THE EFFECT OF GLUCOSE ON THE URINARY EXCRETION OF SODIUM AND HYDROGEN ION IN MAN

E. S. GARNETT AND C. NAHMIAS

Department of Nuclear Medicine, McMaster University Medical Centre, Hamilton, Ontario, Canada

(Received 27 June 1974)

SUMMARY

1. Urinary sodium and hydrogen ion excretion was measured in four normal subjects before and after they had ingested 25 g of glucose. The subjects were studied during a sustained water diuresis after an overnight fast and after a 40 h fast.

2. After glucose had been ingested, urinary sodium excretion was reduced by approximately 40% but there was no change in urine flow. The decrease in sodium excretion was associated with a rise in hydrogen ion excretion.

3. These results suggest that sodium ion is retained in exchange for hydrogen ion in the distal segment of the nephron.

4. It is postulated that the increased renal bicarbonate threshold and the metabolic alkalosis which develop when glucose is given to fasted subjects are a consequence of this exchange.

Key words: urine, sodium, hydrogen, glucose.

If obese subjects fast for at least 4 days they reduce their urinary excretion of sodium when they are given carbohydrate (Weinsier, 1971; Gozansky & Herman, 1971). It has generally been assumed that a period of total starvation is necessary to produce the effect. Consequently, the reduction in urinary sodium has always been associated with a reduction in keto anion excretion since both effects occur when carbohydrate is given to fasted subjects. In the present study, in which subjects were fasted overnight, it has been possible to investigate the effect of glucose on the urinary excretion of sodium and hydrogen ion in the absence of any change in keto anion excretion.

METHODS

Two male and two female subjects were studied. Their ages ranged from 27 to 40 years. They
were healthy members of the laboratory staff who understood the nature of the experiment and volunteered freely. One of the females was overweight.

Each experiment began at 10.00 hours. Subjects emptied their bladders and then were given an oral water load (20 ml/kg body weight). After 100 min, and at 20 min intervals thereafter, each subject emptied his or her bladder and drank a volume of water equal to that passed. After 4 h, when a diuresis was well established, each subject drank 500 ml of a 0.278 mol/l (5%) solution of glucose instead of the replacement water. The original routine was then resumed for a further 3 h. The subjects remained seated in an air-conditioned room except when they emptied their bladders. Central venous blood samples were taken from an indwelling catheter at intervals throughout each experiment.

At least two experiments were performed on each subject. One experiment was done after an overnight fast. The other experiments, which were performed at intervals of at least 1 week, were done after a 40 h fast, when only salt and calorie-free fluids were consumed. To avoid sodium and potassium depletion on the day of the study, 50 mmol of sodium and 25 mmol of potassium, as the chlorides, were ingested at 08.00 hours. To avoid depletion during the 40 h fast sodium and potassium were given as chlorides in amounts equivalent to the usual dietary intake, as previously determined from 24 h urine collections. These electrolytes were given in equally divided doses at intervals of 8 h.

A control experiment in which 500 ml of water was drunk instead of glucose solution was performed on each subject after an overnight fast.

The following measurements were made on each specimen of urine: pH was determined with a Radiometer pH meter, titratable acid was measured by back titration with NaOH to pH 7.4 (Nutbourne, 1961), and bicarbonate was measured by an AutoAnalyser technique (Skeggs & Hochstrasser, 1964), which had been validated by comparison with the Natelson (1951) gasometric method. Sodium and potassium were determined by flame photometry (Unicam SP. 250), ammonium as indophenol by spectrophotometry (Bolleter, Bushman & Tidwell, 1961), creatinine by the Jaffé reaction after adsorption on to fuller's earth (Owen, Iggo, Scandrett & Stewart, 1954). 3-Hydroxybutyrate was determined by fluorimetry (modified from Williamson, Mellanby & Krebs, 1962), glucose by fluorimetry (modified from Slein, 1965) and osmolality by depression of freezing point (Advanced Osmometer, 3L).

pH and PCO₂ were measured on whole blood. Bicarbonate, glucose, 3-hydroxybutyrate, creatinine, osmolality and insulin (Hales & Randle, 1963) were determined in plasma.

RESULTS

Four studies were performed after an overnight fast and seven studies after a 40 h fast.

A control period was started once diuresis had been established. Urine flow rates were maintained in excess of 8 ml/min. In any one subject the urine flow rate was relatively constant throughout the study (coefficient of variation, CV = 10%, SD = 1.1 ml/min). The urinary osmolality ranged from 50 to 65 mosmol/kg before glucose ingestion and from 40 to 50 mosmol/kg after glucose. Plasma osmolality was always less than 275 mosmol/kg and remained constant. True creatinine clearance also remained relatively constant (CV = 12%, SD = 10 ml/min). Glucose was never detected in the urine.

During the control period, the urinary sodium excretion remained constant. After glucose had been given, it decreased. The mean decrease at 60 min was 35% of the control value (range
Glucose-induced hydrogen ion excretion

20–60%). In seven of the eleven studies, the sodium excretion then returned towards the control value, whereas in the remainder it continued to fall. In one study the urinary sodium excretion fell by 90%. There was no difference in the results obtained after an overnight fast and those obtained after a 40 h fast (Fig. 1).

The excretion of ammonium, titratable acid and bicarbonate was relatively constant before glucose was given. After glucose the excretion of ammonium and titratable acid rose and the excretion of bicarbonate fell ($P = 0.025; n = 8$). The reduction in bicarbonate excretion occurred in the absence of any significant change ($P > 0.5; n = 8$) in plasma bicarbonate (Fig. 2). Net hydrogen ion excretion was calculated by subtracting the bicarbonate from the sum of the ammonium and titratable acid excretion. It reached a maximum within an hour of glucose
administration and then fell (Fig. 3). The central venous blood hydrogen ion concentration fell by no more than 6% during the time of increased hydrogen ion excretion and there was no significant change in $P_{CO_2}$.

In those studies done after an overnight fast, the urinary 3-hydroxybutyrate concentration was lower than the limit of detectability (0·02 μmol/ml) both before and after glucose. In contrast, in those studies done after a 40 h fast, the urinary excretion of 3-hydroxybutyrate ranged from 5·0 to 12·0 μmol/min during the control period and fell to less than 2·0 μmol/min within 80 min of glucose ingestion (Fig. 3). Similarly the plasma 3-hydroxybutyrate concentration was negligible after an overnight fast but, after a 40 h fast, it was elevated at 0·36–1·20 μmol/ml and fell to less than 0·05 μmol/ml when glucose was given.

During the control period, the plasma glucose concentration was never greater than 4·16 mmol/l and the plasma insulin concentration was less than 5 μunits/ml, except in the overweight subject in whom it was 15 μunits/ml. When glucose was given, the plasma glucose concentration rose but did not exceed 5·83 mmol/l. The plasma insulin also rose. In the lean subjects, it reached 15 μunits/ml; in the overweight subject, it reached 63 μunits/ml.

None of the subjects developed a negative potassium balance during the study.

When the glucose was omitted in the control experiments (Fig. 1) the urinary sodium excretion remained unchanged ($P>0·5$) and there was no significant change in net hydrogen ion excretion ($P>0·5$).

![Graph](image)

**Fig. 2.** Plasma and urinary bicarbonate before and after glucose. The urinary bicarbonate before glucose is the mean of the bicarbonate excretion during the last three collections of the control period. The urinary bicarbonate after glucose is the mean of three sequential urine collections in which the middle collection contained the lowest bicarbonate excretion of the study.
Glucose-induced hydrogen ion excretion

Fig. 3. Effect of ingestion of 25 g of glucose on urinary 3-hydroxybutyrate excretion, net hydrogen ion excretion and sodium excretion. (a), (b), (c) and (d) show paired results obtained in four subjects. Continuous lines indicate data obtained after a 40 h fast; broken lines indicate data obtained after an overnight fast.
DISCUSSION

The results of these experiments show that the effect of glucose ingestion on the urinary excretion of sodium is not a consequence of prolonged starvation. Nor is it confined to obese subjects. A group of obese subjects and two volunteers of normal weight studied by Veverbrants & Arky (1969) fasted for 3 days, but it is not clear from their results whether the normal subjects retained sodium to the same extent as the obese subjects when each was re-fed. Lindeman, Adler, Yiengst & Beard (1970) fasted normal weight subjects overnight and although they were able to demonstrate carbohydrate-induced sodium retention, this occurred, with one exception, only in patients older than 50 years. However, Hoffman, Martino, Wahl & Arky (1969) did see the effect in young obese subjects after 1 day of fasting. The reason for these differences is not apparent.

| TABLE 1. Mean urinary sodium and hydrogen ion excretion before and after glucose ingestion and in control studies |
| 'Before' represents mean of the three consecutive collection periods preceding ingestion of glucose. 'After' represents mean of the six consecutive periods after ingestion of glucose. Control values are from those studies in which no glucose was ingested. |

Excretion (μmol/min)

<table>
<thead>
<tr>
<th></th>
<th>Sodium</th>
<th></th>
<th>Hydrogen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>40 h fast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject A</td>
<td>76.0</td>
<td>58.0</td>
<td>26.7</td>
<td>37.0</td>
</tr>
<tr>
<td>Subject B</td>
<td>112.7</td>
<td>61.7</td>
<td>19.3</td>
<td>35.0</td>
</tr>
<tr>
<td>Subject C</td>
<td>66.3</td>
<td>49.7</td>
<td>20.7</td>
<td>30.8</td>
</tr>
<tr>
<td>Subject D</td>
<td>86.0</td>
<td>67.3</td>
<td>17.7</td>
<td>23.5</td>
</tr>
<tr>
<td>Overnight fast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject A</td>
<td>140.0</td>
<td>113.0</td>
<td>27.0</td>
<td>27.4</td>
</tr>
<tr>
<td>Subject B</td>
<td>111.0</td>
<td>89.0</td>
<td>6.7</td>
<td>17.7</td>
</tr>
<tr>
<td>Subject C</td>
<td>68.3</td>
<td>44.0</td>
<td>5.6</td>
<td>18.7</td>
</tr>
<tr>
<td>Subject D</td>
<td>89.7</td>
<td>54.3</td>
<td>7.0</td>
<td>21.2</td>
</tr>
<tr>
<td>Paired t</td>
<td>t = 6.47</td>
<td>t = 7.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject A</td>
<td>253.0</td>
<td>220.0</td>
<td>19.5</td>
<td>15.9</td>
</tr>
<tr>
<td>Subject B</td>
<td>70.0</td>
<td>80.0</td>
<td>16.1</td>
<td>15.9</td>
</tr>
<tr>
<td>Subject C</td>
<td>52.0</td>
<td>53.5</td>
<td>12.4</td>
<td>13.9</td>
</tr>
<tr>
<td>Subject D</td>
<td>104.3</td>
<td>128.3</td>
<td>28.1</td>
<td>24.2</td>
</tr>
<tr>
<td>Paired t</td>
<td>t = 0.02</td>
<td>t = 0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P &gt; 0.5</td>
<td>P &gt; 0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the present study, a 40 h fast produced a rise in the plasma 3-hydroxybutyrate concentration, whereas 3-hydroxybutyrate could not be detected in the plasma or urine after an overnight fast. In spite of these differences, the two fasts could not be distinguished from each other on the basis of the time-course and the magnitude of the glucose-induced reduction in urinary sodium (Fig. 1). This implies that the sodium-retaining effect of glucose is not dependent upon a pre-existing keto-acidosis. Similarly, Lemieux & Plante (1968) showed that dogs which have been fasted retain sodium when they are re-fed, although they do not develop a keto-acidosis during starvation.

The striking feature of the present study was the increase in net hydrogen excretion, which was observed when glucose was given (Table 1). This increase was mainly due to a rise in ammonium and titratable acid excretion. It was seen in all of the studies and it occurred whilst the urinary sodium was falling (Fig. 3). This would suggest that the mechanism responsible for the excretion of hydrogen ions was also responsible for the retention of sodium ions. However,
since the number of \( \mu \text{mol} \) of sodium retained was always greater than the number of \( \mu \text{mol} \) of hydrogen excreted, an exchange of sodium for hydrogen ion was not the mechanism by which all of the sodium was retained. In most studies, approximately half of the sodium ions could have been retained in exchange for hydrogen ions. The relation between the excretion of sodium ions and hydrogen ions is represented by the regression equation \( \text{Na}^+ = -2.4 \text{H}^+ + 120 \) (\( r = -0.55, n = 72, P<0.01 \)) (Fig. 4).

It should be noted that the maximal hydrogen ion excretion always occurred within 40 min of glucose ingestion and before minimal sodium excretion. This suggests that the mechanism whereby hydrogen ions are excreted is actuated very soon after the ingestion of glucose. It should also be noted that even after the longer fast the initial increase in hydrogen ion excretion and the decrease in sodium ion excretion occurred before any perceptible change in the excretion of 3-hydroxybutyrate.

After 40 h of total starvation, the hydrogen ion excretion during the control period was greater than after an overnight fast. The excretion of 3-hydroxybutyrate was also greater and it is therefore reasonable to suppose that the elevated hydrogen ion excretion was a consequence of an increased production of ketone body anions. Thus, when the need to excrete 3-hydroxybutyrate was reduced as a result of the increase in insulin produced by the ingestion of glucose, a concomitant reduction in hydrogen ion excretion would be expected.

The fall in hydrogen ion excretion which occurred during the later stages of the experiment was therefore a result of two processes. One was the reduction in hydrogen ion excretion associated with the return of sodium excretion towards pre-glucose values. The other was the decreased need to excrete 3-hydroxybutyric acid. Since two mechanisms contribute to the regulation of the net hydrogen ion excretion after glucose is ingested it is apparent that, if one of the mechanisms plays the major role, the likelihood of detecting the other is decreased. It is also apparent from these experiments that the initial increase in hydrogen ion excretion may not be detected unless urine is collected over short time-intervals.

Katz, Hollingsworth & Epstein (1968) re-fed subjects who had been starved for 4 days and compared the effects of carbohydrate and protein on sodium excretion. Both carbohydrate and protein caused a reduction in urinary sodium but protein did not correct the ketonuria. In those subjects in whom ketonuria persisted, the retention of sodium was associated with a marked increase in the excretion of ammonium, whereas in those subjects in whom the ketonuria was corrected there was a marked decrease in ammonium excretion. The evidence of Katz et al. (1968) therefore supports the present hypothesis that hydrogen ions exchange for sodium ions in the urine when food is ingested. It also supports the conclusion that the rise in hydrogen ion excretion will be detected only if there is no change in ketone body anion excretion. When Sapir, Owen, Cheng, Ginsberg, Boden & Walker (1972) starved patients for more than 2 weeks they found that as little as 7.5 g of carbohydrate/day reduced both the excretion of ketone body anion and ammonium and there was a significant positive correlation between these measurements. This is not surprising since the daily excretion of ketone body anion was in excess of 150 mmol/day. Furthermore, since 24 h collection periods were used and since sodium excretion would already have been reduced to a minimum, because the subjects were not given any sodium during the fast, an initial increase in hydrogen ion excretion would not have been noticed.

Lennox (1926) first reported a systemic alkalosis when fasted patients were re-fed. The mechanism of this alkalosis was investigated by Stinebaugh & Schloeder (1972), who found that
Glucose-induced hydrogen ion excretion

the bicarbonate threshold already increased by starvation rose even higher when glucose was administered. These workers gave their subjects a daily sodium supplement in excess of 100 mmol and when glucose was administered more than half of this was retained. After 4 days of re-feeding, the subjects became oedematous and positive sodium balances of almost 400 mmol were recorded. Our results suggest that approximately half of the sodium which is retained by the kidney when glucose is given is exchanged for hydrogen ions. Since these hydrogen ions are excreted into the urine, the amount of the filtered bicarbonate that can be excreted will be reduced. In other words there will be an increase in the so-called renal bicarbonate threshold, if filtered bicarbonate remains constant. This is illustrated in Fig. 2, in which it can be seen that glucose produced a significant fall in urinary bicarbonate excretion at a time when there was no significant change in plasma bicarbonate and the true creatinine clearance remained relatively constant. Furthermore, since sodium is reabsorbed in exchange for hydrogen ion, an amount of bicarbonate will be formed in the tubule cells which is equivalent to the amount of hydrogen ion exchanged. If the results of the present study can be extrapolated to the longer studies of Stinebaugh & Schloeder (1972), it would suggest that the kidney could have generated up to 200 mmol of bicarbonate as a direct result of the exchange of hydrogen ion for sodium. The loss of hydrogen ion in the urine and the generation of bicarbonate by the kidney would then be sufficient to explain the metabolic alkalosis during the first 4 days of re-feeding.

During the present studies, in which a water diuresis was sustained, it may be supposed that the distal segment of each nephron was impervious to water. Therefore the glucose-induced reduction in urinary sodium excretion which occurred without change of urine flow must have been due to an increase in sodium reabsorption from the distal segment. This conclusion is supported by Wright, Gann & Albertsen (1963), Hoffman et al. (1969) and Schloeder & Stinebaugh (1970), although the last two groups noted glucose-induced changes in the amount of sodium reabsorbed in the proximal segment as well as in the distal segment.

ACKNOWLEDGMENTS

We thank Dominion Foundries and Steel Company Ltd for financial support. We are grateful to Dr C. J. Toews for 3-hydroxybutyrate measurements and to Dr Christopher Walker for bicarbonate measurements.

REFERENCES


LENNOX, W.G. (1926) Chemical changes in the blood during fasting in the human subject. Archives of Internal Medicine, 38, 553–565.


