the infusion period (stippled block) is the mean of the theoretical curves of rise of blood lactate calculated for each rat from the parameters of the exponential decay after cessation of infusion (see Appendix). The continuous line after infusion represents the mean double-exponential decay. The experimental points have been calculated by converting individual measurements into a percentage of the predicted value, taking means of the percentages so obtained, and multiplying the predicted value by this percentage. Vertical lines represent ±SEM.

Fig. 4. Relation of blood lactate half-life (T½) to hydrogen ion activity in sham-operated (○) and nephrectomized (●) rats. Hydrogen ion activity was measured on pre-infusion right atrial blood, and lactic acid was administered as a half-neutralized solution. The linear regression lines are, for sham-operated rats, T½ = 5·60 +0·0045[H+] (P>0·4) and, for nephrectomized rats, T½ = 5·02 +0·035[H+] (P<0·001).
centration of 10 mmol/l, lactate removal in the sham-operated rats was $453 \pm 45.3 \mu$mol min$^{-1}$ (kg body weight)$^{-1}$ and in the nephrectomized rats $320 \pm 28.1 \mu$mol min$^{-1}$ (kg body weight)$^{-1}$ ($P<0.05$).

In the control group of animals, which had had neither sham operation nor nephrectomy, the lactate removal rate was $548 \pm 25.3 \mu$mol min$^{-1}$ (kg body weight)$^{-1}$. The mean lactate space in these animals was $332 \pm 21.5$ ml/kg body weight, which was not statistically different from the value in the sham-operated animals.

**Acidotic animals**

**Effect of acidosis on lactate half-life.** Severely acidotic rats will not tolerate the extra acid load imposed by infusion of 3-6 mol/l lactic acid. For this reason, the studies in acidotic animals were performed with half-neutralized lactic acid; in these animals it was possible to undertake observations with a lower pre-infusion pH than would have been the case if un-neutralized lactic acid had been used. The pre-infusion right atrial blood pH varied between 6.7 and 7.5. During the infusion the mean pH fall was $0.066 \pm 0.086$ ($n = 20$) in the sham-operated group and $0.108 \pm 0.101$ ($n = 18$) in the nephrectomized rats. There is no significant difference between these figures ($P>0.1$). Fig. 4 shows the effects of metabolic acidosis on the blood lactate half-life in nephrectomized and control rats after infusion of half-neutralized lactic acid. In the sham-operated rats, increasing blood hydrogen ion activity has no significant effect on blood lactate half-life ($P>0.4$) whereas in the nephrectomized animals there is a significant positive regression of blood lactate half-life on pre-infusion blood hydrogen ion activity ($P<0.001$). The difference between the slopes of the regression lines in the two groups is significant ($P<0.005$).

**Lactate space and lactate removal in acidotic rats.** Lactate space was calculated as shown in the Appendix. There was no significant relation in either group between lactate space and hydrogen ion activity. Absolute lactate removal rates, calculated as before, show a decrease (slope of regression significant at $P<0.02$) with acidosis in nephrectomized rats, and only slight but insignificant ($P>0.1$) slowing with acidosis in sham-operated rats (Fig. 5). In experiments in which blood pH was greater than 7.0 there was no significant difference in lactate removal rate between the two groups ($P>0.1$); however, at lower blood pH nephrectomized animals showed a highly significant decrease ($P<0.001$) in removal rate compared with the sham-operated group. The error due to the use of blood water lactate rather than plasma lactate results in a 12-7% underestimate of the lactate removal rate in severely acidotic animals (compared with 10-9% in animals at normal pH). This estimate has been calculated assuming that, as in human erythrocytes (Huckabee,
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TABLE 1. Relation of basal blood lactate concentration to hydrogen ion activity in sham-operated and nephrectomized rats

Results shown are mean values ±SEM. pH values are for pre-infusion samples of right atrial blood. * Significantly different from basal blood lactate at pH > 7.40 in sham-operated rats (P < 0.02). ** Significantly different from basal blood lactate at pH > 7.40 in nephrectomized rats (P < 0.02).

<table>
<thead>
<tr>
<th>Blood lactate (mmol/l)</th>
<th>pH &gt; 7.40</th>
<th>pH 7.20–7.40</th>
<th>pH 7.00–7.20</th>
<th>pH 6.80–7.00</th>
<th>pH &lt; 6.80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-operated rats</td>
<td>0.856</td>
<td>0.764</td>
<td>0.405*</td>
<td>0.345*</td>
<td>0.280*</td>
</tr>
<tr>
<td></td>
<td>±0.044 (n = 48)</td>
<td>±0.071 (n = 21)</td>
<td>±0.026 (n = 42)</td>
<td>±0.024 (n = 26)</td>
<td>±0.029 (n = 16)</td>
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<tr>
<td>Nephrectomized rats</td>
<td>0.749</td>
<td>0.576**</td>
<td>0.472**</td>
<td>0.402**</td>
<td>0.450**</td>
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<td>±0.043 (n = 36)</td>
<td>±0.050 (n = 22)</td>
<td>±0.034 (n = 41)</td>
<td>±0.035 (n = 22)</td>
<td>±0.043 (n = 13)</td>
</tr>
<tr>
<td>Comparison between groups</td>
<td>P = 0.1–0.2</td>
<td>P &lt; 0.05</td>
<td>P = 0.1–0.2</td>
<td>P = 0.1–0.2</td>
<td>P &lt; 0.005</td>
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1956), the ratio of plasma water lactate to erythrocyte water lactate is not affected by acute lactic acidosis.

Effect of acidosis on renal excretion of lactate. Renal lactate clearance was measured in three rats previously made acidic by oral administration of ammonium chloride. The mean blood pH in these rats during the experiments was 7.10 (range pH 6.87–7.26). The results are shown in Fig. 2(b). It may be seen by comparison with Fig. 2(a) that lactate clearance is decreased by metabolic acidosis. In two of the acidic animals the sampling cannula was in the inferior vena cava rather than the right atrium, and our unpublished observations have indicated that blood lactate concentration is somewhat lower in the inferior vena cava than the right atrium. The values for clearance shown in Fig. 2(b) may therefore be somewhat higher than the true clearance values.

Effect of acidosis on basal lactate concentration. This is shown in Table 1. Included in this table are data from some rats which were made acidic to varying degrees but did not subsequently receive a lactate infusion. There is a significant fall in blood lactate concentration in both sham-operated and nephrectomized rats; in severe acidosis (pH 6.5–6.8) blood lactate concentrations in nephrectomized animals are approximately 1.7 times the values seen in sham-operated rats, a difference which is significant (P < 0.005).

Effect of acidosis on blood pressure. There is a significant positive regression of blood pressure on blood pH in the sham-operated (P < 0.02) and nephrectomized group (P < 0.01). Both groups were lightly anaesthetized with ether for the blood pressure measurement. The gradients of these regression lines are very similar. Heart rate slows with acidosis in both sham-operated and nephrectomized rats to a similar extent, with a positive linear regression of heart rate on blood pH in both groups that is highly significant (P < 0.001). A fall in blood pH from 7.4 to 6.7 causes a mean fall of blood pressure of approximately 18 mmHg and a mean decrease of heart rate of approximately 140 beats/min.

Discussion

These experiments were designed to study the behaviour of the lactate disposal mechanisms under load conditions; in terms of blood lactate concentrations they simulated approximately the situation during and after a brief spell of strenuous exercise. They differ from previous animal studies in being made in conscious animals. However, the animals cannot be regarded as completely 'normal' because of the performance of sham-operation or nephrectomy 4–6 h before the infusion studies. Thus the half-life of blood lactate was shorter in animals which had not had a sham operation; comparable effects of operation on hepatic lactate removal have been demonstrated by Lee, Ross & Haines (1972).

The decay curves of blood lactate after a short lactic acid infusion are better described by the sum of two exponential terms than by a single exponential, though the first component has negligible effect on blood lactate concentration at times greater than 2.5 min after cessation of the infusion. We have assumed that the second component represents the major phase of metabolic removal of lactate and that any alteration of body lactate production during the observations has a negligible effect on the decay
curve; the observed conformity of the latter part of the curve to single exponential behaviour is consistent with these assumptions but does not exclude other possibilities. A method is described for estimation of the initial volume of distribution of lactate necessary for the calculation of absolute rate of removal of lactate. The more usual technique of single bolus injection for study of disappearance curves, with extrapolation to \( t = 0 \) for space calculation, was impracticable, since rats will not tolerate a bolus injection of lactic acid in the quantities required for the present study.

In a group of conscious sham-operated rats, the mean absolute lactate removal rate at a blood lactate concentration of 10 mmol/l is 453 \( \mu \text{mol min}^{-1} \) (kg body weight)\(^{-1}\). This compares with a figure of 624 \( \mu \text{mol min}^{-1} \) (kg body weight)\(^{-1}\) derived from the equation of Freminet, Bursaux & Poyart (1972), a primed constant infusion of \([U-^{14}C]\)lactate being used in ventilated anaesthetized rats with intact kidneys. At normal blood pH the kidney apparently contributes about one-quarter of the removal of a lactic acid load or about 133 \( \mu \text{mol min}^{-1} \) (kg body weight)\(^{-1}\). This could occur in one of three ways: first, the kidney might contribute directly to the metabolic removal of lactate ions; secondly, the kidney might excrete substantial quantities of lactate; thirdly, nephrectomy might influence lactate removal in the remainder of the body, either through circulatory changes or by some humoral mechanism.

Renal excretion of lactate ion in three rats (not sham-operated) at a blood lactate concentration of 10 mmol/l accounts for a mean removal of only 15 \( \mu \text{mol min}^{-1} \) (kg body weight)\(^{-1}\), or approximately 12\% of the renal component of lactate removal. At lower blood concentrations, the renal component is smaller. Even at high blood lactate concentrations, the clearance is only about 25\% of expected glomerular filtration rate. It can be shown that lactate reabsorption from the glomerular filtrate reaches a plateau when blood lactate concentration is around 10 mmol/l. This compares with the work of Craig (1946), who showed saturation of tubular transport of lactate at blood concentrations of 10 mmol/l in the dog.

The similarity of blood pressure in the nephrectomized and sham-operated groups of rats does not preclude the possibility of circulatory differences between the two groups, but demonstrates that the slowing of lactate removal in the nephrectomized group is not due to a gross degree of circulatory insufficiency. We have not excluded the possibility that the presence of the kidneys may permit a more rapid lactate removal elsewhere in the body through some other mechanism.

It may be noted that when half-neutralized lactic acid was used in the studies of the effect of acidosis there was no significant difference in lactate removal between the two groups at normal pH. The reason for this is not clear but could be related to the small numbers studied at normal pH values in this series.

Metabolic acidosis of 4-6 h duration produces only slight and insignificant slowing of lactate removal in sham-operated rats; in nephrectomized animals, however, lactate removal is slowed by one half when blood pH falls from 7.45 to 6.75. These differences between the sham and nephrectomized animals are unlikely to be due to circulatory effects since metabolic acidosis caused similar reductions in heart rate and mean arterial pressure in the nephrectomized and sham-operated groups. With the calculated regression equations, it may be shown that the renal contribution to lactate removal increased from 16\% at pH 7.45 to 44\% at pH 6.75. There is concurrently a marked slowing (49\%) of extra-renal lactate removal, approximately half of which is compensated for by the increase in renal lactate removal. The observations on renal lactate excretion demonstrate an absolute reduction in clearance in acidotic rats compared with those at normal pH.

It seems likely that the liver is the main organ responsible for removal of a lactic acid load in the nephrectomized rat. Other organs, such as cardiac and skeletal muscle, and brain, have been demonstrated under certain conditions, both in vivo and in vitro, to take up lactate in small amounts and to use it as a metabolic fuel (Carlsten, Hallgren, Jagenburg, Svanborg & Werkö, 1961; Harris, Bateman & Gloster, 1962; Rowe, Maxwell, Castillo, Freeman & Crumpton, 1959). Fig. 6 makes comparisons between values taken from the literature for maximally stimulated removal rates of lactate by perfused rat liver (Ross, Hems & Krebs, 1967) and kidney (Bowman, 1970; Nishiitsutsuji-Uwo, Ross & Krebs, 1967), and the eviscerated rabbit (Drury, Wick & Morita, 1955) on the one hand, and our own results showing the components of removal of a lactic acid load at normal starting pH in the conscious animal. Removal rates are expressed per kg body weight. Because our animals were relatively well fed, gluconeogenesis from lactate
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The effect of metabolic acidosis on lactate removal in the nephrectomized rat is similar to but not identical with that in the isolated perfused rat liver. In the isolated liver, lactate uptake falls markedly when the systemic pH is below 7.1 and is converted into output when perfusion medium pH is less than 7.0 (Lloyd et al., 1973); in the nephrectomized animal, however, lactate uptake continues even at more severe levels of acidosis.

The present observations may have relevance to the pathogenesis of clinical lactic acidosis. It has been suggested (Mulhausen, Eichenholz & Blumentals, 1967; Perret, Enrico, Montani & Pappalardo, 1967; Cohen, Iles, Barnett, Howell & Strunnin, 1971; Lloyd et al., 1973) that a major factor in the production of this syndrome is failure of hepatic removal of lactate. It is clear that such explanations must take into account the very considerable potential contribution of the kidney to lactate removal in acidosis. Thus in lactic acidosis due to phenformin, when interference with hepatic gluconeogenesis from lactate has been suggested as being responsible (Altschuld & Kruger, 1968; Haeckel & Haeckel, 1971), there would have to be a similar interference with renal lactate uptake. It is therefore of interest that phenformin has been demonstrated to inhibit renal gluconeogenesis both in vivo (Meyer, Ipaktchi & Clauser, 1967) and in tissue slices (Alleyne, Besterman & Flores, 1971). In addition, most patients with phenformin-associated lactic acidosis have had impaired renal function (Oliva, 1970; MacGregor, Poole-Wilson & Jones, 1972; Cohen, Ward, Brain, Murray, Savage & Iles, 1973). In lactic acidosis due to circulatory failure, the ability of the kidneys to remove lactate might be impaired by the low renal blood flow.

Basal blood lactate concentration is significantly lowered by acidosis in both sham-operated and nephrectomized rats. In the latter, lactate levels at pH 6.5–6.8 are approximately one and a half times those in the sham-operated group; this is as might be expected from the marked slowing of lactate removal in nephrectomized rats made severely acidic 4–6 h previously. The fall in basal lactate concentrations in acidosis must be related to a reduced production of lactate. It is probable that this fall of lactate production is due to inhibition of glycolysis at the step catalysed by phosphofructokinase, which has been shown to be inhibited by acidosis in many tissues (Trivedi & Danforth, 1966; Ui, 1966).

would be slow, so that the total removal rates seen in our experiments are considerably less than they would be in starved animals, in which gluconeogenesis is maximally stimulated. Even so, the removal in vivo is more than twice the sum of removal rates by individual organs. This would suggest that isolated perfused organ experiments underestimate the capacity of these organs in vivo to remove lactate.

The present studies provide no information concerning the fate of lactate removed from the circulation by the kidney. Studies of the proportions of lactate converted into glucose on the one hand, or oxidized on the other, have given variable results according to the conditions used (Bowman, 1970; Nishiitsutsuji-Uwo et al., 1967; Leal-Pinto, Park, King, MacLeod & Pitts, 1973). Most studies of lactate uptake by isolated perfused liver, however, indicate that the major part of the lactate metabolized is converted into glucose (Hems, Ross, Berry & Krebs, 1966; Exton & Park, 1967). If it is assumed that under the conditions of the present studies a substantial fraction of lactate is converted into glucose, then a possible explanation for the increased renal lactate uptake in acidosis could be the stimulation of renal phosphoenolpyruvate carboxy-kinase activity in acidosis observed by Alleyne (1970); it is noteworthy that the activity of this enzyme in the liver is little affected by acidosis (Alleyne & Scullard, 1969).
Appendix

Calculation of lactate space

Let $I$ be the infusion rate, $L$ the lactate concentration in the lactate space above basal; $t$, time; $V$, volume of lactate space.

Two assumptions are made: (a) that distribution time within the lactate space is negligible compared with metabolic removal, and (b) that the kinetics of lactate disappearance are quantitatively identical during and after the infusion.

During the infusion the rate of rise of $L$ is equal to the sum of the rates of concentration changes due to the infusion $(I/V)$ and to removal processes $(R)$ (eqn. 1).

$$\frac{dL}{dt} = \frac{I}{V} + R \quad (1)$$

If the decay of blood lactate (lactate space) concentration after cessation of infusion is represented by eqn. (2),

$$L = Ae^{-k_1t} + Be^{-k_2t} \quad (2)$$

$R$ could be obtained by simply differentiating the right-hand side of eqn. (2); but eqn. (1) would not then be in a form amenable to simple solution. However, by two successive differentiations of eqn. (2) it may be shown that $R$, the first differential of $L$, is given by eqn. (3).

$$-\frac{1}{(k_1 + k_2)} \left( \frac{d^2L}{dt^2} + k_1k_2L \right) \quad (3)$$

Substituting in eqn. (1)

$$\frac{dL}{dt} = \frac{I}{V} - \frac{1}{(k_1 + k_2)} \left( \frac{d^2L}{dt^2} + k_1k_2L \right) \quad (4)$$

The solution of eqn. (4) is

$$L = \left[ \frac{I \cdot (k_1 + k_2)}{V \cdot k_1k_2(k_1 - k_2)} \right] \left( (k_1 - k_2) + (k_2e^{-k_1t} - k_1e^{-k_2t}) \right) \quad (5)$$

Thus $V$ may be calculated from the lactate concentration at the end of infusion, the infusion rate and the two exponents of the decay curve of blood lactate after the end of infusion. The validity of assumption (b) made above is confirmed by the close correspondence (Fig. 3) of the measured blood lactate concentration during infusion and the theoretical curve of blood lactate during infusion calculated from eqn. (5)

using the value for $V$ obtained as described. This correspondence also makes it likely that assumption (a) is reasonable. If for instance the changes in concentration of lactate in the extravascular part of the lactate space lagged behind the intravascular lactate concentration after the end of infusion, it would be expected that during the infusion the measured intravascular concentrations would exceed the theoretically calculated values.

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References


Renal lactate removal in acidosis


