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Regulation of growth hormone during exercise by oxygen demand and availability

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Summary. Five normal men performed seven sets of seven squats at a load equal to 80% of their seven repetition maximum. Plasma growth hormone (GH) and lactate levels increased during and after the completion of the exercise. A significant ($r=0.93$, $P<0.001$) linear correlation was found between GH changes and the corresponding oxygen Demand/Availability (D/A) ratio expressed by $\left[\int_0^x \dot{V}_{O_2} \cdot dt\right] \cdot f$ (where f=[lactate at time x]/[lactate at time 0]). A retrospective examination of previously published data from our laboratory and others also demonstrated the existence of a significant correlation between changes in plasma GH levels and the D/A ratios over a wide variety of exercise; aerobic and anaerobic, continuous and intermittent, weight lifting and cycling, in both fit and unfit subjects under normoxic and hypoxic conditions. It is suggested that the balance between oxygen demand and availability may be an important regulator of GH secretion during exercise.

Key words: Growth hormone — Lactic acid — Oxygen demand — Oxygen availability — Exercise

Introduction

Although extensively studied, the regulation of the growth hormone (GH) response to exercise is still not well understood (Shephard and Sidney 1975; Lassare et al. 1974; Sutton 1977 and 1978; Raynaud et al. 1981; Kozlowski et al. 1983). Whereas some workers have reported that the GH response is proportional to the intensity and duration of an exercise (Galbo 1983), others are not in accord with this proposal (Kinderman et al. 1982; Koivisto et al. 1982). Recently, it has been shown that in exercise of equal total work output of the same duration, intermittent exercise produces a higher GH response than a continuous one (VanHelder et al. 1984a), and a slower heavier weightlifting exercise results in higher GH levels than a faster lighter one (VanHelder et al. 1984b). Furthermore, continuous exercises differing in load and speed but of equal $\dot{V}_{O_2}$ below the anaerobic threshold, produce similar GH responses (VanHelder et al. 1986). In many of these studies (Kozlowski et al. 1983; VanHelder et al. 1984a and 1984b), correlations have been observed between blood lactate concentrations and GH responses during exercise.

Although various mechanisms have been proposed for the regulation of GH secretion during exercise, the exact physiological factor or factors regulating the GH response during exercise has eluded investigators. It is known that GH levels increase as oxygen demand increases (Lassare et al. 1974), and as oxygen availability decreases (Raynaud et al. 1981; Sutton 1977). Therefore, it follows that the GH response should be proportional to the ratio of oxygen demand/oxygen availability. If one accepts that oxygen availability is inversely proportional to the change in blood lactate concentration during exercise, then oxygen availability can be expressed as $1/f$ where f=[lactate at time $t=x$]/[lactate at time $t=0$]). Oxygen demand would be proportional to the cumulative oxygen consumption over the time (t) of the exercise expressed as $\int_0^x \dot{V}_{O_2} \cdot dt$. Therefore,

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the oxygen demand/availability ratio (D/A) would be defined as:

$$D/A = \int_0^x \dot{V}_{O_2} \cdot dt/(1/f) \text{ or } \left[\int_0^x \dot{V}_{O_2} \cdot dt\right] \cdot f \qquad (1)$$

This D/A ratio should reflect the relationship between the aerobic requirements of a given exercise weighted by the inability of the system to meet these requirements.

In order to test the hypothesis that the GH response during exercise is related to the D/A ratio, we reanalyzed previously published data where GH, $\dot{V}_{O_2}$ and lactate data were available and examined the relationship between the GH response to given exercises and the corresponding D/A ratios. In addition, new data points were obtained on a weight-lifting type of exercise and are included in our analysis.

Experimental approach

Weight lifting experiment. Five male volunteers were trained several weeks prior to the experiment to correctly perform squats with a barbell on their shoulders. The lowest position of a squat was based on each subject's thighs being parallel to the floor in order to minimize the use of elastic energy stored in the tendons. The Seven Repetition Maximum (RM) was then determined for each subject by a previously published method (Delmore and Watkins 1948; VanHelder et al. 1984b; VanHelder et al. 1985).

On the experimental day, each subject ate a standardized meal six hours before the exercise protocol. Indwelling catheters were placed in the antecubital vein 45 min prior to the onset of exercise. Blood (10 ml) was sampled at −10, −3, 0, 4, 7, 10, 16, 20, 30, 60 and 90 minutes with respect to the beginning of the exercise (0 min). At time zero, each subject performed seven squats with a barbell on his shoulders at a load equivalent to 80% of his seven RM, the exercise lasting approximately 30 sec. This was followed by a rest period of 2.5 min with no load on their shoulders. This sequence of squat-rest was repeated seven times by each subject. The total external work was calculated as per VanHelder et al. (1985). Oxygen consumption ($\dot{V}_{O_2}$) was measured by continuous gas volume measurement and analysis (Ergo Oxyscreen, Jaeger). The sampled blood was centrifuged and the plasma assayed for GH (Diagnostics products Corp. kit) and lactate (Sigma kit) by well standardized and routine techniques.

The oxygen demand was calculated by measuring the cumulative oxygen consumption over the time of the exercise period and was expressed by the following equation:

$$\text{Oxygen Demand} = \int_0^x \dot{V}_{O_2} \cdot dt \text{ (where } x = \text{exercise time)}$$

Blood lactate concentrations were measured for the corresponding time period and oxygen availability expressed as being inversely proportion to the blood lactate concentration at that time:

$$\text{Oxygen Availability} = 1/f$$

(where f = [lactate at time x]/[lactate at time 0].

The oxygen demand/availability ratio (D/A) was then expressed as:

$$D/A = \left[\int_0^x \dot{V}_{O_2} \cdot dt\right] \cdot f$$

The relationship of this D/A ratio to changes in GH levels (GH = [GH at time x]/[GH at time 0]) during exercise were then subjected to correlation analysis and the statistical significance determined by the Z statistic.

Analysis of published data. Identical analysis was applied to our previously published data on the comparison of intermittent and continuous exercise of equal duration and output (VanHelder et al. 1984a) as well as on the comparison of different continuous exercises of equal $\dot{V}_{O_2}$ performed below the anaerobic threshold (VanHelder et al. 1986). The same analysis was applied to the data of other authors, namely: aerobic exercise in normal males (Lassare et al. 1974; Karagiorgos et a. 1979); aerobic exercise in fit and unfit males (Sutton 1978); and exercise under normoxic and hypoxic conditions (Sutton 1977; Raynaud et al. 1981).

Results

In the squat exercise reported in this paper, GH began to increase after 10 min of exercise, peaking 10 min after cessation of the exercise (Fig. 1a). Lactate increased immediately upon exercise and increased continuously to the end of the exercise period (Fig. 1b). Oxygen consumption varied between approximately 20 and 12 $ml \cdot min^{-1} \cdot kg^{-1}$ during exercise and rest (Fig. 2). Examination of the relationship of GH to the oxygen D/A ratio for the present data and other published data from our laboratory (VanHelder et al. 1984a) demonstrated a highly significant ($r = 0.93$; $P < 0.001$) correlation (Fig. 3).

A similar analysis of data published by others revealed the same highly significant ($P < 0.001$) linear relationship between the changes in GH levels and the corresponding D/A ratio (Fig. 4 and 5), for fit and unfit subjects (Fig. 4) and for normoxic and hypoxic conditions (Fig. 5).

A global analysis of all of the previously mentioned data was performed and the correlation analysis is shown in Fig. 6. The highly significant ($r = 0.78$; $P < 0.001$) linear relationship between GH changes and the D/A ratio was found to persist.

Discussion

The current experimental data and that previously published by our laboratory demonstrate (Fig. 3)

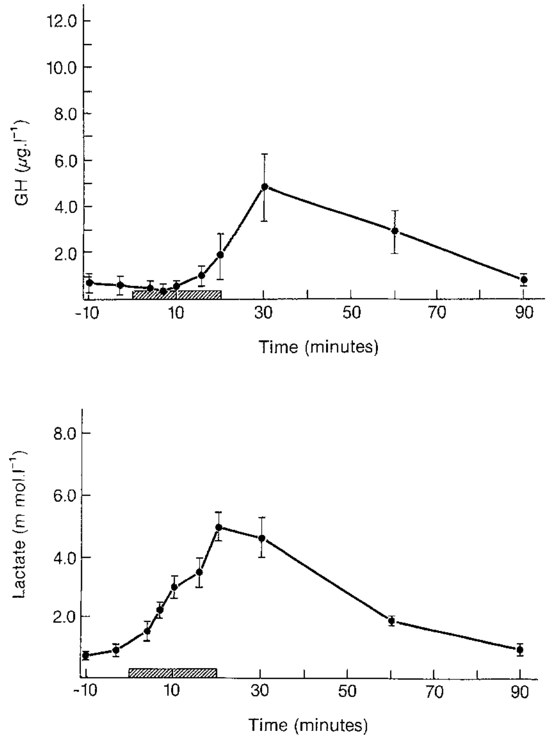

Fig. 1. a GH concentrations during exercise and recovery. The shaded bar on the abscissa represents the period of the exercise and values are expressed as the mean ±SEM ($n=5$). **b** Lactate concentrations during exercise and recovery

that a highly significant ($r=0.93$; $P<0.001$) linear relationship exists between the GH response and the oxygen D/A ratio for different types of exercise; squats, continuous aerobic and intermittent anaerobic cycling (VanHelder et al. 1984a). Although the GH, lactate, and $\dot{V}_{O_2}$ levels were strik-

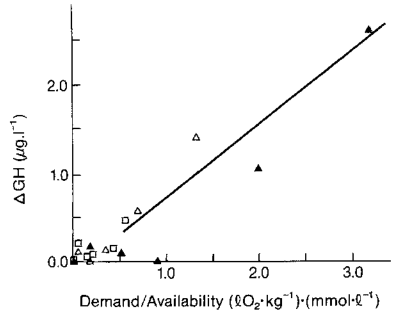

Fig. 3. Correlation between changes in GH levels and the oxygen demand/availability ratio in subjects performing squats and continuous and intermittent cycling ($r=0.93$; Z-statistic$=6.57$; $n=18$). △ squats (this study); □ continuous cycling (VanHelder et al. 1984); ▲ intermittent cycling (VanHelder et al. 1984)

ingly different in the above exercises, the association between GH changes and the D/A ratio persisted.

This relationship was found to exist upon analysis of the data published by other workers. Sutton (1978) examined the GH responses of unfit and fit subjects to 20 min of continuous cycling at 85% and 35% of their respective $\dot{V}_{O_{2\,max}}$ and found significant differences between the two groups not only in their GH responses but also in their lactate production. We found a close correlation between GH and D/A in their data (Fig. 4; $P<0.001$). Karagiorgos et al. (1979) examined continuous and intermittent cycling of 40 min duration and although GH and lactate increased in both protocols, they found no significant relationship between GH and lactate or GH and oxygen

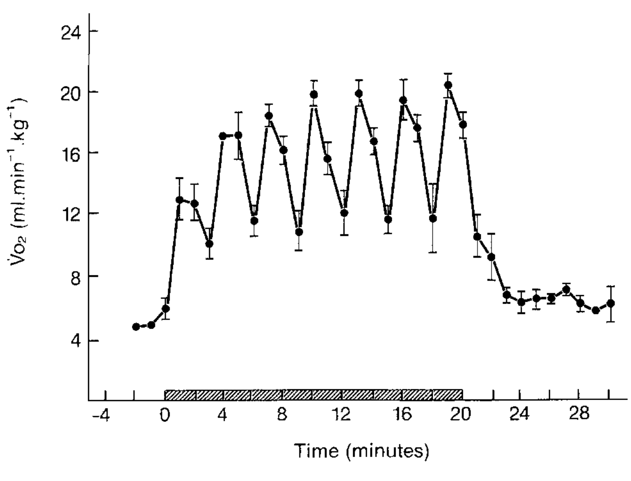

Fig. 2. Oxygen consumption during the squat exercises and recovery. Values are expressed as mean ±SEM

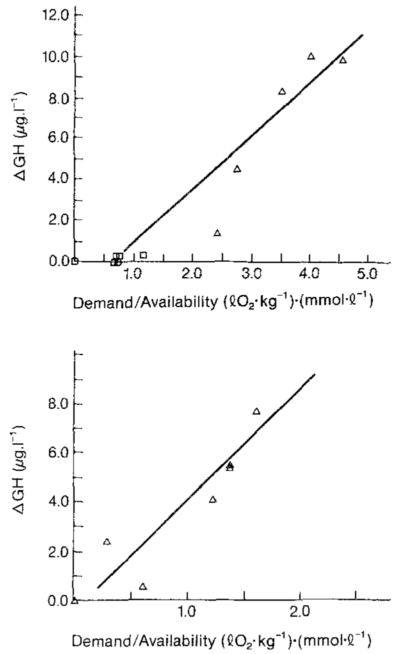

Fig. 4. Correlation between exercise-evoked changes in GH levels and the oxygen D/A ratio: **a** in unfit and fit exercising men ($r=0.94$; Z-statistic $=5.41$; $n=12$). △ unfit (Sutton 1978); □ fit (Sutton 1978). **b** During continuous cycling ($r=0.92$; Z-statistic $=3.19$; $n=7$) (Karagiorgos et al. 1979)

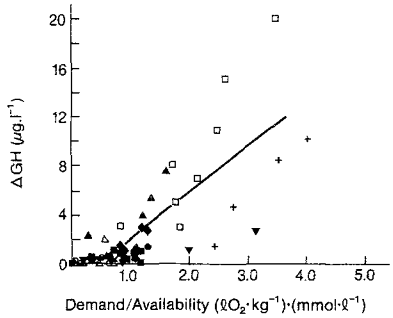

Fig. 6. Global correlation analysis of the relationship between GH changes and the oxygen D/A of data taken from ten published studies ($r=0.78$; Z-statistic $=8.64$; $n=71$); △ normoxia, continuous cycling (Sutton 1977); □ continuous cycling (Lassare et al. 1974); ▲ continuous cycling (Karagiorgos et al. 1979); ■ low frequency cycling (VanHelder et al. 1986); ◆ high frequency cycling (VanHelder et al. 1986); ● squats (this study); ○ continuous cycling (VanHelder et al. 1984a); ▼ intermittent cycling (VanHelder et al. 1984a); + unfit, continuous cycling (Sutton 1978); × fit, continuous cycling (Sutton 1978)

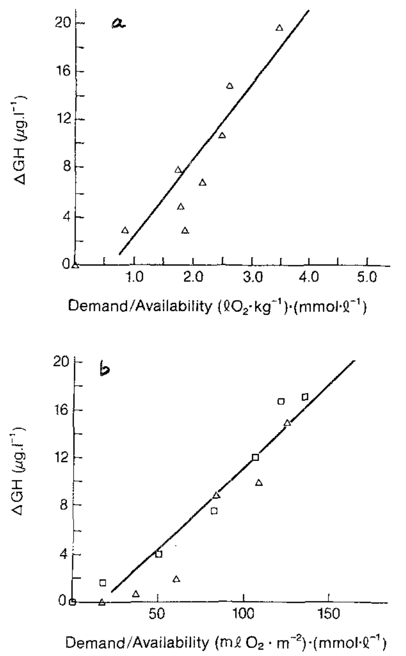

Fig. 5. Correlation between exercise-evoked GH changes and the oxygen D/A ratio under: **a** normoxia ($r=0.89$; Z-statistic $=3.59$; $n=9$) (Lassare et al. 1974). **b** Normoxia and acute hypoxia ($r=0.95$; Z-statistic $=6.29$; $n=14$) (Raynaud et al. 1981). △ ... normoxia; □ ... acute hypoxia

deficit. They concluded that the GH response to exercise was not directly related to "anaerobiosis" and that blood lactate levels were not a determinant in the control of the GH response to exercise. However, we found a highly significant relationship in their data between GH and the oxygen D/A ratio (Fig. 4; $r=0.92$, $P<0.001$) for their continuous exercise. These authors did not report any data on $\dot{V}_{O_2}$ for their intermittent exercise.

This relationship between GH responses and the oxygen D/A ratio was also found whether the exercise was performed under normoxic or hypoxic conditions. Raynaud et al. (1981) examined the GH responses to 60 min of cycling exercise under both normoxic and hypoxic ($F_{IO_2}=15\%$) conditions and found significantly higher GH and lactate responses under hypoxic conditions during most of the exercise period. They found no significant correlation between maximal lactate and GH levels regardless of the level of inspired oxygen. Our analysis of their data revealed a highly significant relationship between GH and the D/A ratio for both normoxic and hypoxic conditions (Fig. 5).

A plot of all of the above data (Fig. 6) demonstrated that the significant relationship between GH and D/A persists for exercises of widely varying duration, intensity, aerobic and anaerobic components, levels of fitness, and subjects. It should be noted that all of the above exercises were of a duration of 20 to 60 min. This same relationship may or may not be evident for exercises of very short (Kinderman et al. 1982) or long

(Koivisto et al. 1982) duration lasting several hours. Increases in GH are not detectable until after 10 to 15 min of exercise, and in exercise lasting several hours, GH levels may decrease due to factors such as depletion of GH in the pituitary or desensitization of receptors regulating GH secretion.

The close association found between GH and the oxygen D/A ratio over a wide range of exercise and studies cited above suggests a causal relationship between the GH response to exercise and the oxygen D/A ratio, further supporting the suggestion that metabolic receptors exist in the muscle which play a role in GH regulation during exercise (Kozlowski et al. 1983; VanHelder et al. 1984a, b). A role for similar receptors which are activated by local changes in lactate concentration, oxygen concentration, or pH has been implied in the regulation of the cardiovascular system (Stegeman and Kenner 1971; McCloskey and Mitchell 1972; Longhurst and Zelis 1979). The supposition that these changes would have to be detected locally in the muscle rather than systemically is further supported by the observation that no relationship appears to exist between externally administered (injected) lactate and GH secretion (Vigas et al. 1974).

In summary, we have shown that the regulation of GH during exercise is closely associated with the oxygen demand/availability ratio for a large variety of aerobic and anaerobic, continuous and intermittent, weight-lifting and cycling exercises of a duration of at least 20 to 60 min, in both fit and unfit subjects and under both normoxic and hypoxic conditions. This persistent relationship suggests that differences between oxygen demand and supply are an important regulator at the muscle site of GH secretion during exercise.

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