The growth hormone response to repeated bouts of sprint exercise with and without suppression of lipolysis in men

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Stokes KA, Tyler C, Gilbert KL. The growth hormone response to repeated bouts of sprint exercise with and without suppression of lipolysis in men. J Appl Physiol 104: 724–728, 2008. First published January 10, 2008; doi:10.1152/japplphysiol.00534.2007.—A single 30-s sprint is a potent physiological stimulus for growth hormone (GH) release. However, repeated bouts of sprinting attenuate the GH response, possibly due to negative feedback via elevated systemic free fatty acids (FFA). The aim of the study was to use nicotinic acid (NA) to suppress lipolysis to investigate whether serum FFA can modulate the GH response to exercise. Seven nonobese, healthy men performed two trials, consisting of two maximal 30-s cycle ergometer sprints separated by 4 h of recovery. In one trial (NA), participants ingested NA (1 g 60 min before, and 0.5 g 60 and 180 min after sprint 1); the other was a control (Con) trial. Serum FFA was not significantly different between trials before sprint 1 but was significantly lower in the NA trial immediately before sprint 2 [NA vs. Con: mean (SD); 0.08 (0.05) vs. 0.75 (0.34) mmol/l, P < 0.05]. Peak and integrated GH were significantly greater following sprint 2 compared with sprint 1 in the NA trial [peak GH: 23.3 (7.0) vs. 7.7 (11.9) μg/l, P < 0.05; integrated GH: 1.076 (350) vs. 316 (527) μg·l⁻¹·60 min⁻¹, P < 0.05] and compared with sprint 2 in the Con trial [peak GH: 23.3 (7.0) vs. 5.2 (2.3) μg/l, P < 0.05; integrated GH: 1.076 (350) vs. 206 (118) μg·l⁻¹·60 min⁻¹, P < 0.05]. In conclusion, suppressing lipolysis resulted in a significantly greater GH response to the second of two sprints, suggesting a potential role for serum FFA in negative feedback control of the GH response to repeated exercise.

nicotinic acid; endocrinology; negative feedback; humans...
Approximately 600 ml of serum was recovered and stored in 500-μl microcentrifuge tubes at −20°C for later determination of GH (ACTIVE Human Growth Hormone, DSL-10–1900, DSL) by routine ELISA, and FFA (nonesterified fatty acid concentration [NEFA]; Wako, Germany) by spectrophotometry (Cobas Mira N; Roche, Switzerland). Samples were not analyzed in duplicate because of limited sample volume. The GH standards for the GH assay were calibrated to the World Health Organization International Reference Preparation 88/624, and the kit had a sensitivity of 0.03 μg/l, an intra-assay coefficient of variation (CV) of 3.3–4.3%, and an inter-assay CV of 6.3–6.6%. It has recently been shown that capillary blood sampling is an appropriate method of blood sampling when determining GH concentration (12).

Statistical analysis. Repeated-measures ANOVA was performed, and specific differences were identified using paired t-tests with Bonferroni correction for multiple comparisons. Statistical significance was accepted at $P < 0.05$. Effect size ($d$) was also calculated, and a large effect taken when $d > 0.8$ (5). All data are presented as means (SD). Peak GH refers to the mean of the highest measured values for each individual. Integrated GH was calculated by the trapezium method.

RESULTS

Performance. No significant differences were found in peak or mean power, total work done, or fatigue index between trials or between sprints (Table 1).

Serum hormone and metabolite responses. Serum FFA concentrations were not significantly different between trials before NA administration, or immediately before exercise (Fig. 2). However, serum FFA concentrations were significantly lower in the NA trial compared with the Con trial 45 min [NA vs. Con: 0.07 (0.03) vs. 0.24 (0.09) mmol/l, $P < 0.05$; $d = 2.6$] and 60 min [NA vs. Con: 0.06 (0.03) vs. 0.20 (0.07) mmol/l, $P < 0.05$; $d = 2.5$] after sprint 1, and immediately before sprint 2 [NA vs. Con: 0.08 (0.05) vs. 0.75 (0.34) mmol/l, $P < 0.05$; $d = 2.8$].

Peak GH and integrated GH were significantly greater following sprint 2 in the NA trial compared with sprint 1 in the

Table 1. Peak and mean power, total work done, and fatigue index in sprints 1 and 2 in the NA and control trials

<table>
<thead>
<tr>
<th></th>
<th>Sprint 1</th>
<th>Sprint 2</th>
<th>Sprint 1</th>
<th>Sprint 2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>NA</td>
<td>Control</td>
<td>NA</td>
<td>Control</td>
</tr>
<tr>
<td>Peak power, W</td>
<td>1.065 (123)</td>
<td>1.042 (94)</td>
<td>1.077 (112)</td>
<td>1.091 (98)</td>
</tr>
<tr>
<td>Mean power, W</td>
<td>655 (102)</td>
<td>645 (96)</td>
<td>667 (94)</td>
<td>670 (96)</td>
</tr>
<tr>
<td>Work done, J</td>
<td>19.657 (3,063)</td>
<td>19.357 (2,891)</td>
<td>20.008 (2,826)</td>
<td>20.109 (2,884)</td>
</tr>
<tr>
<td>Fatigue index, %</td>
<td>58 (7)</td>
<td>60 (8)</td>
<td>57 (6)</td>
<td>57 (6)</td>
</tr>
</tbody>
</table>

Data presented are means (SD); $n = 7$ subjects. NA, nicotinic acid.
NA trial [peak GH: 23.3 (7.0) vs. 7.7 (11.9) µg/l, P < 0.05; d = 1.6; integrated GH: 1,076 (350) vs. 316 (527) µg·l⁻¹·60 min⁻¹, P < 0.05; d = 1.7] and compared with sprint 2 in the Con trial [peak GH: 23.3 (7.0) vs. 5.2 (2.3) µg/l, P < 0.05; d = 3.5; integrated GH: 1,076 (350) vs. 206 (118) µg·l⁻¹·60 min⁻¹, P < 0.05; d = 3.3]. However, peak and integrated GH were not different after sprint 1 and sprint 2 during the Con trial. Immediately before sprint 2, GH was higher in the NA trial than the Con trial, and although this was not significant, there was a large effect (d = 1.3) (Fig. 3).

There were no differences in blood lactate (Fig. 4) or blood glucose (Fig. 5) concentrations between trials.

**DISCUSSION**

In the present study, oral administration of NA resulted in a significant reduction in serum FFA concentrations. When serum FFA were low as a result of NA ingestion, the GH response to the second of two sprints was augmented compared with when NA had not been ingested. These findings support the concept that GH release in response to exercise plays a role in the regulation of substrate availability in the hours after exercise and that circulating FFAs, in turn, play a role in regulating the GH response to a subsequent stimulus.

Recent evidence suggests that an important role for the GH response to exercise is to stimulate lipolysis during the postexercise period (8, 24). The findings of the present study support this evidence, since FFA was elevated 4 h after exercise in the Con trial, and when circulating FFA concentrations were very low in the NA trial the GH response to a second bout of exercise was dramatically increased. In an evolutionary sense, the ability to store fat has been vital for survival (25), and lipolysis must, therefore, be closely regulated. It is possible that the interaction between GH and FFA observed after exercise in the present study reflects one aspect of this regulation, whereby exercise stimulates GH secretion and, consequently, increased lipolysis to meet energy demands during recovery that are above typical resting levels. However, in an example of negative feedback that might represent one means by which postexercise energy metabolism is regulated, FFA act to influence the magnitude of the GH response to a subsequent stimulus.

Increased circulating levels of FFA reduce both basal and stimulated GH secretion (7). Conversely, blocking lipolysis with the NA analog acipimox was a strong stimulus for GH.
secretion in healthy young men (17). During the NA trial in the present study, serum GH concentrations were elevated before sprint 2, which was performed 300 min after the ingestion of the first dose of NA. When the Bonferroni correction for multiple comparisons is applied, this elevation in GH is not significant, although there was a large effect size. Elevated serum GH concentrations would be expected to increase somatostatin synthesis and secretion from the hypothalamus. At the same time, GH would be expected to inhibit GH-releasing hormone (GHRH) synthesis, and both GH and somatostatin would be expected to inhibit release of GHRH from the hypothalamus (9). However, serum GH concentrations were significantly elevated following sprint 2 in the NA compared with the Con trial, not simply as a function of a greater concentration of GH at the start of exercise (i.e., a higher “baseline”), but due to the magnitude of the response itself being greater. These findings show that low circulating FFA concentrations are associated with an enhanced GH response to a physiological stimulus (exercise) in addition to enhanced spontaneous GH secretion.

The fact that there was a GH response to sprint 2 in the NA trial despite elevated GH concentrations immediately before exercise could be taken as evidence that exercise is sufficiently potent to overcome GH autonegative feedback (14, 19); however, GH responses to repeated bouts of sprint exercise have previously been found to be attenuated (21, 22). An alternative explanation is that very low circulating FFA concentrations offer a sufficiently potent stimulus to overcome GH autoinhibitory mechanisms. The mechanisms by which FFA exert an effect on GH secretion have not been fully elucidated, and both a somatostatin-related and a direct pituitary-related effect of FFA have been suggested (1), with the latter receiving most attention. In vitro, FFA inhibit somatotroph function in a dose-related manner (4). The most likely mechanism is that FFA interfere with the function of integral proteins in the lipid bilayer of somatotroph cells. Specifically, the angular structure of cis-unsaturated FFA is likely to affect the way in which they are packed when inserted into the lipid bilayer; in contrast, trans-unsaturated FFA have a linear structure and, as a result, do not interfere with protein function or postreceptor signaling (18). When the gradient of FFA from the plasma toward a cell membrane is not maintained, FFA molecules rapidly disappear from the plasma membrane (3). Therefore, a reduction in plasma (cis-unsaturated) FFA, achieved through blocking lipolysis, might result in a parallel reduction in (cis-unsaturated) FFA in the plasma membrane of the somatotroph cell, altering the state of proteins in the membrane, and increasing the binding affinity of pituitary receptors for GHRH and somatostatin (17). This would, however, be likely to increase pituitary sensitivity to both GHRH and somatostatin. Therefore, a further somatostatin-related mechanism might be important, since it is recognized that FFA can alter somatostatinergic tone (1). In the present study, therefore, we might speculate that a reduction in circulating FFA concentrations using NA enhanced somatotroph sensitivity to GHRH, while inhibiting somatostatin release.

Although an effect of NA on GH release via a direct action of FFA at the pituitary is possible, other mechanisms might be responsible such as NA induced activation of dopaminergic neurons, leading to secretagogue-mediated GH secretion (15). In addition, it must be considered that the altered GH responses to sprint 2 in the present study might be reflected in the response of other counterregulatory hormones that have been shown to be blunted when euglycemia is maintained during exercise that is preceded by prior exercise (11) or by hypoglycemia (6). Administration of NA might have prevented or reversed any overall blunting of coordinated counterregulatory responses via FFA-mediated or other mechanisms, but it was not possible to explore these possibilities in the present study.

In the control trial of the present study, the GH response to the second sprint was not attenuated when compared with the response to the first sprint, which is in contrast to previous findings (21). In fact, in the present study, there was a decrease in peak GH and integrated GH between sprint 1 and sprint 2 in the control trial for only three of the seven subjects, compared with seven of the eight subjects in the previous study (21). The differing findings may be the result of the fact that, in the present study, the response to the first sprint was relatively small compared with the GH response to sprint exercise previously reported (21). This might be explained by the fact that participants in the present study consumed a high-fat diet for 2 days before the main trials. In adults, a single high-fat meal has been found to result in increased circulating somatostatin and a 54% reduction in integrated GH concentrations in response to 10 min of high-intensity submaximal exercise (2), and substantially the same findings are reported for children (10). Furthermore, fasting FFA concentrations have been reported to be significantly higher following 3 days of a high-fat diet (carbohydrate, ~18%; fat, ~66%; protein, ~18%) compared with an isoenetic high-carbohydrate diet (carbohydrate, ~68%; fat, ~18%; protein, ~14%) [0.30 (0.04) and 0.21 (0.03) mmol/l, respectively] (16). In the present study, serum FFA concentrations were elevated above normal resting concentrations at the start of both trials, which might account for the lower GH response to the first sprint than seen in previous studies. The lack of a difference in the GH response to sprint 1 and sprint 2 in the control trial might, therefore, be a result of an already attenuated response to sprint 1.

In conclusion, suppression of lipolysis using NA in young adult men resulted in a significantly greater GH response to the second of two sprints, suggesting a potential role for serum FFA in negative-feedback control of the GH response to a physiological stimulus. The responsible mechanisms might be an increase in the binding affinity of pituitary receptors for both GHRH and somatostatin accompanied by a decrease in somatostatinergic tone. The apparent interaction between GH and FFA indicates that GH plays a role in the regulation of substrate availability in the hours after exercise and that this is represents one of a series of coordinated regulatory pathways that control postexercise metabolism.

GRANTS

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REFERENCES


