

# 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/jappphysiol.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)  $\mu\text{g/l}$ ,  $P < 0.05$ ; integrated GH: 1,076 (350) vs. 316 (527)  $\mu\text{g}\cdot\text{l}^{-1}\cdot 60\text{ min}^{-1}$ ,  $P < 0.05$ ] and compared with *sprint 2* in the Con trial [peak GH: 23.3 (7.0) vs. 5.2 (2.3)  $\mu\text{g/l}$ ,  $P < 0.05$ ; integrated GH: 1,076 (350) vs. 206 (118)  $\mu\text{g}\cdot\text{l}^{-1}\cdot 60\text{ min}^{-1}$ ,  $P < 0.05$ ]. 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

EXERCISE is one of the most potent physiological stimuli for growth hormone (GH) secretion, and a single 30-s sprint on a cycle ergometer elicits a marked increase in serum GH (20). The physiological role for exercise-induced GH release is not known, but recent evidence suggests that one key effect is elevated adipose tissue lipolysis and mobilization of free fatty acids (FFA) for use as an energy resource during recovery (24). This assertion is supported by the finding that blockade of GH release using a somatostatin analog inhibits FFA release from subcutaneous abdominal adipose tissue 3 h after exercise (8).

When two sprints are performed separated by 60 min (21, 22) or 240 min (21) of recovery, the GH response to the second sprint is attenuated. Because serum GH remains elevated for between 90 and 120 min after a single 30-s sprint (23), it is possible that the suppression of the GH response to a second sprint performed within this period is a result of GH autoinhibition at the level of the pituitary (22). The attenuation of the GH response to a second sprint performed after this time (e.g., after 240 min of recovery) may be due to elevated concentra-

tions of systemic FFA (21), which can inhibit GH release at the level of the pituitary (4).

The evidence that exercise-induced GH release stimulates FFA mobilization from adipose tissue in the hours after exercise and that elevated FFA can inhibit GH release suggests that the interaction between GH and FFA might represent an important facet of the coordinated regulation of substrate availability during recovery from exercise. Employing nicotinic acid (NA) as an intervention to acutely suppress lipolysis, the aim of this study is to examine the interaction between GH and FFA and to determine whether serum FFA has a negative-feedback role in the regulation of the GH response to repeated exercise. It is hypothesized that when FFA are high as a result of lipolysis following prior exercise (in the control trial), the GH response to a second bout of sprint exercise will be blunted, and when FFA levels are low as a result of NA ingestion (in the intervention trial), the GH response to exercise will be augmented.

## MATERIALS AND METHODS

**Subjects.** Seven nonobese, healthy male volunteers aged 21 to 30 yr [mean (SD); 26 (3) yr] gave their written informed consent for this study, which conformed to the standards set by the Declaration of Helsinki and had the approval of the local research ethics committee. All subjects were physically active (taking part in physical training between 3 and 6 times per week) but were not specifically trained for a particular sport. Body mass was 81 (8) kg, height was 1.77 (0.05) m, and body mass index was 25.6 (1.6)  $\text{kg/m}^2$ .

**Equipment.** The exercise tests were carried out on a friction-loaded cycle ergometer (Monark 824E), which was interfaced to a microcomputer, allowing instantaneous power output, corrected for fly-wheel acceleration, to be recorded and averaged over 1-s intervals (Wingate Power Testing Software, Cranlea). The same saddle height was used for each trial, and toe-clips held the subjects' feet securely in the pedals.

**Preexperimental procedures.** Subjects visited the laboratory on two occasions before the experimental trials. The purpose of the first visit was to familiarize the subjects with sprinting on a cycle ergometer. On the second visit, subjects performed a single all-out 30-s sprint following NA ingestion (described subsequently). Their responses to NA were monitored over the following hours to confirm their tolerance to oral NA administration. During familiarization (and experimental trials), NA ingestion resulted in all subjects experiencing the mild, transient side effects that have been reported in the literature (13), including flushing, a sensation of heat, and a tingling sensation.

**Protocol.** Two experimental trials were carried out in a random order, separated by at least 7 days. For 2 days before each trial, subjects consumed a prescribed high-fat diet that was isoenergetic with their normal diet (carbohydrate, ~20%; fat, ~60%; protein,

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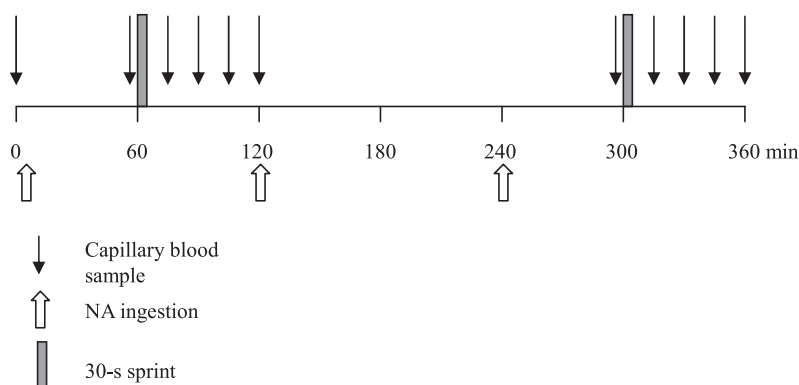


Fig. 1. Schematic outline of the study protocol. NA, nicotinic acid.

~20%) and refrained from exercise, caffeine, and alcohol. They then arrived at the laboratory for each trial after an overnight fast. In one trial (NA), participants ingested a total of 2 g of NA (Niacin 500 mg; Solgar Vitamin and Herbs) over three doses: 1 g ingested 60 min before *sprint 1* and 0.5 g at 60 and 180 min after *sprint 1*. The other trial was a control (Con) trial. The mild side effects of NA (described above) made it impossible to disguise the intervention, which negated any benefit of asking subjects to consume placebo capsules during the Con trial. However, it is unlikely that such knowledge would affect the physiological response to exercise.

On arrival at the laboratory, subjects rested in a seated position for 15 min before a resting finger-prick capillary blood sample was taken (Fig. 1). The first dose of NA was then consumed in the NA trial, and the subjects rested for 60 min in a seated position. A further capillary blood sample was then taken before the subjects moved to the cycle ergometer and performed a standardized, submaximal warm-up consisting of cycling for 4 min at 60 W, 30 s at 80 W, and then 30 s at 100 W. Following a 5-min rest period, an all-out 30-s sprint from a rolling start was performed against an applied resistance equivalent to 7.5% (75 N/kN) of the subject's body mass (*sprint 1*). Capillary blood samples were then taken while the subjects rested in a seated position, and in the NA trial the second and third doses of NA were ingested 60 and 180 min after *sprint 1*. After 240 min of recovery from *sprint 1*, the warm-up routine was repeated followed by a second all-out 30-s sprint (*sprint 2*). Subjects then rested in a seated position for a further 60 min, during which time further capillary blood samples were taken. Subjects were instructed to sprint maximally for the duration of each sprint and were encouraged verbally while they were sprinting. During their first trial, subjects were allowed to drink ad libitum, and the volume and timing of consumption were recorded. During their second trial, subjects were provided with the same amount of water that they consumed during the first trial.

**Blood sampling and analysis.** Capillary blood samples were taken before the first dose of NA, immediately before the warm-up routine before each sprint, and 15, 30, 45, and 60 min after each sprint. Approximately 600 µl of blood was collected in plain microvette tubes (Sarsedt, Germany) and immediately analyzed for blood glucose and lactate concentrations (Yellow Springs Instruments 2300 STAT PLUS). Whole blood was then centrifuged at 10,000 rpm for 3 min,

and ~300 µl 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

	NA		Control	
	<i>Sprint 1</i>	<i>Sprint 2</i>	<i>Sprint 1</i>	<i>Sprint 2</i>
Peak power, W	1,065 (123)	1,042 (94)	1,077 (112)	1,091 (98)
Mean power, W	655 (102)	645 (96)	667 (94)	670 (96)
Work done, J	19,657 (3,063)	19,357 (2,891)	20,008 (2,826)	20,109 (2,884)
Fatigue index, %	58 (7)	60 (8)	57 (6)	57 (6)

Data presented are means (SD); *n* = 7 subjects. NA, nicotinic acid.

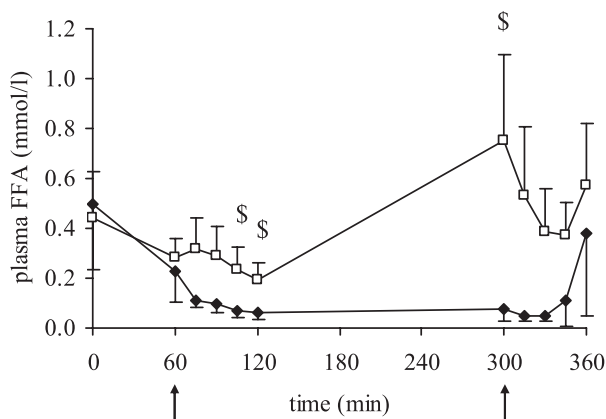


Fig. 2. Serum free fatty acid (FFA) concentrations at rest and during recovery from *sprint 1* and *sprint 2* (represented by arrows) in the NA (closed symbols) and control (Con; open symbols) trials. Data presented are means (SD);  $n = 7$  subjects. \$Significantly different from the corresponding time point in the Con trial.

NA trial [peak GH: 23.3 (7.0) vs. 7.7 (11.9)  $\mu\text{g/l}$ ,  $P < 0.05$ ;  $d = 1.6$ ; integrated GH: 1,076 (350) vs. 316 (527)  $\mu\text{g}\cdot\text{l}^{-1}\cdot 60 \text{ min}^{-1}$ ,  $P < 0.05$ ;  $d = 1.7$ ] and compared with *sprint 2* in the Con trial [peak GH: 23.3 (7.0) vs. 5.2 (2.3)  $\mu\text{g/l}$ ,  $P < 0.05$ ;  $d = 3.5$ ; integrated GH: 1,076 (350) vs. 206 (118)  $\mu\text{g}\cdot\text{l}^{-1}\cdot 60 \text{ min}^{-1}$ ,  $P < 0.05$ ;  $d = 3.3$ ]. 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

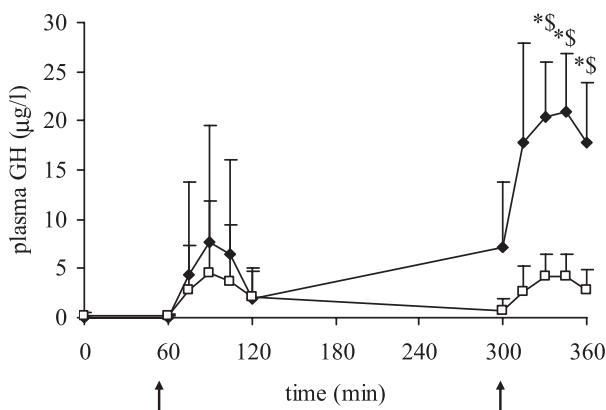


Fig. 3. Serum growth hormone (GH) concentrations at rest and during recovery from *sprint 1* and *sprint 2* (represented by arrows) in the NA (closed symbols) and Con (open symbols) trials. Data presented are means (SD);  $n = 7$  subjects. \*Significantly different from preexercise. \$Significantly different from the corresponding time point in the Con trial.

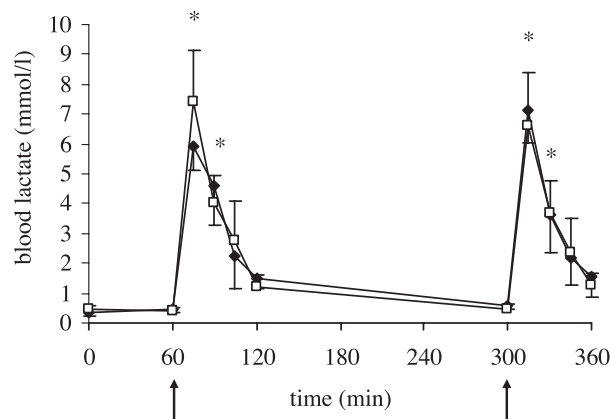


Fig. 4. Blood lactate concentrations at rest and during recovery from *sprint 1* and *sprint 2* (represented by arrows) in the NA (closed symbols) and Con (open symbols) trials. Data presented are means (SD);  $n = 7$  subjects. \*Significantly different from preexercise.

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

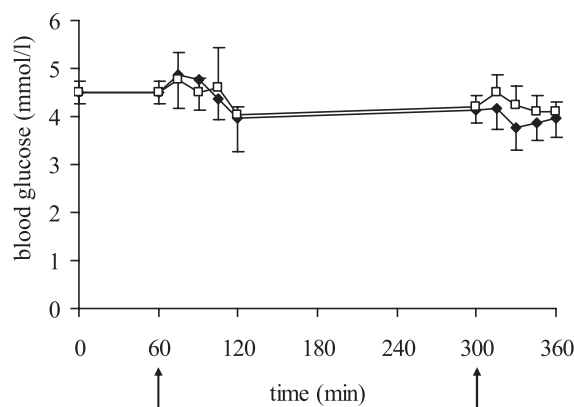


Fig. 5. Blood glucose concentrations at rest and during recovery from *sprint 1* and *sprint 2* (represented by arrows) in the NA (closed symbols) and Con (open symbols) trials. Data presented are means (SD);  $n = 7$  subjects.

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 autoinhibition. 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 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, ~16%) compared with an isoenergetic 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 represents one of a series of coordinated regulatory pathways that control postexercise metabolism.

#### GRANTS

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