Growth hormone secretion in acid–base alterations at rest and during exercise

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Summary
1. Seven healthy males were studied during cycle ergometer exercise at 33%, 66% and 90% of $\dot{V}O_2$ max. on three occasions when NH$_4$Cl, NaHCO$_3$ or CaCO$_3$ (as a control substance) were administered in gelatin capsules double blind and in randomized order. Plasma growth hormone (HGH), lactic acid and hydrogen ion concentration ([H$^+$]) were measured at frequent intervals.

2. Ammonium chloride produced highest blood [H$^+$] and NaHCO$_3$ the lowest. These differences were maintained during exercise and in recovery. Plasma lactic acid concentrations were similar at rest. At 66%, 90% $\dot{V}O_2$ max. and recovery lactic acid was highest with NaHCO$_3$ and lowest with NH$_4$Cl.

3. Exercise stimulated HGH secretion in all studies and the elevation was proportional to the intensity of the exercise. NH$_4$Cl caused a variable elevation of HGH at rest and 33% $\dot{V}O_2$ max. At 66% $\dot{V}O_2$ max., plasma HGH was significantly elevated to similar concentrations in all studies and, at 90% $\dot{V}O_2$ max., HGH was highest with NaHCO$_3$.

4. An infusion of sodium L(+)--lactate producing plasma lactate concentrations of 3–5 mmol/l did not influence HGH secretion.

5. Exercise is a physiological stimulus to HGH secretion and the mechanism is independent of blood [H$^+$] and lactate concentrations.

Key words: acid–base, exercise, growth hormone.

Introduction
Plasma human growth hormone concentration is increased in clinical states associated with metabolic acidosis such as renal failure (Horton, Johnson & Lebovitz, 1968; Wright, Lowy, Russell-Fraser, Spitz, Rubenstein & Bersohn, 1968; Samaan & Freeman, 1970) and diabetes mellitus (Gerich, Martin & Recant, 1970). Exercise also stimulates HGH$^{(1)}$ secretion (Roth, Glick, Yalow & Berson, 1963; Hunter, Fonseka & Passmore, 1965; Schalch, 1967). The magnitude of HGH elevation is related to the duration and intensity of the exercise (Sutton & Lazarus, 1974), and the 'fitness' of the individual, being greater and sustained for longer in the 'unfit' (Sutton, Young, Lazarus, Hickie & Maksvytis, 1969; Rennie, Jennett & Johnson, 1974).

Greater increases are found in submaximal exercise during hypoxia (Sutton, 1971). As lactic acid levels are higher in hypoxic exercise (Jones, Robertson, Kane & Hart, 1972) and in unfit individuals during exercise, we have examined the relationship between the lactic acidosis associated with exercise and changes in HGH. By inducing metabolic acidosis with ammonium chloride and metabolic alkalosis with sodium bicarbonate, we have separated the effects of increasing plasma lactate concentrations from those of increasing blood hydrogen ion concentration ([H$^+$]).

Subjects and methods
Seven healthy males aged 22–42 years, who gave informed consent, were studied on three occasions in

$^{(1)}$ Abbreviation: HGH, human growth hormone.
the space of 6 weeks. The subjects were receiving no drugs at the time of the study, which was approved by the hospital ethics committee. Metabolic acidosis and alkalosis were induced by NH₄Cl or NaHCO₃ and the response of HGH at rest and during exercise was compared with results of a control study in which CaCO₃ was administered. The studies were randomized and conducted double blind by administering these agents as a powder in gelatin capsules. In a preliminary study, maximal oxygen uptake (\( \dot{V}_{O_2} \max \)) was measured with a progressive exercise test on a cycle ergometer. After an overnight fast, NH₄Cl (acidosis), NaHCO₃ (alkalosis) or CaCO₃ (control) were given in a dose of 0·3 g/kg over 3 h. After the 3 h rest period, the subjects exercised on a cycle ergometer at 33% and 66% of \( \dot{V}_{O_2} \max \), each sustained for 20 min. After this, the subjects exercised at 90% of \( \dot{V}_{O_2} \max \) until exhaustion. The individual power output and time to exhaustion at 90% \( \dot{V}_{O_2} \max \) are shown in Table 1. The electrocardiogram (V₃) was displayed on a multichannel recorder and the heart rate calculated by averaging five consecutive R–R intervals. Venous blood was collected from an indwelling intravenous polyethylene catheter inserted into an antecubital vein. The blood was collected during the 3 h after the administration of the capsules, with the subjects at rest, during the exercise, and in the post-exercise period. Venous pH was measured with a Radiometer Blood Gas analyser (BMS 3), plasma lactate was determined by enzymic fluorometric assay (Toews, Lowy & Ruderman, 1970) and plasma growth hormone by double antibody radioimmunoassay (Molinatti, Massara, Strumia, Pennisi, Scassellati & Vancheri, 1969). All samples from the one subject were measured in the same assay to avoid interassay variance. The mean ± 2 SD for low and high control sera in the growth hormone assay were 0·5 ± 0·4 ng/ml and 20·0 ± 4·0 ng/ml.

In a second study, the influence of lactate on HGH secretion was investigated. Sodium L(+)-lactate, pH 7·4 (1 mmol/ml), was infused intravenously at 0·1 mmol min⁻¹ kg⁻¹ by a Harvard constant-infusion syringe pump in six normal fasting subjects at rest and the response in plasma HGH was measured.

**Results**

Acidosis and alkalosis produced by the capsule administration regime achieved significant separation in blood [H⁺] (P < 0·01), which was maintained throughout the study (Fig. 1). Little additional changes in [H⁺] occurred with exercise at the two lower levels of power output, but at 90% \( \dot{V}_{O_2} \max \) a marked increase in [H⁺] occurred in all studies and was greatest in the alkalosis study and least in the acidosis study.

Plasma lactic acid concentrations were similar at rest in all studies (Fig. 2). During exercise, lactic acid was highest with alkalosis and lowest with acidosis and this difference was accentuated at higher levels.

### Table 1. Clinical and exercise data for subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Power output (J s⁻¹)</th>
<th>Exhaustion time at 90% ( \dot{V}_{O_2} \max ) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33%</td>
<td>66%</td>
</tr>
<tr>
<td>J.M.</td>
<td>28</td>
<td>174</td>
<td>65</td>
<td>65</td>
<td>131</td>
</tr>
<tr>
<td>R.H.</td>
<td>24</td>
<td>177</td>
<td>63</td>
<td>97</td>
<td>196</td>
</tr>
<tr>
<td>N.J.</td>
<td>42</td>
<td>188</td>
<td>98</td>
<td>97</td>
<td>196</td>
</tr>
<tr>
<td>R.R.</td>
<td>22</td>
<td>185</td>
<td>90</td>
<td>114</td>
<td>229</td>
</tr>
<tr>
<td>J.R.</td>
<td>23</td>
<td>178</td>
<td>62·5</td>
<td>90</td>
<td>180</td>
</tr>
<tr>
<td>J.S.</td>
<td>33</td>
<td>188</td>
<td>82</td>
<td>82</td>
<td>229</td>
</tr>
<tr>
<td>R.T.</td>
<td>27</td>
<td>185</td>
<td>80</td>
<td>82</td>
<td>163</td>
</tr>
<tr>
<td>Mean</td>
<td>28·4</td>
<td>182</td>
<td>77·2</td>
<td>94·6</td>
<td>189</td>
</tr>
<tr>
<td>SD</td>
<td>7·0</td>
<td>5·7</td>
<td>14·1</td>
<td>17·6</td>
<td>35·1</td>
</tr>
<tr>
<td>SEM</td>
<td>2·7</td>
<td>2·2</td>
<td>5·3</td>
<td>6·6</td>
<td>13·3</td>
</tr>
</tbody>
</table>

(1) Highest power output = 100% of previous maximum power output.
(2) Different from CaCO₃ study (P < 0·005).
(3) Different from CaCO₃ study (P < 0·01).
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**FIG. 1.** Hydrogen ion concentrations at rest and during exercise at 33%, 66% and 90% of \( \dot{V}O_2 \) max. after administration of CaCO\(_3\) (● – ●), NH\(_4\)Cl (■ – ■) and NaHCO\(_3\) (○ – ○). Results are plotted as mean values ± SEM.

**FIG. 2.** Plasma lactic acid concentrations at rest and during exercise with CaCO\(_3\), NH\(_4\)Cl and NaHCO\(_3\). Symbols, etc., are the same as in Fig. 1.
of power output, and maintained in recovery. Lactic acid concentrations were significantly different from control at 66%, 90% \( \dot{V}O_2 \) max. and in recovery (\( P < 0.01 \)). Heart rates were similar in all studies.

Basal levels of HGH were low and similar in all studies, although considerable interindividual differences were seen thereafter (Table 2). After capsule administration, but still at rest, elevations in HGH occurred in the acidosis study in six of seven subjects, but only in three subjects was the elevation above 10 ng/ml. During exercise, HGH levels increased with increasing power output in all studies (Fig. 3). At 33% \( \dot{V}O_2 \) max., the elevation seen at rest with acidosis was maintained, at 66% \( \dot{V}O_2 \) max., the level of HGH was similar in all studies and at exhaustion was highest with alkalosis and lowest with acidosis. Peak HGH levels were correlated with peak lactate levels (\( P < 0.01 \)) (Fig. 4).

### Table 2. Plasma growth hormone response to exercise after calcium carbonate, ammonium chloride and sodium bicarbonate

Mean values are shown ± SD with SEM in parentheses.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>CaCO(_3)</th>
<th>NH(_4)Cl</th>
<th>NaHCO(_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-180 Rest</td>
<td>1.2 ± 2.3 (0.9)</td>
<td>1.4 ± 2.4 (0.9)</td>
<td>1.2 ± 2.1 (0.8)</td>
</tr>
<tr>
<td>-120 Rest</td>
<td>1.1 ± 1.9 (0.7)</td>
<td>5.6 ± 7.9 (3.0)</td>
<td>1.9 ± 2.5 (1.0)</td>
</tr>
<tr>
<td>-60 Rest</td>
<td>0.4 ± 0.2 (0.1)</td>
<td>6.8 ± 8.6 (3.2)</td>
<td>0.5 ± 0.3 (0.1)</td>
</tr>
<tr>
<td>0 Rest</td>
<td>0.7 ± 0.5 (0.2)</td>
<td>9.3 ± 8.8 (3.3)</td>
<td>0.4 ± 0.2 (0.1)</td>
</tr>
<tr>
<td>Exercise</td>
<td>3.4 ± 4.9 (1.8)</td>
<td>8.5 ± 7.9 (3.0)</td>
<td>3.5 ± 6.5 (2.5)</td>
</tr>
<tr>
<td>10 33% ( \dot{V}O_2 ) max.</td>
<td>5.7 ± 4.6 (1.8)</td>
<td>10.2 ± 8.8 (3.3)</td>
<td>5.6 ± 7.4 (2.8)</td>
</tr>
<tr>
<td>20 ( \dot{V}O_2 ) max.</td>
<td>5.7 ± 4.6 (1.8)</td>
<td>10.2 ± 8.8 (3.3)</td>
<td>5.6 ± 7.4 (2.8)</td>
</tr>
<tr>
<td>Exercise</td>
<td>19.6 ± 11.6 (4.4)</td>
<td>19.4 ± 5.8 (2.2)</td>
<td>19.6 ± 12.4 (4.7)</td>
</tr>
<tr>
<td>30 66% ( \dot{V}O_2 ) max.</td>
<td>30.6 ± 14.0 (5.3)</td>
<td>25.8 ± 13.4 (5.1)</td>
<td>29.4 ± 10.9 (4.1)</td>
</tr>
<tr>
<td>40 ( \dot{V}O_2 ) max.</td>
<td>35.2 ± 17.8 (6.7)</td>
<td>28.3 ± 13.4 (5.1)</td>
<td>36.8 ± 7.9 (3.0)</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>21.2 ± 10.5 (4.0)</td>
<td>17.4 ± 7.0 (2.7)</td>
<td>25.6 ± 11.8 (4.5)</td>
</tr>
<tr>
<td>10 Recovery</td>
<td>21.2 ± 10.5 (4.0)</td>
<td>17.4 ± 7.0 (2.7)</td>
<td>25.6 ± 11.8 (4.5)</td>
</tr>
</tbody>
</table>
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\[ y = 15.6 + 2.23x \]
\[ r = 0.6130 \]
\[ P < 0.01 \]

Fig. 4. Correlation between peak plasma growth hormone and peak plasma lactate in all studies.

Fig. 5. Plasma lactate and growth hormone after sodium l(+)-lactate infusion (0.1 mmol min\(^{-1}\) kg\(^{-1}\); horizontal line between arrowheads).

In the subjects receiving sodium l(+)-lactate infusions at rest, there was no increase in plasma HGH in spite of significant elevation in plasma lactate to concentrations found in moderately severe exercise (Fig. 5).

Discussion

This study confirmed that exercise is a potent physiological stimulus to HGH secretion and that the elevation in plasma HGH concentration is proportional to the intensity of the exercise. Nevertheless, the mechanism of such stimulation remains unclear.

Lactic acid has been suggested as a possible trigger to HGH secretion in exercise (Sutton et al., 1969; Lassarre, Girard, Durand & Raynaud, 1974; Vigas, Nemeth, Jurcovicova, Mikulaj & Komadel, 1974), although elevations in HGH have been reported during submaximal exercise insufficient to elevate plasma lactic acid (Hartley, Mason, Hogan, Jones, Kotchen, Mougey, Wherry, Pennington & Ricketts, 1972; Sutton, Coleman, Casey & Lazarus, 1973).

As an increase in plasma [H\(^+\)] will usually occur if plasma lactate is elevated, the extent to which elevations in plasma HGH are related to increases in lactic acid per se or to concomitant changes in [H\(^+\)] has been uncertain.

The design of the present study enabled us to separate the effects of high lactic acid from those of high [H\(^+\)]. The greatest elevation in lactic acid followed NaHCO\(_3\) administration in which [H\(^+\)] was lowest, whereas NH\(_4\)Cl administration led to the least increase in lactic acid, but highest concentrations of [H\(^+\)]. Subjects were also able to exercise longest at 90% \( \dot{V}O_2 \) max. after NaHCO\(_3\), endurance being least with NH\(_4\)Cl (Jones, Sutton, Taylor & Toews, 1975).

The elevation of plasma HGH in the resting state with NH\(_4\)Cl but not with CaCO\(_3\) or NaHCO\(_3\) is consistent with [H\(^+\)] being a stimulus to HGH secretion. As there were no consistent differences in the symptoms or resting heart rates of the subjects during the three studies, it is unlikely that this elevation in HGH could be attributed to non-specific stress reaction associated with the administration of NH\(_4\)Cl (Greenwood & Landon, 1966).

It is possible that the increased HGH secretion at rest with NH\(_4\)Cl may be related to the secondary effects of a lowered P\(CO_2\) through the ventilatory effects of acidosis, which may become particularly important during heavy exercise. A low P\(CO_2\) might influence HGH release directly or via an effect on cerebral and hypothalamic blood flow. Preliminary studies during voluntary hyperventilation are consistent with this theory (J. R. Sutton, A. P. Powles & N. L. Jones, unpublished observations).

Although an increase in blood [H\(^+\)] at rest appears to be associated with increased HGH secretion, there was marked variation among individuals. In four subjects, the rise was less than 10 ng/ml (20 \( \mu \)units/ml), an increase which is considered to be of doubtful physiological significance in normal subjects (Tanner, Whitehouse, Hughes & Vince, 1971). During exercise at low intensity (33% \( \dot{V}O_2 \) max.), the rise in HGH
associated with an increase in [H\(^+\)] was maintained, but at higher levels of power output, [H\(^+\)] did not appear to have an effect independent of exercise. If absolute concentrations of [H\(^+\)] stimulated HGH secretion at rest, clearly, other factors must operate to override the [H\(^+\)] effect at the higher intensities of exercise as the highest HGH concentrations were found at exhaustion in alkalosis and the lowest with acidosis. As the greatest increase in [H\(^+\)] and also in HGH during exercise at 90% \(\dot{V}O_2\) max. occurred in the alkalosis study, it is possible that an acute increase in [H\(^+\)] may be a more important HGH stimulus than a persistently elevated [H\(^+\)].

The correlation between peak HGH levels and peak lactate levels suggests that the two may be causally related. However, this hypothesis was not supported by the study in which an elevation in lactate concentration produced by sodium L(-)-lactate infusions were not associated with evidence of increased HGH secretion. These findings are in apparent conflict with a previous study of Sutton et al. (1969), in which infusions of sodium Dl-lactate were stated to provoke HGH secretion. Although we are unable to explain the reasons for this discrepancy, the amount of lactate infused was less than in the present study; only half of sodium DL-lactate were stated to provoke HGH secretion during exercise at 90% \(\dot{V}O_2\) max. occurred in alkalosis. As the greatest increase in [H\(^+\)] and lactate concentrations also in HGH during exercise at 90% \(\dot{V}O_2\) max. occurred in the alkalosis study, it is possible that an acute increase in [H\(^+\)] may be a more important HGH stimulus than a persistently elevated [H\(^+\)].

We suggest that HGH secretion during exercise is independent of lactate. The correlation between peak HGH levels and peak lactate levels suggests that the two may be causally related. However, this hypothesis was not supported by the study in which an elevation in lactate concentration produced by sodium L(-)-lactate infusions were not associated with evidence of increased HGH secretion. These findings are in apparent conflict with a previous study of Sutton et al. (1969), in which infusions of sodium Dl-lactate were stated to provoke HGH secretion. Although we are unable to explain the reasons for this discrepancy, the amount of lactate infused was less than in the present study; only half of sodium DL-lactate were stated to provoke HGH secretion during exercise at 90% \(\dot{V}O_2\) max. occurred in alkalosis. As the greatest increase in [H\(^+\)] and lactate concentrations also in HGH during exercise at 90% \(\dot{V}O_2\) max. occurred in the alkalosis study, it is possible that an acute increase in [H\(^+\)] may be a more important HGH stimulus than a persistently elevated [H\(^+\)].

We have previously emphasized the importance of work load, duration of exercise and physical fitness of the subjects in assessing the HGH response to exercise (Sutton et al., 1969; Sutton & Lazarus, 1974). The present study has confirmed the effects of intensity and duration of exercise, but by separating the influences of [H\(^+\)] and lactate, has shown that the increase in plasma HGH with exercise cannot be explained by changes in blood [H\(^+\)] or lactate concentrations. Although adrenergic (Sutton & Lazarus, 1974) and serotonergic (Smythe & Lazarus, 1974) neurotransmission appears important in the growth hormone secretion with exercise, the exact stimulus remains unknown.

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