Plasma Nitrate/Nitrite Response to an Oral Glucose Load and the Effect of Endurance Training

Edward P. Weiss, Jung-Jun Park, Jennifer A. McKenzie, Joon-Young Park, Onanong Kulaputana, Michael D. Brown, Dana A. Phares, and James M. Hagberg

To assess the role of circulating nitric oxide (NO) production in glucose homeostasis, plasma nitrate/nitrite (NO_x) was assessed during oral glucose tolerance tests (OGTTs) on 64 sedentary subjects and in a subset 40 subjects before and after 6 months of endurance exercise training. NO_x decreased with the oral glucose load ($P \leq .001$ for linear and quadratic effects). OGTT NO_x response indices (NO_x response area (NO_x AREA), change in NO_x from baseline to the minimum (ΔNO_x), and NO_x time-to-minimum) were not associated with OGTT insulin or glucose areas under the curve (AUCs) or with insulin sensitivity index (ISI). Training did not alter NO_x AREA, or ΔNO_x, however, NO_x time-to-minimum occurred later after training ($P = .038$). Training-induced insulin AUC and ISI changes were not associated with OGTT NO_x index changes; however, glucose total AUC changes were associated with changes in NO_x AREA ($r = .42$, $P = .007$) and ΔNO_x ($r = .37$, $P = .019$). In conclusion, these data suggest that circulating NO production is not involved in glycemic control after an oral glucose load in sedentary adults. In response to endurance training, however, it appears that the time required to reach minimum NO_x levels after a glucose load is greater after training. Furthermore, although the magnitude of NO_x response (as indicated by NO_x AREA and ΔNO_x) to an oral glucose load does not appear to change with training for all individuals, individual training-induced changes in the NO_x response magnitude are partly explained by training-induced changes in OGTT glucose responses.

NITRIC OXIDE (NO) may be involved in the modulation of postprandial glucose homeostasis. First, at the tissue level, NO increases blood flow,[1] which facilitates the delivery of glucose and insulin to the capillary beds of skeletal muscle, where both glucose and insulin may directly stimulate cellular glucose uptake. Secondly, NO may directly stimulate glucose uptake at the cellular level in resting muscle, although existing reports are contradictory.[2,3] Lastly, NO may affect glucose homeostasis by altering insulin and/or glucagon responses to glucose ingestion,[4,5] which have their own effects on glucose metabolism.

Despite the evidence that suggests that NO may facilitate postprandial glucose disposal, it is not clear if NO production is increased in the postprandial state. To the best of our knowledge, only one study has assessed the role of NO in physiologic hyperglycemia and hyperinsulinemia in humans. Kawano et al[6] measured plasma nitrate/nitrite (NO_x) concentration as a marker for vascular NO production and found that circulating NO_x concentration did not increase in response to an oral glucose load. However, it should be noted that the subjects all had cardiovascular disease (CVD) and might have already had endothelial dysfunction,[7,8] which could conceivably compromise insulin-mediated NO production.

Hypothetically, if NO enhances glucose delivery to muscle and myocellular glucose uptake, it is reasonable to hypothesize that plasma NO_x levels would increase in response to a standard oral glucose load. Additionally, although it is well accepted that exercise training can improve glucoregulatory function in individuals at risk for the development of type 2 diabetes,[9] it is not known if changes in postprandial NO production contribute to this improvement. The purpose of the present study, therefore, was to determine if plasma NO_x concentration, as a marker for NO production, increases in response to an oral glucose load in subjects who are free from cardiovascular disease and diabetes. Furthermore, because insulin and glucose may affect NO production,[10] we sought to determine if the plasma NO_x response to oral glucose would be associated with plasma insulin and/or glucose responses to an oral glucose load. Lastly, because endurance exercise training is known to improve glucoregulatory function,[11,12] we studied the effect of 6 months of endurance exercise training on the plasma NO_x response to oral glucose load in previously sedentary individuals who were at an increased risk for type 2 diabetes due to their age and body mass index (BMI).

MATERIALS AND METHODS

Subjects

Sixty-four sedentary, nondiabetic, healthy men (n = 23) and women (n = 41) gave their written consent to participate in the study after the nature of all procedures was explained. All provisionally qualified candidates were screened for diabetes using fasting and 2-hour post-glucose load plasma glucose concentrations according to published guidelines.[13] No subjects were taking medications known to affect glucose metabolism. Further details on subject screening and recruitment are published elsewhere.[14] Of the 64 subjects who completed testing at baseline, a subset of 40 subjects (15 men, 25 women) completed 6 months of endurance training as described below. Among the 24 subjects for which posttraining data are not reported, 16 (25%) dropped out of the study before or during the exercise intervention, and 8 were excluded from the training-effects analyses because of missing glucose tolerance test data.

From the Department of Kinesiology, University of Maryland, College Park, MD.

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Address reprint requests to Edward P. Weiss, PhD, Campus Box 8113, 4566 Scott Ave, Washington University School of Medicine, St. Louis, MO 63110.

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Dietary Control

All 64 subjects underwent 6 weeks of a dietary stabilization period during which they attended twice weekly dietary classes and were taught to consume a diet consistent with the American Heart Association Dietary Recommendations for the General Population.[15] Compliance with the diet was monitored using 7-day diet records and food frequency questionnaires.

Dietary nitrate/nitrite consumption was not assessed or controlled in the present study, however, it is unlikely to have affected the study outcomes because our assessments were performed after a 12- to 16-hour fast and because the half-life of plasma NO_x is 3 to 8 hours.[16,17] Furthermore, because we assessed the acute response of plasma NO_x concentrations to an oral glucose load, it is unlikely that a time-specific postprandial change in plasma NO_x concentrations could be due to random ingestion of dietary nitrate/nitrite from food consumed 12 or more hours before the oral glucose load.

Exercise Intervention

The 6-month, supervised endurance exercise training program utilized exercises, such as treadmill walking, stationary cycling, and stationary rowing. The training program has been described in detail previously.[14] In brief, the subjects were gradually progressed, over the first 10 weeks, to 3 sessions of exercise per week for 40 minutes of exercise per session at 65% to 75% of heart rate reserve.

Dependent Measures

Dependent measures were assessed when the subjects completed the 6-week dietary stabilization class, but before starting their exercise training, and again at the end of the 6-month exercise intervention. Only subjects who had at least a 75% attendance rate for exercise training were retested in the trained state, and exercise training was continued until the last of the dependent measures were made. All assessments at the end of the training intervention were made within 24 to 36 hours after an exercise bout.

Subjects underwent a 3-hour, oral glucose tolerance test (OGTT) before and after the training intervention. For 3 days prior to each OGTT, subjects consumed at least 250 g carbohydrates per day. All tests were started between 6:30 AM and 9 AM and were performed after a 12- to 16-hour overnight fast. A 20-gauge intravenous catheter was placed in an arm vein at or distal to the antecubital fossa. The catheter and extension line were flushed after each draw with 0.9% sodium chloride. Blood samples for glucose, insulin, and NO_x were drawn before and 30, 60, 90, 120, and 180 minutes after an oral glucose load of 75 g of dextrose in a 296-mL (10 fluid oz) solution. Blood samples were immediately mixed with 15% potassium EDTA and stored on ice. Whole blood samples were later centrifuged at 4°C and 1,800 *g* for 20 minutes. Supernatant plasma was transferred to separate tubes for glucose, insulin, and NO_x assays and stored at −80°C for later analyses.

Sample Analysis

For glucose, insulin, and NO_x assays, each subject's OGTT plasma samples from before and after training were analyzed in a single assay to eliminate interassay variability. Glucose was analyzed using the glucose oxidase method and a semiautomatic analyzer (model 2300 Stat Plus; YSI, Yellow Springs, OH). Insulin was assayed via competitive radioimmunoassay (kit HI-14K; Linco Research, St. Charles, MO). Plasma for determination of NO_x concentration was filtered with 10,000 molecular weight cut-off centrifugal ultrafilters at 9,000 *g* and 4°C for 50 minutes. NO_x concentration in the filtered plasma was analyzed via a modification of the Greiss Assay as described elsewhere.[18] For all assays, samples were run in duplicate, and the mean of duplicates was used to represent the sample value for the respective analyte. When results for duplicate measures of a sample were discrepant (>2 mg/dL for glucose or a coefficient of variation of >0.10 for insulin and NO_x), the sample was reassessed in a subsequent assay.

Calculations

Total and incremental areas under the curve (AUC_{total} and $AUC_{partial}$, respectively) were calculated for the OGTT plasma glucose and insulin responses using the trapezoidal rule. Insulin sensitivity index (ISI) was calculated as described by Matsuda and DeFronzo[19] and as follows: $ISI = 10{,}000[(FPG \times FPI) \times (MPG \times MPI)]^{0.5}$, where FPG is fasting plasma glucose in mg/dL, FPI is fasting plasma insulin in μU/mL, MPG is mean plasma glucose during minutes 0 to 120 of the OGTT in mg/dL, and MPI is the mean plasma insulin during minutes 0 to 120 of the OGTT in μU/mL.

Plasma NOx levels decreased in response to the oral glucose load (see below), therefore, the area between baseline and the plasma NO_x concentration curve (NO_x AREA) was calculated as the total area below baseline minus the area below the curve where the area below the curve was calculated using the trapezoidal rule. The maximum change in NO_x (ΔNO_x) was calculated as the lowest postglucose load NO_x concentration minus fasting NO_x concentration. NO_x time-to-minimum was the postprandial time point (ie, 30, 60, 90, 120, or 180) at which the NO_x concentration was at its minimum.

Maximum Oxygen Uptake

Maximum oxygen uptake ($\dot{V}O_{2max}$) was determined via indirect calorimetry during a progressive, incremental treadmill exercise test to exhaustion as described previously.[20]

Statistics

NO_x response to the oral glucose load was evaluated using analysis of variance (ANOVA) and regression analysis with repeated measures over time. Post hoc means comparisons were performed using protected least significant difference tests. For the regression analysis, the time-dependent NO_x response to oral glucose was evaluated for the presence of linear, quadratic, and cubic effects. The effects of endurance training on outcomes from the OGTT were studied in subjects who had paired baseline, and final data and were evaluated using repeated measures ANOVA. Pearson product-moment correlation analyses were used to identify associations between variables with results being presented as correlation coefficients. All outcome data analyses were performed at a type I error rate of 0.05. Error terms are presented as standard error of the mean. All statistical analyses were performed using SAS software (SAS version 8, SAS Institute, Cary, NC).

RESULTS

Subjects

Mean age for the subjects was 58 ± 1 year and $\dot{V}O_2$ max was 25 ± 1 mL/kg/min for both the 64 sedentary subjects (Table 1) and for the 40 training study subjects at baseline (Table 2). Exercise training increased $\dot{V}O_2$ max by 17% to 29 ± 1 mL/kg/min ($P < .001$). Mean BMI for the 64 sedentary subjects was 28.2 kg/m^2 indicating that many of the subjects were overweight. In the training group, body weight decreased from 79.8 ± 14.1 to 78.7 ± 13.7 kg ($P < .01$) following the intervention.

Effect of oral glucose load on plasma NO_x concentration in sedentary individuals. The dependency of plasma NO_x concentration on OGTT time is described by the equation: $NO_x = 15.54411 - 0.02043t + 0.00007719t^2$, where NO_x is NO_x in μmol/L and t is OGTT time in minutes ($P \leq .0001$ for linear

Table 1. Characteristics of 64 Sedentary Subjects

Sex (F/M)	41/23
Age (yr)	58 ± 1
Weight (kg)	79.9 ± 1.7
BMI (kg/m^2)	28.2 ± 0.5
Vo_{2max} (L/min)	2.0 ± 0.1
Vo_{2max} (mL/kg/min)	25 ± 1
Fasting NO_x (μmol/L)	15.6 ± 0.8
Fasting insulin (pmol/L)	79 ± 4
Fasting glucose (mmol/L)	5.0 ± 0.1
120-min glucose (mmol/L)	6.2 ± 0.2
Insulin sensitivity index	3.74 ± 0.22

NOTE. Data are means ± SEM. Insulin sensitivity index determined according to Matsuda and DeFronzo.[19]

and quadratic effects; $P = .01$ for cubic effects) (Fig 1). Plasma NO_x concentration decreased in response to the oral glucose load from 15.6 ± 0.8 μmol/L at 0 minutes to 15.1 ± 0.8 μmol/L at 30 minutes ($P = .068$) and to 14.3 ± 0.7 μmol/L at 60 minutes ($P \leq .001$ compared with NO_x concentrations at 0 and 30 minutes). No further change in NO_x occurred after the 60-minute time point, but the 90-, 120-, and 180-minute NO_x values were all significantly lower than the 0- and 30-minute NO_x values ($P \leq .05$ for all pairwise comparisons).

Association between NO_x response and glucose and insulin responses to the oral glucose load in sedentary individuals. NO_x AREA, ΔNO_x, and NO_x time-to-minimum were not associated with the insulin or glucose responses to the oral glucose load (all P values ≥ 0.58). Furthermore, fasting plasma NO_x concentrations were not associated with the OGTT insulin or glucose responses, with fasting plasma glucose concentrations or with fasting plasma insulin concentrations.

Effects of endurance training on glucose and insulin responses to the oral glucose load. Endurance training resulted in decreases in insulin AUC_{total} (71 ± 4 μmol/L · min before training *v* 55 ± 4 μmol/L · min after training; $P < .01$) and glucose AUC_{total} (1.2 ± 0.04 mmol/L · min · 10^3 before training *v* 1.1 ± 0.04 mmol/L · min · 10^3 after training; $P < .01$). Furthermore, training decreased the plasma insulin concentrations for all OGTT time points (Fig 2) and decreased the plasma glucose concentrations at most OGTT time points (Fig 3).

Table 2. Characteristics of 40 Subjects Before and After Endurance Training

	Before Training	After Training
Sex (F/M)	25/15	—
Age (yr)	58 ± 1	—
Weight (kg)	79.8 ± 2.2	78.7 ± 2.2*
BMI (kg/m^2)	27.8 ± 0.6	27.4 ± 0.6*
Vo_{2max} (L/min)	2.0 ± 0.1	2.3 ± 0.1*
Vo_{2max} (mL/kg/min)	25 ± 1	29 ± 1*
Fasting NO_x (μmol/L)	15.5 ± 1.1	15.3 ± 1.1
Fasting insulin (pmol/L)	82 ± 4	70.8 ± 4*
Fasting glucose (mmol/L)	5.0 ± 0.1	5.0 ± 0.1
120-min glucose (mmol/L)	6.1 ± 0.3	5.7 ± 0.3*
Insulin sensitivity index	3.75 ± 0.32	4.47 ± 0.29*

NOTE. Data are means ± SEM. Insulin sensitivity index determined according to Matsuda and DeFronzo.[19]

*Different from before training at $P \leq .05$

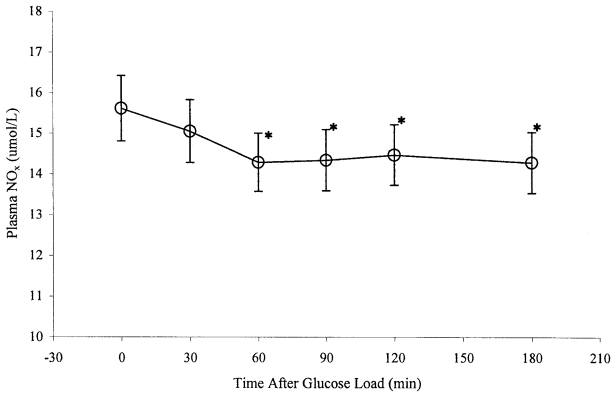

Fig 1. Time-dependent change in plasma NO_x in response to an oral glucose load in 64 sedentary subjects. NO_x, nitrate/nitrite. Bars represent SEM. *$P \leq .05$ *v* NO_x at 0 minutes and NO_x at 30 minutes.

Effects of endurance training on plasma NO_x response to the oral glucose load. NO_x time-to-minimum occurred later during the OGTT after training versus before training (94 ± 9 *v* 114 ± 9 min for the before and after training tests, respectively; $P = .04$) (Fig 4). Neither NO_x AREA nor ΔNO_x changed in response to endurance training. Furthermore, NO_x concentrations at individual OGTT time points were not affected by endurance training.

Association between training-induced changes in NO_x response and glucose and insulin responses to the oral glucose load. None of changes in OGTT NO_x indices with training were associated with changes in insulin AUC_{total} or insulin $AUC_{partial}$ (Table 3). However, training-induced changes in glucose AUC_{total} were positively related to changes in NO_x AREA ($r = .42$, $P = .007$) and ΔNO_x ($r = .37$, $P = .02$), which indicates that individuals who demonstrated the largest training-induced reductions in the OGTT glucose response also had

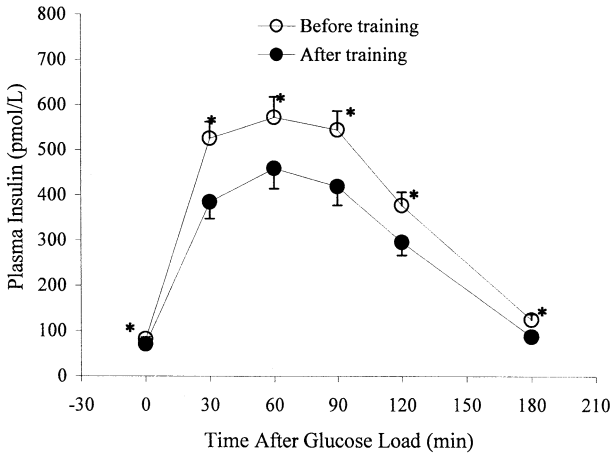

Fig 2. Plasma insulin response to an oral glucose load in 40 subjects before and after endurance exercise training. *$P \leq .05$ between before training and after training at a given OGTT time point.

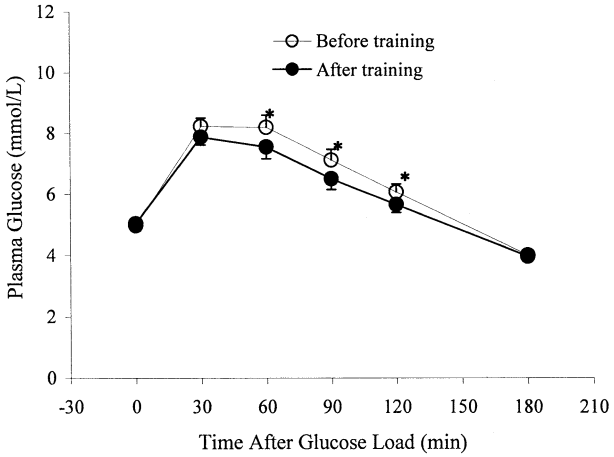

Fig 3. Plasma glucose response to an oral glucose load in 40 subjects before and after endurance exercise training. *$P \leq .05$ between before training and after training at a given OGTT time point.

the greatest upward shifts in the OGTT NO_x response curves (ie, if the glucose curve shifts downward, the NO_x curve shifts upward). Furthermore, the training-induced changes in ISI and NO_x AREA were negatively related ($r = -.32$, $P = .05$) indicating that individuals who increased ISI with training tended to have training-induced upward shifts in their OGTT NO_x curves. The training-induced changes in $\dot{V}O_{2max}$ were not related to changes in NO_x AREA ($r = .02$, $P = .91$), ΔNO_x ($r = .06$, $P = .71$) or NO_x time-to-minimum ($r = -.07$, $P = .67$) or with fasting plasma NO_x concentrations ($r = -.03$, $P = .88$).

DISCUSSION

Sedentary, middle- to older-aged men and women were studied to determine the plasma NO_x response to a physiologic oral glucose load and to determine if the NO_x response to an oral glucose load is related to the insulin and glucose responses to an oral glucose load. Furthermore, a subset of men and women underwent endurance-exercise training for 6 months to determine the effect of endurance training on the NO_x response to oral glucose.

Responses to Oral Glucose in Sedentary Individuals

A reasonable case can be made to suggest that NO production should increase postprandially to facilitate blood glucose disposal. In theory, postprandial hyperinsulinemia increases systemic NO production which, in turn, facilitates glucose disposal via its effects on muscle blood flow,[1] cellular glucose uptake,[2] and systemic insulin and glucagon levels.[4,5] Despite these premises, we failed to identify a postprandial increase in systemic NO production as determined by plasma NO_x concentrations. Furthermore, our data suggest that systemic NO production acutely decreases postprandially as evidenced by a small, but significant, decrease in plasma NO_x concentrations in the 60 minutes following oral glucose ingestion.

The only others to report the plasma NO_x concentration response to an oral glucose load were Kawano et al,[6] however, they studied patients with CVD who might have had endothelial dysfunction as is often found in CVD patients[7,8]; and endothelial dysfunction could possibly explain the lack of a postprandial increase in plasma NO_x concentration in their study. The present study, however, advances the findings of Kawano et al[6] in that our CVD-free subjects exhibited a decrease, rather than an increase, in plasma NO_x concentrations in response to an oral glucose load. It is perhaps noteworthy that although Kawano et al[6] did not detect a statistically significant decline in plasma NO_x concentrations in response to an oral glucose load, mean plasma NO_x concentrations decreased by 5% to 7%, which is a relative decrease of similar magnitude to the statistically significant 8% decrease found in the present study. The 3-fold larger sample size used in the present study may be the reason for the difference in statistical results between the present study and that of Kawano et al.[6]

While the reason for the postprandial decrease in plasma NO_x concentrations is not clear, it is possible that acute hyperglycemia impairs systemic NO production. Although too little evidence is available to conclude with regard to this possibility, it is worthwhile to note that several studies have found that an oral glucose load impairs endothelium-dependent vasodilation.[21-23] Because endothelium-dependent vasodilation is thought to depend primarily on NO production and signaling, these studies suggest that physiologic hyperglycemia impairs NO production and/or NO signaling. Furthermore, in cultured endothelial cells, it has been shown that physiologic glucose concentrations fully mitigate the stimulatory effects of insulin on endothelial NO production.[10] The results of the present study support the possibility that an oral glucose load reduces systemic NO production and suggest that NO production is not increased to facilitate postprandial blood glucose disposal.

If plasma glucose concentrations do influence NO production, it might be expected that plasma NO_x concentrations would be restored to basal levels in a time course that is similar

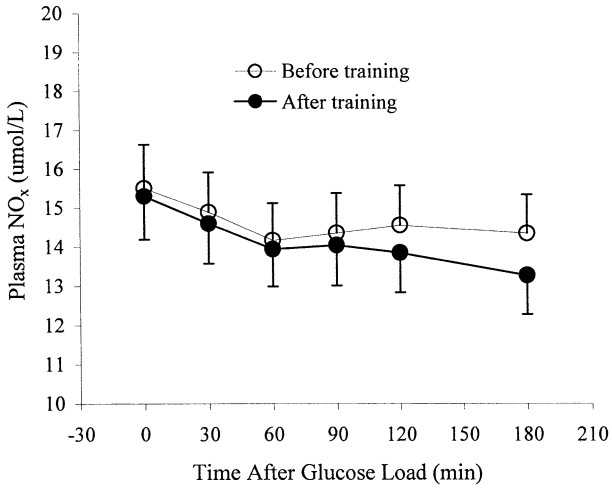

Fig 4. Plasma NO_x response to an oral glucose load in 40 subjects before and after endurance exercise training.

Table 3. Correlation Matrix for Training-Induced Changes in Indices of the NO_x Response to Oral Glucose Load and Glucoregulatory Indices

	Change in NO_x AREA (μmol/L · min · 10^2)	Change in ΔNO_x (μmol/L)	Change in NO_x time-to-minimum (min)	Change in Fasting NO_x (μmol/L)
Change in insulin AUC_{total} (μmol/L · min)	0.11 (.51)	0.16 (.32)	0.25 (.12)	0.09 (.60)
Change in insulin $AUC_{partial}$ (μmol/L · min)	0.08 (.64)	0.14 (.38)	0.24 (.14)	0.10 (.55)
Change in glucose AUC_{total} (mmol/L · min · 10^3)	0.42 (<.01)	0.37 (.02)	−0.05 (.75)	−0.06 (.73)
Change in glucose $AUC_{partial}$ (mmol/L · min · 10^3)	0.24 (.14)	0.27 (.09)	−0.07 (.69)	0.02 (.89)
Change in ISI	−0.32 (.05)	−0.27 (.10)	0.01 (.95)	−0.09 (.57)

NOTE. Values are Pearson correlation coefficients with corresponding *P* values in parentheses.

to that for the restoration of plasma glucose levels to baseline values. In the present study, however, plasma NO_x concentrations remained below baseline levels despite the fact the plasma glucose concentrations had returned to baseline values. While it is not clear why the time courses for plasma glucose and NO_x recovery are not parallel in the present study, it is possible that changes in plasma NO_x concentrations lag behind those for plasma glucose concentrations. Indeed, during the early stages of the OGTT, plasma glucose concentrations peaked by the 30-minute time point, while the decrease in plasma NO_x concentration was not complete until the 60-minute time point. If a similar time-lag is maintained during the 3 to 4 hours after glucose ingestion, plasma NO_x concentrations would not be expected to return to baseline until after the OGTT was terminated, because plasma glucose values in the present study did not return to baseline values until the end of the 180-minute test.

Because NO production has been suggested to be part of the mechanism for insulin-mediated glucose disposal,[24] we hypothesized that the NO_x response to oral glucose would be associated with the plasma insulin response. NO_x decreased in response to the oral glucose, rather than increasing, as we hypothesized. Furthermore, the NO_x and insulin responses to a glucose load were not correlated (data not shown). These data suggest that physiologic hyperinsulinemia, in the presence of physiologic hyperglycemia, is not related to circulatory NO production.

Endurance Training Responses

To date, no studies have assessed the effect of endurance training on the plasma NO_x concentration response to an oral glucose load. Endurance training was hypothesized to alter the NO_x response to an oral glucose load because it is thought that insulin is involved in NO production in vivo[25-28] and because the insulin response to oral glucose is attenuated with endurance training.[29,30] Training resulted in clear improvements in insulin action as evidenced by a 19% increase in ISI, a 23% decrease in insulin AUC_{total}, and a 6% decrease in glucose AUC_{total}. However, while the OGTT NO_x time-to-minimum occurred 20 minutes later as a result of endurance training, training did not affect NO_x AREA or ΔNO_x. Taken together, these findings suggest that circulating NO and its control systems are not involved in training-induced adaptations in postprandial glucose control.

Despite the lack of training-induced changes in the NO_x response to oral glucose for the group as a whole, it is interesting to note that the individual responses varied widely with some individuals demonstrating large decreases in NO_x AREA, while others increased (range, −13.8 to 4.7 μmol/L · min · 10^2). To identify potential determinants of individual changes in NO_x response to oral glucose, we assessed the associations between glucoregulatory indices and the OGTT NO_x response and found weak to moderate associations between training-induced changes in glucose AUC_{total} and training-induced changes in NO_x AREA and ΔNO_x. These correlations suggest that training-induced attenuations in the OGTT glucose response are associated with training-induced upward shifts in the OGTT NO_x response curves. Despite the association between training-induced changes in glucose AUC_{total} and OGTT NO_x response indices, training-induced changes in the OGTT insulin response indices were not associated with changes in any of the OGTT NO_x response indices.

Limitations

An assumption in our study is that a change in venous plasma NO_x concentration reflects a change in NO production in vivo. Several studies have concluded that changes in plasma NO_x concentrations validly reflect changes in NO production[16,17,31,32]; however, it has been suggested that because NO_x is distributed in a large volume pool, only large changes in NO production would be detectable.[16,17] Despite the low sensitivity of plasma NO_x concentration to changes in NO production, we demonstrated a small, but significant, reduction in NO_x levels in response to an oral glucose load.

Another limitation in the present study is that decreases in circulating NO_x during the OGTT may simply reflect diurnal variation in plasma NO_x concentrations. While this possibility cannot be fully ruled out, it seems an unlikely explanation because 2 studies have demonstrated that circulating NO_x concentrations increase during daytime hours after reaching a nadir during the early morning sleeping hours,[33,34] and 2 additional studies reported that plasma NO_x concentrations do not exhibit diurnal variation.[35,36] OGTTs in the present study were started in the morning waking hours between 6:30 AM and 9 AM and concluded between 10 AM and 12:30 PM. Therefore, diurnal variation in circulating NO_x concentrations, if existent at all, would counter the decreases in plasma NO_x concentrations reported in the present study, not explain them. Lastly, because all of the decreases in plasma NO_x concentrations during the OGTT occurred during the 0- to 60-minute time periods of the OGTT and then remained constant through the rest of the 180-minute test, it seems unlikely that this rapid and time-point specific change is reflective of diurnal change.

In conclusion, it appears that production of circulating NO is not a major contributor to glucoregulatory function in seden-

tary, nondiabetic, middle- to older-aged men and women following a physiologic glucose load and that the NO_x response after a physiologic glucose load is not related to the OGTT insulin or glucose responses.

In response to endurance training, however, it appears that the time required to reach minimum NO_x levels after a glucose load is greater after training. Furthermore, although the magnitude of NO_x response (as indicated by NO_x AREA and ΔNO_x) to an oral glucose load does not appear to change with training for all individuals, individual training-induced changes in the NO_x response magnitude are partly explained by training-induced changes in OGTT glucose responses. Lastly, it is important to qualify these conclusions as preliminary due to the inherent limitations involved in studying the role of circulatory NO in metabolism. It is important that future studies use complementary methods, such as NO donor infusions, to contribute to our understanding of the role of NO in glucoregulatory function.

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