Effects of exercise on neuroendocrine secretions and glucose regulation at different times of day

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Division of Diabetes, Nutrition and Metabolic Diseases, Department of Medicine, University of Liège, B-4000 Liège; Center for the Study of Biological Rhythms, Université Libre de Bruxelles, B-1070 Brussels, Belgium; and Section of Endocrinology, Department of Medicine, University of Chicago, Illinois 60637

Scheen, André J., Orfeu M. Buxton, Maria Jison, Olivier Van Reeth, Rachel Leprout, Mireille L’Hermite-Balériaux, and Eve Van Cauter. Effects of exercise on neuroendocrine secretions and glucose regulation at different times of day. Am. J. Physiol. 274 (Endocrinol. Metab. 37): E1040–E1049, 1998.—To study the effects of time of day on neuroendocrine and metabolic responses to exercise, body temperature, plasma glucose, insulin secretion rates (ISR), and plasma cortisol, growth hormone (GH) and thyrotropin (TSH) were measured in young men, both at bed rest and during a 3-h exercise period (40–60% maximal O2 uptake). Exercise was performed at three times of day characterized by marked differences in cortisol levels, i.e., early morning (n = 5), afternoon (n = 8), and around midnight (n = 9). The subjects were kept awake and fasted, but they received a constant glucose infusion to avoid hypoglycemia. Exercise-induced elevations of temperature were higher in the early morning than at other times of day. The exercise-induced glucose decrease was 50% greater around midnight, when cortisol was minimal and not stimulated by exercise, than in the afternoon or early morning (P < 0.05). This effect of time of day appeared unrelated to decreases in ISR or increases in temperature and GH. Robust TSH increases occurred in all exercise periods and were maximal at night. The results demonstrate the existence of circadian variations in neuroendocrine and metabolic responses to exercise.

circadian rhythms

insulin secretion; cortisol; growth hormone; thyrotropin; circadian rhythms

PHYSICAL EXERCISE is associated with marked metabolic changes and elicits a variety of neuroendocrine responses, including increases in the release of cortisol and growth hormone (GH), which have been extensively studied (8, 15). Some, but not all, studies have also reported an elevation of plasma thyrotropin (TSH) levels during exercise (7–9, 11, 18). Diurnal variations in pituitary hormone secretions and of parameters of glucose regulation, including glucose tolerance, insulin secretion, and insulin sensitivity, have been well demonstrated in normal subjects studied at bed rest or with minimal amounts of physical activity (25). Although effects of time of day on components of sports performance have been well documented (1), it is not known whether metabolic and hormonal responses to exercise vary according to time of day, because almost all detailed studies have been performed in the morning (8). Interestingly, on the basis of extensive observations, optimal performance in both training and competition occurs in the afternoon and early evening for the vast majority of sports (17). An appreciation of daytime vs. nighttime differences in metabolic and neuroendocrine responses to physical exercise is also relevant to the millions of shift workers who are repeatedly confronted with a misalignment between the enforced rest-activity cycle and endogenous 24-h biological rhythms.

In normal subjects studied under resting conditions, glucose tolerance and insulin sensitivity are optimal in the morning, a time when cortisol secretion is maximal, the propensity for GH release is minimal, and TSH levels are declining (24, 25). Later in the day, glucose tolerance is decreased, cortisol levels are lower, and the propensity for GH secretion appears to be higher than in the morning, and TSH levels are low and stable. The early part of the night is associated with reduced glucose tolerance, minimal cortisol levels, maximal GH pulsatility, and peak TSH concentrations. Whether these major diurnal variations in neuroendocrine status in resting conditions are associated with differences in hormonal and metabolic responses to exercise at different times of day is not known. Therefore, the aim of the present study, performed in young healthy male volunteers, was to investigate the metabolic and hormonal responses to a 3-h exercise bout [40–60% maximal O2 uptake (VO2max)] compared with continuous bed rest, at three different times of the 24-h cycle period, i.e., in the early morning, in the afternoon, and around midnight. Although not typical of laboratory studies, this type of exercise, including variable workloads and short breaks, is very common in real life (e.g., hiking, biking and the like). To avoid influences of different meal schedules among the three groups, all subjects remained fasted and received a constant glucose infusion as the sole energy supply. This experimental condition prevented the appearance of exercise-induced hypoglycemia and therefore permitted the evaluation of neuroendocrine effects of exercise in the absence of secretory responses to hypoglycemia.

SUBJECTS AND METHODS

Subjects

Twenty-two normal young men were studied. All were nonobese and in good physical condition, obtained through regular exercise of moderate intensity. Competitive athletes were not included. All subjects were nonsmokers who did not take any drugs, had regular life habits, and had no personal history of endocrine or metabolic illness. Shift workers and subjects having experienced a transmeridian flight <6 wk before the start of the study were excluded. The subjects were subdivided into three groups to study the effects of a 3-h period of exercise at three different times of day: in the early
morning (n = 5; exercise initiated at 0500 in four subjects and at 0740 in one subject), in the afternoon (n = 8; exercise initiated at 1430), and around midnight (n = 9; exercise initiated at 2330 in eight subjects and at 0040 in one subject).

Experimental Protocol

Each subject participated in two separate studies, one baseline study with continuous bed rest and one study with exposure to a 3-h exercise period. All studies were performed in the Clinical Research Center of the University of Chicago. The protocol was approved by the Institutional Review Board, and all subjects gave informed consent. For 7 days before the study, the volunteers were asked to comply (within ±30 min) with a fixed schedule of bedtime and mealtimes designed in accordance with their usual habits.

Except during the exercise session, the subjects remained at bed rest throughout the studies. They were exposed to normal indoor light (<300 lux), and caloric intake was exclusively in the form of an intravenous glucose infusion at a constant rate of 5 g·kg⁻¹·24 h⁻¹. Naps were not allowed. In each study, the glucose infusion was initiated 6–12 h before the beginning of the study period to attain stable levels of blood glucose. Blood sampling at 20-min intervals started 60 min before the exercise period and continued for >140 min after the end of the 3-h exercise session (or the corresponding period of bed rest).

Body temperature was continuously recorded using either a telemetry system (early morning studies; Cortemp, Human Technologies, St. Petersburg, FL) or an ambulatory monitor with a rectal probe (all other studies; Mini-Logger, Mini-Mitter, Sunriver, OR).

Exposure to Exercise

The exercise period was chosen to be 3 h in duration, i.e., long enough to be consistently associated with metabolic and hormonal changes but short enough to be compatible with the expected level of endurance of young healthy volunteers who were not competitive athletes. Workloads during the periods of exercise were individually tailored to the subject's exercise capacity. During the week preceding the exercise study, each subject was studied as an outpatient in the University of Chicago Cardiac Exercise Physiology Laboratory with the same exercise equipment (Schwinn Airdyne arm and leg exerciser) as used during the study itself to determine his peak O₂ uptake (peak VO₂) for the cycling exercise. A symptom-limited maximal upright exercise study was performed for the maximum expected level of endurance of young healthy volunteers who were not competitive athletes.


Calculations

Insulin secretion rate. In each 20-min blood sampling interval, the insulin secretion rate (ISR) was mathematically derived from plasma C-peptide levels by use of a two-compartment model for C-peptide disappearance kinetics (16). The kinetic parameters for the group of normal subjects were derived from published demographic data adjusted for sex, age, and body surface area (23). The long half-life for C-peptide averaged 32.6 ± 0.1 min.

GH secretion rate. The amount of GH secreted during each exercise/bed rest period was estimated by deconvolution based on a one-compartment model for GH clearance and variable individual half-life values, as previously described (22). The half-life values averaged 18.2 ± 0.6 min. A volume of distribution of 7% of body weight was used in these calculations.

Quantification of Effects of Exercise on Body Temperature, Plasma Glucose, and Hormonal Levels

For body temperature, glucose, ISR, cortisol, and TSH, the baseline level was calculated as the mean of the values measured during the 60-min period preceding the scheduled period of exercise (or bed rest). Baseline levels were similarly defined for GH secretory rates, except when the 60-min prestudy period corresponded to the declining limb of a GH pulse, in which case the lowest GH secretory rate measured during this prestudy period was taken to represent the baseline secretory rate.

The effects of exercise vs. rest were quantified by calculating the area above the curve (positive area) or below (negative area) the baseline level during the 3-h exercise or rest period. For TSH, these calculations were performed using the percentages of baseline levels to avoid confounding effects of differences in assay performance. The effects of exercise at different times of the 24-h cycle were quantified by calculating the area between the rest and exercise curves.
during the 3-h study period as well as by calculating the maximum difference between the exercise and rest conditions for body temperature and plasma concentrations (glucose, cortisol, TSH) or secretory rates (insulin, GH) observed during this same 3-h period (20). For each individual study and each parameter, the duration of the response to exercise was defined as the time interval between the scheduled onset of exercise and the time when values observed during exercise were no longer different from those observed during rest.

**Statistical Analysis**

Unless otherwise indicated, all results are expressed as means ± SE. At each time of day, the significance of the effects of exercise vs. rest was determined by comparing the corresponding areas above and below baseline by paired t-test. Differences in effects of exercise at different time points of the 24-h cycle were analyzed by ANOVA for repeated measures (SuperAnova, Abacus Concepts, Berkeley, CA).

**RESULTS**

The timings of the three exercise sessions relative to the normal diurnal variation in body temperature, plasma cortisol, plasma glucose, ISR, plasma GH, and plasma TSH observed in comparable groups of subjects studied at bed rest under the same experimental conditions (13, 21) as in the present study are illustrated in Fig. 1.

**Effects of Exercise on Body Temperature**

Preexercise temperature levels were similar in the afternoon (1330–1430: 37.06 ± 0.06°C) and at night (2230–2330: 37.13 ± 0.09°C) but were significantly lower in the early morning (0400–0500: 36.37 ± 0.07°C), consistent with the well-known diurnal variation in resting core body temperature (Fig. 2). Exercise-induced elevations of temperature were higher in the early morning (1.31 ± 0.08°C) than in the afternoon (0.96 ± 0.09°C, P < 0.05) or at night (0.89 ± 0.10°C, P < 0.05), probably because the exercise-induced elevation was superimposed on the normal early morning increase. The areas under the curve for body temperature during exercise were similar at each time of day.

**Metabolic and Neuroendocrine Effects of Exercise vs. Rest**

At all three times of day, there were no significant differences in baseline levels of plasma glucose and ISR levels between the exercise and rest conditions (Table 1). Both glucose and ISR declined significantly during exercise compared with rest, irrespective of time of day. As illustrated in Fig. 3, the major part of the decline in plasma glucose occurred during the 1st h of exercise, but the return toward baseline levels was not initiated.
until the end of the exercise session. It is noteworthy that, in the conditions of continuous intravenous glucose infusion used in the present protocol, minimal glucose concentrations measured during the exercise periods remained well above the hypoglycemic threshold at all times of day (mean: 83.3 mg/dl; range 67.5–94.0 mg/dl). The magnitude of the exercise-induced decrease in glucose levels was highly correlated with the preexercise baseline glucose level ($r = 0.81$, $P < 0.0001$) and appeared independent of the level of ISR prevailing before the exercise session ($r = 0.07$, not significant (NS)).

Baseline levels of plasma cortisol, GH secretory rates, and plasma TSH were similar in the rest and exercise conditions at each time of day (Table 2). As expected, baseline plasma cortisol levels were minimal when the subjects were studied around midnight and, in the absence of exercise, increased toward the morning maximum. When subjects were studied in the early morning, baseline cortisol levels were higher than at night and continued to increase, even in the absence of exercise. In contrast, when subjects were studied in the afternoon, baseline cortisol levels were intermediate and, in the absence of exercise, declined toward the evening quiescent period.

A significant stimulatory effect of exercise on cortisol levels was observed in the afternoon only (Table 2). As illustrated in Fig. 4, increasing cortisol levels were observed only during the 1st h of afternoon exercise, with declining levels observed during the remainder of the exercise period. Exercise was associated with significant increases in GH secretion and plasma TSH levels at each time of day. Increases in GH secretion were confined to the first one-half of the exercise period. Increments in plasma GH levels averaged $14.3 \pm 4.1 \mu g/l$ in the morning, $14.2 \pm 2.6 \mu g/l$ in the afternoon, and $21.0 \pm 8.1 \mu g/l$ at night (NS). In contrast, the effects of exercise on TSH levels persisted throughout the entire exercise session (Fig. 4).

Differences in Effects of Exercise at Various Times of Day

Exercise-associated decreases in ISR and increases in GH secretion were similar in the afternoon, at night, and in the morning. In contrast, effects of exercise on plasma glucose, plasma cortisol, and plasma TSH were different depending on time of day (Tables 1 and 2, Figs. 3 and 4).

When measured by the difference in area between the exercise and rest curves during the 3-h exercise period, changes in plasma glucose levels and insulin secretion rates during bed rest and exercise studies at different times of 24-h cycle were significant ($P < 0.05$).

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Rest</th>
<th>Exercise</th>
<th>$P$ Level</th>
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</thead>
<tbody>
<tr>
<td>Baseline level, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afternoon</td>
<td>109.8 ± 4.5</td>
<td>106.1 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Night</td>
<td>117.7 ± 3.0</td>
<td>118.3 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Early morning</td>
<td>112.9 ± 5.2</td>
<td>114.1 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>3-h Area above (+) or below (−) baseline, mg·min·dl$^{-1}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afternoon</td>
<td>255 ± 336</td>
<td>$-2,690 \pm 483$</td>
<td>$&lt;0.005$</td>
</tr>
<tr>
<td>Night</td>
<td>527 ± 253</td>
<td>$-4,424 \pm 567$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Early morning</td>
<td>$-739 \pm 510$</td>
<td>$-3,404 \pm 569$</td>
<td>$&lt;0.04$</td>
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<tr>
<td>Insulin secretion rates</td>
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<tr>
<td>Baseline level, pmol/min</td>
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<tr>
<td>Afternoon</td>
<td>191 ± 23</td>
<td>196 ± 24</td>
<td>NS</td>
</tr>
<tr>
<td>Night</td>
<td>205 ± 25</td>
<td>221 ± 42</td>
<td>NS</td>
</tr>
<tr>
<td>Early morning</td>
<td>153 ± 17</td>
<td>184 ± 28</td>
<td>NS</td>
</tr>
<tr>
<td>3-h Area above (+) or below (−) baseline, pmol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afternoon</td>
<td>1,580 ± 2,372</td>
<td>$-14,417 \pm 3,672$</td>
<td>$&lt;0.02$</td>
</tr>
<tr>
<td>Night</td>
<td>1,756 ± 1,755</td>
<td>$-17,218 \pm 2,989$</td>
<td>$&lt;0.002$</td>
</tr>
<tr>
<td>Early morning</td>
<td>3,030 ± 2,040</td>
<td>$-13,649 \pm 2,754$</td>
<td>$&lt;0.02$</td>
</tr>
</tbody>
</table>

Data are means ± SE.

Table 1. Changes in plasma glucose levels and insulin secretion rates during bed rest and exercise studies at different times of 24-h cycle.
period, the effects of exercise on glucose were nearly 50% greater at night than during the afternoon or the early morning (Fig. 3). A similar effect was observed for the maximum difference in plasma glucose concentration during the 3-h period of exercise vs. rest (Table 3). Additionally, recovery from the effects of exercise was significantly slower in the afternoon and at night than in the morning. Although the mean ISR profiles during exercise and rest appeared to show the same tendency for greater and more prolonged effects of exercise at night than either during the afternoon or in the early morning, the differences failed to reach significance because of large interindividual variability (Fig. 3).

Somewhat surprisingly, the 3-h period of sustained moderate-intensity exercise elicited a significant response in cortisol secretion only when the exercise was performed in the afternoon (Table 2). Accordingly, the comparison of the exercise vs. rest conditions indicated that the difference in area under the curves and the maximum difference in plasma levels were higher in the afternoon than at night or in the early morning (Table 3).

As was the case for glucose, the effects of exercise on TSH levels were more pronounced at night than during the daytime (Table 2). When measured by the difference in area between the exercise and rest curves, the exercise-induced TSH increases were nearly 100% larger at night than during the afternoon or the early morning (Table 3). Similarly, the maximum difference in plasma TSH concentration between the exercise and the rest conditions was also almost twofold higher at night than during the afternoon or the early morning. Additionally, recovery from the effects of exercise was significantly slower at night than in the afternoon (Table 3).

Correlations Between Metabolic and Neuroendocrine Responses

Possible relationships between the magnitudes of changes in ISR and neuroendocrine variables (as dependent variables) and the magnitude of the glucose changes (as an independent variable) were examined by simple linear regression at each time of day and for all times of day combined. Both the areas between the exercise and rest curves and the maximum exercise vs. rest differences in concentrations (or secretory rate for insulin and GH) were used as estimations of the magnitude of the effects of exercise in these calculations. The results were concordant for both estimations but were more robust for the maximum differences between the exercise and rest curves than for the areas between the exercise and rest curves, and therefore only the results of regression analyses using the maximum exercise vs. rest differences will be described below.

No significant correlations were observed between the exercise-associated changes in plasma glucose concentrations and ISR at any time of day and for all studies taken together (r = 0.07, NS). With all studies considered together, a positive relationship was ob-

Fig. 3. Mean (+ SE) profiles of plasma glucose levels and ISR in the resting condition (○) and in the exercise condition (●) for 3 groups of subjects exercising in the early morning (0530–0830), in the afternoon (1430–1730), and around midnight (2330–0230).
observed between the maximum glucose decrease and the increase in GH secretion (Fig. 5, middle). Similarly, the exercise-associated elevation in plasma TSH appeared positively correlated with the maximum decrease in glucose level (Fig. 5, bottom). The same positive trends for the relationships GH-glucose and TSH-glucose were observed during each of the three time periods but failed to reach significance because of the small number of subjects studied in each experimental condition. Contrasting with the positive relationships seen between the magnitudes of the glucose, GH, and TSH responses, a trend toward a negative relationship between cortisol changes and exercise-induced decreases in plasma glucose concentrations was observed when all study periods were considered together (Fig. 5, top). This trend was, however, entirely due to the impact of observations obtained in the afternoon group \( r = -0.59, \text{n} = 8, P < 0.13 \), at a time when a strong stimulatory effect of exercise on plasma cortisol response was observed. At night and in the early morning, when plasma cortisol responses were not significantly influenced by exercise, no relationship was observed between plasma cortisol and glucose changes \( r = 0.06, \text{NS} \).

No significant relationships were seen between changes in ISR, on the one hand, and changes in the other hormones, GH, TSH, and cortisol, on the other, when studies were either all considered together or during each time period separately.

There were also no correlations between the magnitude of the exercise-induced temperature elevation and the magnitudes of the decreases in glucose and ISR or increases in GH, cortisol, and TSH.

**DISCUSSION**

Despite the facts that most components of sports performance appear to peak in the early evening (1, 17) and that around-the-clock operations have resulted in a wide range of timings of physical exercise for the large population of shift workers, almost all detailed physiological studies investigating fuel-hormonal responses to exercise have been restricted to the morning period (8). The present study compared the effects of prolonged moderate-intensity exercise at three different times of day that are characterized, under resting conditions, by marked differences in neuroendocrine secretions known to be stimulated by exercise (i.e., cortisol and GH, and possibly TSH) as well as by robust differences in parameters of glucose regulation (25). This type of exercise, although very common in everyday life, has been relatively understudied in laboratory conditions. At each time of day, neuroendocrine and metabolic profiles during exercise were compared with those obtained in the same subjects under otherwise identical resting conditions to take into account the effects of baseline circadian rhythmicity as well as duration of prior wakefulness (20). Furthermore, because plasma glucose, insulin, and, to a lesser extent, cortisol levels are influenced by the timing, size, and composition of the preceding meal, caloric intake was replaced by an intravenous glucose infusion at a constant rate, initiated \( \geq 6 \text{ h} \) before the exercise session and maintained throughout the exercise and recovery periods. This condition also prevented the occurrence of hypoglycemia and of its related hormonal responses (19).

The results clearly demonstrate the existence of marked effects of time of day on the neuroendocrine and metabolic responses to prolonged moderate-intensity exercise in healthy human volunteers. Whether similar differences would be apparent for responses to high-intensity short-duration exercise routines remains to be demonstrated. The exercise-induced glucose decrease was \( \pm 50\% \) greater around midnight than in the afternoon or in the early morning. This day-night difference cannot be explained by differences in nutritional status or in exercise intensity, or by commensurate changes in insulin secretion. Consequently, the diurnal variation in exercise-induced metabolic responses observed in the present study probably results from differences in counterregulatory hormones.

Preexercise GH levels and GH responses to exercise were similar at all three times of day in our experimental conditions, suggesting that metabolic effects of GH did not play a major role in the different glycemic response seen at night compared with the morning and the afternoon. Cortisol levels normally exhibit a high-amplitude circadian rhythm (Fig. 1), which could under-
lie the differences in metabolic responses to exercise at different times of day. In the present study, cortisol concentrations were minimal and not significantly stimulated by exercise when the latter was performed around midnight, at a time when the hypothalamo-pituitary-adrenal (HPA) axis is quiescent. When the exercise was performed in the early morning, cortisol levels were high and still in a rising phase, and no further stimulation by moderate-intensity exercise could be detected, possibly because the HPA axis is already maximally stimulated during the daily circadian surge. The only time of day when effects of moderate-intensity exercise on plasma cortisol could be clearly evidenced was in the afternoon, i.e., during the declining phase of

![Fig. 4. Mean (+ SE) profiles of plasma cortisol, GH secretory rates, and plasma TSH in the resting condition (○) and in the exercise condition (●) for the 3 groups of subjects exercising in early morning (0530–0830), in afternoon (1430–1730), and around midnight (2330–0230).](image)

**Table 3. Effects of time of day on metabolic and neuroendocrine effects of exercise**

<table>
<thead>
<tr>
<th></th>
<th>Early Morning (n = 5)</th>
<th>Afternoon (n = 8)</th>
<th>Night (n = 9)</th>
<th>Afternoon vs. Early Morning</th>
<th>Night vs. Early Morning</th>
<th>Afternoon vs. Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in area under the curve or amount secreted</td>
<td></td>
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</tr>
<tr>
<td>Plasma glucose, mg·min·dl⁻¹</td>
<td>-2.665 ± 0.400</td>
<td>-2.945 ± 0.713</td>
<td>-4.952 ± 0.584</td>
<td>NS</td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Insulin secretion, nmol</td>
<td>-16.7 ± 4.1</td>
<td>-16.0 ± 4.6</td>
<td>-19.0 ± 3.9</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma cortisol, µg·min·dl⁻¹</td>
<td>-64 ± 194</td>
<td>+950 ± 318</td>
<td>+146 ± 237</td>
<td>P &lt; 0.05</td>
<td>NS</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>GH secretion, µg</td>
<td>158 ± 54</td>
<td>191 ± 46</td>
<td>183 ± 81</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma TSH, % of basal·min</td>
<td>+6229 ± 958</td>
<td>+6376 ± 1333</td>
<td>+13532 ± 1936</td>
<td>NS</td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Maximum difference in concentration or secretory rate</td>
<td></td>
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<tr>
<td>Plasma glucose, mg/dl</td>
<td>-31.2 ± 4.7</td>
<td>-27.2 ± 4.9</td>
<td>-41.0 ± 3.9</td>
<td>NS</td>
<td>NS</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Insulin secretion, pmol/min</td>
<td>-164 ± 23</td>
<td>-195 ± 35</td>
<td>-191 ± 25</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma cortisol, µg/dl</td>
<td>+3.7 ± 1.6</td>
<td>+9.9 ± 2.2</td>
<td>+5.3 ± 2.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>GH secretory rate, µg/min</td>
<td>3.4 ± 1.0</td>
<td>3.6 ± 0.6</td>
<td>4.5 ± 1.9</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma TSH, % of basal</td>
<td>+49 ± 11</td>
<td>+55 ± 12</td>
<td>+92 ± 10</td>
<td>NS</td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Duration of response to exercise, min</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Plasma glucose</td>
<td>228 ± 29</td>
<td>298 ± 18</td>
<td>316 ± 12</td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>276 ± 28</td>
<td>300 ± 21</td>
<td>318 ± 15</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma cortisol</td>
<td>80 ± 30</td>
<td>223 ± 47</td>
<td>113 ± 35</td>
<td>P &lt; 0.05</td>
<td>NS</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>GH secretory rate</td>
<td>112 ± 21</td>
<td>113 ± 21</td>
<td>120 ± 16</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma TSH</td>
<td>236 ± 32</td>
<td>198 ± 30</td>
<td>291 ± 19</td>
<td>NS</td>
<td>NS</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>
cortisol secretion. It is therefore conceivable that the effects of time of day on the exercise-induced glucose decreases are due to the diurnal variation of cortisol levels before and during exercise. In the early morning, decreases in glucose concentrations were probably limited by the high circulating cortisol levels, which could not be further increased by the moderate-intensity exercise stimulus. In the afternoon, the initial decrease in glucose level may have been limited by the exercise-induced stimulation of cortisol secretion, as suggested by the inverse relationship between the maximal glucose decline and the maximal cortisol increase. Around midnight, low cortisol levels and failure of moderate-intensity exercise to stimulate HPA activity may explain the greater and longer glycemic decrements observed in response to exercise at that time of day.

Interestingly, the time of day at which maximal effects of exercise on plasma glucose levels were observed (i.e., the first few hours of the usual bedtime period) corresponds to the timing of the minimum of glucose tolerance under resting conditions. Numerous studies, using different methodological approaches, have provided consistent data indicating that one of the mechanisms underlying the diurnal variation in glucose tolerance is a morning-to-evening decrease in insulin sensitivity (24). Consistent with the direction of this diurnal variation in insulin sensitivity, but in apparent contrast to the findings of the present study, an earlier report using a 30-min exercise bout at 70% $\dot{V}O_2_{\text{max}}$ in fasting subjects described a more pronounced glucose decline at 0800 than at 2000 (3). The differences in experimental conditions (including timing and nature of exercise and caloric intake) do not permit speculations on the underlying causes of the discrepancies between this earlier study and the present one. However, it can be argued that the observations of the present study are not inconsistent with the diurnal variation of insulin sensitivity observed in resting conditions, because it is well established that glucose disposal during muscular exercise is largely insulin independent (8). The results of the present study indicate that endurance exercise is able to overcome the resistance to insulin-mediated glucose disposal observed in the late evening under resting conditions.

The present study was performed under constant glucose infusion, a condition that permitted evaluation of neuroendocrine effects of prolonged exercise in the absence of hypoglycemia (19) but was associated with a modest hyperglycemia and hyperinsulinemia. Under this condition, in subjects maintained at bed rest, plasma glucose levels mainly reflect glucose disposal by the brain and the peripheral tissues, because hepatic

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**Fig. 5.** Relationships between maximum exercise vs. rest difference in plasma glucose (abscissa) and the maximum difference in plasma cortisol (top), maximum difference in GH secretory rate (middle), and maximum difference in plasma TSH (bottom). Relationships were quantified by simple linear regression. For GH secretory rates, 2 subjects were excluded from this calculation, 1 because of a negative exercise vs. rest difference due to a large preexercise GH pulse, and 1 because maximum GH level postexercise was 64.0 µg/l compared with 14.1 ± 8.5 µg/l, i.e., >5 SD from group mean.
glucose production is largely inhibited by the endogenous glucose supply (27). Under the same conditions but in the presence of prolonged moderate-intensity exercise, plasma glucose concentrations reflect a balance between the endogenous glucose supply, a contribution of endogenous glucose production facilitated by the decline in ISR, and glucose utilization, primarily by the exercising skeletal muscles. In the present study, the examination of the time course of the plasma glucose profiles at each time of day shows that plasma glucose decreased during the 1st h and then remained stable or slightly increased until the end of the exercise bout (Fig. 3). This reproducible pattern suggests that the rate of glucose utilization by the skeletal muscles is greater than the rate of intravenous glucose infusion during the 1st h of exercise and that an increase in hepatic glucose production occurs later on to avoid hypoglycemia (12). Another explanation for the stabilization of glucose levels during the second half of the exercise period may be a progressive switch from glucose to free fatty acids (FFA) as the fuel used by the skeletal muscles when exercise is prolonged (8, 10, 14). It is likely that both processes, i.e., late stimulation of hepatic glucose production and reduction of muscular glucose uptake, explain the stabilization of plasma glucose levels after the initial sharp drop observed during the 1st h of exercise. A well-documented study has reported 10–20% decreases in hepatic glucose production and circulating glycerol and FFA levels during the early part of the night in subjects maintained awake at bed rest (5). In the present study, the larger and more prolonged exercise-induced glucose decreases observed around midnight compared with other times of day could partly reflect the impact of these normal nocturnal declines in hepatic glucose output and lipolysis.

Previous studies have indicated that exercise-induced elevations in plasma GH levels may be totally eliminated if the associated rise in core body temperature is prevented (4). Conversely, increases in core temperature by ~1°C obtained by external heating in the absence of physical activity result in robust elevations of plasma GH concentrations (4). However, in the present study, there were no correlations between the magnitude of the GH responses and the elevations of core body temperature, which averaged 0.9–1.3°C. In contrast, the positive correlation between maximal difference in glucose level and maximal difference in GH secretory rate (Fig. 5) suggests that metabolic factors play a role in the exercise-induced GH release, even in the absence of hypoglycemia (19).

A consistent rise in plasma TSH levels was observed during each exercise session and was maintained throughout the duration of the exercise. The magnitude of the changes averaged 50% during the early morning and the afternoon (when TSH levels are normally declining or stable in resting conditions) and 100% around midnight (when, in resting conditions, TSH levels are high and still in a rising phase). These findings confirm the observations from a limited number of previous studies that had reported exercise-induced increases in plasma TSH levels (9, 11, 18) and suggest that the stimulating effects of exercise are more pronounced during the evening and early part of the night, i.e., during the normal circadian increase in thyrotropic activity. Interestingly, the magnitude of the TSH elevation was directly related to the magnitude of the glucose decrease, suggesting that metabolic factors are involved in the exercise-induced TSH response.

In conclusion, the present study demonstrates the existence of a circadian modulation of glucose, cortisol, and TSH responses to exercise when the physical activity is performed at three different times of the 24-h cycle period characterized by widely different circulating levels of neuroendocrine hormones under resting conditions. Metabolic and hormonal responses to exercise were generally of smaller magnitude in the morning than in the afternoon and at night. Further studies are necessary to determine whether improvements in physical performance in the latter part of the day may be related to the circadian variations in exercise-induced metabolic and hormonal responses.

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