Carbohydrate Metabolism During Exercise in Females: Effect of Reduced Fat Availability

Kirsten F. Howlett, Lawrence L. Spriet, and Mark Hargreaves

This study examined the effect of reduced plasma free fatty acid (FFA) availability on carbohydrate metabolism during exercise. Six untrained women cycled for 60 minutes at approximately 58% of maximum oxygen uptake after ingestion of a placebo (CON) or nicotinic acid (NA), 30 minutes before exercise (7.4 ± 0.5 mg·kg^{-1} body weight), and at 0 minutes (3.7 ± 0.3 mg·kg^{-1}) and 30 minutes (3.7 ± 0.3 mg·kg^{-1}) of exercise. Glucose kinetics were measured using a primed, continuous infusion of [6,6-^{2}H] glucose. Plasma FFA (CON, 0.86 ± 0.12; NA, 0.21 ± 0.11 mmol·L^{-1} at 60 minutes, $P < .05$) and glycerol (CON, 0.34 ± 0.05; NA, 0.10 ± 0.04 mmol·L^{-1} at 60 minutes, $P < .05$) were suppressed throughout exercise. Mean respiratory exchange ratio (RER) during exercise was higher ($P < .05$) in NA (0.89 ± 0.02) than CON (0.83 ± 0.02). Plasma glucose and glucose production were similar between trials. Total glucose uptake during exercise was greater ($P < .05$) in NA (1,876 ± 161 μmol·kg^{-1}) than in CON (1,525 ± 107 μmol·kg^{-1}). Total fat oxidation was reduced ($P < .05$) by approximately 32% during exercise in NA. Total carbohydrate oxidized was approximately 42% greater ($P < .05$) in NA (412 ± 40 mmol) than CON (290 ± 37 mmol), of which, approximately 16% (20 ± 10 mmol) could be attributed to glucose. Plasma insulin and glucagon were similar between trials. Catecholamines were higher ($P < .05$) during exercise in NA. In summary, during prolonged moderate exercise in untrained women, reduced FFA availability results in a compensatory increase in carbohydrate oxidation, which appears to be due predominantly to an increase in glycogen utilization, although there was a small, but significant, increase in whole body glucose uptake.

DURING PROLONGED SUBMAXIMAL exercise, oxidative metabolism of both carbohydrate and fat is important in providing energy for contracting skeletal muscle. The exact mechanism that regulates the relative contribution of these substrates to energy production during exercise is equivocal (for review, see Wolfe[1] and Spriet and Odland[2]). However, it has been proposed that there is an inverse relationship between the availability of circulating fatty acids and carbohydrate metabolism.[3,4] Numerous studies in exercising humans have shown that increased fat availability results in reduced muscle glycogen utilization.[5-8] Furthermore, increased fat availability may also decrease muscle glucose uptake during exercise,[9] although this has not always been observed.[7,10] In contrast, relatively few studies have examined the effect of reduced fat availability on carbohydrate metabolism during exercise. A study in dogs that used the antilipolytic drug, nicotinic acid (NA), to inhibit free fatty acid (FFA) mobilization, showed that whole body glucose uptake was elevated during exercise.[11] In addition, hepatic glucose production was also increased during exercise when fat availability was reduced.[11] Studies in humans that have used NA to reduce fat availability have found an increase in muscle glycogen utilization during prolonged submaximal exercise,[12] but no effect on muscle glucose extraction during dynamic forearm exercise.[13] To our knowledge, no studies have been undertaken in humans to specifically examine the effect of reduced fat availability on whole body glucose uptake or hepatic glucose production during exercise.

Although limited data are available, it appears that at given relative submaximal exercise intensities, women oxidize a greater proportion of fat relative to carbohydrate than when compared with men, as indicated by lower respiratory exchange ratios (RER).[14-16] In light of this, it was proposed that if a reduction in fat availability resulted in a compensatory increase in carbohydrate metabolism, then this would be more marked in women than in men. Thus, the aim of this study was to examine the effect of reduced plasma FFA availability, as a result of NA ingestion, on carbohydrate metabolism during prolonged moderate exercise in untrained women. It was hypothesized that reduced FFA availability would increase carbohydrate utilization during exercise.

MATERIALS AND METHODS

Subjects

Six active, but untrained, females (23 ± 1 years, 62 ± 5 kg, mean ± SEM) volunteered to participate in the experiment. Subjects were not taking oral contraceptives and had a normal (≈ 28 day) menstrual cycle. The experimental procedures and possible risks of the study were explained to each subject verbally and in writing. All subjects gave their informed, written consent, and the experiment was approved by the Deakin University Human Ethics Committee.

Pre-Experimental Protocol

To reduce the impact of ovarian hormone variability on substrate utilization, all subjects were studied in the midfollicular phase of the menstrual cycle. Subjects performed an incremental workload test to exhaustion on an electromagnetically braked cycle ergometer (LODE Instrument, Groningen, The Netherlands) on day 5 ± 1 (where day 1 is the first day of menses) of the menstrual cycle to determine their maximum pulmonary oxygen uptake ($V_{O_{2max}}$). Maximum V_{O_2} was the highest V_{O_2} attained during the latter stages of the test and was accompanied by a RER that was greater than 1.1. Mean $V_{O_{2max}}$ was 2.59 ± 0.27 L·min^{-1}. From the $V_{O_{2max}}$ test, the relationship between the measured steady state submaximal V_{O_2} values and the corresponding workload for each individual was determined using a linear regression equation. From this equation, the estimated experimental trial workload

From the From the School of Health Sciences, Deakin University, Burwood, Australia.

Submitted July 31, 2000; accepted October 2, 2000.

Address correspondence to Professor Mark Hargreaves, PhD, School of Health Sciences, Deakin University, Burwood, 3125, Australia.

0026-0495/01/5004-0029$35.00/0
doi:10.1053/meta.2001.21035

that would elicit the required exercise intensity (%$V_{O_{2max}}$) for each individual was derived. For the day preceding each trial, the subjects consumed a food package (≈ 80% carbohydrate [CHO]) and abstained from exercise, tobacco, caffeine, and alcohol. In addition, they were instructed to consume approximately 5 mL of tap water per kilogram body weight upon waking to ensure euhydration. The subjects reported to the laboratory in the morning after a 10- to 12-hour overnight fast.

Experimental Protocol

Each subject performed 2 exercise trials that were separated by approximately 28 days and undertaken on a similar day (control trial, 9 ± 0; drug trial, 9 ± 1 days) during the follicular phase of the menstrual cycle. Subjects were instructed to maintain similar activity levels for the duration of the study. The exercise trials were performed on the same cycle ergometer used in the $V_{O_{2max}}$ test. Subjects performed all exercise tests in the laboratory at a mild temperature.

On arrival at the laboratory, all subjects rested quietly in a supine position on a couch. A catheter was introduced percutaneously into the antecubital vein for blood sampling. The catheter was kept patent by regular flushing with isotonic saline. In addition, a catheter was inserted into the contralateral forearm vein for a primed (3.3 mmol) continuous (44.3 ± 0.8 μmol·min^{-1}) infusion of [6,6-^{2}H] glucose (Cambridge Isotope Laboratories, Cambridge, MA) that was maintained for the duration of the resting period (2.5 hours) and exercise. Subjects then exercised for 60 minutes at a power output (98 ± 14 W) requiring 58% ± 1% $V_{O_{2max}}$. Venous blood samples were obtained at 10-minute intervals during the final 30 minutes of the rest period and throughout exercise for later analysis of plasma glucose, lactate, and ^{2}H glucose enrichment. Additional blood samples were obtained before drug/placebo (-30 minutes) administration, immediately before the onset of exercise, at 10 minutes, 30 minutes, and at the completion of exercise for analysis of FFA, glycerol, insulin, glucagon, and catecholamines. Blood for glucose, lactate, insulin, and glycerol was placed in lithium heparin tubes. For analysis of catecholamines and FFA, blood was placed in plain tubes containing ethylene glycol-bis (β-aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA) and reduced glutathione, and for glucagon, in lithium heparin tubes containing a protease inhibitor (10% Trasylol). Upon completion of exercise, the blood samples were spun and the plasma removed and stored at -20°C for later analysis. Plasma for catecholamine analysis was stored at -80°C. In preparation for the glycerol assay, 250 μL of plasma were deproteinised in 250 μL of 3 mol/L perchloric acid and spun. The supernatant (400 μL) was then mixed with 100 μL of 6 mol/L potassium hydroxide (KOH), spun again, and the supernatant removed and stored at -80°C. Expired gases were sampled during exercise for measurement of V_{O_2}, V_{CO_2}, and ventilation using an on-line system (Gould 2900 Metabolic System; Gould, Dayton, OH). Heart rate was measured continuously using telemetry (Polar Sports Tester, Polar Electro, Kempele, Finland). During exercise, the intensity of effort was quantified by a rating of perceived exertion on a scale from 6 (minimum effort) to 20 (maximum effort). Subjects were permitted to drink water ad libitum during the first experimental trial, and this was replicated in the following exercise trial.

Table 1. VO_2, Ve, RER, and Heart Rate During 60 Minutes of Moderate Exercise Without (CON) and With (NA) Oral Ingestion of NA

	10 Minutes	30 Minutes	60 Minutes
V_{O_2} (L · min^{-1})			
CON	1.47 ± 0.14	1.50 ± 0.15	1.50 ± 0.15
NA	1.45 ± 0.15	1.47 ± 0.15	1.50 ± 0.15
Ve (L · min^{-1})			
CON	36.6 ± 3.6	36.5 ± 2.8	36.1 ± 2.9
NA	38.6 ± 2.8	40.6 ± 3.2	39.7 ± 3.0
RER			
CON	0.87 ± 0.01	0.82 ± 0.00	0.80 ± 0.01
NA	0.92 ± 0.02*	0.89 ± 0.01*	0.87 ± 0.01*
Heart rate (bpm)			
CON	139 ± 3	144 ± 2	150 ± 1
NA	149 ± 4	154 ± 4	155 ± 3

NOTE. Values are mean ± SEM (n = 6 subjects).

Abbreviations: V_{O_2}, oxygen uptake; Ve, ventilation; RER, respiratory exchange rate.

* Denotes difference ($P < .05$) from CON.

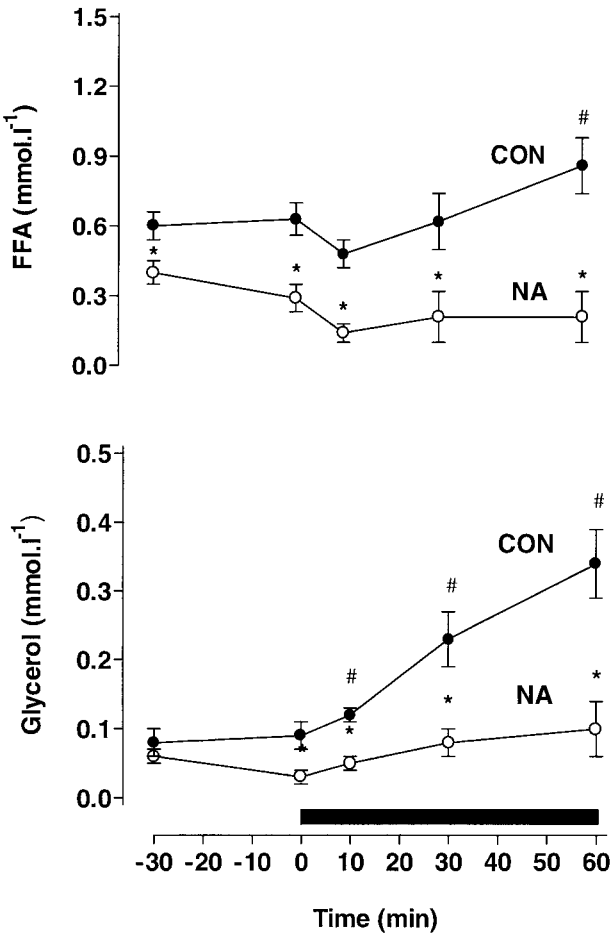

Fig 1. Plasma FFA and glycerol at rest and during 60 minutes of moderate exercise without (CON) and with (NA) oral ingestion of NA. Values are mean ± SEM (n = 6 subjects). Solid bar denotes exercise. * Denotes difference ($P < .05$) from CON. # Denotes difference from –30 minutes.

Drug Administration

Using a randomized, crossover design, subjects ingested a capsule containing either a placebo (CON) or the antilipolytic drug, NA, Rhône-Poulenc Rorer, Baulkham Hills, Australia) 30 minutes before exercise (7.4 ± 0.5 mg·kg^{-1} body weight), at the onset of exercise (3.7 ± 0.3 mg·kg^{-1}), and after 30 minutes of exercise (3.7 ± 0.3 mg·kg^{-1}). A recent study[17] in women showed that oral administration of NA at a similar dosage (500 mg) to that used in the present study resulted in a significant reduction in FFA concentration and in the rate

of appearance (Ra) of FFA and glycerol. In the present study, after oral administration of NA, all subjects experienced an acute flushing reaction (a reddening of the skin affecting the entire body) and an associated sensation of heat. These symptoms were transient and subsided within 1 to 2 hours of administering the drug. One subject vomited after exercise in the drug trial. Another subject developed hypotension after administration of the drug before exercise and experienced abdominal cramps and diarrhea. These symptoms were acute and subsided within 1 hour after withdrawal of the drug. After reducing the drug dosage, the latter subject completed the trial on another occasion.

Analytical Techniques

Plasma FFA were measured by an enzymatic colorimetric method (Wako NEFA C test kit, Wako Chemicals, Osaka, Japan) and glycerol by an enzymatic method.[18] Plasma glucose and lactate were measured using an automated glucose-lactate analyzer (EML 105 Radiometer, Copenhagen, Denmark). Plasma insulin (Phadeseph; Pharmacia & Upjohn, Uppsala, Sweden) and glucagon[19] were measured by radioimmunoassay. To express the glucagon-insulin molar ratio, the measured glucagon was dividied by 3.485 and then by the corresponding plasma insulin concentration. Plasma catecholamines were determined using a single isotope, radioenzymatic method (TRK 995, Amersham, Buckinghamshire, UK). Plasma ^2H glucose enrichment was measured as previously described.[20] Rates of plasma glucose appearance (glucose Ra) and disappearance (glucose Rd) at rest and during exercise were calculated using a modified 1-pool nonsteady-state model[21] assuming a pool fraction of 0.65 and estimating the apparent glucose space as 25% of body weight. The metabolic clearance rate (MCR) of glucose was calculated by dividing glucose Rd by the corresponding plasma glucose concentration. For the duration of exercise, total glucose Ra and Rd were determined by calculating the area under the curve. From V_{O_2} and V_{CO_2}, total carbohydrate and fat oxidation were calculated using the nonprotein respiratory quotient.[22] Assuming complete oxidation of glucose Rd, total glycogen oxidation was calculated as the difference between total carbohydrate oxidation and total plasma glucose Rd. Data from the 2 trials were compared by a 2-way analysis of variance (ANOVA) for repeated measures. Specific differences were determined using the Student-Newman-Keuls post hoc test. The level of significance was set at $P < .05$. Where appropriate, paired comparisons were made using *t* tests. All data are reported as mean ± SEM.

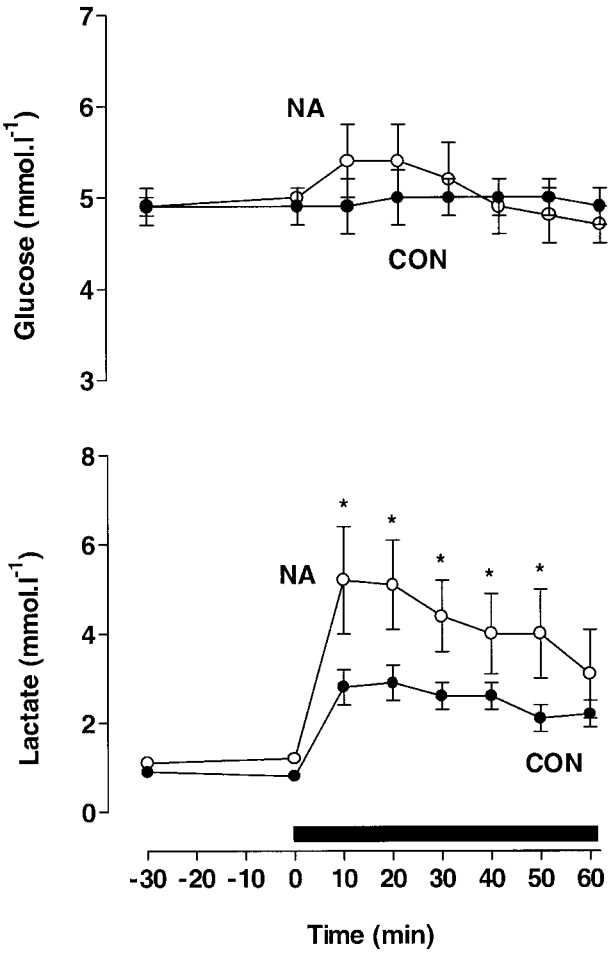

Fig 2. Plasma glucose and lactate at rest and during 60 minutes of moderate exercise without (CON) and with (NA) oral ingestion of NA. Values are mean ± SEM (n = 6 subjects). Solid bar denotes exercise. * Denotes difference ($P < .05$) from CON.

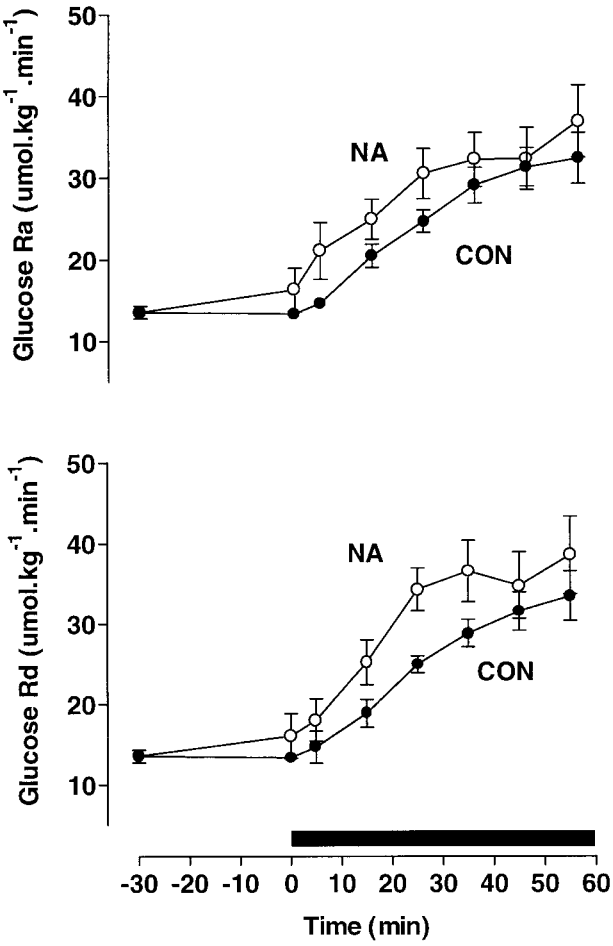

Fig 3. Rates of whole body glucose appearance (Ra) and glucose disappearance (Rd) at rest and during 60 minutes of moderate exercise without (CON) and with (NA) oral ingestion of NA. Values are mean ± SEM (n = 6 subjects). Solid bar denotes exercise.

RESULTS

At rest, before drug/placebo administration, plasma glycerol levels were similar between trials, whereas, plasma FFA were

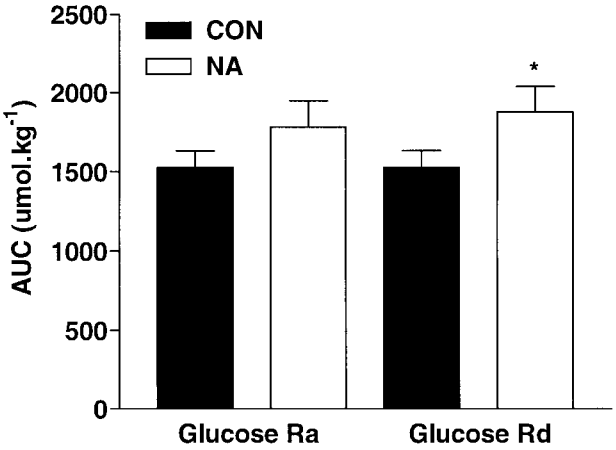

Fig 4. Total glucose Ra and Rd during 60 minutes of moderate exercise without (CON) or with (NA) oral ingestion of NA. Values are mean ± SEM (n = 6 subjects). AUC, area under the curve. * Denotes difference ($P < .05$) from CON.

lower ($P < .05$) in NA compared with that in CON (Fig 1). There is no clear explanation for this latter finding given that trials were conducted on a similar day during the follicular phase of the menstrual cycle using a randomized, crossover design. Furthermore, subjects consumed the same diet for the day before each trial and maintained similar activity levels for the duration of the study. During exercise in CON, there was an increase ($P < .05$) in plasma FFA and glycerol levels. Ingestion of NA 30 minutes before the onset of exercise resulted in a reduction ($P < .05$) in circulating levels of FFA and glycerol before exercise (0 minutes) when compared with that in CON and attenuated ($P < .05$) the exercise-induced increase in fat mobilization as FFA and glycerol levels did not increase significantly above pre-exercise levels.

There were no differences between trials in oxygen uptake (Table 1). Heart rate increased ($P < .05$, time effect) during exercise, and there was a tendency for heart rate ($P = .06$, treatment effect) and ventilation ($P = .07$, treatment effect) to be higher in NA (Table 1). RER was markedly higher ($P < .05$) in NA than in CON (Table 1). Rating of perceived exertion during exercise was similar between CON (10 minutes, 11 ± 0; 30 minutes, 12 ± 0; and 60 minutes, 13 ± 1) and NA (10 minutes, 11 ± 0; 30 minutes, 13 ± 0; and 60 minutes, 13 ± 1).

Plasma lactate was similar at rest between trials (Fig 2). During exercise, lactate levels increased ($P < .05$), however, the increase was greater ($P < .05$) in NA than in CON. Plasma glucose levels were similar at rest and during exercise in CON and NA (Fig 2). During exercise, glucose Ra and Rd increased ($P < .05$, time effect), and although not significantly different, there was a tendency for glucose Ra and Rd to be greater in NA than CON (Fig 3). Subsequently calculated total glucose Ra for the duration of exercise was not different between trials, whereas total glucose Rd was significantly greater in NA than in CON (Fig 4). MCR was similar between trials at rest and during exercise (data not shown).

During exercise, total fat oxidized was approximately 32% lower ($P < .05$) in NA (17 ± 3 g) than in CON (25 ± 2 g). Total carbohydrate oxidized was approximately 42% greater ($P < .05$) in NA (412 ± 40 mmol or 74 ± 7 g) than in CON (290 ± 37 mmol or 52 ± 7 g) (Fig 5). Of this increase in carbohydrate oxidation in NA, approximately 16% (20 ± 10 mmol) could be attributed to glucose. The amount of whole body glucose (CON, 96 ± 12; NA, 116 ± 12 mmol; $P < .05$) and glycogen (CON, 194 ± 30; NA, 296 ± 32 mmol; $P < .05$) oxidized was approximately 21% and approximately 53% greater in NA than CON, respectively.

Plasma insulin was similar at rest between trials (Table 2). Insulin levels decreased ($P < .05$, time effect) during exercise, but were not different between CON and NA. Plasma glucagon and the glucagon-insulin molar ratio increased ($P < .05$, time effect) during exercise, but were similar between CON and NA (Table 2). Plasma epinephrine was similar between trials at rest, but increased ($P < .05$) during exercise and were significantly higher during the final 30 minutes of exercise in NA compared with CON (Table 2). Plasma norepinephrine increased ($P < .05$, time effect) during exercise and was higher ($P < .05$, treatment effect) in NA than CON (Table 2).

DISCUSSION

The findings of the present study show that during prolonged moderate exercise in untrained women a reduction in plasma FFA availability, as a result of NA ingestion, significantly increased carbohydrate oxidation due to an increase in both whole body glucose uptake and glycogen utilization.

The current finding in women that whole body glucose uptake was increased during prolonged exercise when plasma FFA availability was reduced with NA supports a previous study in exercising dogs.[11] However, in the animal study, reduced fat availability did not affect limb glucose uptake and fractional extraction during exercise. Similarly, during 15 minutes of dynamic forearm exercise in healthy men, muscle glucose extraction was not affected when arterial FFA concentrations were decreased after infusion of NA.[13] Direct comparison with the present study is complicated because both the hindlimb[11] and forearm[13] are of relatively small muscle mass,

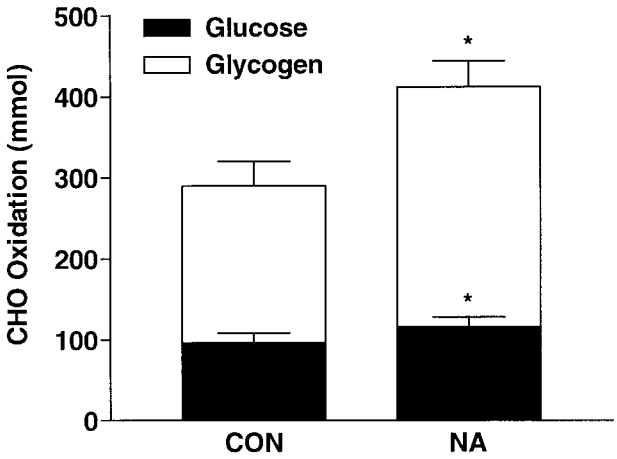

Fig 5. CHO oxidation during 60 minutes of moderate exercise without (CON) or with (NA) oral ingestion of NA. Values are mean ± SEM (n = 6 subjects). * Denotes difference ($P < .05$) from CON.

Table 2. Plasma Hormones at Rest and During 60 Minutes of Moderate Exercise Without (CON) and With (NA) Oral Ingestion of NA

	−30 Minutes	0 Minutes	10 Minutes	30 Minutes	60 Minutes
Insulin (pmol · L^{-1})					
CON	37.8 ± 2.6	35.2 ± 3.2	38.8 ± 3.4	30.1 ± 1.7	29.7 ± 2.1
NA	41.1 ± 3.4	43.2 ± 3.8	37.8 ± 3.4	37.1 ± 2.6	26.8 ± 2.1
Glucagon (ng · L^{-1})					
CON	18 ± 3	35 ± 21	17 ± 3	58 ± 34	54 ± 15
NA	25 ± 6	53 ± 15	55 ± 24	42 ± 11	75 ± 27
G-I molar ratio					
CON	0.14 ± 0.02	0.25 ± 0.12	0.13 ± 0.02	0.58 ± 0.35	0.53 ± 0.15
NA	0.17 ± 0.04	0.35 ± 0.10	0.44 ± 0.20	0.32 ± 0.09	0.86 ± 0.35
Epinephrine (nmol · L^{-1})					
CON	0.10 ± 0.04	0.11 ± 0.02	0.31 ± 0.06	0.37 ± 0.04	0.62 ± 0.09
NA	0.07 ± 0.03	0.18 ± 0.04	0.61 ± 0.09	0.58 ± 0.07*	1.08 ± 0.22*
Norepinephrine (nmol · L^{-1})					
CON	1.12 ± 0.29	0.93 ± 0.33	4.13 ± 0.62	4.16 ± 0.79	5.46 ± 1.01
NA	1.09 ± 0.26	1.88 ± 0.44	7.44 ± 0.95	6.63 ± 1.59	7.18 ± 1.72†

Values are mean ± SEM (n = 6 subjects).

* Denotes difference ($P < 0.05$) from CON.

† Denotes difference ($P < .05$, treatment effect) from CON.

such that substrate demand may be smaller than compared with whole body exercise requirements. In addition, forearm work in the men[13] was of relatively short duration in which energy requirements may not be as marked as that during more prolonged exercise. Despite this, it is possible that a tissue other than contracting skeletal muscle could be the site of increased glucose uptake and utilization. The heart has been shown to be sensitive to changes in fat availability.[4,23] Thus, this tissue could be responsible, in part, for the increase in glucose uptake and oxidation during exercise in the present study when FFA availability was reduced. However, during exercise, it is likely that the major site of enhanced glucose uptake is active skeletal muscle.[24]

Although whole body glucose uptake and estimated glucose oxidation during exercise were increased with NA, this could only account for a small (≈ 16%), but nonetheless significant, proportion of the increase in total carbohydrate oxidation in the present study. Previously, when fat availability was reduced with NA, muscle glycogen utilization and whole body carbohydrate oxidation was increased during prolonged exercise in men.[12] Furthermore, in swimming rats, muscle glycogen utilization was also increased after treatment with NA.[25] Indeed, in the present study, estimated glycogen utilization accounted for approximately 84% of the increase in total carbohydrate oxidation during exercise with NA. Furthermore, plasma lactate, albeit an indirect measure of glycogen breakdown, was also found to be significantly elevated during exercise with NA. It is likely that the marked increase in estimated glycogen utilization after NA ingestion was due to reduced FFA availability. However, it should be noted that plasma epinephrine levels were significantly elevated during the final 30 minutes of exercise in NA. Given that the effect of physiologic epinephrine levels on muscle glycogen breakdown during exercise are equivocal,[26,27] it is unclear as to whether this increase in epinephrine contributed to the enhanced glycogen utilization.

Despite a greater increase in total whole body glucose Rd during exercise in NA, plasma glucose levels remained relatively constant during exercise. The maintenance of glucose homeostasis reflects a similar increase in glucose Ra, although in the present study, the increase in total glucose Ra during exercise in NA was not statistically different from that in CON. When FFA availability was reduced with NA in exercising dogs, glucose homeostasis was maintained by an increase in hepatic glucose production that was probably due to elevated glucagon levels.[11] In contrast, pancreatic hormones were not different between trials at rest and during exercise in the present study.

Ingestion of NA resulted in a reduction of approximately 32% in total fat oxidation during exercise in untrained women. This finding is likely to be attributed to a reduction in circulating fat availability because FFA levels were significantly reduced during exercise with NA than when compared with that in the control trial. Intramuscular triglyceride utilization could not be determined in the present study, and although the exact contribution of muscle triglyceride to skeletal muscle oxidation during exercise has been difficult to ascertain, it is likely to be relatively small, especially in untrained subjects (for review, see Turcotte[28]). It has been suggested that reduced fat availability with NA may result in a compensatory increase in intramuscular triglyceride utilization.[13] Arguing against this, a study in swimming rats found that intramuscular triglyceride utilization was similar between NA-treated and control animals.[25] However, a recent study using isotopic tracer methodology has suggested that intramuscular triglyceride oxidation was increased during moderate intensity exercise to compensate for reductions in plasma FFA oxidation after administration of Acipimox, a NA analog.[29] However, in contrast to the present study, Coyle et al[29] found that despite a reduction in FFA availability, total fat oxidation was maintained during exercise. Furthermore, endurance-trained men were used in the latter study[29] and are likely to have a different metabolic response compared with that of untrained women used in the present study.

The mechanism of action of NA is not completely understood.[30] However, it is likely that the direct effects of NA are primarily restricted to fat mobilization from adipose tissue. In

mice, intravenous injection of [^{3}H]-NA has been found to be highly concentrated in adipose tissue.[31] In the present study, there was a tendency for ventilation and heart rate to be higher during exercise in NA, which may be due to increased sympathetic activity. A previous study in humans has also shown that heart rate was elevated ($\approx$ 20 beats per minute) during exercise after the administration of NA.[12] Subcutaneous adipose tissue blood flow may be reduced in exercising humans treated with NA.[32] However, NA has been shown to have no effect on peak postexercise blood flow in the forearm muscle.[13] Indeed, the vasodilatation in skin and muscle that may occur as a result of NA at rest is small compared with that caused by dynamic exercise.[33]

It should be noted that the observation of increased carbohydrate metabolism during exercise in females under conditions of reduced FFA availability may not necessarily apply to other population groups such as males, the elderly, or those with obesity and/or type 2 diabetes. Because females oxidize more lipids during exercise than males,[14,34] their metabolic responses may be more readily affected by alterations in FFA availability.

In summary, during prolonged moderate exercise in untrained women, a reduction in FFA availability after ingestion of NA resulted in a compensatory increase in carbohydrate oxidation. The increase in carbohydrate oxidation during exercise appears to be due predominantly to an increase in glycogen utilization, although there was a small, but significant, increase in whole body glucose uptake.

ACKNOWLEDGMENT

The authors wish to thank Andrew Garnham, School of Health Sciences, Deakin University, for medical support; Dom Caridi, Department of Chemistry and Biology, Victoria University of Technology, for assistance in measuring the glucose enrichments; and Michael Christopher, Department of Endocrinology, St. Vincents Hospital, for glucagon analysis.

REFERENCES

1. Wolfe RR: Metabolic interactions between glucose and fatty acids in humans. Am J Clin Nutr 67:519S-526S, 1998

2. Spriet LL, Odland LM: Biochemical regulation of carbohydrate-lipid interaction in skeletal muscle during low and moderate intensity exercise, in Hargreaves M, Thompson M (eds): Biochemistry of Exercise. Champaign, IL, Human Kinetics, 1998, pp 241-262

3. Randle PJ, Hales CN, Garland PB, et al: The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1:785-789, 1963

4. Randle PJ, Newsholme EA, Garland PB: Regulation of glucose uptake by muscle: 8. Effects of fatty acids, ketone bodies and pyruvate, and of alloxan-diabetes and starvation, on the uptake and metabolic fate of glucose in rat heart and diaphragm muscles. Biochem J 93:652-665, 1964

5. Costill DL, Coyle E, Dalsky G, et al: Effects of elevated plasma FFA and insulin on muscle glycogen usage during exercise. J Appl Physiol 43:695-699, 1977

6. Dyck DJ, Putman CT, Heigenhauser GJF, et al: Regulation of fat-carbohydrate interaction in skeletal muscle during intense exercise. Am J Physiol 265:E852-E859, 1993

7. Odland LM, Heigenhauser GJ, Wong D, et al: Effects of increased fat availability on fat-carbohydrate interaction during prolonged exercise in men. Am J Physiol 274:R894-902, 1998

8. Vukovich MD, Costill DL, Hickney MS, et al: Effect of fat emulsion infusion and fat feeding on muscle glycogen utilization during cycle exercise. J Appl Physiol 75:1513-1518, 1993

9. Hargreaves M, Kiens B, Richter EA: Effect of increased plasma free fatty acid concentrations on muscle metabolism in exercising men. J Appl Physiol 70:194-201, 1991

10. Romijn JA, Coyle EF, Sidossis LS, et al: Relationship between fatty acid delivery and fatty acid oxidation during strenuous exercise. J Appl Physiol 79:1939-1945, 1995

11. Bracy DP, Zinker BA, Jacobs JC, et al: Carbohydrate metabolism during exercise: Influence of circulating fat availability. J Appl Physiol 79:506-513, 1995

12. Bergström J, Hultman E, Jorfeldt L, et al: Effect of nicotinic acid on physical working capacity and on metabolism of muscle glycogen in man. J Appl Physiol 26:170-176, 1969

13. Kaijser L, Nye ER, Eklund B, et al: The relation between carbohydrate extraction by the forearm and arterial free fatty acid concentration in man. Forearm work with nicotinic acid infusion. Scand J Clin Lab Invest 38:41-47, 1978

14. Horton TJ, Pagliassotti MJ, Hobbs K, et al: Fuel metabolism in men and women during and after long-duration exercise. J Appl Physiol 85:1823-1832, 1998

15. Tarnopolsky LJ, MacDougall JD, Atkinson SA, et al: Gender differences in substrate for endurance exercise. J Appl Physiol 68:302-308, 1990

16. Friedlander AL, Casazza GA, Horning MA, et al: Training-induced alterations of carbohydrate metabolism in women: Women respond differently from men. J Appl Physiol 85:1175-1186, 1998

17. Wang W, Basinger A, Neese R, et al: Effects of nicotinic acid on fatty acid kinetics, fuel selection, and pathways of glucose production in women. Am J Physiol 279:E50-E59, 2000

18. Chernick SS: Determination of glycerol in acyl glycerols, in Colowick SP, Kaplan ND (eds): Methods in Enzymology, vol 14. New York, NY, Academic, 1969, pp 627-630

19. Alford FP, Bloom SR, Nabarro: Glucagon levels in normal and diabetic subjects: Use of specific immunoabsorbent for glucagon radioimmunoassay. Diabetologia 13:1-6, 1977

20. McConell G, Fabris S, Proietto J, et al: Effect of carbohydrate ingestion on glucose kinetics during exercise. J Appl Physiol 77:1537-1541, 1994

21. Steele R, Wall JS, DeBodo RC, et al: Measurement of the size and turnover rate of body glucose pool by isotope dilution method. Am J Physiol 187:15-24, 1956

22. Peronnet F, Massicotte D: Table of non-protein respiratory quotient. An update. Can J Sports Sci 16:23-29, 1991

23. Lassers BW, Wahlqvist ML, Kaijser L, et al: Effect of nicotinic acid on myocardial metabolism in man at rest and during exercise. J Appl Physiol 33:72-80, 1972

24. Kjær M, Kiens B, Hargreaves M, et al: Influence of active muscle mass on glucose homeostasis during exercise in humans. J Appl Physiol 71:552-557, 1991

25. Stankiewicz-Choroszucha B, Górski J: Effect of decreased availability of substrates on intramuscular triglyceride utilization during exercise. Eur J Appl Physiol 40:27-35, 1978

26. Wendling PS, Peters SJ, Heigenhauser GJF, et al: Epinephrine infusion does not enhance net muscle glycogenolysis during prolonged aerobic exercise. Can J Appl Physiol 21:271-284, 1996

27. Febbraio MA, Lambert DL, Starkie RL, et al: Effect of epinephrine on muscle glycogenolysis during exercise in trained men. J Appl Physiol 84:465-470, 1998

28. Turcotte LP: Role of fats in exercise. Types and quality. Clin Sports Med 18:485-498, 1999

29. Coyle EF, Jeukendrup AE, Wagenmakers AJM, et al: Intramuscular triglyceride oxidation during exercise acutely increases with reduced plasma FFA mobilization and oxidation. FASEB J 10:A143, 1998

30. Hotz W: Nicotinic acid and its derivatives: A short story. Adv Lipid Res 20:195-217, 1983

31. Carlson LA, Hanngren A: Initial distribution in mice of ^{3}H-labeled nicotinic acid studied with autoradiography. Life Sci 3:867-871, 1964

32. Bulow J: Human adipose tissue blood flow during prolonged exercise. Effect of beta-adrenergic blockade, nicotinic acid and glucose infusion. Scand J Clin Lab Invest 41:415-424, 1981

33. Kaijser L, Eklund B, Olsson AG, et al: Dissociation of the effects of nicotinic acid on vasodilation and lipolysis by a prostoglandin synthesis inhibitor, indomethacin, in man. Med Biol 57:114-117, 1979

34. Tarnopolsky LJ, MacDougall JD, Atkinson SA et al: Gender differences in substrate for endurance exercise. J Appl Physiol 68:302-308, 1990