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Plasma Growth Hormone and Prolactin Responses to Graded Levels of Acute Exercise and to a Lactate Infusion

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Abstract
The effect of acute exercise at three graded intensities on plasma growth hormone (GH) and prolactin (PRL) concentrations was examined in three groups of healthy male volunteers. According to their training status these subjects were divided into untrained, moderately trained and highly trained. A clear response of GH to exercise was registered already at an intensity of 50% of maximal oxygen uptake (V_{O_2max}) with a maximal response at 70% V_{O_2max} and no further effect at 90% V_{O_2max}. In contrast, no PRL response was observed at 50% V_{O_2max}, a small PRL rise was seen at 70% V_{O_2max} and the highest response occurred at 90% V_{O_2max}. Basal and exercise-stimulated plasma GH and PRL concentrations were similar in the three groups tested at similar relative workloads, suggesting that physical training induces adaptive changes whereby higher absolute workloads induce similar hormonal and metabolic changes. To examine a potential causative role of lactate in inducing the GH and PRL responses, sodium *L*-lactate was infused intravenously to normal sedentary volunteers at doses producing plasma lactate concentrations within the range of those seen between 70 and 90% V_{O_2max}. This resulted in a significant elevation of plasma GH and PRL concentrations, which, however, were smaller than those obtained at an exercise-induced matched plasma lactate concentration. We conclude that physical training causes adaptive changes in highly trained runners so that identical GH and PRL responses to exercise are recorded at higher absolute workloads. Lactate may be involved in the exercise-induced GH and PRL response; however, it does not appear to play an exclusive role.

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Acute exercise is a potent stimulus of pituitary growth hormone (GH) and prolactin (PRL) release [1–3]. Physical training has been shown to modulate the acute responses to exercise, generally leading to increased tolerance to a given workload [4–12]. Thus, trained subjects can perform more strenuous exercise with the same acute hemodynamic, metabolic and endocrine changes as untrained subjects. Among the metabolic factors involved in the response of the organism to an acute bout of exercise, a causative role for lactate in mediating PRL release has been postulated recently [13].

The purpose of this study was to examine the response of GH and PRL to acute exercise. To test for possible effects of chronic dynamic exercise on these two hormones, sedentary subjects and runners at two levels of training were studied at graded intensities of treadmill exercise. In addition, the possible role of lactate in the exercise-induced endocrine changes was tested by infusing intravenously sodium lactate to normal healthy sedentary volunteers.

Material and Methods

Exercise Study

Subjects. Twenty-one healthy men participated in the study after giving informed consent. Seven of these volunteers were sedentary (untrained); the rest were runners who were classified as moderately trained (25–40 km/week) or highly trained (more than 75 km/week). The characteristics of these men are given in table 1. Studies on other hormonal and metabolic responses in these subjects have been reported elsewhere [6–8].

Protocol. The precise protocol has been described in detail previously [6]. In a screening visit all subjects provided their medical and physical training history and had a physical examination. All volunteers accepted into the study had their body fat content and their V_{O_2max} determined. The former was accomplished by measuring underwater weight und residual volume by spirometry using the formula of Siri [14]. The latter was determined by treadmill exercise to exhaustion according to the protocol described by Bruce et al. [15]. Oxygen consumption during the screening and subsequent visits was measured by a metabolic measurement cart (Sensormedics, Anaheim, Calif., USA). Electrocardiogram and heart rate were monitored continuously throughout the exercise period and the ensuing 15 min. On three sequential weekly evening visits the volunteers were subjected, thereafter, in a randomized order to three different intensities of treadmill exercise (50, 70 and 90% V_{O_2max}).

The effect of running at three different exercise intensities on the secretion of GH and PRL as well as on the lactate production was examined. All subjects fasted for 6 h before the exercise which was started at 6 p.m. and runners refrained from running on the day of the tests to exclude the variation of possible factors influencing GH and PRL release [2, 16–18]. An intravenous catheter was inserted 30 min prior to the test, blood was collected in prechilled glass tubes for lactate measurements and glass tubes maintained at room temperature for determination of GH and PRL. The tubes were stored on ice or at room temperature until plasma was separated by centrifugation (within 1 h). Plasma samples were stored at $-20\,^{\circ}C$ until assayed.

Lactate Infusion Study

Subjects. Seven different healthy sedentary (untrained) male subjects (aged 25–30 years) participated in this part of the study after informed consent was obtained.

Protocol. All studies were started at 5 p.m. when an intravenous catheter was inserted in each arm. At 6 p.m. an intravenous infusion of 250 ml of 1 *M* sodium *L*-lactate (obtained from Sigma Chemical Co., St. Louis, Mo., USA, and prepared by our pharmacy) was given over a 15-min period. All subjects tolerated the infusion well without any side effects. The choice of sodium lactate over lactic acid was warranted by the highly irritant local properties of the latter. Blood for determination of lactate, GH and PRL was drawn at -20, 0, 10, 20, 30, 45, 60, 90 and 120 min from the contralateral arm of the infusion, stored on ice or at room temperature (for GH and PRL), respectively, and separated within 1 h by centrifugation. Plasma samples were stored at $-20\,^{\circ}C$ until assayed.

Assays. Plasma lactate concentrations were analyzed by a commercial kit obtained from Sigma Chemical Co., GH and PRL were measured as previously described [19, 20]. The intraassay coefficients of variation were 0.4, 6.5 and 7.3%, respectively, the interassay coefficients of variations were 3.6, 9.7 and 9.5%, respectively.

Statistical Analyses. All data are expressed as mean ± SEM. Differences among groups were evaluated by multiple Student t-tests with the Bonferroni correction for the exercise study [21]. In the lactate infusion study differences between the two groups were evaluated by Tukeys studentized range test [21].

Results

Exercise Study

Growth Hormone (fig. 1a). A significant increase of GH was observed already at the lowest exercise intensity of 50% V_{O_2max} (basal values; 1.4 ± 0.6 µg/l in the untrained subjects (UT); 0.9 ± 0.2 µg/l in the moderately trained subjects (MT), and 2.2 ± 1.2 µg/l in the highly trained subjects (HT), respectively; peak levels: UT, 6.1 ± 2.0 µg/l; MT, 8.1 ± 3.6 µg/l, and HT, 11.5 ± 4.3 µg/l; $p < 0.05$ between basal and peak levels). The maximal GH response was registered at 70% V_{O_2max} (UT, 12.6 ± 4.8 µg/l; MT, 16.8 ± 4.5 µg/l; HT, 13.8 ± 5.2 µg/l) with no further stimulation at 90% (UT, 15.8 ± 5.6 µg/l; MT, 18.7 ± 5.9 µg/l; HT, 17.3 ± 5.5 µg/l; NS, when compared to peak levels at 70% V_{O_2max}). Basal and exercise-stimulated plasma GH concentrations as well as the mean GH responses to exercise expressed as time integrated stimulation over the basal value were similar in the three groups of subjects with different training status at a given relative workload.

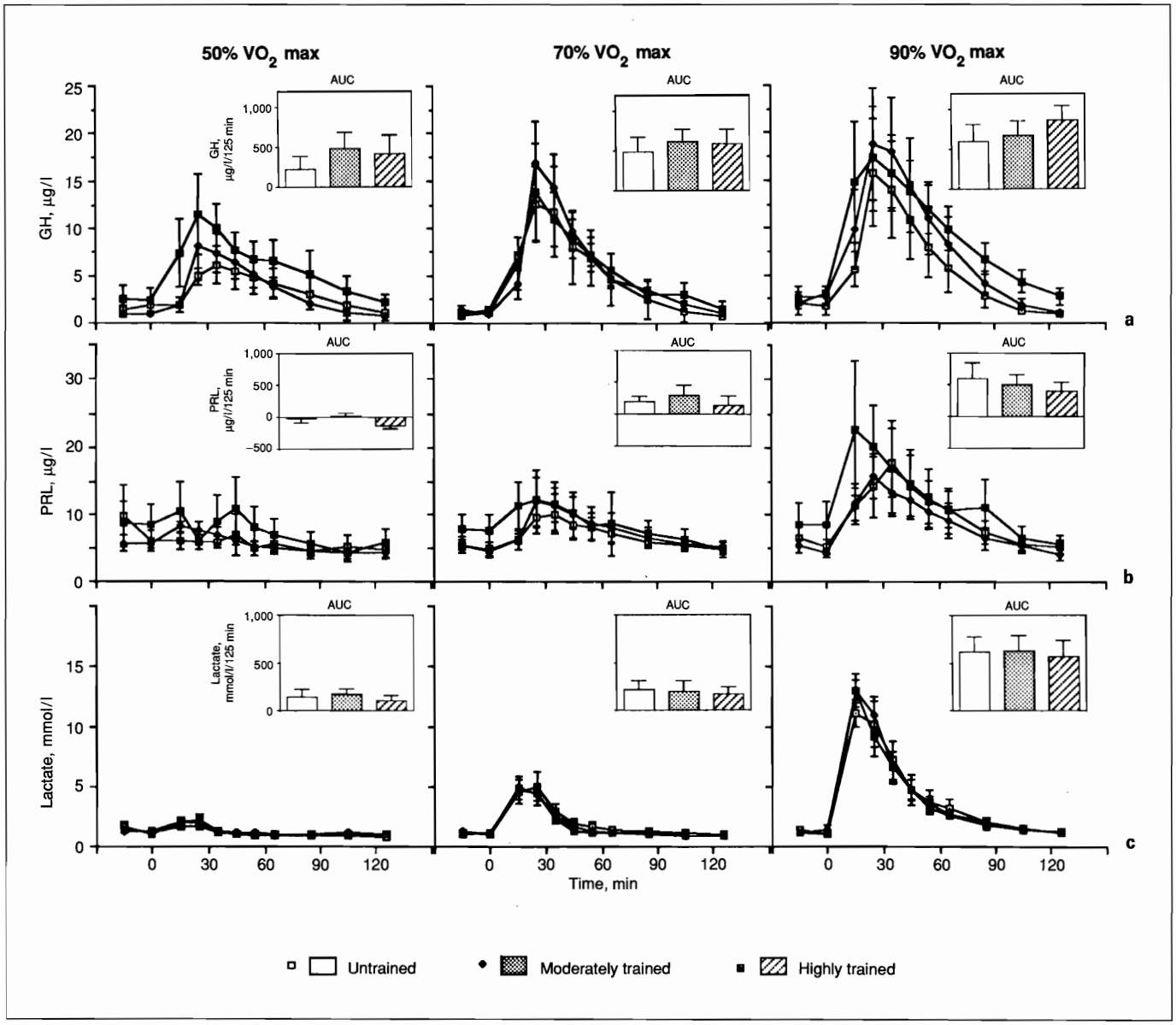

Fig. 1. a Mean (±SE) plasma GH responses to graded intensities (50, 70 and 90% V_{O_2max}) of treadmill exercise. Inserts represent time integrated GH stimulation above baseline values in response to the grades exercise intensities expressed as area under the curve (AUC). **b** Mean (±SE) plasma PRL responses to graded intensities (50, 70 and 90% V_{O_2max}) of treadmill exercise. Inserts represent time integrated PRL stimulation above baseline values in response to the graded exercise intensities expressed as area under the curve (AUC). **c** Mean (±SE) plasma lactate responses to graded intensities (50, 70 and 90% V_{O_2max}) of treadmill exercise. Inserts represent time integrated lactate stimulation above baseline values in response to the graded exercise intensities expressed as area under the curve (AUC). The lactate data have been reported elsewhere in a different context [6, 8]. They are included here for the sake of comparisons with the lactate concentrations from the sodium lactate infusions (cf. fig. 2).

Prolactin (fig. 1b). Exercise at a relative intensity of 50% V_{O_2max} did not stimulate PRL release (NS). However, a significant increase in plasma PRL concentration was recorded at 70% V_{O_2max} (basal values: UT, 5.5 ± 1.2 µg/l; MT, 5.4 ± 0.8 µg/l; HT, 7.7 ± 2.2 µg/l; peak levels: UT, 10.1 ± 2.9 µg/l; MT, 11.9 ± 3.6 µg/l; HT, 12.3 ± 3.6 µg/l; $p < 0.05$ when peak levels are compared to basal values). A greater stimulation occurred at a relative exercise intensity of 90% V_{O_2max} (UT, 17.8 ± 5.2 µg/l; MT, 15.9 ± 3.3 µg/l; HT, 22.8 ± 6.2 µg/l) but the difference to

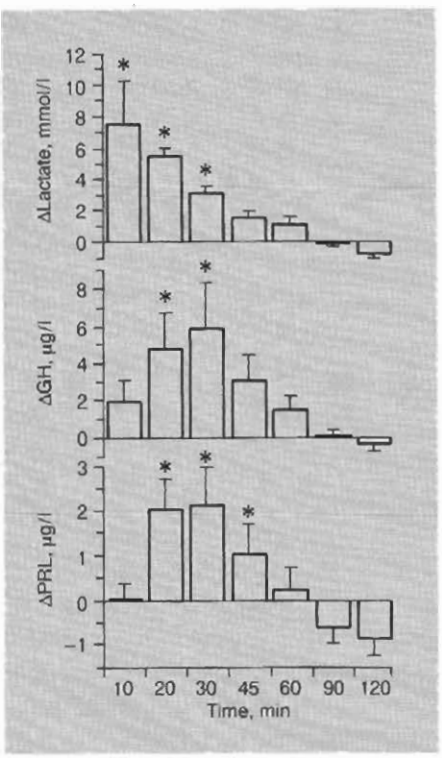

Fig. 2. Mean (± SE) plasma lactate, GH, and PRL responses to the intravenous infusion of 250 ml 1 *M* sodium lactate in 7 untrained healthy volunteers. *$p < 0.05$ when compared to the basal values.

Table 1. General characteristics of subjects tested

	Untrained men	Moderately trained runners	Highly trained runners
Age, years	35.7 ± 0.9	30.0 ± 3.4	31.6 ± 2.8
Height, cm	177.3 ± 2.4	176.3 ± 3.3	174.9 ± 2.6
Weight, kg	78.0 ± 3.2	73.8 ± 3.1	68.6 ± 1.9[a]
Body fat, %	19.4 ± 2.1	9.8 ± 2.3[b]	8.1 ± 1.2[b]
V_{O_2max}, ml/min/kg	33.5 ± 1.5	47.3 ± 2.5[c]	57.4 ± 1.7[c]

[a]$p < 0.05$; [b]$p < 0.01$, and [c]$p < 0.001$ as compared with untrained subjects.

PRL peak levels recorded at 70% V_{O_2max} failed to reach statistical significance. As observed for GH, basal and exercise-stimulated PRL levels as well as the mean PRL responses to exercise expressed as time integrated stimulation over the basal values were similar in the three groups tested at a given relative workload.

Lactate (fig. 1c). The plasma lactate concentrations followed the expected pattern and are shown here to be compared with the lactate levels achieved with the lactate infusion. No increase in plasma lactate concentrations was registered below the anaerobic threshold (at 50% V_{O_2max}, NS), a significant, approximately fourfold increase took place when the workload was around the anaerobic threshold (at 70% V_{O_2max} basal values; UT, 1.1 ± 0.1 mmol/l; MT, 1.2 ± 0.1 mmol/l; HT, 1.0 ± 0.1 mmol/l; peak values: UT, 5.0 ± 1.2 mmol/l; MT, 4.9 ± 0.7 mmol/l; HT, 4.7 ± 1.1 mmol/l; $p < 0.05$ when peak levels were compared to basal values). A steep, approximately tenfold increase occurred when work was performed at 90% V_{O_2max} (UT, 11.1 ± 1.2 mmol/l; MT, 12.9 ± 1.0 mmol/l; HT, 13.0 ± 1.4 mmol/l; $p < 0.05$ when compared to peak levels at 70% V_{O_2max}). The plasma lactate concentrations were similar in the three groups tested. Correlations between plasma lactate and GH and PRL were examined and were, respectively, $r = 0.34$, $p < 0.14$, and $r = 0.39$, $p < 0.08$.

Lactate Infusion (fig. 2)

The maximal plasma lactate levels that could be achieved with sodium *L*-lactate infusion (9.2 ± 2.8 mmol/l) ranged between those seen at an exercise intensity of 70 and 90% V_{O_2max}, i.e. well above the anaerobic threshold. The increase in plasma lactate concentrations was closely paralleled by significant increases in GH (9.2 ± 2.8 µg/l; $p < 0.05$ when compared to basal values) and PRL levels (2.2 ± 0.9 µg/l; $p < 0.05$ when compared to basal values) with a delay of 30 min. In contrast, infusion of 250 ml 0.9% sodium chloride was without any effect on GH and PRL release (data not shown).

Discussion

Acute treadmill exercise induced elevations of plasma GH and PRL concentrations in all subjects tested. There was an intensity-dependent stimulation of PRL, reminiscent of the data previously recorded for ACTH, cortisol [6], and epinephrine and norepinephrine [8], i.e. no response to exercise at a relative intensity of 50% V_{O_2max}, a significant response at 70% V_{O_2max} and a greater response at 90% V_{O_2max}. In contrast, a significant GH response to exercise was obtained already at 50% V_{O_2max}, with a maximal stimulation at 70% V_{O_2max}, which was not different from the one observed at 90% V_{O_2max}. The GH findings

are reminiscent of those of aldosterone [7]. Together these observations indicate that several different mechanisms and/or mediators are involved in the exercise-induced hormonal changes or that the threshold sensitivity to exercise is different in these different hormone systems. One of these might be the exercise-induced increase in body core temperature, as suggested previously [22]. It is interesting that the GH response to exercise tended to be lower than the one observed after exogenous administration of the hypothalamic releasing factor for GH, GH-releasing hormone [23, 24], suggesting stimulation via an alternate pathway or simultaneous release of an inhibiting factor, possibly somatostatin. The latter is quite possible since corticotropin-releasing hormone (CRH) which is expected to rise in exercise [6] has been shown to stimulate release of somatostatin [25]. Also the PRL response to exercise was smaller when compared to other established releasers such as TRH, or metoclopramide [26]. This is in contrast to previous findings from the hypothalamic-pituitary-adrenal axis, in which the response of ACTH to exercise was clearly higher than the one noted after exogenous administration of CRH [6] and further suggests the involvement of other mechanisms.

Chronic physical training led to adaptive changes in GH and PRL secretion. Thus, hormonal responses to absolute workloads were inversely proportional to the degree of training, i.e. at a workload where the GH and PRL response was already maximal in untrained subjects no response could be registered in the highly trained subjects. However, when corrected for the training level, by expressing the workload as percentage of the individual maximal workload (V_{O_2max}), similar GH and PRL responses occurred at similar relative work intensities in the three groups of subjects tested. This shift of the dose-response curve of GH and PRL to graded levels of exercise to the right, after training, appears to be a general mechanism by which the sympathetic system, several hormonal systems, and serum lactate adapt to different levels of chronic training.

An alternative mechanism of PRL release in exercise was previously proposed, attributing a role to lactate or other metabolic factors [13]. To test this hypothesis, lactate was infused intravenously in normal healthy volunteers. An infusion of 1 *M* sodium lactate was selected, because lactic acid was not tolerated at all and this concentration of the salt was the highest one tolerated locally by the veins. With this infusion, lactate concentrations in plasma ranged between those registered at an exercise intensity of 70 and 90% V_{O_2max}. Although this was followed by a significant rise in plasma PRL and GH concentrations, the increases observed were clearly smaller than those following exercise at intensities causing similar plasma lactate concentrations. It seems, therefore, as suggested previously [27], that lactate may play some, but not an exclusive, role in the exercise-induced release of GH and PRL. This view is supported by the fact that GH release was observed also when exercise was performed at an intensity below the anaerobic threshold (i.e. at 50% V_{O_2max}), at which no significant lactate production was observed.

In summary, exercise represents a potent stimulus of GH and PRL release. Because of the low exercise intensity needed to obtain a maximal GH response, exercise can be regarded as a suitable stimulation test for GH. Activation of GH and PRL release occurs at different exercise intensities, GH being more sensitive than PRL. Physical training leads to adaptive changes, whereby higher absolute workloads in highly trained than sedentary or moderately trained subjects are associated with identical GH and PRL responses. Lactate seems to play a role in the exercise-induced stimulation of GH and PRL; however, other factors appear to be involved as well.

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